

# **Integrated Science Assessment for Sulfur Oxides—Health Criteria**

**(Second External Review Draft)**

December 2016

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

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# Integrated Science Assessment Team for Sulfur Oxides—Health Criteria

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## Executive Direction

- Dr. John Vandenberg (Director, RTP Division)—National Center for Environmental Assessment—Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC
- Ms. Debra Walsh (Deputy Director, RTP Division)—National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC
- Dr. Reeder Sams II (Acting Deputy Director, RTP Division)—National Center for Environmental Assessment, 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. Steven J. Dutton (Branch Chief)—National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC
- Dr. Ellen Kirrane (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. Tom Long (Team Leader, Integrated Science Assessment for Sulfur Oxides)—National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC
- Dr. James Brown—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. Steven J. Dutton—National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC
- Dr. Brooke L. Hemming—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. Ellen Kirrane—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. Thomas Luben—National Center for Environmental Assessment, Office of Research and Development, 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

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 M. 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

Dr. Jennifer Richmond-Bryant—National Center for Environmental Assessment, Office of Research and Development, 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. David Svendsgaard—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**

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

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

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

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

Mr. Samuel S. Thacker—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

---

---

## **Authors, Contributors, and Reviewers**

---

### **Authors**

- Dr. Tom Long (Team Leader, Integrated Science Assessment for Sulfur Oxides)—National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC
- Dr. Michael Breen—National Exposure Research Laboratory, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC
- Dr. James Brown—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
- Mr. Evan Coffman—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. Laura Datko-Williams—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. Steven J. Dutton—National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC
- Dr. Rachelle Duvall—National Exposure Research Laboratory, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC
- Dr. Brooke L. Hemming—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. Ellen Kirrane—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. Thomas Luben—National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC
- Dr. Jennifer Nichols—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. Michelle Oakes—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. Elizabeth Oesterling Owens—National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC
- Dr. Molini M. Patel—National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC
- Dr. Steven Perry—National Exposure Research Laboratory, 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
- Dr. Kristen Rappazzo—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. Jennifer Richmond-Bryant—National Center for Environmental Assessment, Office of Research and Development, 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. Tina Stevens—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. 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. Gregory Wellenius†—Department of Community Health (Epidemiology Section), Brown University, Providence, RI

†Under Sub-contract, through ICF International

---

## Contributors

- Ms. Breanna Alman—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. Adam Benson—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. Candis Edwards—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. Charlene Finley—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. Beth Gatling—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. William Griffin—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. Rachel Housego—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. Satoru Ito—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. Emily Lau—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. Meagan Madden—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. April Maxwell—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. Ihab Mikati—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. Danielle Moore—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. Kyle Painter—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. Adam Reff—Office of Air Quality Planning and Standards, Office of Air and Radiation, U.S. Environmental Protection Agency, Research Triangle Park, NC

Ms. Alexandra Ross—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. Kaylyn Siporin—Curriculum for the Environment and Ecology, University of North Carolina, Chapel Hill, NC

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

Ms. Adrien Wilkie—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. Brianna Young—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

---

## Reviewers

Dr. Sara Adar—School of Public Health, University of Michigan, Ann Arbor, MI

Mr. Ed Avol—Keck School of Medicine, University of Southern California, Los Angeles, CA

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

Dr. Jeffrey Brook—Environment Canada, Toronto, ON

Mr. Matthew Davis—Office of Children’s Health Protection, U.S. Environmental Protection Agency, Washington, DC

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

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

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

Dr. Douglas Johns—Division of Respiratory Disease Studies, National Institute for Occupational Safety and Health, Morgantown, WV

Mr. William Keene—Department of Environmental Sciences, University of Virginia, Charlottesville, VA

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

Dr. Leila Lackey—Office of Science Policy, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Mr. John Langstaff—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

Dr. Qingyu Meng—School of Public Health, Rutgers University, Piscataway, NJ

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

Dr. Jennifer Peel—Colorado School of Public Health, Colorado State University, Fort Collins, CO

Dr. Edward Schelegle—School of Veterinary Medicine, University of California—Davis, Davis, CA

- Dr. Michael Stewart—Office of Air Quality Planning and Standards, Office of Air and Radiation, U.S. Environmental Protection Agency, Research Triangle Park, NC
- Dr. James Thurman—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 Wagner—College of Veterinary Medicine, Michigan State University, East Lansing, MI
- Dr. Lewis Weinstock—Office of Air Quality Planning and Standards, Office of Air and Radiation, U.S. Environmental Protection Agency, Research Triangle Park, NC
- Ms. Debra Walsh—National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC
- Ms. Melina Williams—Air and Radiation Law Office, Office of General Counsel, U.S. Environmental Protection Agency, Washington, DC

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# Clean Air Scientific Advisory Committee Sulfur Oxides NAAQS Review Panel

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## Chair of the Sulfur Oxides Review Panel

Dr. Ana Diez-Roux\*, Drexel University, Philadelphia, PA

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## Sulfur Oxides Review Panel Members

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

Dr. John R. Balmes—University of California, San Francisco, CA

Dr. James Boylan—Georgia Department of Natural Resources, Atlanta, GA

Dr. Judith Chow\*\*—Desert Research Institute, Reno, NV

Dr. Aaron Cohen—Health Effects Institute, Boston, MA

Dr. Alison Cullen—University of Washington, Seattle, WA

Dr. Delbert Eatough—Brigham Young University, Provo, UT

Dr. Christopher Frey\*\*\*—North Carolina State University, Raleigh, NC

Dr. William Griffith—University of Washington, Seattle, WA

Dr. Steven Hanna—Hanna Consultants, Kennebunkport, ME

Dr. Jack Harkema\*\*—Michigan State University, East Lansing, MI

Dr. Daniel Jacob—Harvard University, Cambridge, MA

Dr. Farla Kaufman—California Environmental Protection Agency, Sacramento, CA

Dr. David Peden—University of North Carolina at Chapel Hill, Chapel Hill, NC

Dr. Richard Schlesinger—Pace University, New York, NY

Dr. Elizabeth A. (Lianne) Sheppard\*\*—University of Washington, Seattle, WA

Dr. Frank Speizer—Harvard Medical School, Boston, MA

Dr. James Ultman—Pennsylvania State University, University Park, PA

Dr. Ronald Wyzga\*\*—Electric Power Research Institute, Palo Alto, CA

\*Chair of the statutory Clean Air Scientific Advisory Committee (CASAC) appointed by the U.S. EPA Administrator

\*\*Members of the statutory CASAC appointed by the U.S. EPA Administrator

\*\*\*Immediate Past CASAC Chair

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## Science Advisory Board Staff

Mr. Aaron Yeow (Designated Federal Officer)—U.S. Environmental Protection Agency, Science Advisory Board (1400R), 1200 Pennsylvania Avenue, NW, Washington, DC 20460-0001, Phone: 202-564-2050, Fax: 202-565-2098, (yeow.aaron@epa.gov) (FedEx: 1300 Pennsylvania Avenue, NW, Suite 31150, Washington, DC 20004)

# Acronyms and Abbreviations

<b>Acronym/ Abbreviation</b>	<b>Meaning</b>	<b>Acronym/ Abbreviation</b>	<b>Meaning</b>
$\alpha$	alpha, exposure factor	BALF	bronchoalveolar lavage fluid
A4	not classifiable for humans or animals	B[a]P	benzo[a]pyrene
AA	adenine-adenine genotype	bax	B-cell lymphoma 2-like protein 4
ACS	American Cancer Society	BC	black carbon
AER	air exchange rate; Atmospheric and Environmental Research	Bcl-2	B-cell lymphoma 2
AERMOD	American Meteorological Society/U.S. EPA Regulatory Model	BHR	bronchial hyperreactivity
ag	agriculture	BK	Bangkok
AG	adenine-guanine genotype	BMA	Bayesian Model Averaging
AGL	above ground level	BMI	body mass index
AHR	airway hyperresponsiveness	BP	blood pressure
AIRS	Aerometric Information Retrieval System; Atmospheric Infrared Sounder	BrO	bromine oxide
AL	Alabama	BS	black smoke
ALRI	acute lower respiratory infection	C	degrees Celsius; the product of microenvironmental concentration; carbon
a.m.	ante meridiem (before noon)	C1	sulfur dioxide + nitrogen dioxide
APEX	Air Pollution Exposure model	C2	sulfur dioxide + PM <sub>10</sub>
APHEA	Air Pollution and Health: A European Approach study	C3	sulfur dioxide + ozone
APIMS	atmospheric pressure ionization mass spectrometry	CA	California
AQCD	air quality criteria document	C <sub>a</sub>	central site ambient SO <sub>2</sub> concentration
AQS	air quality system	<i>C<sub>a,csm</sub></i>	ambient concentration at a central site monitor
ARIES	Aerosol Research Inhalation Epidemiology Study	CAA	Clean Air Act
ARP	Acid Rain Program	CAIR	Clean Air Interstate Rule
ASM	airway smooth muscle	CAPES	China Air Pollution and Health Effects Study
AT	Atascadero	CASAC	Clean Air Scientific Advisory Committee
ATD	atmospheric transport and dispersion	CBSA	core-based statistical area
ATS	American Thoracic Society	CCN	cloud condensation nuclei
avg	average	CDC	Centers for Disease Control and Prevention
AZ	Arizona	CFR	Code of Federal Regulations
$\beta$	beta	cGMP	cyclic guanosine monophosphate
BAL	bronchoalveolar lavage	CH <sub>3</sub> SH	methyl mercaptan

<b>Acronym/ Abbreviation</b>	<b>Meaning</b>	<b>Acronym/ Abbreviation</b>	<b>Meaning</b>
CH <sub>3</sub> -S-CH <sub>3</sub>	dimethyl sulfide	DFA	detrended fluctuation analysis
CH <sub>3</sub> -S-S-CH <sub>3</sub>	dimethyl disulfide	DL	distributed lag
(CH <sub>3</sub> ) <sub>2</sub> SO	dimethyl sulfoxide	DMDS	dimethyl disulfide
CH <sub>3</sub> SO <sub>3</sub> H	methanesulfonic acid	DMS	dimethyl sulfide
CHAD	Consolidated Human Activity Database	DNA	deoxyribonucleic acid
CHD	coronary heart disease	DOAS	differential optical absorption spectroscopy
CHF	congestive heart failure	DVT	deep vein thrombosis
CI(s)	confidence interval(s)	e.g.	exempli gratia (for example)
cIMT	carotid intima-media thickness	<i>E<sub>a</sub></i>	exposure to SO <sub>2</sub> of ambient origin
<i>C<sub>j</sub></i>	airborne SO <sub>2</sub> concentration at microenvironment <i>j</i>	EBC	exhaled breath condensate
Cl	chlorine radical	EC	elemental carbon
CMAQ	Community Multiscale Air Quality	ECG	electrocardiographic
CO	carbon monoxide; Colorado	ECRHS	European Community Respiratory Health Survey
CO <sub>2</sub>	carbon dioxide	ED	emergency department
COH	coefficient of haze	EGF	epidermal growth factor
Conc	concentration	EGFR	epidermal growth factor receptor
Cong.	congress	EGU	electric power generating unit
COPD	chronic obstructive pulmonary disease	EIB	exercise-induced bronchospasm
COX-2	cyclooxygenase-2	EKG	electrocardiogram
C-R	concentration-response (relationship)	ELF	epithelial lining fluid
CRDS	cavity ring-down spectroscopy	EMSA	electrophoretic mobility shift assay
CRP	c-reactive protein	<i>E<sub>na</sub></i>	exposure to SO <sub>2</sub> of nonambient origin
CS <sub>2</sub>	carbon disulfide	eNO	exhaled nitric oxide
CT	Connecticut	EP	entire pregnancy
CTM	chemical transport models	EPA	U.S. Environmental Protection Agency
CVD	cardiovascular disease	<i>E<sub>T</sub></i>	total exposure over a time period of interest
D.C. Cir	District of Columbia Circuit	EWPM	emission-weighted proximity model
d	day	Exp(B)	odds ratio of bivariate associations
DBP	diastolic blood pressure	F	female
DC	District of Columbia	FB	fractional bias
DEcCBP	diesel exhaust particle extract-coated carbon black particles	FC	fuel combustion
DEP	diesel exhaust particles		
df	degrees of freedom		

<b>Acronym/ Abbreviation</b>	<b>Meaning</b>	<b>Acronym/ Abbreviation</b>	<b>Meaning</b>
FEF <sub>25-75%</sub>	forced expiratory flow at 25–75% of exhaled volume	H <sub>2</sub> SO <sub>4</sub>	sulfuric acid
FEF <sub>50%</sub>	forced expiratory flow at 50% of forced vital capacity	HERO	Health and Environmental Research Online
FEF <sub>75%</sub>	forced expiratory flow at 75% of forced vital capacity	HF	high frequency component of HRV
FEF <sub>max</sub>	maximum forced expiratory flow	HI	Hawaii
FEM	federal equivalent method	HK	Hong Kong
FeNO	fractional exhaled nitric oxide	HO <sub>2</sub>	hydroperoxyl radical
FEV	forced expiratory volume	HR	hazard ratio(s); heart rate
FEV <sub>1</sub>	forced expiratory volume in 1 second	HRV	heart rate variability
FL	Florida	HS	hemorrhagic stroke
FOXp3	forkhead box P3	HSO <sub>3</sub> <sup>-</sup>	bisulfite
FPD	flame photometric detection	HSC	Harvard Six Cities
FR	Federal Register	i.p.	intraperitoneal
FRC	functional residual capacity	IARC	International Agency for Research on Cancer
FRM	federal reference method	i.e.	id est (that is)
func	functional residual capacity	ICAM-1	intercellular adhesion molecule 1
FVC	forced vital capacity	ICC	intraclass correlation coefficient
g	gram	ICD	International Classification of Diseases; implantable cardioverter defibrillators
GA	Georgia	IDW	inverse distance weighting
GALA II	Genes-Environments and Admixture in Latino Americans	IFN- $\gamma$	interferon gamma
GG	guanine-guanine genotype	IgE	immunoglobulin E
GIS	geographic information system	IgG	immunoglobulin G
GM	geometric mean	IHD	ischemic heart disease
GP	general practice	IKK $\beta$	inhibitor of nuclear factor kappa-B kinase subunit beta
GPS	global positioning system	IL	Illinois
GSD	geometric standard deviation	IL-4	interleukin-4
GSTM1	glutathione S-transferase Mu 1	IL-5	interleukin-5
GSTP	glutathione S-transferase P	IL-6	interleukin-6
GSTP1	glutathione S-transferase Pi 1	IL-8	interleukin-8
h	hour(s)	Ile	isoleucine
H <sup>+</sup>	hydrogen ion	IQR	interquartile range
H <sub>2</sub> O	water	IS	ischemic stroke
H <sub>2</sub> O <sub>2</sub>	hydrogen peroxide	ISA	Integrated Science Assessment
H <sub>2</sub> S	hydrogen sulfide	ISAAC	International Study of Asthma and Allergies in Children
H <sub>2</sub> SO <sub>3</sub>	sulfurous acid		

<b>Acronym/ Abbreviation</b>	<b>Meaning</b>	<b>Acronym/ Abbreviation</b>	<b>Meaning</b>
IUGR	intrauterine growth restriction	max	maximum
I $\kappa$ B $\alpha$	nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha	MAX-DOAS	multiaxis differential optical absorption spectroscopy
<i>j</i>	microenvironment	MCh	methacholine
JE	joint model estimate	MD	Maryland
<i>k</i>	reaction rate; decay constant derived from empirical data; rate of SO <sub>2</sub> loss in the microenvironment	MDL	method detection limit
K <sub>ATP</sub>	adenosine triphosphate (ATP)-sensitive potassium channel	ME	Maine
kg	kilogram(s)	med	median
km	kilometer(s)	mg	milligram
KS	Kansas	MI	myocardial infarction (“heart attack”); Michigan
L	liter(s)	min	minimum; minute
LBW	low birth weight	MINAP	Myocardial Ischaemia National Audit Project
LED	light-emitting diode	MISA	Meta-analysis of the Italian studies on short-term effects of air pollution
LF	low-frequency component of HRV	mL	milliliter(s)
LF/HF	ratio of LF and HF components of HRV	mm	millimeters
LIF	laser induced fluorescence	MMEF	maximum midexpiratory flow
ln	natural logarithm	MMFR	Maximal midexpiratory flow rate
LOD	limit of detection	mmHg	millimeters of mercury
LOESS	locally weighted scatterplot smoothing	MN	Minnesota
Lp-PLA <sub>2</sub>	lipoprotein-associated phospholipase A <sub>2</sub>	MN	micronuclei formation
LUR	land use regression	MNPCE	polychromatophilic erythroblasts of the bone marrow
LX	lung adenoma-susceptible mouse strain	mo	month(s)
$\mu$	mu; micro	MO	Missouri
$\mu\text{g}/\text{m}^3$	micrograms per cubic meter	MOA	mode(s) of action
m	meter	MODIS	Moderate Resolution Imaging Spectroradiometer
M	male	mRNA	messenger ribonucleic acid
MA	Massachusetts	MS	Mississippi
M1	Month 1	MSA	methane sulfonic acid
M2	Month 2	MSE	mean standardized error
M3	Month 3	MUC5AC	mucin 5AC glycoprotein
M12	average of M1 and M2	<i>n</i>	sample size; total number of microenvironments that the individual has encountered
		N	population number

<b>Acronym/ Abbreviation</b>	<b>Meaning</b>	<b>Acronym/ Abbreviation</b>	<b>Meaning</b>
N <sub>2</sub>	molecular nitrogen	OHCA	out-of-hospital cardiac arrests
N/A	not applicable	OMI	Ozone Monitoring Instrument
NA	not available	OR	odds ratio(s)
NAAQS	National Ambient Air Quality Standards	OVA	ovalbumin
NaCl	sodium chloride	<i>p</i>	probability
NALF	nasal lavage fluid	P	Pearson correlation
NBP	NO <sub>x</sub> Budget Program	P53	tumor protein 53
NC	North Carolina	PA	Pennsylvania
NCORE	National Core network	PAH(s)	polycyclic aromatic hydrocarbon(s)
NEI	National Emissions Inventory	PAPA	Public Health and Air Pollution in Asia
NFκB	nuclear factor kappa-light-chain-enhancer of activated B cells	Pb	lead
NH	New Hampshire	PC(SO <sub>2</sub> )	provocative concentration of SO <sub>2</sub>
NH <sub>3</sub>	ammonia	PE	pulmonary embolism
NH <sub>4</sub> <sup>+</sup>	ammonium ion	PEF	peak expiratory flow
NHAPS	National Human Activity Pattern Survey	Penh	enhanced pause
NHLBI	National Heart, Lung, and Blood Institute	PEFR	peak expiratory flow rate
NJ	New Jersey	PM	particulate matter
NLCS	Netherlands Cohort Study on Diet and Cancer	PM <sub>10</sub>	In general terms, particulate matter with a nominal aerodynamic diameter less than or equal to 10 μm; a measurement of thoracic particles (i.e., that subset of inhalable particles thought small enough to penetrate beyond the larynx into the thoracic region of the respiratory tract). In regulatory terms, particles with an upper 50% cutpoint of 10 ± 0.5 μm aerodynamic diameter (the 50% cutpoint diameter is the diameter at which the sampler collects 50% of the particles and rejects 50% of the particles) and a penetration curve as measured by a reference method based on Appendix J of 40 CFR Part 50 and designated in accordance with 40 CFR Part 53 or by an equivalent method designated in accordance with 40 CFR Part 53.
nm	nanometer		
NMMAAPS	The National Morbidity Mortality Air Pollution Study		
NO	nitric oxide		
NO <sub>2</sub>	nitrogen dioxide		
NO <sub>3</sub> <sup>-</sup>	nitrate		
NO <sub>3</sub>	nitrate radical		
non-HS	non-hemorrhagic stroke		
NO <sub>x</sub>	the sum of NO and NO <sub>2</sub>		
NR	not reported		
NY	New York		
O <sub>3</sub>	ozone		
obs	observations		
OC	organic carbon		
OCS	carbonyl sulfide		
OH	hydroxide; Ohio		

<b>Acronym/ Abbreviation</b>	<b>Meaning</b>	<b>Acronym/ Abbreviation</b>	<b>Meaning</b>
PM <sub>10-2.5</sub>	In general terms, particulate matter with a nominal aerodynamic diameter less than or equal to 10 µm and greater than a nominal 2.5 µm; a measurement of thoracic coarse particulate matter or the coarse fraction of PM <sub>10</sub> . In regulatory terms, particles with an upper 50% cutpoint of 10 µm aerodynamic diameter and a lower 50% cutpoint of 2.5 µm aerodynamic diameter (the 50% cutpoint diameter is the diameter at which the sampler collects 50% of the particles and rejects 50% of the particles) as measured by a reference method based on Appendix O of 40 CFR Part 50 and designated in accordance with 40 CFR Part 53 or by an equivalent method designated in accordance with 40 CFR Part 53.	Q3	3rd quartile or quintile
		Q4	4th quartile or quintile
		Q5	5th quintile
		QT interval	time between start of Q wave and end of T wave in ECG
		R <sup>2</sup>	square of the correlation coefficient
		RI	Rhode Island
		RMB	renminbi
		rMSSD	root-mean-square of successive differences
		RR	risk ratio(s), relative risk
		RSP	respirable suspended particles
		RT	total respiratory resistance
		sec	second(s)
		S <sub>2</sub> O	disulfur monoxide
		S. Rep	Senate Report
		SDCCE	simulated downwind coal combustion emissions
		SE	standard error
		SEARCH	Southeast Aerosol Research Characterization
		Sess.	session
		SGA	small for gestational age
		SH	Shanghai
		SHEDS	Stochastic Human Exposure and Dose Simulation
		SHEEP	Stockholm Heart Epidemiology Programme
		SLAMS	state and local air monitoring stations
		SO <sub>2</sub>	sulfur dioxide
		SO <sub>3</sub> <sup>2-</sup>	sulfite
		SO <sub>3</sub>	sulfur trioxide
		SO <sub>4</sub>	sulfur tetroxide
		SO <sub>4</sub> <sup>2-</sup>	sulfate
		SO <sub>x</sub>	sulfur oxides
		SPE	single-pollutant model estimate
		SPM	source proximity model; suspended particulate matter
		sRaw	specific airway resistance
PM <sub>2.5</sub>	In general terms, particulate matter with a nominal aerodynamic diameter less than or equal to 2.5 µm; a measurement of fine particles. In regulatory terms, particles with an upper 50% cutpoint of 2.5 µm aerodynamic diameter (the 50% cutpoint diameter is the diameter at which the sampler collects 50% of the particles and rejects 50% of the particles) and a penetration curve as measured by a reference method based on Appendix L of 40 CFR Part 50 and designated in accordance with 40 CFR Part 53, by an equivalent method designated in accordance with 40 CFR Part 53, or by an approved regional method designated in accordance with Appendix C of 40 CFR Part 58.		
PMR	peak-to-mean ratio		
PNC	particle number concentration		
PR	prevalence ratio		
PRB	policy-relevant background		
PWEI	Population Weighted Emissions Index		
Q2	2nd quartile or quintile		

<b>Acronym/ Abbreviation</b>	<b>Meaning</b>	<b>Acronym/ Abbreviation</b>	<b>Meaning</b>
ST segment	segment of the electrocardiograph between the end of the S wave and beginning of the T wave	wk	week
STN	Speciation Trends Network	WHI	Women's Health Initiative
subj	subject	WI	Wisconsin
<i>t</i>	fraction of time spent in a microenvironment across an individual's microenvironmental exposures, time	yr	year(s)
TBARS	thiobarbituric acid reactive substances (species)	Z*	the true concentration
T1	first trimester		
T2	second trimester		
T3	third trimester		
T1–T1	correlation between 1st trimester SO <sub>2</sub> and copollutants		
TC	total hydrocarbon		
Tg	teragram(s)		
Th1	T-helper 1		
Th2	T-helper 2		
TIA	transient ischemic attack		
TN	Tennessee		
TNF- $\alpha$	tumor necrosis factor alpha		
TX	Texas		
U.S.C.	U.S. Code		
U.K.	United Kingdom		
U.S.	United States of America		
UT	Utah		
V <sub>max50</sub>	maximal expiratory flow rate at 50%		
V <sub>max75</sub>	maximal expiratory flow rate at 75%		
V <sub>max25</sub>	maximal expiratory flow rate at 25%		
VA	Virginia		
Val	valine		
VOC	volatile organic compound		
VSGA	very small for gestational age		
VTE	venous thromboembolism		
WBC	white blood cell		
WH	Wuhan		

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## Preface

### Legislative Requirements for the Review of the National Ambient Air Quality Standards

1 Two sections of the Clean Air Act (CAA) govern the establishment, review, and revision  
2 of the National Ambient Air Quality Standards (NAAQS). Section 108 [42 U.S. Code  
3 (U.S.C.) 7408] directs the Administrator to identify and list certain air pollutants and then  
4 to issue air quality criteria for those pollutants. The Administrator is to list those air  
5 pollutants that in her “judgment, cause or contribute to air pollution which may  
6 reasonably be anticipated to endanger public health or welfare,” “the presence of which  
7 in the ambient air results from numerous or diverse mobile or stationary sources,” and  
8 “for which ... [the Administrator] plans to issue air quality criteria ...” [42 U.S.C.  
9 7408(a)(1); [CAA, 1990a](#)]. Air quality criteria are intended to “accurately reflect the  
10 latest scientific knowledge useful in indicating the kind and extent of all identifiable  
11 effects on public health or welfare, which may be expected from the presence of [a]  
12 pollutant in the ambient air ...” [42 U.S.C. 7408(b)]. Section 109 [42 U.S.C. 7409;  
13 [CAA, 1990b](#)] directs the Administrator to propose and promulgate “primary” and  
14 “secondary” NAAQS for pollutants for which air quality criteria are issued.

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

22 The requirement that primary standards provide an adequate margin of safety was  
23 intended to address uncertainties associated with inconclusive scientific and technical  
24 information available at the time of standard setting. It was also intended to provide a

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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, 91st Cong., 2d Sess. 10 (1970).

<sup>2</sup> Section 302(h) of the Act [42 U.S.C. 7602(h)] provides that all language referring to effects on welfare includes, but is not limited to, “effects on soils, water, crops, vegetation, man-made materials, animals, wildlife, weather, visibility and climate, damage to and deterioration of property, and hazards to transportation, as well as effects on economic values and on personal comfort and well-being ...” ([CAA, 2005](#)).

1 reasonable degree of protection against hazards that research has not yet identified.<sup>1</sup> Both  
2 kinds of uncertainty are components of the risk associated with pollution at levels below  
3 those at which human health effects can be said to occur with reasonable scientific  
4 certainty. Thus, in selecting primary standards that provide an adequate margin of safety,  
5 the Administrator is seeking not only to prevent pollution levels that have been  
6 demonstrated to be harmful but also to prevent lower pollutant levels that may pose an  
7 unacceptable risk of harm, even if the risk is not precisely identified as to nature or  
8 degree. The CAA does not require the Administrator to establish a primary NAAQS at a  
9 zero-risk level or at background concentration levels, but rather at a level that reduces  
10 risk sufficiently so as to protect public health with an adequate margin of safety.<sup>2</sup> In so  
11 doing, protection is provided for both the population as a whole and those groups and  
12 lifestages potentially at increased risk for health effects from exposure to the air pollutant  
13 for which each NAAQS is set.

14 In addressing the requirement for an adequate margin of safety, the U.S. Environmental  
15 Protection Agency (U.S. EPA) considers such factors as the nature and severity of the  
16 health effects involved, the size of the sensitive group(s), and the kind and degree of the  
17 uncertainties. The selection of any particular approach to providing an adequate margin  
18 of safety is a policy choice left specifically to the Administrator’s judgment.<sup>3</sup>

19 In setting standards that are “requisite” to protect public health and welfare as provided in  
20 Section 109(b), the U.S. EPA’s task is to establish standards that are neither more nor less  
21 stringent than necessary for these purposes. In so doing, the U.S. EPA may not consider  
22 the costs of implementing the standards.<sup>4</sup> Likewise, “[a]ttainability and technological  
23 feasibility are not relevant considerations in the promulgation of national ambient air  
24 quality standards.”<sup>5</sup>

25 Section 109(d)(1) requires that “not later than December 31, 1980, and at 5-year intervals  
26 thereafter, the Administrator shall complete a thorough review of the criteria published  
27 under Section 108 and the national ambient air quality standards ... and shall make such  
28 revisions in such criteria and standards and promulgate such new standards as may be

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<sup>1</sup> See *Lead Industries Association v. EPA*, 647 F.2d 1130, 1154 [District of Columbia Circuit (D.C. Cir.) 1980]; *American Petroleum Institute v. Costle*, 665 F.2d 1176, 1186 (D.C. Cir. 1981); *American Farm Bureau Federation v. EPA*, 559 F. 3d 512, 533 (D.C. Cir. 2009); *Association of Battery Recyclers v. EPA*, 604 F. 3d 613, 617–18 (D.C. Cir. 2010).

<sup>2</sup> See *Lead Industries v. EPA*, 647 F.2d at 1156 n.51; *Mississippi v. EPA*, 744 F. 3d 1334, 1339, 1351, 1353 (D.C. Cir. 2013).

<sup>3</sup> See *Lead Industries Association v. EPA*, 647 F.2d at 1161–62; *Mississippi v. EPA*, 744 F. 3d at 1353.

<sup>4</sup> See generally, *Whitman v. American Trucking Associations*, 531 U.S. 457, 465–472, 475–476 (2001).

<sup>5</sup> See *American Petroleum Institute v. Costle*, 665 F. 2d at 1185.

1 appropriate ....” Section 109(d)(2) requires that an independent scientific review  
2 committee “shall complete a review of the criteria ... and the national primary and  
3 secondary ambient air quality standards ... and shall recommend to the Administrator any  
4 new ... standards and revisions of existing criteria and standards as may be  
5 appropriate ....” Since the early 1980s, this independent review function has been  
6 performed by the Clean Air Scientific Advisory Committee (CASAC).<sup>1</sup>

## Overview and History of the Reviews of the Primary National Ambient Air Quality Standard for Sulfur Dioxide

7 NAAQS are defined by four basic elements: indicator, averaging time, level, and form.  
8 The indicator defines the pollutant to be measured in the ambient air for the purpose of  
9 determining compliance with the standard. The averaging time defines the time period  
10 over which air quality measurements are to be obtained and averaged or cumulated,  
11 considering evidence of effects associated with various time periods of exposure.  
12 The level of a standard defines the air quality concentration used (i.e., an ambient  
13 concentration of the indicator pollutant) in determining whether the standard is achieved.  
14 The form of the standard defines the air quality statistic that is compared to the level of  
15 the standard in determining whether an area attains the standard. For example, the form  
16 of the current primary 1-hour sulfur dioxide (SO<sub>2</sub>) standard is the 3-year average of the  
17 99th percentile of the annual distribution of 1-hour daily maximum SO<sub>2</sub> concentrations.  
18 The Administrator considers these four elements collectively in evaluating the protection  
19 to public health provided by the primary NAAQS.

20 The U.S. EPA considers the term sulfur oxides to refer to multiple gaseous oxidized  
21 sulfur species such as SO<sub>2</sub> and sulfur trioxide (SO<sub>3</sub>). SO<sub>2</sub> was chosen as the indicator for  
22 sulfur oxides because as in previous reviews, the presence of other sulfur oxides in the  
23 atmosphere has not been demonstrated, and SO<sub>2</sub> has a large body of health effects  
24 evidence associated with it. The atmospheric chemistry, exposure, and health effects  
25 associated with sulfur compounds present in particulate matter (PM) were most recently  
26 considered in the U.S. EPA’s review of the NAAQS for PM. Some of the welfare effects  
27 resulting from deposition of sulfur oxides (e.g., effects associated with ecosystem  
28 loading) are being considered in a separate assessment as part of the review of the  
29 secondary NAAQS for nitrogen dioxide and SO<sub>2</sub> ([U.S. EPA, 2013d](#)).

30 The U.S. EPA completed the initial review of the air quality criteria for sulfur oxides in  
31 1969 [34 Federal Register (FR) 1988; ([HEW, 1969](#))]. Based on this review, the U.S. EPA  
32 promulgated NAAQS for sulfur oxides in 1971, establishing the indicator as SO<sub>2</sub> [36 FR

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<sup>1</sup> Lists of CASAC members and of members of the CASAC Augmented for Sulfur Oxides Panel are available at:  
<http://yosemite.epa.gov/sab/sabproduct.nsf/WebCASAC/CommitteesandMembership?OpenDocument>.

1 8186; ([U.S. EPA, 1971](#))]. The 1971 primary standards were set at 365 µg/m<sup>3</sup> [equal to  
 2 0.14 parts per million (ppm)] averaged over a 24-hour period, not to be exceeded more  
 3 than once per year, and at 80 µg/m<sup>3</sup> (equal to 0.03 ppm) annual arithmetic mean.<sup>1</sup> Since  
 4 then, the Agency has completed multiple reviews of the air quality criteria and standards,  
 5 as summarized in [Table I](#).

**Table I History of the primary National Ambient Air Quality Standards for sulfur dioxide since 1971.**

Final Rule/ Decisions	Indicator	Averaging Time	Level	Form
1971 36 FR 8186 Apr 30, 1971	SO <sub>2</sub>	24 h	140 ppb <sup>a</sup>	One allowable exceedance
		1 yr	30 ppb <sup>a</sup>	Annual arithmetic average
1996 61 FR 25566 May 22, 1996	Both the 24-h and annual average standards retained without revision.			
2010 75 FR 35520 June 22, 2010	SO <sub>2</sub>	1 h	75 ppb	3-yr average of the 99th percentile of the annual distribution of daily maximum 1-h concentrations
	24-h and annual SO <sub>2</sub> standards revoked.			

FR = Federal Register; SO<sub>2</sub> = sulfur dioxide.

<sup>a</sup>The initial level of the 24-h SO<sub>2</sub> standard was 365 µg/m<sup>3</sup> which is equal to 0.14 parts per million (ppm) or 140 parts per billion (ppb). The initial level of the annual SO<sub>2</sub> standard was 80 µg/m<sup>3</sup> which is equal to 0.03 ppm or 30 ppb. The units for the standard level were officially changed to ppb in the final rule issued in 2010 (75 FR 35520).

6 In 1982, the U.S. EPA published the Air Quality Criteria for Particulate Matter and  
 7 Sulfur Oxides ([U.S. EPA, 1982a](#)) along with an addendum of newly published controlled  
 8 human exposure studies, which updated the scientific criteria upon which the initial  
 9 standards were based ([U.S. EPA, 1982b](#)). In 1986, a second addendum was published  
 10 presenting newly available evidence from epidemiologic and controlled human exposure  
 11 studies ([U.S. EPA, 1986a](#)). In 1988, the U.S. EPA published a proposed decision not to  
 12 revise the existing standards (53 FR 14926). However, the U.S. EPA specifically  
 13 requested public comment on the alternative of revising the current standards and adding  
 14 a new 1-hour primary standard of 0.4 ppm to protect against short-term peak exposures.

<sup>1</sup> Note that 0.14 parts per million (ppm) is equivalent to 140 parts per billion (ppb) and 0.03 ppm is equivalent to 30 ppb.

1 As a result of public comments on the 1988 proposal and other post-proposal  
2 developments, the U.S. EPA published a second proposal on November 15, 1994 (59 FR  
3 58958). The 1994 re-proposal was based in part on a supplement to the second addendum  
4 of the criteria document, which evaluated new findings on the respiratory effects of  
5 short-term SO<sub>2</sub> exposures in individuals with asthma ([U.S. EPA, 1994](#)). As in the 1988  
6 proposal, the U.S. EPA proposed to retain the existing 24-hour and annual standards.  
7 The U.S. EPA also solicited comment on three regulatory alternatives to further reduce  
8 the health risk posed by exposure to high 5-minute peaks of SO<sub>2</sub> if additional protection  
9 were judged to be necessary. The three alternatives were: (1) revising the existing  
10 primary SO<sub>2</sub> NAAQS by adding a new 5-minute standard of 0.60 ppm SO<sub>2</sub>;  
11 (2) establishing a new regulatory program under Section 303 of the Act to supplement  
12 protection provided by the existing NAAQS, with a trigger level of 0.60 ppm SO<sub>2</sub> with  
13 one expected exceedance; and (3) augmenting implementation of existing standards by  
14 focusing on those sources or source types likely to produce high 5-minute concentrations  
15 of SO<sub>2</sub>.

16 In assessing the regulatory options mentioned above, the Administrator concluded that  
17 the likely frequency of 5-minute concentrations of concern should also be a consideration  
18 in assessing the overall public health risks. Based upon an exposure analysis conducted  
19 by the U.S. EPA, the Administrator concluded that exposure of individuals with asthma  
20 to SO<sub>2</sub> at levels that can reliably elicit adverse health effects was likely to be a rare event  
21 when viewed in the context of the entire population of individuals with asthma. Thus, the  
22 Administrator judged that high 5-minute SO<sub>2</sub> concentrations did not pose a broad public  
23 health problem when viewed from a national perspective, and a 5-minute standard was  
24 not promulgated. In addition, no other regulatory alternative was finalized, and the  
25 24-hour and annual average primary SO<sub>2</sub> standards were retained in 1996 (61 FR 25566).

26 The American Lung Association and the Environmental Defense Fund challenged the  
27 U.S. EPA's decision not to establish a 5-minute standard. On January 30, 1998, the Court  
28 of Appeals for the District of Columbia ("D.C. Circuit") found that the U.S. EPA had  
29 failed to adequately explain its determination that no revision to the SO<sub>2</sub> NAAQS was  
30 appropriate and remanded the decision back to the U.S. EPA for further explanation.<sup>1</sup>  
31 Specifically, the court found that the U.S. EPA had failed to provide adequate rationale to  
32 support the Agency judgment that exposures to high 5-minute concentrations of SO<sub>2</sub> do  
33 not pose a public health problem from a national perspective even though these peaks  
34 will likely cause adverse health impacts in a subset of individuals with asthma. Following  
35 the remand, the U.S. EPA requested that states voluntarily submit 5-minute SO<sub>2</sub>  
36 monitoring data to be used to conduct air quality analyses in order to gain a better

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<sup>1</sup> See *American Lung Ass'n v. EPA*, 134 F. 3d 388 (D.C. Cir. 1998).

1 understanding of the magnitude and frequency of high, 5-minute peak SO<sub>2</sub>  
2 concentrations. The data submitted by states and the analyses based on this data helped  
3 inform the last review of the SO<sub>2</sub> NAAQS, which ultimately addressed the issues raised  
4 in the 1998 remand.

5 The last review of the health-related air quality criteria for sulfur oxides and the primary  
6 SO<sub>2</sub> standard was initiated in May 2006 (71 FR 28023).<sup>1,2</sup> The Agency's plans for  
7 conducting the review were presented in the Integrated Review Plan (IRP) for the  
8 Primary National Ambient Air Quality Standards for Sulfur Oxides ([U.S. EPA, 2007a](#)),  
9 which included consideration of comments received during a CASAC consultation as  
10 well as public comment on a draft IRP. The science assessment for the review was  
11 described in the 2008 ISA for Sulfur Oxides—Health Criteria ([U.S. EPA, 2008d](#)),  
12 multiple drafts of which received review by CASAC and the public. The U.S. EPA also  
13 conducted quantitative human risk and exposure assessments after having consulted with  
14 CASAC and receiving public comment on a draft analysis plan ([U.S. EPA, 2007b](#)). These  
15 technical analyses were presented in the Risk and Exposure Assessment (REA) to  
16 Support the Review of the SO<sub>2</sub> Primary National Ambient Air Quality Standards ([U.S.  
17 EPA, 2009b](#)), multiple drafts of which were reviewed by CASAC and the public.

18 On June 22, 2010, the U.S. EPA revised the primary SO<sub>2</sub> NAAQS to provide requisite  
19 protection of public health with an adequate margin of safety (75 FR 35520).  
20 Specifically, after concluding that the then-existing 24-hour and annual standards were  
21 inadequate to protect public health with an adequate margin of safety, the U.S. EPA  
22 established a new 1-hour SO<sub>2</sub> standard at a level of 75 parts per billion (ppb), based on  
23 the 3-year average of the annual 99th percentile of 1-hour daily maximum concentrations.  
24 This standard was promulgated to provide substantial protection against SO<sub>2</sub>-related  
25 health effects associated with short-term exposures ranging from 5 minute to 24 hours.  
26 More specifically, U.S. EPA concluded that a 1-hour SO<sub>2</sub> standard at 75 ppb would  
27 substantially limit exposures associated with the adverse respiratory effects  
28 (e.g., decrements in lung function and/or respiratory symptoms) reported in exercising  
29 asthmatics following 5–10 minute exposures in controlled human exposure studies, as  
30 well as the more serious health associations (e.g., respiratory-related emergency  
31 department visits and hospitalizations) reported in epidemiologic studies that mostly used  
32 daily metrics (1-h daily max and 24-h avg). In the last review, the U.S. EPA also revoked  
33 the then-existing 24-hour and annual primary standards based largely on the recognition

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<sup>1</sup> Documents related to reviews completed in 2010 and 1996 are available at: <https://www.epa.gov/naaqs/sulfur-dioxide-so2-primary-air-quality-standards>.

<sup>2</sup> The U.S. EPA conducted a separate review of the secondary SO<sub>2</sub> NAAQS jointly with a review of the secondary NO<sub>2</sub> NAAQS. The Agency retained those secondary standards, without revision, to address the direct effects on vegetation of exposure to oxides of nitrogen and sulfur (77 FR 20218).

1 that the new 1-hour standard at 75 ppb would generally maintain 24-hour and annual SO<sub>2</sub>  
2 concentrations well below the NAAQS, so that retaining the corresponding standards  
3 would not provide additional public health protection (75 FR 35550). The decision to set  
4 a 1-hour standard at 75 ppb—in part to substantially limit exposure to 5-minute  
5 concentrations of SO<sub>2</sub> resulting in adverse respiratory effects in exercising  
6 asthmatics—also satisfied the remand by the D.C. Circuit in 1998.

7 As mentioned above, the U.S. EPA’s last review placed considerable weight on  
8 substantially limiting health effects associated with high 5-minute SO<sub>2</sub> concentrations.  
9 Thus, as part of the final rulemaking, the U.S. EPA for the first time required the states to  
10 report either the highest 5-minute concentration for each hour of the day, or all twelve  
11 5-minute concentrations for each hour of the day. The rationale for this requirement was  
12 that this additional monitored data could then be used in future reviews to evaluate the  
13 extent to which the 1-hour SO<sub>2</sub> NAAQS at 75 ppb provides protection against 5-minute  
14 concentrations of concern.

15 After publication of the final rule, a number of industry groups and states filed petitions  
16 for review arguing that the U.S. EPA failed to follow notice-and-comment rulemaking  
17 procedures, and that the decision to establish the 1-hour SO<sub>2</sub> NAAQS at 75 ppb was  
18 arbitrary and capricious because it was lower than statutorily authorized. The D.C.  
19 Circuit rejected these challenges, thereby upholding the standard in its entirety [*National*  
20 *Environmental Development Association’s Clean Air Project v. EPA*, 686 F. 3d 803  
21 (D.C. Cir. 2012), cert. denied *Asarco LLC v. EPA*, 133 S. Ct. 983 (Jan. 22, 2013)].

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# Executive Summary

## Purpose and Scope of the Integrated Science Assessment

1 This Integrated Science Assessment (ISA) is a comprehensive evaluation and synthesis of  
2 policy-relevant science aimed at characterizing exposures to ambient sulfur oxides (SO<sub>x</sub>)  
3 and the health effects associated with these exposures.<sup>1</sup> Thus, this ISA serves as the  
4 scientific foundation for the review of the primary (health-based) National Ambient Air  
5 Quality Standard (NAAQS) for sulfur dioxide (SO<sub>2</sub>). The indicator<sup>2</sup> for the current  
6 standard is SO<sub>2</sub> because it is the most prevalent species of SO<sub>x</sub> (a group of closely related  
7 gaseous compounds including SO<sub>2</sub> and SO<sub>3</sub>) in the atmosphere and has health effects for  
8 which there is a large body of scientific evidence. The health effects of sulfate and other  
9 sulfur aerosols are considered as part of the review of the NAAQS for particulate matter  
10 [e.g., in the 2009 Integrated Science Assessment for Particulate Matter ([U.S. EPA,](#)  
11 [2009a](#))].<sup>3</sup> Some of the welfare effects resulting from deposition of sulfur oxides  
12 (e.g., effects associated with ecosystem loading) are being considered in a separate  
13 assessment as part of the review of the secondary (welfare-based) NAAQS for oxides of  
14 nitrogen and sulfur ([U.S. EPA, 2013d](#)).

15 In 2010, the U.S. Environmental Protection Agency (U.S. EPA) established a new 1-hour  
16 SO<sub>2</sub> primary standard of 75 parts per billion (ppb) based on the 3-year average of the 99th  
17 percentile of each year's 1-hour daily maximum concentrations (75 FR 35520).<sup>4</sup>  
18 The 1-hour standard was established to protect against a broad range of respiratory  
19 effects associated with short-term exposures in potential at-risk populations, such as  
20 people with asthma. This standard was based on clear evidence of SO<sub>2</sub>-related effects in  
21 controlled human exposure studies of exercising individuals with asthma, as well as  
22 epidemiologic evidence of associations between ambient SO<sub>2</sub> concentrations and  
23 respiratory-related emergency department visits and hospitalizations. The U.S. EPA also  
24 revoked the existing 24-hour and annual primary SO<sub>2</sub> standards of 140 and 30 ppb,  
25 respectively, based largely on the recognition that the new 1-hour standard would  
26 generally maintain 24-hour and annual SO<sub>2</sub> concentrations well below the NAAQS, and  
27 thus retaining these standards would not provide additional public health protection (75

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<sup>1</sup> The general process for developing an ISA, including the framework for evaluating weight of evidence and drawing scientific conclusions and causal judgments, is described in a companion document, *Preamble to the Integrated Science Assessments* ([U.S. EPA, 2015b](#)), <https://www.epa.gov/isa>.

<sup>2</sup> The four components to a NAAQS are: (1) indicator (e.g., SO<sub>2</sub>), (2) level (e.g., 75 ppb), (3) averaging time (e.g., 1 h), and (4) form (e.g., 3 yr avg of the 99th percentile of each year's daily 1-h max concentrations).

<sup>3</sup> In this ISA, the blue electronic links can be used to navigate to cited chapters, sections, tables, figures, and studies.

<sup>4</sup> The legislative requirements and history of the SO<sub>2</sub> NAAQS are described in detail in the [Preface](#) to this ISA.

1 FR 35550). The U.S. EPA also began requiring states to report 5-min avg SO<sub>2</sub>  
2 concentrations in light of evidence from controlled human exposure studies of health  
3 effects associated with 5-minute SO<sub>2</sub> exposures.

4 This ISA updates the 2008 ISA for Sulfur Oxides [([U.S. EPA, 2008d](#)) hereafter referred  
5 to as the 2008 SO<sub>x</sub> ISA] with studies and reports published from January 2008 through  
6 August 2016. The U.S. EPA conducted in-depth searches to identify peer-reviewed  
7 literature on relevant topics such as health effects, atmospheric chemistry, ambient  
8 concentrations, and exposure. Information was also solicited from subject-matter experts  
9 and the public during a kick-off workshop held at the U.S. EPA in June 2013 and at a  
10 public meeting of the Clean Air Scientific Advisory committee held in January 2015.  
11 To fully describe the state of available science, The U.S. EPA also included in this ISA  
12 the most relevant studies from previous assessments.

13 As in the 2008 SO<sub>x</sub> ISA, this ISA determines the causal nature of relationships with  
14 health effects only for SO<sub>2</sub> ([Chapter 5](#)). Health effects of other SO<sub>x</sub> species are not  
15 considered, because their presence in the atmosphere has not been demonstrated,  
16 ([Chapter 2](#)), transformation products of SO<sub>x</sub> such as sulfate are considered in the ISA for  
17 Particulate Matter ([U.S. EPA, 2009a](#)), and the health literature is focused on SO<sub>2</sub>. Key to  
18 interpreting the health effects evidence is understanding the sources, chemistry, and  
19 distribution of SO<sub>2</sub> in the ambient air ([Chapter 2](#)) that influence exposure, ([Chapter 3](#)),  
20 the uptake of inhaled SO<sub>2</sub> in the respiratory tract, and what biological mechanisms may  
21 subsequently be affected ([Chapter 4](#)). Further, the ISA aims to characterize the  
22 independent effect of SO<sub>2</sub> on health ([Chapter 5](#)). The ISA also informs policy-relevant  
23 issues ([Chapter 1](#) and [Chapter 6](#)), such as (1) exposure durations and patterns associated  
24 with health effects; (2) concentration-response relationship(s), including evidence of  
25 potential thresholds for effects; and (3) populations or lifestages at increased risk for  
26 health effects related to SO<sub>2</sub> exposure ([Section 1.7.4](#) and [Chapter 6](#)).

## Sources and Human Exposure to Sulfur Dioxide

27 The main objective of the ISA is to characterize health effects related to ambient SO<sub>2</sub>  
28 exposure. This requires understanding the factors that affect both the exposure to ambient  
29 SO<sub>2</sub> and the uncertainty in estimating exposure. These factors include spatial variability  
30 in SO<sub>2</sub> concentrations, exposure to copollutants, and uncharacterized time-activity  
31 patterns.

32 Emissions of SO<sub>2</sub> have decreased by approximately 72% from 1990 to 2011 due to  
33 several federal air quality regulatory programs. Coal-fired electricity generation units are  
34 the dominant sources, emitting 4.6 million tons of SO<sub>2</sub> in 2011, nearly 10 times more  
35 than the next largest source (coal-fired boilers for industrial fuel combustion);

1 [Section 2.2](#)). In addition to emission rate, important factors that affect ambient SO<sub>2</sub>  
2 concentrations at downwind locations include local meteorology (e.g., wind, atmospheric  
3 stability, humidity, and cloud/fog cover) and chemistry in the plume ([Section 2.3](#)).

4 The national average daily 1-hour max SO<sub>2</sub> concentration reported during 2013–2015  
5 was 5.4 ppb with a 99th percentile concentration of 64 ppb ([Section 2.5](#)). However,  
6 1-hour daily max SO<sub>2</sub> concentrations were 75 ppb or higher at some monitors located  
7 near point sources, such as power plants or metals processing facilities, or natural  
8 sources, such as volcanoes. The national average of 5-minute hourly max concentrations  
9 during 2013–2015 was 2.1 ppb, with a 99th percentile concentration of 24 ppb. Hourly  
10 5-minute max concentrations tracked closely with their corresponding 1-h avg  
11 concentrations, with 75% of sites having a correlation above 0.9, indicating that  
12 fluctuations in 5-minute hourly max concentrations are well represented by changes in  
13 1-h avg concentrations. The ratio of 5-minute hourly max concentrations to their  
14 corresponding 1-h avg concentrations was generally in the range of 1–3, although higher  
15 ratios were also observed during some hours. Background SO<sub>2</sub> concentrations due to  
16 natural sources and man-made sources located outside the U.S. are very low across most  
17 of the U.S. (less than 0.03 ppb) except in areas affected by volcanoes, such as Hawaii and  
18 the West Coast.

19 Air quality models are used to estimate SO<sub>2</sub> concentrations in locations without ambient  
20 SO<sub>2</sub> monitors ([Section 2.6](#)). As part of the implementation program for the 2010 primary  
21 SO<sub>2</sub> NAAQS, air quality modeling may be used to characterize air quality for  
22 determining compliance with the standard where existing ambient SO<sub>2</sub> monitors may not  
23 capture peak 1-hour concentrations (75 FR 35520). The widely used dispersion model  
24 American Meteorological Society/U.S. EPA Regulatory Model (AERMOD) is based on  
25 Gaussian dispersion models with enhancements to improve modeling of SO<sub>2</sub> plumes.  
26 AERMOD is relatively unbiased in estimating upper-percentile 1-hour concentration  
27 values over averaging times from 1 hour to 1 year. Lagrangian puff dispersion models,  
28 such as CALPUFF, have been developed as an alternative to Gaussian dispersion models.  
29 Uncertainties in model predictions are influenced by uncertainties in model inputs,  
30 particularly emissions data and meteorological conditions.

31 Correlations between ambient concentrations of SO<sub>2</sub> and copollutants are generally low  
32 (<0.4), although they vary across location, study, and SO<sub>2</sub> averaging time and are greater  
33 than 0.7 at some monitoring sites ([Section 3.4.3](#)). Median correlations of  
34 1-hour daily maximum and 24-h avg SO<sub>2</sub> concentrations with particulate matter, nitrogen  
35 dioxide (NO<sub>2</sub>), and carbon monoxide (CO) during 2013–2015 ranged from 0.2–0.4,  
36 while for ozone (O<sub>3</sub>) the median daily copollutant correlation with SO<sub>2</sub> was less than 0.1  
37 ([Figure 3-5](#)).

1 Estimating exposure to ambient SO<sub>2</sub> for use in epidemiologic studies can be done in  
2 multiple ways. Common techniques include using air quality monitoring data, personal  
3 SO<sub>2</sub> monitoring, and modeling. Air quality monitoring data from central site monitors  
4 (rather than near-source monitors), which are assumed to represent population exposure,  
5 are frequently used, but these monitors may not capture the spatial variation in ambient  
6 SO<sub>2</sub> concentrations across an urban area, which can be relatively high in areas affected by  
7 large point sources. Modeling approaches combining air quality data with geographic  
8 information or time-activity patterns, or both, can provide estimates of local ambient  
9 concentration or exposure concentration, although more complex approaches need more  
10 detailed inputs and have the potential for uncertainty related to missing sources, overly  
11 smooth concentration gradients, and other factors.

12 “Exposure error,” which refers to the bias and uncertainty associated with using exposure  
13 metrics to represent the actual exposure of an individual or population, can contribute to  
14 error in health effect estimates in epidemiologic studies ([Section 3.4.4](#)). Several  
15 exposure-related factors (including uncharacterized time-activity patterns, spatial and  
16 temporal variability of SO<sub>2</sub> concentrations, and distance of individuals and populations  
17 from air quality monitors used in the statistical analyses) contribute to error in estimating  
18 exposure to ambient SO<sub>2</sub>. Variation in activity patterns across individuals and over time  
19 results in corresponding variations in exposure concentration. Uncharacterized spatial  
20 variability in SO<sub>2</sub> concentrations can contribute to exposure error that tends to add  
21 uncertainty and reduce the magnitude of effect estimates in daily time-series  
22 epidemiologic studies. For long-term (e.g., annual) studies, the effect estimate may be  
23 increased or reduced by using central site monitoring data, depending on the relative  
24 locations of sources, monitors, and exposed people. The exposure error associated with  
25 using central site monitors is generally expected to widen confidence intervals beyond the  
26 nominal coverage of those intervals that would be produced had the true exposure been  
27 used for all study types.

## **Dosimetry and Mode of Action of Inhaled Sulfur Dioxide**

28 Understanding the absorption and fate of SO<sub>2</sub> in the body (dosimetry) and the biological  
29 pathways that potentially underlie health effects (mode of action) is crucial to provide  
30 biological plausibility for linking SO<sub>2</sub> exposure with observed health effects.

31 Inhaled SO<sub>2</sub> is readily absorbed in the nasal passages of resting humans and laboratory  
32 animals ([Section 4.2](#)). As physical activity increases, there is an increase in breathing rate  
33 and a shift to breathing through the mouth, resulting in greater SO<sub>2</sub> penetration into the  
34 lower airways. Relative to healthy adults, children, and individuals with asthma or  
35 allergic rhinitis have an increased amount of oral breathing, and thus, may be expected to

1 have greater SO<sub>2</sub> penetration into the lungs. Children also generally have a greater intake  
2 dose of SO<sub>2</sub> per body mass than adults.

3 The distribution and clearance of inhaled SO<sub>2</sub> from the respiratory tract involves several  
4 chemical transformations, particularly the formation of sulfite and S-sulfonates. Sulfite is  
5 metabolized into sulfate, which is rapidly excreted through the urine, while S-sulfonates  
6 are cleared more slowly from the circulation over a period of days. Although SO<sub>2</sub>-derived  
7 products have been found in the blood and urine within minutes of an inhalation  
8 exposure, a substantial portion of these products appear to be retained within the upper  
9 airways, particularly during nasal breathing, with only slow absorption into the blood.

10 Although inhaled SO<sub>2</sub> produces sulfite that is distributed through the circulation, overall  
11 sulfite levels are heavily influenced by production within the body (endogenous  
12 production) and by eating food with sulfur-containing amino acids or sulfite itself  
13 ([Section 4.2.6](#)). For both adults and children, metabolism of sulfur-containing amino  
14 acids produces much more sulfite than is ingested as food additives. Sulfite produced  
15 endogenously generates levels two or more orders of magnitude higher than  
16 inhalation-derived sulfite levels for both children and adults, even for full-day exposures  
17 to 75 ppb SO<sub>2</sub> (i.e., the level of the 1-hour NAAQS). Sulfite ingestion from food  
18 additives varies widely, but is generally expected to exceed sulfite intake from inhalation  
19 in both adults and children, even for full-day exposures to 75 ppb SO<sub>2</sub>. However, an  
20 important distinction is that inhalation-derived SO<sub>2</sub> products can accumulate in the  
21 respiratory tract, whereas sulfite from ingestion or endogenous production does not.

22 SO<sub>2</sub> inhalation produces bronchoconstriction in both healthy adults and those with  
23 asthma ([Section 4.3](#)), but the underlying processes are somewhat different. The response  
24 to SO<sub>2</sub> in healthy adults occurs primarily from activation of sensory nerves in the  
25 respiratory tract resulting in neural reflex responses through the vagus nerve. In adults  
26 with asthma, the response is only partly due to this neural reflex response, with  
27 inflammatory mediators also being involved. Inhalation of SO<sub>2</sub> increases allergic  
28 inflammation in adults with asthma and in animals with allergic airways disease, which  
29 shares many features with asthma. Furthermore, SO<sub>2</sub> inhalation increases allergic  
30 sensitization in animals not already allergic, and once allergic, these animals respond to  
31 an allergen challenge with greater allergic inflammation and airway obstruction (likely  
32 due to bronchoconstriction) compared to animals who were not exposed to SO<sub>2</sub>. These  
33 findings suggest that allergic inflammation and increased airway responsiveness due to  
34 short-term SO<sub>2</sub> exposure (minutes up to 1 month) may be linked to asthma exacerbation  
35 seen in epidemiologic studies.

36 For long-term SO<sub>2</sub> exposure (more than 1 month to years), animal studies provide  
37 additional evidence of airway inflammation, airway remodeling, AHR, and allergic

1 sensitization. In animals that are not allergic, SO<sub>2</sub> inhalation leads to airway inflammation  
2 and allergic sensitization. In animals with allergic airway disease, SO<sub>2</sub> exposure increases  
3 airway responsiveness and airway remodeling. Thus, inhalation of SO<sub>2</sub> may lead to the  
4 development and worsening of allergic airway disease. The development of AHR may  
5 link long-term exposure to SO<sub>2</sub> to the epidemiologic outcome of physician-diagnosed  
6 asthma (new onset asthma).

7 While there is some evidence for extrapulmonary effects of inhaled SO<sub>2</sub>, the mode of  
8 action underlying these responses is uncertain. Controlled human exposure studies  
9 provide evidence suggesting activation of sensory nerves in the respiratory tract resulting  
10 in a neural reflex response by SO<sub>2</sub> exposure, which could lead to changes in heart rate or  
11 heart rate variability. Additionally, the transport of sulfite into the circulation could result  
12 in redox stress, but this is likely to only occur at elevated or prolonged exposures due to  
13 the body's efficient metabolism of sulfite to sulfate.

## Health Effects of Sulfur Dioxide Exposure

14 This ISA integrates information on SO<sub>2</sub> exposure and health effects from controlled  
15 human exposure, epidemiologic, and toxicological studies to form conclusions about the  
16 causal nature of relationships between SO<sub>2</sub> exposure and health effects. For most health  
17 effect categories, with the exception of reproductive and developmental effects, effects  
18 are evaluated separately for short-term exposures and long-term exposures. Health effects  
19 are considered in relation to the full range of SO<sub>2</sub> concentrations relevant to ambient  
20 conditions. Based on upper-percentile ambient concentrations ([Section 2.5](#)) and the ISA's  
21 emphasis on ambient-relevant exposures within one to two orders of magnitude of current  
22 conditions [[Preamble](#) to the ISAs ([U.S. EPA, 2015b](#)), Section 5c], SO<sub>2</sub> concentrations up  
23 to 2,000 ppb<sup>1</sup> are defined to be ambient-relevant. A consistent and transparent framework  
24 [[Preamble](#) to the ISAs ([U.S. EPA, 2015b](#)), Table II] is applied to classify the health  
25 effects evidence according to a five-level hierarchy:

- 26 1. Causal relationship
- 27 2. Likely to be a causal relationship
- 28 3. Suggestive of, but not sufficient to infer, a causal relationship
- 29 4. Inadequate to infer the presence or absence of a causal relationship
- 30 5. Not likely to be a causal relationship

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<sup>1</sup> The 2,000-ppb upper limit applies mostly to animal toxicological studies and also a few controlled human exposure studies. Experimental studies examining SO<sub>2</sub> exposures greater than 2,000 ppb were included if they provided information on the uptake of SO<sub>2</sub> in the respiratory tract or on potential biological mechanisms.

1 The causal determinations presented in [Table ES-1](#) are informed by recent findings and  
2 whether these recent findings, integrated with information from the 2008 SO<sub>x</sub> ISA,  
3 support a change in causal conclusions. Important considerations include: (1) determining  
4 whether laboratory studies of humans and animals demonstrate an independent health  
5 effect of SO<sub>2</sub> exposure and what the potential underlying biological mechanisms are;  
6 (2) determining whether there is consistency in epidemiologic evidence across various  
7 methods used to estimate SO<sub>2</sub> exposure; (3) examining epidemiologic studies of the  
8 potential influence of factors that could bias associations observed with SO<sub>2</sub> exposure;  
9 (4) determining the coherence of findings integrated across controlled human exposure,  
10 epidemiologic, and toxicological studies; and (5) making judgments regarding error and  
11 uncertainty in the collective body of available studies.

**Table ES-1 Causal determinations for relationships between sulfur dioxide exposure and health effects from the 2008 and current draft Integrated Science Assessment for Sulfur Oxides.**

Health Effect Category <sup>a</sup> and Exposure Duration	Causal Determination	
	2008 SO <sub>x</sub> ISA	Current Draft ISA
Respiratory effects—Short-term exposure <a href="#">Section 5.2.1, Table 5-21</a>	Causal relationship	Causal relationship
Respiratory effects—Long-term exposure <a href="#">Section 5.2.2, Table 5-24</a>	Inadequate to infer the presence or absence of a causal relationship	Suggestive of, but not sufficient to infer, a causal relationship
Cardiovascular effects—Short-term exposure <a href="#">Section 5.3.1, Table 5-34</a>	Inadequate to infer the presence or absence of a causal relationship	Inadequate to infer the presence or absence of a causal relationship
Cardiovascular effects—Long-term exposure <a href="#">Section 5.3.2, Table 5-35</a>	Not included	Inadequate to infer the presence or absence of a causal relationship
Reproductive and developmental effects <sup>b</sup> <a href="#">Section 5.4, Table 5-38</a>	Inadequate to infer the presence or absence of a causal relationship	Inadequate to infer the presence or absence of a causal relationship
Total mortality—Short-term exposure <a href="#">Section 5.5.1, Table 5-41</a>	Suggestive of, but not sufficient to infer, a causal relationship	Suggestive of, but not sufficient to infer, a causal relationship
Total mortality—Long-term exposure <a href="#">Section 5.5.2, Table 5-43</a>	Inadequate to infer the presence or absence of a causal relationship	Inadequate to infer the presence or absence of a causal relationship
Cancer—Long-term exposure <a href="#">Section 5.6, Table 5-44</a>	Inadequate to infer the presence or absence of a causal relationship	Inadequate to infer the presence or absence of a causal relationship

ISA = Integrated Science Assessment; SO<sub>x</sub> = sulfur oxides.

Previous causal determinations taken from the 2008 SO<sub>x</sub> ISA ([U.S. EPA, 2008d](#)).

<sup>a</sup>An array of outcomes is evaluated as part of a broad health effect category: physiological measures (e.g., airway responsiveness), clinical outcomes (e.g., hospital admissions), and cause-specific mortality. Total mortality includes all nonaccidental causes of mortality and is informed by findings for the spectrum of morbidity effects (e.g., respiratory, cardiovascular) that can lead to mortality. The sections and tables referenced include a detailed discussion of the evidence that supports the causal determinations and the SO<sub>2</sub> concentrations with which health effects have been associated.

<sup>b</sup>Reproductive and developmental effects studies consider a wide range of exposure durations.

## Sulfur Dioxide Exposure and Respiratory Effects

1 As in the 2008 SO<sub>x</sub> ISA ([U.S. EPA, 2008d](#)), the current ISA concludes that there is a  
2 causal relationship between short-term SO<sub>2</sub> exposure and respiratory effects, particularly  
3 in individuals with asthma ([Section 5.2.1](#)). This determination is based on consistent,  
4 coherent, and biologically plausible evidence for asthma exacerbation due to SO<sub>2</sub>  
5 exposure. The clearest evidence for this conclusion comes from controlled human  
6 exposure studies available at the time of the 2008 SO<sub>x</sub> ISA showing lung function  
7 decrements and respiratory symptoms in adults with asthma exposed to SO<sub>2</sub> for  
8 5–10 minutes at elevated breathing rates. The effects observed in these studies are  
9 consistent with the processes leading to asthma exacerbation described in the mode of  
10 action section ([Section 4.3](#)). Epidemiologic evidence, including recent studies not  
11 available at the time of the 2008 SO<sub>x</sub> ISA, also supports a causal relationship, primarily  
12 due to studies reporting positive associations for asthma hospital admissions and  
13 emergency department visits with short-term SO<sub>2</sub> exposures, specifically for children.  
14 This is coherent with studies showing that children have increased airway responsiveness  
15 to a trigger and have greater oral breathing and body-mass-adjusted intake dose relative  
16 to adults, suggesting they will have a greater response to SO<sub>2</sub> exposure than adults.  
17 Hospital admissions and emergency department visits studies that examined potential  
18 copollutant confounding reported associations were generally unchanged in copollutant  
19 models. Additional support comes from studies reporting positive associations between  
20 short-term SO<sub>2</sub> exposures and respiratory symptoms in children with asthma, although  
21 the evidence from respiratory symptoms studies in adults with asthma is less consistent.  
22 Finally, epidemiologic studies that report consistent positive associations between  
23 short-term SO<sub>2</sub> concentrations and respiratory mortality indicate a potential continuum of  
24 effects.

25 For long-term SO<sub>2</sub> exposure and respiratory effects the evidence is suggestive of, but not  
26 sufficient to infer, a causal relationship ([Section 5.2.2](#)). The strongest evidence is  
27 provided by coherence among findings of epidemiologic studies showing associations  
28 between long-term SO<sub>2</sub> exposure and increases in asthma incidence among children and  
29 results of animal toxicological studies that provide a pathophysiologic basis for the  
30 development of asthma. Some evidence regarding respiratory symptoms and/or  
31 respiratory allergies among children provides limited support for a possible relationship  
32 between long-term SO<sub>2</sub> exposure and the development of asthma. This represents a  
33 change in the causal determination made in the 2008 SO<sub>x</sub> ISA from inadequate to  
34 suggestive, based on a limited body of new evidence.

## Sulfur Dioxide Exposure and Other Health Effects

1           There is more uncertainty regarding relationships between SO<sub>2</sub> exposure and health  
2           effects outside of the respiratory system. SO<sub>2</sub> itself is unlikely to enter the bloodstream;  
3           however, its reaction products, such as sulfite, may do so. The amount of circulating  
4           sulfite due to inhalation of ambient-relevant concentrations of SO<sub>2</sub> is far less than the  
5           contribution from metabolism of sulfur-containing amino acids.

6           For short-term SO<sub>2</sub> exposure and total mortality, the current ISA reaches the same  
7           conclusion as the 2008 SO<sub>x</sub> ISA ([U.S. EPA, 2008d](#)); that the evidence is suggestive of,  
8           but not sufficient to infer, a causal relationship ([Section 5.5.1](#)). This conclusion is based  
9           on previous and recent multicity epidemiologic studies providing consistent evidence of  
10          positive associations. While recent multicity studies have analyzed some key  
11          uncertainties and data gaps identified in the 2008 SO<sub>x</sub> ISA, questions remain regarding  
12          the potential for SO<sub>2</sub> to have an independent effect on mortality, considering issues such  
13          as the limited number of studies that examined copollutant confounding, evidence for a  
14          decrease in the size of SO<sub>2</sub>-mortality associations in copollutant models with NO<sub>2</sub> and  
15          PM<sub>10</sub>, and the lack of a potential biological mechanism for mortality following short-term  
16          exposures to SO<sub>2</sub>.

17          For the remaining health effect categories (short-term and long-term SO<sub>2</sub> exposure and  
18          cardiovascular effects, long-term exposure and total mortality, reproductive and  
19          developmental effects, and long-term exposure and cancer), the evidence is inadequate to  
20          infer the presence or absence of a causal relationship, mainly due to inconsistent evidence  
21          across specific outcomes and uncertainties regarding exposure measurement error,  
22          copollutant confounding, and potential modes of action. These conclusions are consistent  
23          with those made in the 2008 SO<sub>x</sub> ISA, as illustrated in [Table ES-1](#).

## Policy-Relevant Considerations for Health Effects Associated with Sulfur Dioxide Exposure

24          This section describes issues relevant for considering the potential importance of impacts  
25          of ambient SO<sub>2</sub> exposure on public health, including exposure durations observed to  
26          cause health effects, the shape of the concentration-response relationship, regional  
27          differences, and at-risk populations and lifestages.

28          Evidence from controlled human exposure studies of respiratory effects after exposures  
29          of 5–10 minutes indicates a rapid onset of SO<sub>2</sub>-related effects and provides support for  
30          the 1-h avg time used in the primary SO<sub>2</sub> NAAQS ([Section 5.2.1](#)). Epidemiologic studies  
31          of asthma hospital admissions and emergency department visits using daily exposure  
32          metrics (24-h avg and 1-h daily max) show positive associations that are generally

1 unchanged in copollutant models, although these associations could be due to very short  
2 duration exposures (5–10 minutes) experienced during the day. The rapid onset of effects  
3 is also coherent with the limited number of epidemiologic studies that examined lag  
4 structures and reported associations within the first few days of exposure.

5 Substantial interindividual variability was observed in controlled human exposure studies  
6 of SO<sub>2</sub> and respiratory effects, but there was a clear increase in the magnitude of  
7 respiratory effects with increasing exposure concentrations between 200 and 1,000 ppb  
8 during 5–10 minute SO<sub>2</sub> exposures ([Section 5.2.1.2](#)). Both the number of affected  
9 individuals with asthma and the severity of the response increased as SO<sub>2</sub> concentrations  
10 increased. Epidemiologic studies evaluating the shape of the concentration-response  
11 function have found no evidence for a population-level threshold or nonlinearity,  
12 although the evidence is limited.

13 SO<sub>2</sub> concentrations are highly spatially heterogeneous, with SO<sub>2</sub> concentrations at some  
14 monitors possibly not highly correlated with the community average concentration  
15 ([Section 3.4.2.2](#)). The predominance of point sources results in an uneven distribution of  
16 SO<sub>2</sub> concentrations across an urban area. This spatial and temporal variability in SO<sub>2</sub>  
17 concentrations can contribute to exposure error in epidemiologic studies, whether the  
18 studies rely on central site monitor data or concentration modeling for exposure  
19 assessment.

20 Consistent with the findings of the 2008 SO<sub>x</sub> ISA ([U.S. EPA, 2008d](#)), this ISA concludes  
21 there is adequate evidence that people with asthma, particularly children, are at increased  
22 risk for SO<sub>2</sub>-related health effects compared with those without asthma ([Chapter 6](#)). This  
23 conclusion is based on the evidence for short-term SO<sub>2</sub> exposure and respiratory effects  
24 (specifically lung function decrements), for which a causal relationship has been  
25 determined. The ISA concludes there is suggestive evidence that children are at increased  
26 risk for SO<sub>2</sub>-related health effects, based on their increased ventilation rates relative to  
27 body mass and increased oral breathing, together with some epidemiologic evidence of  
28 increased associations between SO<sub>2</sub> and respiratory effects relative to adults, even though  
29 recent epidemiologic evidence is less consistent. There is also evidence suggestive of  
30 increased risk of SO<sub>2</sub>-related health effects for older adults relative to other lifestages.

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# Chapter 1 Integrative Synthesis of the ISA

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## 1.1 Purpose and Overview of the Integrated Science Assessment

1 The Integrated Science Assessment (ISA) is a comprehensive evaluation and synthesis of  
2 the policy-relevant science “useful in indicating the kind and extent of all identifiable  
3 effects on public health or welfare which may be expected from the presence of [a]  
4 pollutant in the ambient air,” as described in Section 108 of the Clean Air Act ([CAA,](#)  
5 [1990a](#)).<sup>1</sup> This ISA communicates critical science judgments of the health-related air  
6 quality criteria for the broad category of sulfur oxides (SO<sub>x</sub>). As such, this ISA serves as  
7 the scientific foundation for the review of the current primary (health-based) National  
8 Ambient Air Quality Standard (NAAQS) for sulfur dioxide (SO<sub>2</sub>). SO<sub>x</sub> include several  
9 related gaseous compounds such as SO<sub>2</sub> and sulfur trioxide (SO<sub>3</sub>) ([Section 2.3](#)). SO<sub>2</sub> was  
10 chosen as the indicator<sup>2</sup> for the NAAQS because as in previous reviews, the presence of  
11 other sulfur oxides in the atmosphere has not been demonstrated ([U.S. EPA, 1996b](#);  
12 [HEW, 1969](#)),<sup>3</sup> and there is a large body of evidence on health effects following exposure  
13 to SO<sub>2</sub>. In addition, the 2010 Final Rule concluded that “measures leading to reductions  
14 in population exposures to SO<sub>2</sub> can generally be expected to lead to reductions in  
15 population exposures to SO<sub>x</sub>.” (75 FR 35536). Health effects of particulate  
16 sulfur-containing species (e.g., sulfate) are being considered in the current review of the  
17 NAAQS for particulate matter (PM) and were previously evaluated in the 2009 ISA for  
18 PM ([U.S. EPA, 2009a](#)). Some of the welfare effects resulting from deposition of SO<sub>x</sub>  
19 (e.g., effects associated with ecosystem loading) are being evaluated in a separate  
20 assessment conducted as part of the review of the secondary (welfare-based) NAAQS for  
21 oxides of nitrogen (NO<sub>x</sub>) and SO<sub>x</sub> ([U.S. EPA, 2013d](#)).

22 This ISA evaluates relevant scientific literature published since the 2008 ISA for Sulfur  
23 Oxides [([U.S. EPA, 2008d](#)), or 2008 SO<sub>x</sub> ISA], integrating key information and  
24 judgments contained in the 2008 SO<sub>x</sub> ISA and the 1982 *Air Quality Criteria Document*  
25 (*AQCD*) for Particulate Matter and Sulfur Oxides ([U.S. EPA, 1982a](#)) and its Addenda  
26 ([U.S. EPA, 1994, 1986a, 1982b](#)). Thus, this ISA updates the state of the science that was

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<sup>1</sup> The general process for developing an ISA, including the framework for evaluating weight of evidence and drawing scientific conclusions and causal judgments, is described in a companion document, *Preamble to the Integrated Science Assessments* ([U.S. EPA, 2015b](#)).

<sup>2</sup> The four components to a NAAQS are: (1) indicator (e.g., SO<sub>2</sub>); (2) level (e.g., 75 ppb); (3) averaging time (e.g., 1 h), and (4) form (e.g., 3 yr avg of the 99th percentile of each year’s 1-h daily max concentrations).

<sup>3</sup> In this ISA, the blue electronic links can be used to navigate to cited chapters, sections, tables, figures, and studies.

1 available for the 2008 SO<sub>x</sub> ISA, which informed decisions on the primary SO<sub>2</sub> NAAQS  
2 in the review completed in 2010. In 2010, the U.S. Environmental Protection Agency  
3 (U.S. EPA) established a new 1-hour standard of 75 parts per billion (ppb) SO<sub>2</sub> based on  
4 the 3-yr avg of the 99th percentile of each year's 1-hour daily max concentrations.<sup>1</sup>  
5 The 1-hour standard was established to protect against a broad range of respiratory  
6 effects associated with short-term exposures in potential at-risk populations such as  
7 people with asthma. This standard was based on clear evidence of SO<sub>2</sub>-related effects in  
8 controlled human exposure studies of exercising individuals with asthma, as well as  
9 epidemiologic evidence of associations between ambient SO<sub>2</sub> concentrations and  
10 respiratory-related emergency department visits and hospitalizations. The U.S. EPA also  
11 revoked the existing 24-hour and annual primary SO<sub>2</sub> standards of 140 and 30 ppb,  
12 respectively. The 24-hour and annual primary standards were revoked largely based on  
13 the recognition that the new 1-hour standard at 75 ppb would generally maintain 24-hour  
14 and annual SO<sub>2</sub> concentrations well below the NAAQS, and thus, retaining these  
15 standards would not provide additional public health protection (75 FR 35550). In light of  
16 considerable weight being placed on health effects associated with 5-minute peak SO<sub>2</sub>  
17 concentrations, the U.S. EPA for the first time required state reporting of either the  
18 highest 5-minute concentration for each hour of the day, or all twelve 5-minute  
19 concentrations for each hour of the day ([U.S. EPA, 2010b](#)).

20 This new review of the primary SO<sub>2</sub> NAAQS is guided by several policy-relevant  
21 questions that are identified in *The Integrated Review Plan for the Primary National*  
22 *Ambient Air Quality Standard for Sulfur Dioxide* ([U.S. EPA, 2014a](#)). To address these  
23 questions and update the scientific judgments in the 2008 ISA for Sulfur Oxides ([U.S.](#)  
24 [EPA, 2008d](#)), this ISA aims to:

- 25 • Characterize the evidence for health effects associated with short-term (minutes  
26 up to 1 month) and long-term (more than 1 month to years) exposure to SO<sub>x</sub> by  
27 integrating findings across scientific disciplines and across related health  
28 outcomes and by considering important uncertainties identified in the  
29 interpretation of the scientific evidence, including the role of SO<sub>2</sub> within the  
30 broader ambient mixture of pollutants.
- 31 • Inform policy-relevant issues related to quantifying health risks, such as exposure  
32 concentrations, durations, and patterns associated with health effects;  
33 concentration-response (C-R) relationships and existence of thresholds below  
34 which effects do not occur; and populations and lifestages potentially with  
35 increased risk of health effects related to exposure to SO<sub>x</sub>.

36 Sulfur dioxide is the most abundant species of SO<sub>x</sub> in the atmosphere, while the presence  
37 of other SO<sub>x</sub> species in the atmosphere has not been demonstrated ([Section 2.1](#)). Most  
38 studies on the health effects of SO<sub>x</sub> focus on SO<sub>2</sub>. In evaluating the health evidence, this

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<sup>1</sup> The legislative requirements and history of the SO<sub>2</sub> NAAQS are described in detail in the [Preface](#) to this ISA.

1 ISA considers possible influences of other atmospheric pollutants, including interactions  
2 of SO<sub>2</sub> with co-occurring pollutants such as PM, NO<sub>x</sub>, carbon monoxide (CO), and ozone  
3 (O<sub>3</sub>).

4 In addressing policy-relevant questions, this ISA aims to characterize the independent  
5 health effects of SO<sub>2</sub>. As described in this ISA, recent evidence continues to support a  
6 causal relationship between short-term SO<sub>2</sub> exposure and respiratory effects based on the  
7 consistency of findings, coherence among evidence from controlled human exposure,  
8 epidemiologic, and toxicological studies, and biological plausibility for effects  
9 specifically related to asthma exacerbation. The information summarized in this ISA will  
10 serve as the scientific foundation for the review of the current primary 1-hour SO<sub>2</sub>  
11 NAAQS.

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## 1.2 Process for Developing Integrated Science Assessments

12 The U.S. EPA uses a structured and transparent process for evaluating scientific  
13 information and determining the causal nature of relationships between air pollution  
14 exposures and health effects [details provided in the [Preamble to the Integrated Science  
15 Assessments \(U.S. EPA, 2015b\)](#)]. The ISA development process describes approaches for  
16 literature searches, criteria for selecting and evaluating relevant studies, and a framework  
17 for evaluating the weight of evidence and forming causal determinations. As part of this  
18 process, the ISA is reviewed by the Clean Air Scientific Advisory Committee (CASAC),  
19 which is a formal independent panel of scientific experts, and by the public. As this ISA  
20 informs the review of the primary SO<sub>2</sub> NAAQS, it integrates and synthesizes information  
21 characterizing exposure to SO<sub>2</sub> and potential relationships with health effects. Relevant  
22 studies include those examining atmospheric chemistry, spatial and temporal trends, and  
23 exposure assessment, as well as U.S. EPA analyses of air quality and emissions data.  
24 Relevant health research includes epidemiologic, controlled human exposure, and  
25 toxicological studies on health effects, as well as studies on dosimetry and modes of  
26 action.

27 The U.S. EPA initiated the current review of the primary NAAQS for SO<sub>2</sub> in August  
28 2013 with a call for information from the public ([U.S. EPA, 2013d](#)). Thereafter, the  
29 U.S. EPA routinely conducted literature searches to identify relevant peer-reviewed  
30 studies published since the previous ISA (i.e., from January 2008 through August 2016).  
31 Multiple search methods were used [[Preamble to the ISAs \(U.S. EPA, 2015b\)](#), Section 2],  
32 including searches in the PubMed and Web of Science databases. Subject-area experts  
33 and the public were also able to recommend studies and reports during a science/policy  
34 issue “kick-off” workshop held at the U.S. EPA in June 2013. The U.S. EPA identified

1 additional studies considered to be the definitive work on particular topics from previous  
2 assessments to include in this ISA. Studies that did not address a topic described in the  
3 preceding paragraph based on title were excluded. Studies that were judged to be  
4 potentially relevant based on review of the abstract or full text and “considered” for  
5 inclusion in the ISA are documented and can be found at the Health and Environmental  
6 Research Online (HERO) website. The HERO project page for this ISA  
7 (<https://hero.epa.gov/hero/sulfur-oxides>) contains the references that are cited in the ISA,  
8 the references that were considered for inclusion but not cited, and electronic links to  
9 bibliographic information and abstracts.

10 Categories of health effects were considered for evaluation in this ISA if they were  
11 examined in previous U.S. EPA assessments for SO<sub>x</sub> or in multiple recent studies. For  
12 other categories of health effects, literature searches were conducted to determine the  
13 extent of available health evidence. These searches identified a few recently published  
14 epidemiologic studies on outcomes such as migraine/headache, depression, suicide, eye  
15 irritation/conjunctivitis, rheumatic disease, and gastrointestinal disorders [Supplemental  
16 Table 5S-1 ([U.S. EPA, 2016l](#))]. Literature searches have also identified a few recently  
17 published toxicological studies on hematological effects, mRNA and protein expression  
18 in the brain, sensory symptoms, and effects in other organs (e.g., liver, spleen)  
19 [Supplemental Table 5S-2 ([U.S. EPA, 2015e](#))]. These health effects are not evaluated in  
20 the current draft ISA because of the lack of relationship between the toxicological and  
21 epidemiological health effects examined, as well as a large potential for publication bias  
22 (i.e., a greater likelihood of publication for studies showing effects compared with those  
23 showing no effect).

24 The [Preamble](#) to the ISAs ([U.S. EPA, 2015b](#)) describes the general framework for  
25 evaluating scientific information, including criteria for assessing study quality and  
26 developing scientific conclusions. Aspects specific to evaluating studies of SO<sub>x</sub> are  
27 described in the [Annex for Chapter 5](#). For epidemiologic studies, emphasis is placed on  
28 studies that (1) characterize quantitative relationships between SO<sub>2</sub> and health effects,  
29 (2) examine exposure metrics that well represent the variability in concentrations in the  
30 study area, (3) consider the potential influence of other air pollutants and factors  
31 correlated with SO<sub>2</sub>, (4) examine potential at-risk populations and lifestages, or  
32 (5) combine information across multiple cities. With respect to the evaluation of  
33 controlled human exposure and toxicological studies, emphasis is placed on studies that  
34 examine effects relevant to humans and SO<sub>2</sub> concentrations relevant to ambient  
35 exposures. Based on peak ambient concentrations ([Section 2.5](#)) and the ISA’s emphasis  
36 on ambient-relevant exposures within one to two orders of magnitude of current ambient

1 concentrations, SO<sub>2</sub> concentrations of 2,000 ppb<sup>1</sup> or less are defined to be  
2 ambient-relevant. Experimental studies with higher exposure concentrations were  
3 included if they contributed to an understanding of dosimetry or potential modes of  
4 action. For the evaluation of human exposure to ambient SO<sub>2</sub>, emphasis is placed on  
5 studies that examine the quality of data sources used to assess exposures, such as central  
6 site monitors, personal exposure monitors, and dispersion models. The ISA also  
7 emphasizes studies that examine factors that influence exposure such as time-activity  
8 patterns and building ventilation characteristics.

9 Integrating information across scientific disciplines and related health outcomes and  
10 synthesizing evidence from previous and recent studies, the ISA draws conclusions about  
11 relationships between SO<sub>2</sub> exposure and health effects. Determinations are made about  
12 causation, not just association, and are based on judgments of aspects such as the  
13 consistency, coherence, and biological plausibility of observed effects (i.e., evidence for  
14 effects on key events in the mode of action) as well as related uncertainties. The ISA uses  
15 a formal causal framework [Table II of the [Preamble](#) to the ISAs ([U.S. EPA, 2015b](#))] to  
16 classify the weight of evidence according to the five-level hierarchy summarized below.

- 17 • **Causal relationship:** the consistency and coherence of evidence integrated  
18 across scientific disciplines and related health outcomes are sufficient to rule out  
19 chance, confounding, and other biases with reasonable confidence.
- 20 • **Likely to be a causal relationship:** there are studies in which results are not  
21 explained by chance, confounding, or other biases, but uncertainties remain in the  
22 evidence overall. For example, the influence of other pollutants is difficult to  
23 address, or evidence across scientific disciplines may be limited or inconsistent.
- 24 • **Suggestive of, but not sufficient to infer, a causal relationship:** evidence is  
25 generally supportive but not entirely consistent or is limited overall. Chance,  
26 confounding, and other biases cannot be ruled out.
- 27 • **Inadequate to infer the presence or absence of a causal relationship:** there is  
28 insufficient quantity, quality, consistency, or statistical power of results from  
29 studies.
- 30 • **Not likely to be a causal relationship:** several adequate studies, examining the  
31 full range of anticipated human exposure concentrations and potential at-risk  
32 populations and lifestyles, consistently show no effect.

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<sup>1</sup> The 2,000-ppb upper limit applies largely to animal toxicological studies but also a few controlled human exposure studies.

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## 1.3 Organization of the Integrated Science Assessment

1 This ISA comprises the [Preface](#) (legislative requirements of the NAAQS and history of  
2 the primary SO<sub>2</sub> NAAQS), [Executive Summary](#), and six chapters. This chapter  
3 ([Chapter 1](#)) synthesizes the scientific evidence that best informs policy-relevant questions  
4 that frame this review of the primary SO<sub>2</sub> NAAQS. [Chapter 2](#) characterizes the sources,  
5 atmospheric processes involving SO<sub>x</sub>, and trends in ambient concentrations. [Chapter 3](#)  
6 describes methods to estimate human exposure to SO<sub>x</sub> and the impact of error in  
7 estimating exposure on relationships with health effects. [Chapter 4](#) describes the  
8 dosimetry and modes of action for SO<sub>2</sub>. [Chapter 5](#) evaluates and integrates  
9 epidemiologic, controlled human exposure, and toxicological evidence for health effects  
10 related to short-term and long-term exposure to SO<sub>x</sub>. [Chapter 6](#) evaluates information on  
11 potential at-risk populations and lifestyles. In addition, the [Preamble](#) to the ISAs ([U.S.](#)  
12 [EPA, 2015b](#)) describes the general process for developing an ISA.

13 The purpose of this chapter is not to summarize each of the aforementioned chapters but  
14 to synthesize the key findings for each topic that informed the characterization of SO<sub>2</sub>  
15 exposure and relationships with health effects. This chapter also integrates information  
16 across the ISA to inform policy-relevant issues such as SO<sub>2</sub> exposure metrics associated  
17 with health effects, concentration-response relationships, and the public health impact of  
18 SO<sub>2</sub>-related health effects ([Section 1.7](#)). A key consideration in the health effects  
19 assessment is the extent to which evidence indicates that SO<sub>2</sub> exposure independently  
20 causes health effects. To that end, this chapter draws upon information about the sources,  
21 distribution, and exposure to ambient SO<sub>2</sub> and identifies pollutants and other factors  
22 related to the distribution of or exposure to ambient SO<sub>2</sub> that can potentially influence  
23 epidemiologic associations observed between health effects and SO<sub>2</sub> exposure  
24 ([Section 1.4](#)). The chapter also summarizes information on the dosimetry and mode of  
25 action of inhaled SO<sub>2</sub> that can provide biological plausibility for observed health effects  
26 ([Section 1.5](#)). The discussions of the health effects evidence and causal determinations  
27 ([Section 1.6](#)) describe the extent to which epidemiologic studies accounted for factors  
28 that may influence epidemiologic study results and the extent to which findings from  
29 controlled human exposure and animal toxicological studies support independent  
30 relationships between SO<sub>2</sub> exposure and health effects.

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## 1.4 From Emissions Sources to Exposure to Sulfur Dioxide

31 Characterizing human exposure is key to understanding the relationships between  
32 ambient SO<sub>2</sub> exposure and health effects. The sources of SO<sub>x</sub> and the transformations  
33 that occur in ambient air influence the spatial and temporal pattern of SO<sub>2</sub> concentrations

1 in the air. These patterns have implications for variation in exposure in the population,  
2 the adequacy of methods used to estimate exposure, and in turn, the strength of inferences  
3 that can be drawn about health effects related to SO<sub>2</sub> exposure.

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#### 1.4.1 Emission Sources and Distribution of Ambient Concentrations

4 Emissions of SO<sub>2</sub> have declined by approximately 72% for all sources from 1990 to 2011  
5 as a result of several U.S. air quality regulatory programs. Coal-fired electricity  
6 generation units (EGUs) remain the dominant sources by nearly an order of magnitude  
7 above the next highest source (industrial fuel combustion), emitting 4.6 million tons of  
8 SO<sub>2</sub> annually, according to the 2011 National Emissions Inventory (NEI; [Section 2.2](#)).

9 In addition to emission rate, the two important variables that determine the concentration  
10 of SO<sub>2</sub> downwind of the source are the photochemical and other removal processes (e.g.,  
11 formation of particle-phase reduced sulfur compounds) occurring in the emissions plume  
12 and the local meteorology, including wind, atmospheric stability, humidity, and cloud/fog  
13 cover ([Section 2.3](#)). The primary gas-phase photochemical SO<sub>2</sub> oxidation mechanism  
14 requires the hydroxyl radical (OH). Another oxidation mechanism involves a Criegee  
15 intermediate biradical that participates in converting SO<sub>2</sub> to SO<sub>3</sub>, which rapidly reacts  
16 with water vapor to form sulfuric acid (H<sub>2</sub>SO<sub>4</sub>). The Criegee-based SO<sub>2</sub> oxidation  
17 mechanism may amplify the rate of SO<sub>2</sub> removal and formation of organosulfur  
18 compounds in areas with high concentrations of Criegee precursors (i.e., low-molecular-  
19 weight organic gases, such as biogenic compounds and unsaturated hydrocarbons present  
20 downwind of industrial sites and refineries). Aqueous-phase oxidation of SO<sub>2</sub> is also an  
21 important removal mechanism. Clouds and fog can reduce local SO<sub>2</sub> concentrations by  
22 converting it to H<sub>2</sub>SO<sub>4</sub> in the droplet phase.

23 Changes were undertaken to the existing U.S. EPA monitoring network as a result of the  
24 new 1-hour primary NAAQS standard promulgated in 2010 ([Section 2.4](#)). First, the  
25 automated pulsed ultraviolet fluorescence (UVF) method, the method most commonly  
26 used by state and local monitoring agencies for NAAQS compliance, was designated as a  
27 federal reference method (FRM). Second, new SO<sub>2</sub> monitoring guidelines require states  
28 to report either the highest 5-minute concentration for each hour of the day or all twelve  
29 5-minute concentrations for each hour of the day in light of health effects evidence on  
30 respiratory effects among exercising individuals with asthma following a 5–10-minute  
31 exposure to SO<sub>2</sub>. Analysis of environmental concentrations of SO<sub>2</sub> data reported in  
32 [Section 2.5](#) reflect the monitoring network changes, particularly the analysis of the recent  
33 5-minute data.

1 On a nationwide basis, the average 1-h daily max SO<sub>2</sub> reported during 2013–2015 is  
2 5.4 ppb with a 99th percentile concentration of 64 ppb ([Section 2.5](#)). However, peak  
3 concentrations (99th percentile) of 1-h daily max SO<sub>2</sub> concentrations can be greater than  
4 75 ppb at some monitoring sites located near large anthropogenic sources (e.g., power  
5 plants or metal processing facilities) or natural sources (e.g., volcanoes). The mean  
6 5-minute hourly max concentration across the U.S. in 2013–2015 was 2.1 ppb, with a  
7 99th percentile concentration of 24.0 ppb. Correlations between hourly 5-minute max  
8 SO<sub>2</sub> concentrations and their corresponding 1-h avg concentrations are high, with  
9 approximately 75% of sites having correlations greater than 0.9. Peak-to-mean ratios  
10 (PMRs) between the two metrics are generally less than 3, although higher PMRs are  
11 observed during some hours ([Section 2.5.4](#)). Background concentrations of SO<sub>2</sub> from  
12 natural sources and sources outside the U.S. are very low across most of the country (less  
13 than 0.03 ppb), accounting for less than 1% of ambient SO<sub>2</sub> concentrations except in  
14 areas where volcanic emissions are important, such as Hawaii and the West Coast  
15 ([Section 2.5.5](#)).

16 SO<sub>2</sub> concentrations are highly variable across urban spatial scales, exhibiting moderate to  
17 poor correlations between SO<sub>2</sub> measured at different monitoring sites across a  
18 metropolitan area. This high degree of urban spatial variability may not be fully captured  
19 by central site monitors used in epidemiologic studies, and thus, has implications for the  
20 interpretation of human exposure and health effects data ([Section 2.5.2.2](#) and  
21 [Section 3.4.4](#)).

22 Air quality models, including dispersion models and chemical transport models, can be  
23 used to estimate SO<sub>2</sub> concentrations in locations where monitoring is not practical or  
24 sufficient ([Section 2.6](#)). Because existing ambient SO<sub>2</sub> monitors may not be sited in  
25 locations to capture peak 1-hour concentrations, the implementation program for the 2010  
26 primary SO<sub>2</sub> NAAQS allows for air quality modeling to be used to characterize air  
27 quality for informing designation decisions (75 FR 35520). In addition, modeling is  
28 critical to the assessment of the impact of future sources or proposed modifications where  
29 monitoring cannot inform, and for the design and implementation of mitigation  
30 techniques. Dispersion models have also been used to estimate SO<sub>2</sub> exposure  
31 concentrations in epidemiologic studies, particularly in long-term studies  
32 ([Section 3.3.2.4](#), [Chapter 5](#)). The widely used dispersion model American Meteorological  
33 Society/U.S. EPA Regulatory Model (AERMOD) is based on Gaussian dispersion  
34 models but includes advancements such as boundary layer scaling formulations, surface  
35 and elevated emission points, interactions of plumes with buildings and terrain, and  
36 source geometry. Several evaluations of the performance of AERMOD against field  
37 study data over averaging times from 1 hour to 1 year found the model was relatively  
38 unbiased in estimating upper-percentile 1-hour concentration values. Lagrangian puff

1 dispersion models, such as CALPUFF, have been developed as an alternative to Gaussian  
2 dispersion models. CALPUFF models SO<sub>2</sub> as a tracer and then uses a Lagrangian step  
3 algorithm to model non-steady-state dynamics, using time-varying winds specified by  
4 meteorological models. CALPUFF simulations were found to improve in accuracy with  
5 increasing integration times. Uncertainties in model predictions are influenced by  
6 uncertainties in model input data, particularly emissions and meteorological conditions  
7 (e.g., wind).

---

## 1.4.2 Assessment of Human Exposure

8 Multiple techniques can be used to assign exposure for epidemiologic studies, including  
9 evaluation of data from central site monitoring, personal SO<sub>2</sub> monitoring, and using  
10 various modeling approaches ([Section 3.3](#)). Each has strengths and limitations, as  
11 summarized in [Table 3-1](#). Central site monitors are intended to represent population  
12 exposure, in contrast to near-source monitors, which are intended to capture high  
13 concentrations in the vicinity of a source and are not typically used as the primary data  
14 source in urban-scale epidemiologic studies. Central site monitors may provide a  
15 continuous record of SO<sub>2</sub> concentrations over many years, but they do not fully capture  
16 the relatively high spatial variability in SO<sub>2</sub> concentration across an urban area. Personal  
17 SO<sub>2</sub> monitors can capture the study participants' activity-related exposure across different  
18 microenvironments, but low ambient SO<sub>2</sub> concentrations often result in a substantial  
19 fraction of the samples below the limit of detection for averaging times of 24 hours or  
20 less. The time and expense involved to deploy personal monitors make them suitable for  
21 panel epidemiologic studies and exposure validation studies. Models can be used to  
22 estimate exposure for individuals and large populations when personal exposure  
23 measurements are unavailable. Modeling approaches include estimating concentration  
24 surfaces and time-activity patterns and running microenvironment-based models that  
25 combine air quality data with time-activity patterns. In general, more complex  
26 approaches provide more detailed exposure estimates but require additional input data,  
27 assumptions, and computational resources. Depending on the model type, there is the  
28 potential for bias and reduced precision due to model misspecification, missing sources,  
29 smoothing of concentration gradients, and complex topography. Evaluation of model  
30 results helps demonstrate the suitability of that approach for particular applications.

31 New studies of the relationship between indoor and outdoor SO<sub>2</sub> concentrations have  
32 focused on publicly owned buildings rather than residences ([Section 3.4.1.2](#)). The results  
33 of these studies are consistent with results of previous studies showing that  
34 indoor:outdoor ratios and slopes cover an extremely wide range, from near zero to near  
35 one. Differences in results among studies are due to building characteristics (e.g., forced

1 ventilation, building age, and building type), personal activities such as opening windows  
2 and doors, and SO<sub>2</sub> measurement limitations. When reported, correlations between indoor  
3 and outdoor concentrations were relatively high (>0.75), suggesting that variations in  
4 outdoor concentration drive indoor concentrations, particularly considering the lack of  
5 indoor SO<sub>2</sub> sources. These high correlations were observed across seasons and  
6 geographic locations. The bulk of the evidence for personal-ambient SO<sub>2</sub> relationships  
7 was available at the time of the 2008 ISA for Sulfur Oxides ([U.S. EPA, 2008d](#)) and  
8 showed a wide range of correlations between ambient concentration and personal  
9 exposure, in part due to a large fraction of samples below the method detection limit  
10 (MDL) in several studies ([Section 3.4.1.3](#)). When nearly all of the personal samples are  
11 below the MDL, no correlation can be observed. However, when the bulk of the personal  
12 samples are above the MDL, personal exposure is moderately correlated with ambient  
13 concentration.

14 “Exposure error” refers to the bias and uncertainty associated with using concentration  
15 metrics to represent the actual exposure of an individual or population [([Lipfert and](#)  
16 [Wyzga, 1996](#)) [Section 3.2](#)]. Exposure error has two components: (1) exposure  
17 measurement error derived from uncertainty in the metric being used to represent  
18 exposure, and (2) use of a surrogate target parameter of interest in the epidemiologic  
19 study in lieu of the true exposure, which may be unobservable ([Section 3.2.1](#)). Factors  
20 that could contribute to error in estimating exposure to ambient SO<sub>2</sub> include  
21 time-location-activity patterns, spatial and temporal variability in SO<sub>2</sub> concentrations, and  
22 proximity of populations to monitoring sites and sources ([Section 3.4.2](#)). Activity patterns  
23 vary both among and within individuals, resulting in corresponding variations in  
24 exposure across a population and over time. Variation in SO<sub>2</sub> concentrations among  
25 different microenvironments means that the amount of time spent in each location, as  
26 well as exertion level, will influence an individual’s exposure to ambient SO<sub>2</sub>. Time spent  
27 in different locations has also been found to vary by age, with younger and older age  
28 groups spending a greater percentage of time outdoors than adults of typical working age  
29 (18–64 years). These variations in activity pattern contribute to differences in exposure  
30 and, if uncharacterized, introduce error into population-averaged exposure estimates.

31 Uncharacterized spatial and temporal variability in SO<sub>2</sub> concentrations can contribute to  
32 exposure error in epidemiologic studies. SO<sub>2</sub> has low to moderate spatial correlations  
33 among ambient monitoring sites across urban geographic scales; thus, using central site  
34 monitor data for epidemiologic exposure assessment introduces exposure error into the  
35 resulting health effect estimate. Spatial variability in the magnitude of concentrations  
36 may affect cross-sectional and large-scale cohort studies by assigning exposures from one  
37 or a small number of sites that do not capture all of the spatial variability within a city.

1 This issue may be less important for time-series studies, which rely on day-to-day  
2 temporal variability in concentrations to evaluate health effects.

3 Proximity of populations to ambient monitoring sites may influence how well human  
4 exposure is represented by measurements at the monitors, although factors other than  
5 distance play an important role as well. While many SO<sub>2</sub> monitoring sites are located  
6 near dense population centers, other sites are located near sources and may not fully  
7 represent SO<sub>2</sub> concentrations experienced by populations in epidemiologic studies. Use  
8 of these near-source monitoring sites introduces exposure error into health effect  
9 estimates, although this error can be mitigated by using average concentrations across  
10 multiple sites in an urban area.

11 Exposure to copollutants, such as other criteria pollutants, may result in confounding of  
12 health effect estimates. For SO<sub>2</sub>, daily concentrations generally exhibit low correlations  
13 (median <0.4) with other daily NAAQS pollutant concentrations at collocated monitors  
14 ([Figure 3-5, Section 3.4.3](#)). However, a wide range of copollutant correlations has been  
15 observed across different monitoring sites, from moderately negative to moderately  
16 positive. In studies in which daily SO<sub>2</sub> correlations with NO<sub>2</sub> and CO were observed to be  
17 high, it is possible the data were collected before a rule to reduce sulfur content in diesel  
18 fuel (66 FR 5002) took effect in 2006 and 2007. The minority of sites with stronger  
19 correlations may introduce a greater degree of confounding into epidemiologic results.  
20 A similar impact is expected for epidemiologic studies of long-term SO<sub>2</sub> exposure, which  
21 also report a wide range of copollutant correlations.

22 Exposure error can influence epidemiologic study results by biasing effect estimates  
23 either toward or away from the null and widening confidence intervals beyond the  
24 nominal coverage that would be produced if the true exposure had been used  
25 ([Section 3.4.4](#)). The exposure error varies according to the study design, especially  
26 regarding the study's spatial and temporal aspects. For example, in time-series and panel  
27 studies, low personal-ambient correlations tend to bias the effect estimate toward the null,  
28 while spatial variation in personal-ambient correlations across an urban area contributes  
29 to widening of the confidence interval around the effect estimate beyond the nominal  
30 coverage of the confidence intervals that would be produced if the true exposure had been  
31 used. For long-term studies, bias of the health effect estimate may occur in either  
32 direction depending on whether the monitor is over- or underestimating exposure for the  
33 population of interest. In all study types, use of central site monitors is expected to  
34 decrease precision of the health effect estimate because spatial variation in  
35 personal-ambient correlations across an urban area contributes to widening of the  
36 confidence interval around the effect estimate beyond the nominal coverage that would  
37 be produced if the true exposure had been used.

1 Choice of exposure estimation method also influences the impact of exposure error on  
2 epidemiologic study results. Central site monitors offer a convenient source of time-series  
3 data, but fixed-site measurements do not account for the effects of spatial variation in  
4 SO<sub>2</sub> concentration, differences between indoor and outdoor exposure to ambient SO<sub>2</sub>, and  
5 varying activity patterns on personal exposure to SO<sub>2</sub>. Personal exposure measurements,  
6 such as those made in panel epidemiologic studies, provide accurate and specific  
7 exposure estimates, but sample size is often small and only a limited set of health  
8 outcomes can be studied. Modeled concentrations or exposures offer alternatives to  
9 measurements, with the advantage of estimating exposures over a wide range of scales,  
10 populations, and scenarios, particularly for locations lacking monitoring data. However,  
11 depending on the model type, there is the potential for bias and reduced precision due to  
12 model misspecification, missing sources, smoothing of concentration gradients, and  
13 complex topography. Model estimates are most informative when compared to an  
14 independent set of measured concentrations or exposures. The various sources of  
15 exposure error and their potential impact are considered in the evaluation of  
16 epidemiologic study results in this ISA.

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## 1.5 Dosimetry and Mode of Action of Sulfur Dioxide

17 This ISA summarizes information on the dosimetry of inhaled SO<sub>2</sub>, including the  
18 processes of absorption, distribution, metabolism, and elimination, as well as information  
19 on the mode of action of inhaled SO<sub>2</sub>, covering the processes by which inhaled SO<sub>2</sub>  
20 initiates a cascade of molecular and cellular responses and the organ-level responses that  
21 follow. ([Chapter 4](#)). Together, these sections provide the foundation for understanding  
22 how exposure to inhaled SO<sub>2</sub> may lead to health effects. This understanding may provide  
23 biological plausibility for effects observed in the epidemiologic studies.

---

### 1.5.1 Dosimetry of Inhaled Sulfur Dioxide

24 Dosimetry of inhaled SO<sub>2</sub> refers to the measurement or estimation of the amount of SO<sub>2</sub>  
25 and its reaction products reaching and/or persisting at specific sites within the respiratory  
26 tract and systemically after exposure. Factors affecting the transport and fate of SO<sub>2</sub> in  
27 the respiratory tract include respiratory tract morphology, respiratory functional  
28 parameters, and physicochemical properties of SO<sub>2</sub> and of epithelial lining fluid (ELF).  
29 Health effects may be due to inhaled SO<sub>2</sub> or its chemical reaction products, including  
30 sulfite and S-sulfonates. Few studies have investigated SO<sub>2</sub> dosimetry since the 2008 ISA  
31 for Sulfur Oxides ([U.S. EPA, 2008d](#)), with most studies conducted prior to the 1982  
32 AQCD ([U.S. EPA, 1982a](#)) and the 1986 Second Addendum ([U.S. EPA, 1986b](#)).

1 Because SO<sub>2</sub> is highly soluble in water, it is readily absorbed in the nasal passages of  
2 both humans and laboratory animals under resting conditions ([Section 4.2.2](#)). During  
3 nasal breathing, the majority of available data suggests 95% or greater SO<sub>2</sub> absorption  
4 occurs in the nasal passages, even under ventilation levels comparable to that during  
5 exercise. With increasing physical activity, there is an increase in ventilatory rate and a  
6 shift from nasal to oronasal breathing, resulting in greater SO<sub>2</sub> penetration into the lower  
7 respiratory tract. Even at rest, differences have been observed by age, sex, disease status,  
8 and body mass index in the fraction of oral versus nasal breathing ([Section 4.1.2](#)).  
9 Children inhale a larger fraction of air through their mouth than adults, and males tend  
10 inhale a larger fraction of air through their mouth than females (across all ages).  
11 Individuals with allergies or upper respiratory infections experience increased nasal  
12 resistance, and thus, increased fraction of oral breathing. Obesity, especially in boys, also  
13 contributes to increased nasal resistance and an increased oral fraction of breathing  
14 relative to normal weight children. Due to their increased amount of oral breathing, these  
15 individuals may be expected to have greater SO<sub>2</sub> penetration into the lower respiratory  
16 tract than healthy, normal weight adults. Children may also be expected to have a greater  
17 intake dose of SO<sub>2</sub> per body mass than adults.

18 Following absorption in the respiratory tract, SO<sub>2</sub> rapidly forms a mixture of bisulfite and  
19 sulfite, with the latter predominating. As much as 15–18% of the absorbed SO<sub>2</sub> may be  
20 desorbed and exhaled following cessation of exposure. Although some SO<sub>2</sub> products  
21 rapidly move from the respiratory tract into the blood and are distributed about the body,  
22 experiments using radiolabeled <sup>35</sup>S indicate that the majority of sulfur in SO<sub>2</sub>-derived  
23 products in the body at any given time following exposure is found in the respiratory tract  
24 and may be detected there for up to a week following inhalation ([Section 4.2.3](#)).

25 The distribution and clearance of inhaled SO<sub>2</sub> from the respiratory tract may involve  
26 several intermediate chemical reactions and transformations, particularly the formation of  
27 sulfite and S-sulfonates. Sulfite is metabolized into sulfate, primarily in the liver, which  
28 has higher sulfite oxidase levels than the lung or other body tissues ([Section 4.2.4](#)).  
29 Sulfite oxidase activity is highly variable among species with liver sulfite oxidase activity  
30 in rats being 10–20 times greater than in humans. Urinary excretion of sulfate is rapid  
31 and proportional to the concentration of SO<sub>2</sub> products in the blood ([Section 4.2.5](#)).  
32 S-sulfonates are cleared more slowly from the circulation with a clearance half-time of  
33 days.

34 Sulfite levels in the body are predominately influenced by endogenous production and  
35 ingestion of sulfite in food ([Section 4.2.6](#)). The primary endogenous contribution of  
36 sulfite is from the catabolism of sulfur-containing amino acids (namely, cysteine and  
37 methionine). Endogenous sulfite from ingested sulfur-containing amino acids far exceeds  
38 exogenous sulfite from ingestion of food additives [by 140 and 180 times in adult

1 (19–50 years) females and males, respectively, and by 500 times or more in young  
2 children (1–3 years)]. Endogenous sulfite production is two or more orders of magnitude  
3 higher than inhalation-derived sulfite levels for both children and adults, even for full day  
4 exposures to 75 ppb SO<sub>2</sub> (the level of the 1-hour NAAQS). Ingestion rates of sulfite  
5 added to foods vary widely; however, in general, sulfite ingestion is expected to exceed  
6 sulfite intake from inhalation in adults and children even for full day exposures to 75 ppb  
7 SO<sub>2</sub>. However, inhalation-derived SO<sub>2</sub> products accumulate in respiratory tract tissues,  
8 whereas sulfite and sulfate from ingestion or endogenous production do not.

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## 1.5.2 Mode of Action of Inhaled Sulfur Dioxide

9 Mode of action refers to a sequence of key events, endpoints, and outcomes that result in  
10 a given toxic effect. The mode of action discussion in [Section 4.3](#) of this ISA updates the  
11 basic concepts derived from the SO<sub>2</sub> literature presented in the 1982 AQCD ([U.S. EPA,  
12 1982a](#)) and the 2008 ISA for Sulfur Oxides ([U.S. EPA, 2008d](#)) and introduces the recent  
13 relevant literature. The main effects of SO<sub>2</sub> inhalation are seen at the sites of absorption  
14 (i.e., the respiratory tract) and include (1) activation of sensory nerves in the respiratory  
15 tract resulting in a neural reflex response, (2) injury to airway mucosa, and (3) increased  
16 airway hyperreactivity and allergic inflammation. Effects outside the respiratory tract  
17 may occur at very high concentrations of inhaled SO<sub>2</sub>.

18 Reactive products formed as a result of SO<sub>2</sub> inhalation are responsible for a variety of  
19 downstream key events, which may include activation of sensory nerves in the  
20 respiratory tract, release of inflammatory mediators, and modulation of allergic  
21 inflammation or sensitization. These key events may collectively lead to several  
22 endpoints, including bronchoconstriction and airway hyper-responsiveness (AHR).  
23 A characteristic feature of individuals with asthma is an increased propensity of their  
24 airways to narrow in response to bronchoconstrictive stimuli relative to nonatopic  
25 individuals without asthma. Thus, bronchoconstriction is characteristic of an asthma  
26 attack. However, individuals without asthma may also experience bronchoconstriction in  
27 response to SO<sub>2</sub> inhalation; generally this occurs at higher concentrations (>1,000 ppb)  
28 than in an individual with asthma. Additionally, SO<sub>2</sub> exposure may increase airway  
29 responsiveness to subsequent exposures of other stimuli such as allergens or  
30 methacholine. These pathways may be linked to the epidemiologic outcome of asthma  
31 exacerbation.

32 The strongest evidence for the mode of action for respiratory effects following short-term  
33 exposure comes from controlled human exposure studies. SO<sub>2</sub> exposure resulted in  
34 increased airway resistance due to bronchoconstriction in adults, both with and without

1 asthma. In adults without asthma, this response occurred primarily as a result of  
2 activation of sensory nerves in the respiratory tract resulting in neural reflex responses  
3 ([Section 4.3.1](#)). This is mediated by cholinergic parasympathetic pathways involving the  
4 vagus nerve. However, in adults with asthma, evidence indicates that the response is only  
5 partially due to vagal pathways and that inflammatory mediators such as histamine and  
6 leukotrienes also play an important role. Studies in experimental animals also  
7 demonstrate that SO<sub>2</sub> exposure activates reflexes that are mediated by cholinergic  
8 parasympathetic pathways involving the vagus nerve. However, noncholinergic  
9 mechanisms (i.e., neurogenic inflammation) may also be involved.

10 Evidence demonstrates that SO<sub>2</sub> exposure modulates allergic inflammatory responses  
11 ([Section 4.3.2](#)). Enhancement of allergic inflammation (i.e., leukotriene-mediated  
12 increases in numbers of sputum eosinophils) has been observed in adults with asthma  
13 who were exposed for 10 minutes to 750 ppb SO<sub>2</sub>. In an animal model of allergic airway  
14 disease, repeated exposure to 2,000 ppb SO<sub>2</sub> led to an enhanced inflammatory response,  
15 including allergic inflammation. In naive animals, repeated exposure to SO<sub>2</sub> (as low as  
16 100 ppb) over several days promoted allergic sensitization, inflammation, and AHR when  
17 animals were subsequently sensitized and challenged with an allergen. Thus, allergic  
18 inflammation and increased airway responsiveness may also link short-term SO<sub>2</sub>  
19 exposure to asthma exacerbation.

20 Evidence for the mode of action for respiratory effects due to long-term SO<sub>2</sub> exposure  
21 comes from studies in both naive and allergic experimental animals, which demonstrate  
22 allergic sensitization, allergic inflammation, AHR, and morphologic changes suggestive  
23 of airway remodeling following exposure to SO<sub>2</sub> (i.e., 2,000 ppb) over several weeks  
24 ([Section 4.3.3](#)). These changes, however, are mild compared to histopathological  
25 changes, such as mucous cell metaplasia and intramural fibrosis, which are generally  
26 observed following chronic exposure of naive animals to SO<sub>2</sub> concentrations of 10 ppm  
27 (10,000 ppb) and higher. However, in allergic animals, exposure to SO<sub>2</sub> over several  
28 weeks leads to morphologic responses indicative of airway remodeling and to AHR.  
29 Thus, repeated exposure to SO<sub>2</sub> may lead to the development of allergic airway disease,  
30 which shares many features with asthma, and to the worsening of the allergic airway  
31 disease. The development of AHR may link long-term exposure to SO<sub>2</sub> to the  
32 epidemiologic outcome of new onset asthma.

33 Although there is some evidence that SO<sub>2</sub> inhalation results in extrapulmonary effects,  
34 there is uncertainty regarding the mode of action underlying these responses  
35 ([Section 4.3.4](#)). Evidence from controlled human exposure studies points to SO<sub>2</sub>  
36 exposure-induced activation/sensitization of neural reflexes, possibly leading to altered  
37 heart rate (HR) or heart rate variability (HRV). Evidence also points to transport of sulfite

1 into the circulation. Sulfite is highly reactive and may be responsible for redox stress  
2 (possibly through autoxidation or peroxidase-mediated reactions to produce free radicals)  
3 in the circulation and extrapulmonary tissues. However, this stress is likely to occur only  
4 at very high SO<sub>2</sub> concentrations or during prolonged exposures because circulating sulfite  
5 is efficiently metabolized to sulfate in a reaction catalyzed by hepatic sulfite oxidase.

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## 1.6 Health Effects of Sulfur Dioxide

6 This ISA evaluates relationships between an array of health effects and short-term and  
7 long-term exposures to SO<sub>2</sub> as examined in epidemiologic, controlled human exposure,  
8 and animal toxicological studies. Short-term exposures are defined as those with  
9 durations of minutes up to 1 month, with most studies examining effects related to  
10 exposures in the range of 1 hour to 1 week. Long-term exposures are defined as those  
11 with durations of more than 1 month to years. Drawing from the health effects evidence  
12 described in detail in [Chapter 5](#), information on dosimetry and modes of action presented  
13 in [Chapter 4](#), as well as issues regarding exposure assessment and potential confounding  
14 described in [Chapter 3](#) and [Section 1.4](#), the subsequent sections and [Table 1-1](#) present the  
15 key evidence that informed the causal determinations for relationships between SO<sub>2</sub>  
16 exposure and health effects.

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### 1.6.1 Respiratory Effects

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#### 1.6.1.1 Respiratory Effects Associated with Short-Term Exposure to Sulfur Dioxide

17 Strong scientific evidence indicates that there is a causal relationship between short-term  
18 SO<sub>2</sub> exposure and respiratory morbidity, particularly in individuals with asthma, which is  
19 consistent with the conclusions of the 2008 ISA for Sulfur Oxides ([U.S. EPA, 2008d](#)).  
20 This determination is based on the consistency of findings within disciplines, coherence  
21 among evidence from controlled human exposure, epidemiologic, and toxicological  
22 studies, and biological plausibility for effects specifically related to asthma exacerbation  
23 ([Table 5-21](#)).

24 This conclusion is primarily based on controlled human exposure studies included in the  
25 2008 SO<sub>x</sub> ISA ([U.S. EPA, 2008d](#)) that showed lung function decrements and respiratory  
26 symptoms in adults with asthma exposed to SO<sub>2</sub> for 5–10 minutes under increased  
27 ventilation conditions; no new controlled human exposure studies have been conducted to

1 evaluate the effect of SO<sub>2</sub> on respiratory morbidity among individuals with asthma. These  
2 studies consistently demonstrated that individuals with asthma experience a moderate or  
3 greater decrement in lung function, defined as a  $\geq 100\%$  increase in specific airway  
4 resistance (sRaw) or  $\geq 15\%$  decrease in forced expiratory volume in 1 sec (FEV<sub>1</sub>),  
5 frequently accompanied by respiratory symptoms, following peak exposures of  
6 5–10 minutes with elevated ventilation rates at concentrations of 400–600 ppb  
7 ([Section 5.2.1.2](#)). A fraction of individuals with asthma (~5–30%) was observed in these  
8 studies to have moderate decrements in lung function at lower SO<sub>2</sub> concentrations  
9 (200–300 ppb; [Table 5-2](#)). Lung function decrements at these lower concentrations are  
10 less likely to be accompanied by respiratory symptoms. Some studies have evaluated the  
11 influence of asthma severity on response to SO<sub>2</sub>, but the most severe asthmatics have not  
12 been tested, and thus, their response is unknown. Adults with moderate to severe asthma  
13 demonstrated larger absolute changes in lung function during exercise in response to SO<sub>2</sub>  
14 than adults with mild asthma, although this difference was attributed to a larger response  
15 to the exercise component of the protocol rather than to SO<sub>2</sub> itself. While adults with  
16 moderate to severe asthma may have similar responses to SO<sub>2</sub> as healthy adults (although  
17 at lower concentrations), they have less reserve capacity to deal with an insult compared  
18 with individuals with mild asthma; therefore, the impact of SO<sub>2</sub>-induced decrements in  
19 lung function is greater in individuals with asthma than healthy adults. Although there are  
20 no laboratory studies of children exposed to SO<sub>2</sub>, a number of studies have evaluated  
21 airway responsiveness of children and adults to a bronchoconstrictive stimulus. These  
22 studies indicate that school-aged children, particularly boys and perhaps obese children,  
23 are expected to have greater responses (i.e., greater lung function decrements) following  
24 exposure to SO<sub>2</sub> than adolescents and adults.

25 These findings are consistent with the current understanding of dosimetry and modes of  
26 action ([Section 1.5](#)). Due to their increased fraction of oral breathing, individuals with  
27 asthma may be expected to have greater SO<sub>2</sub> penetration into the lower respiratory tract  
28 than healthy adults. Reactive products formed as a result of SO<sub>2</sub> inhalation, particularly  
29 sulfites and S-sulfonates, are responsible for a variety of downstream key events, which  
30 may include activation of sensory nerves in the respiratory tract resulting in a neural  
31 reflex response, release of inflammatory mediators, and modulation of allergic  
32 inflammation. These key events may lead to several endpoints including  
33 bronchoconstriction and AHR, resulting in the outcome of asthma exacerbation.

34 Epidemiologic evidence also provides support for a causal relationship, including  
35 additional studies that add to the evidence provided by the 2008 ISA for Sulfur Oxides  
36 ([U.S. EPA, 2008d](#)). Studies of asthma hospital admissions and emergency department  
37 (ED) visits report positive associations with short-term SO<sub>2</sub> exposures, particularly for  
38 children (i.e., <18 years of age), with additional evidence from studies that examine

1 potential copollutant confounding that associations are generally unchanged in  
2 copollutant models involving PM and other criteria pollutants ([Section 5.2.1.2](#),  
3 [Figure 5-2](#)). There is also some supporting evidence for positive associations between  
4 short-term SO<sub>2</sub> exposures and respiratory symptoms among children with asthma  
5 ([Section 5.2.1.2](#)). Epidemiologic evidence of associations between short-term SO<sub>2</sub>  
6 exposures and lung function or respiratory symptoms among adults with asthma is less  
7 consistent ([Section 5.2.1.2](#)). Epidemiologic studies of cause-specific mortality that report  
8 consistent positive associations between short-term SO<sub>2</sub> exposures and respiratory  
9 mortality provide support for a potential continuum of effects ([Section 5.2.1.8](#)).

10 There is some support for other SO<sub>2</sub>-related respiratory effects including exacerbation of  
11 chronic obstructive pulmonary disease (COPD) in individuals with COPD and other  
12 respiratory effects including respiratory infection, aggregated respiratory conditions, and  
13 respiratory mortality in the general population ([Section 5.2.1.3](#), [Section 5.2.1.4](#),  
14 [Section 5.2.1.5](#), and [Section 5.2.1.6](#)). The limited and inconsistent evidence for these  
15 nonasthma-related respiratory effects does not contribute heavily to the causal  
16 determination.

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### 1.6.1.2 Respiratory Effects Associated with Long-Term Exposure to Sulfur Dioxide

17 Overall, the evidence is suggestive of, but not sufficient to infer, a causal relationship  
18 between long-term SO<sub>2</sub> exposure and respiratory effects, mainly the development of  
19 asthma in children ([Section 5.2.2](#)). This represents a change from the conclusion in the  
20 2008 ISA for Sulfur Oxides ([U.S. EPA, 2008d](#)) that the evidence was “inadequate to infer  
21 a causal association.” There is a limited number of recent longitudinal epidemiologic  
22 studies that evaluate associations between asthma incidence among children and  
23 long-term SO<sub>2</sub> exposures, with the overall body of evidence lacking consistency.  
24 The evidence from longitudinal studies showing increases in asthma incidence is  
25 coherent with findings from animal toxicological studies that provide a pathophysiologic  
26 basis for the development of asthma. In naive newborn animals, repeated SO<sub>2</sub> exposure  
27 over several weeks resulted in immune responses and airway inflammation, key steps in  
28 allergic sensitization. In allergic newborn animals, studies with several days or several  
29 weeks of repeated SO<sub>2</sub> exposure found enhanced airway inflammation and some evidence  
30 of airway remodeling and AHR. The combined epidemiologic and animal toxicological  
31 evidence provides support for an independent effect of long-term exposure to SO<sub>2</sub> on the  
32 development of asthma in children, but key uncertainties remain, including exposure  
33 measurement error and the potential for copollutant confounding. Some evidence of a  
34 link between long-term exposure to SO<sub>2</sub> and respiratory symptoms and/or respiratory  
35 allergies among children further supports a possible relationship between long-term SO<sub>2</sub>

1 exposure and the development of asthma. Details of the causal determination are  
2 provided in [Table 5-24](#).

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## 1.6.2 Health Effects beyond the Respiratory System

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### 1.6.2.1 Cardiovascular Effects Associated with Short-Term Exposure to Sulfur Dioxide

3 Overall, the available evidence is inadequate to infer the presence or absence of a causal  
4 relationship between short-term exposure to SO<sub>2</sub> and cardiovascular health effects  
5 ([Table 5-34, Section 5.3.1](#)). This conclusion is consistent with that of the 2008 ISA for  
6 Sulfur Oxides ([U.S. EPA, 2008d](#)), which concluded “the evidence as a whole is  
7 inadequate to infer a causal relationship.” Although multiple epidemiologic studies report  
8 positive associations between short-term exposure to SO<sub>2</sub> and a variety of cardiovascular  
9 outcomes, the results are inconsistent across the specific cardiovascular outcomes, and  
10 the associations are generally attenuated after copollutant adjustment. There is some  
11 experimental evidence in humans and animals for SO<sub>2</sub>-induced effects on the autonomic  
12 nervous system and inflammation and other effects in tissues distal to the absorption site.  
13 However, the limited and inconsistent evidence from the available experimental studies  
14 does not demonstrate potentially biologically plausible mechanisms for, and is not  
15 coherent with, cardiovascular effects such as triggering a myocardial infarction. Evidence  
16 for other cardiovascular and related metabolic effects is inconclusive.

---

### 1.6.2.2 Cardiovascular Effects Associated with Long-Term Exposure to Sulfur Dioxide

17 Overall, the evidence is inadequate to infer the presence or absence of a causal  
18 relationship between long-term exposure to SO<sub>2</sub> and cardiovascular health effects  
19 ([Table 5-35, Section 5.3.2](#)). The relationship between long-term SO<sub>2</sub> exposure and  
20 cardiovascular outcomes was not evaluated in the 2008 ISA for Sulfur Oxides ([U.S. EPA,](#)  
21 [2008d](#)). Despite a number of epidemiologic studies that report positive associations  
22 between long-term exposure to SO<sub>2</sub> concentrations and cardiovascular disease and stroke,  
23 the evidence for any one endpoint is limited and inconsistent. Exposure measurement  
24 error and the potential for copollutant confounding are uncertainties in the interpretation  
25 of the evidence. Additionally, there is insufficient experimental evidence to provide

1 coherence or biological plausibility for an independent effect of long-term exposure to  
2 SO<sub>2</sub> on cardiovascular health.

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### 1.6.2.3 Reproductive and Developmental Effects

3 Overall the evidence is inadequate to infer the presence or absence of a causal  
4 relationship between exposure to SO<sub>2</sub> and reproductive and developmental outcomes  
5 ([Table 5-38, Section 5.4](#)), consistent with the conclusion reached in the 2008 ISA for  
6 Sulfur Oxides ([U.S. EPA, 2008d](#)).

7 There are several recent well-designed, well-conducted studies that indicate an  
8 association between SO<sub>2</sub> and reproductive and developmental health outcomes, including  
9 fetal growth metrics, preterm birth, birth weight, and fetal and infant mortality. However,  
10 a number of uncertainties are associated with the observed relationship between exposure  
11 to SO<sub>2</sub> and birth outcomes, such as timing of exposure windows, exposure error, and  
12 spatial and temporal heterogeneity. Few studies have examined other health outcomes,  
13 such as fertility, effects on pregnancy (e.g., pre-eclampsia, gestational diabetes), and  
14 developmental effects, and there is little coherence or consistency among epidemiologic  
15 and toxicological studies for these outcomes. There is limited toxicological evidence at  
16 relevant dose ranges of SO<sub>2</sub>, making it difficult to evaluate the potential modes of action  
17 for reproductive and developmental effects of ambient SO<sub>2</sub>. Studies published since the  
18 2008 SO<sub>x</sub> ISA ([U.S. EPA, 2008d](#)) have not substantially reduced any of the uncertainties  
19 identified in the previous ISA, including exposure measurement error and the potential  
20 for copollutant confounding; therefore, the evidence is inadequate to infer the presence or  
21 absence of a causal relationship between exposure to SO<sub>2</sub> and reproductive and  
22 developmental outcomes.

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### 1.6.2.4 Total Mortality Associated with Short-Term Exposure to Sulfur Dioxide

23 Multicity studies evaluated since the completion of the 2008 ISA for Sulfur Oxides  
24 continue to provide consistent evidence of positive associations between short-term SO<sub>2</sub>  
25 exposures and total mortality ([Section 5.5.1](#)). Although the body of evidence is larger  
26 than at the time of the last review, key uncertainties and data gaps still remain, which  
27 contribute to the conclusion that the evidence for short-term SO<sub>2</sub> exposures and total  
28 mortality is suggestive of, but not sufficient to infer, a causal relationship ([Table 5-41](#)).  
29 This conclusion is consistent with that reached in the 2008 SO<sub>x</sub> ISA ([U.S. EPA, 2008d](#)).  
30 Overall, recent multicity studies evaluated have further informed key uncertainties and  
31 data gaps in the SO<sub>2</sub>-mortality relationship identified in the 2008 SO<sub>x</sub> ISA including

1 confounding, modification of the SO<sub>2</sub>-mortality relationship, potential seasonal  
2 differences in SO<sub>2</sub>-mortality associations, and the shape of the SO<sub>2</sub>-mortality C-R  
3 relationship. However, questions remain regarding whether SO<sub>2</sub> has an independent  
4 effect on mortality, and these lingering questions can be attributed to the limited number  
5 of studies that examined potential copollutant confounding, the relative lack of  
6 copollutant analyses with PM<sub>2.5</sub>, and the evidence indicating attenuation of SO<sub>2</sub>-mortality  
7 associations in copollutant models with NO<sub>2</sub> and PM<sub>10</sub>. Additionally, a biological  
8 mechanism has not been characterized to date that could lead to mortality as a result of  
9 short-term SO<sub>2</sub> exposures.

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### 1.6.2.5 Total Mortality Associated with Long-Term Exposure to Sulfur Dioxide

10 The overall evidence is inadequate to infer the presence or absence of a causal  
11 relationship between long-term exposure to SO<sub>2</sub> and total mortality among adults  
12 ([Table 5-43, Section 5.5.2](#)), consistent with the conclusion reached in the 2008 ISA for  
13 Sulfur Oxides ([U.S. EPA, 2008d](#)). Recent evidence is generally consistent with the  
14 evidence included in the ISA, although some recent cohort epidemiologic studies provide  
15 evidence for improved consistency in the association between long-term exposure to SO<sub>2</sub>  
16 and both respiratory and total mortality. However, none of these recent studies help to  
17 resolve the uncertainties identified in the 2008 SO<sub>x</sub> ISA related to exposure measurement  
18 error, copollutant confounding, or the geographic scale of the analysis.

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### 1.6.2.6 Cancer

19 The overall evidence for long-term SO<sub>2</sub> exposure and cancer is inadequate to infer the  
20 presence or absence of a causal relationship ([Table 5-44, Section 5.6](#)), the same  
21 conclusion reached in the 2008 ISA for Sulfur Oxides ([U.S. EPA, 2008d](#)). Recent studies  
22 include evidence on lung cancer as well as other cancer types. Although some studies of  
23 SO<sub>2</sub> concentrations and lung cancer mortality have reported null results, other studies that  
24 included various cofounders and copollutants reported positive associations. Positive  
25 associations were also observed in a study of SO<sub>2</sub> concentrations and bladder cancer  
26 mortality but not in ecological studies of bladder cancer incidence. Limited supportive  
27 evidence for mode of action is available from genotoxicity and mutagenicity studies, but  
28 animal toxicological studies provide no coherence with epidemiologic findings.

**Table 1-1 Key evidence contributing to causal determinations for sulfur dioxide exposure and health effects evaluated in the current draft Integrated Science Assessment for Sulfur Oxides.**

Health Effect Category <sup>a</sup> and Causal Determination	SO <sub>2</sub> Concentrations Associated with Effects
<p><b>Respiratory Effects and Short-Term Exposure</b> (<a href="#">Section 5.2.1</a>): <u>Causal relationship</u>  <i>No change in causal determination from the 2008 SO<sub>x</sub> ISA (<a href="#">U.S. EPA, 2008d</a>); new evidence is consistent with previous determination.</i></p>	
<p>Key evidence  <a href="#">(Table 5-21)</a></p>	<p>Strongest evidence is for effects on asthma exacerbation. There is consistent evidence from multiple high-quality controlled human exposure studies ruling out chance, confounding, and other biases. These studies show decreased lung function and increased respiratory symptoms following peak exposures of 5–10 min in exercising individuals with asthma. Additional consistent evidence from multiple high quality epidemiologic studies at relevant SO<sub>2</sub> concentrations shows an increase in asthma hospital admissions and ED visits in single- and multicity studies and in studies examining individuals of all ages, including children and older adults. These associations are generally unchanged in copollutant models involving PM and other criteria pollutants. Additionally, there is some supporting epidemiologic evidence of associations with respiratory symptoms among children with asthma. Evidence is available for activation of sensory nerves in the respiratory tract resulting in a neural reflex and/or inflammation leading to bronchoconstriction and allergic inflammation leading to increased airway responsiveness. Enhanced allergic sensitization, allergic inflammation, and airway responsiveness was observed in guinea pigs exposed to SO<sub>2</sub> repeatedly over several days and subsequently sensitized and challenged with an allergen. This evidence represents key events or endpoints in the proposed mode of action linking short-term SO<sub>2</sub> exposure and asthma exacerbation.</p>
<p>Overall study ambient means:  <i>Controlled human exposure studies of decreased lung function:</i> 200–600 ppb, with a subset analysis of responders showing statistically significant responses at 300 ppb  <i>Controlled human exposure studies of increased respiratory symptoms:</i> 400–1,000 ppb  <i>Epidemiologic studies:</i>            1-h max: 9.6–11 ppb            24-h avg: 1.0–37 ppb  <i>Animal studies:</i>            100 ppb</p>	
<p><b>Respiratory Effects and Long-Term Exposure</b> (<a href="#">Section 5.2.2</a>): <u>Suggestive of, but not sufficient to infer, a causal relationship</u>  <i>Change in causal determination from the 2008 SO<sub>x</sub> ISA (<a href="#">U.S. EPA, 2008d</a>) (inadequate to infer a causal relationship) due to new, but limited, evidence.</i></p>	
<p>Key evidence<sup>b</sup>  <a href="#">(Table 5-24)</a></p>	<p>Evidence from epidemiologic studies is generally supportive but not entirely consistent for increases in asthma incidence and prevalence related to SO<sub>2</sub> exposure. Uncertainty remains regarding potential copollutant confounding, so chance, confounding, and other biases cannot be ruled out. The limited animal toxicological evidence provides biological plausibility and coherence across lines of evidence. There is some evidence for a mode of action involving inflammation and allergic sensitization.</p>
<p>Overall epidemiologic study ambient means:            2-4 ppb            Animal toxicological studies:            2,000 ppb</p>	

**Table 1-1 (Continued): Key evidence contributing to causal determinations for sulfur dioxide exposure and health effects evaluated in the current draft Integrated Science Assessment for Sulfur Oxides.**

Health Effect Category <sup>a</sup> and Causal Determination		SO <sub>2</sub> Concentrations Associated with Effects
<p><b>Cardiovascular Effects and Short-Term Exposure</b> (<a href="#">Section 5.3.1</a>) <u>Inadequate to infer a causal relationship</u>  <i>No change in causal determination from the 2008 SO<sub>x</sub> ISA (<a href="#">U.S. EPA, 2008d</a>); new evidence is consistent with previous determination.</i></p>		
<p>Key evidence<sup>b</sup>  <a href="#">(Table 5-34)</a></p>	<p>There is some evidence of increased hospital admissions and ED visits among adults for IHD, MI, and all CVD, coherence with ST-segment depression in adults with pre-existing coronary heart disease, and increased risk of cardiovascular mortality. However, there is inconsistency in results across outcomes, and the associations are generally attenuated after copollutant adjustment. There is insufficient evidence from epidemiologic panel studies and experimental studies for clinical cardiovascular effects and to identify key events in a mode of action linking short-term SO<sub>2</sub> exposure and cardiovascular effects.</p>	<p>Overall epidemiologic study ambient 24-h avg means: 1.2–30 ppb</p>
<p><b>Cardiovascular Effects and Long-Term Exposure</b> (<a href="#">Section 5.3.2</a>) <u>Inadequate to infer a causal relationship</u>  <i>Not included in the 2008 SO<sub>x</sub> ISA (<a href="#">U.S. EPA, 2008d</a>).</i></p>		
<p>Key evidence<sup>b</sup>  <a href="#">(Table 5-35)</a></p>	<p>Results of epidemiologic studies of long-term SO<sub>2</sub> concentrations and MI, CVD, and stroke events are limited and inconsistent. There is limited coherence with evidence for cardiovascular mortality and weak evidence to identify key events in a mode of action linking long-term SO<sub>2</sub> exposure and cardiovascular effects.</p>	<p>Overall epidemiologic study ambient means: 1.3–1.7 ppb</p>
<p><b>Reproductive and Developmental Effects and Exposure</b> (<a href="#">Section 5.4</a>) <u>Inadequate to infer a causal relationship</u>  <i>No change in causal determination from the 2008 SO<sub>x</sub> ISA (<a href="#">U.S. EPA, 2008d</a>); new evidence is consistent with previous determination.</i></p>		
<p>Key evidence<sup>b</sup>  <a href="#">(Table 5-38)</a></p>	<p>Consistent positive associations are observed with near-birth exposures to SO<sub>2</sub> and preterm birth. Although limited evidence is available, positive associations are also reported for fetal growth metrics, birth weight, and infant and fetal mortality. There is insufficient evidence from epidemiologic studies to support an association of SO<sub>2</sub> exposure with detrimental effects on fertility or pregnancy. Thus, the available studies are of insufficient consistency across outcomes. Recent studies have not reduced uncertainties identified in the previous ISA, including exposure measurement error and copollutant confounding. Limited evidence is available for an understanding of key reproductive and developmental events in mode of action.</p>	<p>Overall epidemiologic study ambient means: 1.9–13 ppb</p>

**Table 1-1 (Continued): Key evidence contributing to causal determinations for sulfur dioxide exposure and health effects evaluated in the current draft Integrated Science Assessment for Sulfur Oxides.**

Health Effect Category <sup>a</sup> and Causal Determination		SO <sub>2</sub> Concentrations Associated with Effects
<p><b>Total Mortality and Short-Term Exposure (Section 5.5.1)</b> <u>Suggestive of, but not sufficient to infer, a causal relationship</u>  <i>No change in causal determination from the 2008 SO<sub>x</sub> ISA (U.S. EPA, 2008d); new evidence is consistent with previous determination.</i></p>		
<p>Key evidence<sup>b</sup>  <a href="#">(Table 5-41)</a></p>	<p>There is consistent epidemiologic evidence from multiple high-quality studies at relevant SO<sub>2</sub> concentrations demonstrating increases in mortality in multicity studies conducted in the U.S., Canada, Europe, and Asia. There is limited coherence and biological plausibility with cardiovascular and respiratory morbidity evidence and uncertainty regarding a biological mechanism that would explain the continuum of effects leading to SO<sub>2</sub>-related mortality; thus, chance, confounding, and other biases cannot be ruled out.</p>	<p>Overall epidemiologic study ambient 24-h avg means:  <i>U.S., Canada, South America, Europe:</i>                      0.4–28 ppb  <i>Asia:</i>                      0.7–&gt;200 ppb</p>
<p><b>Total Mortality and Long-Term Exposure (Section 5.5.2)</b> <u>Inadequate to infer a causal relationship</u>  <i>No change in causal determination from the 2008 SO<sub>x</sub> ISA (U.S. EPA, 2008d); new evidence is consistent with previous determination.</i></p>		
<p>Key evidence<sup>b</sup>  <a href="#">(Table 5-43)</a></p>	<p>Some epidemiologic studies report positive associations, but results are not entirely consistent, with some studies reporting null associations. Additionally, there is no evidence for associations between SO<sub>2</sub> exposure and long-term respiratory or cardiovascular health effects to support an association with mortality from these causes.</p>	<p>Overall epidemiologic study ambient means:                      1.6–24 ppb</p>

**Table 1-1 (Continued): Key evidence contributing to causal determinations for sulfur dioxide exposure and health effects evaluated in the current draft Integrated Science Assessment for Sulfur Oxides.**

Health Effect Category <sup>a</sup> and Causal Determination		SO <sub>2</sub> Concentrations Associated with Effects
<b>Cancer and Long-Term Exposure</b> ( <a href="#">Section 5.6</a> ) <u>Inadequate to infer a causal relationship</u> <i>No change in causal determination from the 2008 SO<sub>x</sub> ISA (<a href="#">U.S. EPA, 2008d</a>); new evidence is consistent with previous determination.</i>		
Key evidence <sup>b</sup> <a href="#">(Table 5-44)</a>	Among a small body of evidence, some epidemiologic studies report associations in lung cancer and bladder cancer mortality. There is also some evidence identifying mutagenesis and genotoxicity as key events in a proposed mode of action linking long-term SO <sub>2</sub> exposure and cancer; however, toxicological studies provide limited coherence with epidemiologic studies.	Overall epidemiologic study ambient means: 1.5–28 ppb. Toxicological studies: 5,000, 10,700, 21,400, 32,100 ppb

CVD = cardiovascular disease; ED = emergency department; IHD = ischemic heart disease; ISA = Integrated Science Assessment; MI = myocardial infarction; PM = particulate matter; SD = standard deviation; SO<sub>2</sub> = sulfur dioxide; SO<sub>x</sub> = sulfur oxides.

<sup>a</sup>A large spectrum of outcomes is evaluated as part of a broad health effect category including physiological measures (e.g., airway responsiveness, lung function), clinical outcomes (e.g., respiratory symptoms, hospital admissions), and cause-specific mortality. Total mortality includes all nonaccidental causes of mortality and is informed by the nature of the evidence for the spectrum of morbidity effects (e.g., respiratory, cardiovascular) that can lead to mortality. The sections and tables referenced include a detailed discussion of the available evidence that informed the causal determinations.

<sup>b</sup>Uncertainties remain for many of the studies included as key evidence. Uncertainty remains in some epidemiologic studies. Exposure assessments in epidemiologic studies using central site monitors may not fully capture spatial variability of SO<sub>2</sub>. Spatial and temporal heterogeneity may introduce exposure error in long-term effects. For studies of reproductive and developmental outcomes, associations with exposure to SO<sub>2</sub> at particular windows during pregnancy are inconsistent between studies. Additionally, although SO<sub>2</sub> is generally poorly to moderately correlated with other National Ambient Air Quality Standards pollutants at collocated monitors, copollutant confounding by these and other pollutants cannot be ruled out.

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## 1.7 Policy-Relevant Considerations

1 As described in the [Preamble](#) to the ISAs ([U.S. EPA, 2015b](#)) and [Section 1.1](#), this ISA  
2 informs policy-relevant issues that are aimed at characterizing quantitative aspects of  
3 relationships between ambient SO<sub>2</sub> exposure and health effects and the impact of these  
4 relationships on public health. To that end, this section integrates information from the  
5 ISA to describe SO<sub>2</sub> exposure durations and patterns related to health effects, the shape of  
6 the concentration-response relationship, regional heterogeneity in relationships, the  
7 adverse nature of health effects, and at-risk populations and lifestages. In addressing  
8 these policy-relevant issues, this section focuses on respiratory effects associated with  
9 short-term exposures, for which the evidence indicates there is a causal relationship.

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### 1.7.1 Durations and Lag Structure of Sulfur Dioxide Exposure Associated with Health Effects

10 Effects have been observed in controlled human exposure studies after SO<sub>2</sub> exposures as  
11 brief as 5–10 minutes. Consistent associations between SO<sub>2</sub> concentrations and asthma  
12 hospital admissions and ED visits that are generally unchanged in copollutant models  
13 have been demonstrated in epidemiologic studies using daily exposure metrics (24-h avg  
14 and 1-h daily max), although the observed effects could be related to very short duration  
15 (5–10 minutes) peak exposures experienced during the day.

16 Regarding the lag in effects, the findings from controlled human exposure studies provide  
17 evidence of a rapid onset of effects. The limited number of epidemiologic studies that  
18 examined lag structures reported associations within the first few days of exposure.

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### 1.7.2 Concentration-Response Relationships and Thresholds

19 Characterizing the shape of concentration-response relationships for health effects  
20 associated with SO<sub>2</sub> exposure aids in quantifying the public health impact of SO<sub>2</sub>  
21 exposure. A key issue is often whether the relationship is linear across the full range of  
22 ambient concentrations or whether there are deviations from linearity, and if so, at what  
23 concentrations they occur. Another important issue is the evidence regarding potential  
24 thresholds for key effects. Such thresholds may indicate exposures below which adverse  
25 health outcomes are not elicited. Lack of a discernable threshold in the evidence for

1 health effects of interest precludes the identification of an exposure level without risk of  
2 those effects.

3 Results from controlled human exposure studies indicate wide interindividual variability  
4 in response to SO<sub>2</sub> exposures, with peak (5 to 10 minutes) exposures at concentrations as  
5 low as 200–300 ppb eliciting lung function decrements in some individuals with asthma.  
6 A clear increase in the magnitude of lung function decrements was observed with  
7 increasing exposure concentrations between 200 and 1,000 ppb during 5–10 minute SO<sub>2</sub>  
8 exposures. The limited epidemiologic research on concentration-response functions  
9 relating SO<sub>2</sub> concentrations to respiratory health morbidity does not provide evidence for  
10 a deviation from linearity or a discernable population-level threshold.

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### 1.7.3 Regional Heterogeneity in Effect Estimates

11 The 2008 ISA for Sulfur Oxides ([U.S. EPA, 2008d](#)) discussed spatial variability in SO<sub>2</sub>  
12 concentrations and its impact on effect estimates from epidemiologic studies.

13 Correlations between monitors ranged from very low to very high, suggesting that SO<sub>2</sub>  
14 concentrations at some monitoring sites may not be highly correlated with the community  
15 average concentration. Of particular concern for SO<sub>2</sub> is the predominance of point  
16 sources, resulting in an uneven distribution of SO<sub>2</sub> concentrations across an urban area.  
17 Factors contributing to differences among monitoring sites include proximity to sources,  
18 terrain features, and uncertainty regarding the measurement of low SO<sub>2</sub> concentrations.

19 Spatial and temporal variability in SO<sub>2</sub> concentrations can contribute to exposure error in  
20 epidemiologic studies, whether such studies rely on central site monitor data or  
21 concentration modeling for exposure assessment. SO<sub>2</sub> has low to moderate spatial  
22 correlations between ambient monitoring sites across urban geographic scales; thus, using  
23 central site monitor data for epidemiologic exposure assessment introduces exposure  
24 error into the resulting effect estimate. Spatial variability in the magnitude of  
25 concentrations may affect cross-sectional and large-scale cohort studies by undermining  
26 the assumption that intraurban concentration and exposure differences are less important  
27 than interurban differences. This issue may be less important for time-series studies,  
28 which rely on day-to-day temporal variability in concentrations to evaluate health effects.  
29 Low correlations between monitors contribute to exposure error in time-series studies,  
30 including bias toward the null and wider confidence intervals.

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## 1.7.4 Public Health Significance

1 The public health significance of air pollution-related health effects is informed by the  
2 adverse nature of the health effects that are observed, the size of the population exposed  
3 to the air pollutant or affected by the health outcome, and the presence of populations or  
4 lifestages with higher exposure or increased risk of air pollution-related health effects.

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### 1.7.4.1 Characterizing Adversity of Health Effects

5 Both the World Health Organization (WHO) and the American Thoracic Society (ATS)  
6 have provided guidance in describing what health effects may be considered adverse.  
7 WHO defines health as “the state of complete physical, mental, and social well-being and  
8 not merely the absence of disease or infirmity” ([WHO, 1948](#)). By this definition, changes  
9 in health outcomes that are not severe enough to result in a diagnosis of a clinical effect  
10 or condition can be considered adverse if they affect the well-being of an individual. ATS  
11 also has considered a wide range of health outcomes in defining adverse effects.  
12 Distinguishing between individual and population risk, ATS described its view that small  
13 air pollution-related changes in an outcome observed in individuals might be considered  
14 adverse on a population level. This is because a shift in the distribution of population  
15 responses resulting from higher air pollution exposure might increase the proportion of  
16 the population with clinically important effects or at increased risk of a clinically  
17 important effect that could be caused by another risk factor ([ATS, 2000](#)). Increases in  
18 ambient SO<sub>2</sub> concentrations are associated with a broad spectrum of health effects related  
19 to asthma, including those characterized as adverse by ATS such as ED visits and  
20 hospital admissions.

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### 1.7.4.2 At-Risk Populations and Lifestages for Health Effects Related to Sulfur Dioxide Exposure

21 The primary NAAQS are intended to protect public health with an adequate margin of  
22 safety. In so doing, protection is provided for both the population as a whole and those  
23 groups potentially at increased risk for health effects from exposure to the air pollutant  
24 for which each NAAQS is set ([Preface](#) to this ISA). Hence, the public health significance  
25 of health effects related to SO<sub>2</sub> exposure also is informed by whether specific lifestages  
26 or groups in the population are identified as being at increased risk of SO<sub>2</sub>-related health  
27 effects.

1 At-risk populations or lifestages can be characterized by specific biological,  
2 sociodemographic, or behavioral factors, among others. Since the 2008 ISA for Sulfur  
3 Oxides ([U.S. EPA, 2008d](#)), the U.S. EPA has used a framework for drawing conclusions  
4 about the role of such factors in modifying risk of health effects of air pollution exposure  
5 [Table III of the [Preamble](#) to the ISAs ([U.S. EPA, 2015b](#))]. Similar to the causal  
6 framework, conclusions about at-risk populations are based on judgments of the  
7 consistency and coherence of evidence within and across disciplines ([Chapter 6](#)). Briefly,  
8 the evaluation is based on studies that compared exposure or health effect relationships  
9 among groups that differ according to a particular factor (e.g., people with and without  
10 asthma) and studies conducted in a population or animal model with a particular factor or  
11 pathophysiological condition. Where available, information on exposure, dosimetry, and  
12 modes of action is evaluated to assess coherence with health effect evidence and inform  
13 how a particular factor may contribute to SO<sub>2</sub>-related risk of health effects (e.g., by  
14 increasing exposure, increasing biological effect for a given dose).

15 There is adequate evidence that people with asthma are at increased risk for SO<sub>2</sub>-related  
16 health effects ([Section 6.3.1](#)), which is consistent with the findings of the 2008 ISA for  
17 Sulfur Oxides ([U.S. EPA, 2008d](#)). The conclusions are based on findings for short-term  
18 SO<sub>2</sub> exposure and respiratory effects (specifically lung function decrements), for which a  
19 causal relationship has been determined ([Section 5.2.1.9](#)). There are a limited number of  
20 epidemiologic studies evaluating SO<sub>2</sub>-related respiratory effects that include stratification  
21 by asthma status, but there is evidence for respiratory-related hospital admissions and  
22 emergency department visits ([Section 5.2.1.2](#)). Further support for increased risk in  
23 individuals with asthma is provided by biological plausibility drawn from modes of  
24 action. Children with asthma may be particularly at increased risk relative to adults with  
25 asthma due to their increased responsiveness to methacholine, increased ventilation rates  
26 relative to body mass, and increased proportion of oral breathing, particularly among  
27 boys. Among children in the U.S., asthma is the leading chronic illness (9.5% prevalence)  
28 and largest reason for missed school days.

29 There is also evidence suggestive of increased risk for children and older adults relative  
30 to other lifestages ([Section 6.5.1](#)). Although the 2008 ISA for Sulfur Oxides ([U.S. EPA,](#)  
31 [2008d](#)) discussed several studies indicating stronger associations between SO<sub>2</sub> and  
32 respiratory outcomes for these lifestages, the recent evidence is not entirely consistent  
33 with previous studies. For children, studies comparing SO<sub>2</sub>-associated respiratory  
34 outcomes reported mixed results. For adults, recent evidence generally found similar  
35 associations for SO<sub>2</sub>-related respiratory outcomes or mortality across age groups,  
36 although those over 75 years of age were more consistently at increased risk. In addition,  
37 there was insufficient toxicological evidence regarding the effect of lifestage on

1 respiratory responses to SO<sub>2</sub> to support observations made across epidemiologic studies  
2 that evaluated lifestage.

---

### 1.7.4.3 Summary of Public Health Significance of Health Effects Related to Sulfur Dioxide Exposure

3 Several aspects of the current evidence are important for considering the public health  
4 significance of SO<sub>2</sub>-related health effects. One aspect is adversity of the health effects,  
5 which may include health effects that are clearly adverse such as ED visits and hospital  
6 admissions for asthma and asthma exacerbation. Magnitude of the affected population is  
7 also important. As noted above, in the case of SO<sub>2</sub>-related health effects, the potentially  
8 affected population is large, given the number of people with asthma in the U.S.  
9 The roles of co-occurring risk factors or combined higher SO<sub>2</sub> exposure and health risk in  
10 influencing the risk of SO<sub>2</sub>-related health effects is not well understood. The large  
11 proportions of children and older adults in the U.S. population and the high prevalence of  
12 asthma in children may translate into a large number of people affected by SO<sub>2</sub>, and thus,  
13 magnify the public health impact of ambient SO<sub>2</sub> exposure.

---

## 1.8 Summary and Health Effects Conclusions

14 This ISA is a comprehensive evaluation and synthesis of the policy-relevant science  
15 regarding the potential health effects of ambient sulfur oxides, focusing on SO<sub>2</sub>. The ISA  
16 development process involves review of the scientific literature, selecting and evaluating  
17 relevant studies, and evaluating the weight of evidence to reach causal determinations  
18 regarding the likelihood of independent health effects of SO<sub>2</sub>. Information is included in  
19 the ISA on sources of SO<sub>2</sub>, atmospheric chemistry of SO<sub>2</sub> and other sulfur-containing  
20 compounds, ambient concentrations of SO<sub>2</sub> nationwide and in urban areas, and modeling  
21 approaches for estimating SO<sub>2</sub> concentrations. Approaches for characterizing exposure to  
22 ambient SO<sub>2</sub>, including monitoring and modeling, together with factors affecting ambient  
23 exposure, are described in terms of their potential impact on epidemiologic study results.  
24 Dosimetry of SO<sub>2</sub> and potential modes of action are discussed to provide context for the  
25 consideration of potential health effects of SO<sub>2</sub>, including respiratory effects,  
26 cardiovascular effects, reproductive and developmental effects, cancer, and mortality.

27 Consistent with the findings of the 2008 ISA for Sulfur Oxides ([U.S. EPA, 2008d](#)),  
28 studies continue to support the conclusion that there is a causal relationship between  
29 short-term SO<sub>2</sub> exposure and respiratory effects. This causal determination is based on  
30 consistency of findings within disciplines, coherence among multiple lines of evidence,

1 and biological plausibility indicating that there is a causal relationship between  
2 short-term SO<sub>2</sub> exposure and respiratory effects in individuals with asthma. The primary  
3 evidence for this conclusion comes from controlled human exposure studies that showed  
4 lung function decrements and respiratory symptoms in adult individuals with asthma  
5 exposed to SO<sub>2</sub> for 5–10 minutes under increased ventilation conditions. Supporting  
6 evidence was provided by epidemiologic studies that reported positive associations  
7 between short-term SO<sub>2</sub> exposures and asthma hospital admissions and ED visits that  
8 were generally unchanged in copollutant models involving PM and other criteria  
9 pollutants.

10 For both long-term exposure and respiratory effects, as well as short-term exposure and  
11 total mortality, the evidence is suggestive of, but not sufficient to infer, a causal  
12 relationship. In both cases, there is some evidence of an association between SO<sub>2</sub>  
13 exposure and health outcomes, but the evidence is inconsistent and uncertainties remain,  
14 including exposure error and copollutant confounding. The evidence was considered to  
15 be inadequate to infer the presence or absence of a causal relationship for other health  
16 effects, including cardiovascular morbidity (short- and long-term exposure), reproductive  
17 and developmental effects, total mortality (long-term exposure), and cancer. For these  
18 outcome categories, the evidence generally was not consistent across specific outcomes,  
19 showed a potential for copollutant confounding, and was lacking in biological  
20 plausibility.

21 In considering the effects of SO<sub>2</sub> on various populations and lifestages, there is adequate  
22 evidence that people with asthma are at increased risk for SO<sub>2</sub>-related health effects, as  
23 well as suggestive evidence for increased risk among children and older adults. The large  
24 proportions of children and older adults in the U.S. population and the high prevalence of  
25 asthma in children may translate into a large number of people affected by SO<sub>2</sub>, and thus,  
26 magnify the public health impact of ambient SO<sub>2</sub> exposure.

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## Chapter 2 Atmospheric Chemistry and Ambient Concentrations of Sulfur Dioxide and Other Sulfur Oxides

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### 2.1 Introduction

1 The Clean Air Act requires the U.S. Environmental Protection Agency (U.S. EPA) to  
2 periodically review the air quality criteria and the national ambient air quality standards  
3 (NAAQS) for sulfur oxides (SO<sub>x</sub>), which is one of the six criteria air pollutants, and  
4 revise the standards as may be appropriate. Sulfur oxides are a group of closely related  
5 sulfur-containing gaseous compounds [e.g., sulfur dioxide (SO<sub>2</sub>), sulfur monoxide (SO),  
6 disulfur monoxide (S<sub>2</sub>O), and sulfur trioxide (SO<sub>3</sub>)], and the NAAQS are currently set  
7 using SO<sub>2</sub> as the indicator species. Of the sulfur oxides, SO<sub>2</sub> is the most abundant in the  
8 atmosphere, the most important in atmospheric chemistry, and the one most clearly  
9 linked to human health effects ([U.S. EPA, 2008d](#)). As in previous reviews, the presence  
10 of sulfur oxides other than SO<sub>2</sub> in the atmosphere has not been demonstrated ([U.S. EPA,](#)  
11 [1996b](#); [HEW, 1969](#)). Therefore, the emphasis in this chapter is on SO<sub>2</sub>. Note that the  
12 mechanism of particle-phase SO<sub>4</sub><sup>2-</sup> formation is briefly described in [Section 2.3](#) [for more  
13 detail, see [Seinfeld and Pandis \(2006\)](#), [Finlayson-Pitts and Pitts \(2000\)](#), and other  
14 atmospheric chemistry texts]. The health effects of sulfate aerosol and other  
15 particle-phase sulfur compounds are discussed in the ISA for Particulate Matter ([U.S.](#)  
16 [EPA, 2009a](#)).

17 Sulfur dioxide is both a primary gas-phase pollutant (when formed during fuel  
18 combustion) and a secondary pollutant [the product of atmospheric gas- or droplet-phase  
19 oxidation of reduced sulfur compounds (sulfides)]. Fossil fuel combustion is the main  
20 anthropogenic source of primary SO<sub>2</sub>, while volcanoes and landscape fires (wildfires as  
21 well as controlled burns) are the main natural sources of primary SO<sub>2</sub>. Industrial chemical  
22 and pulp and paper production, natural biological activity (plants, fungi, and  
23 prokaryotes), and volcanoes are among many sources of reduced sulfur compounds that  
24 ultimately lead, through various oxidation reactions in the atmosphere, to the formation  
25 of secondary SO<sub>2</sub>.

26 This chapter provides concepts and findings relating to common sulfur oxides found in  
27 the atmosphere ([Section 2.1](#)), source emissions ([Section 2.2](#)), atmospheric chemistry and  
28 fate ([Section 2.3](#)), measurement methods ([Section 2.4](#)), environmental concentrations  
29 ([Section 2.5](#)), and atmospheric modeling of sulfur oxides ([Section 2.6](#)). It is intended as a  
30 prologue for detailed discussions on exposure and health effects evidence in the

1 subsequent chapters, and as a source of information to help interpret that evidence in the  
2 context of relevant ambient concentrations.

---

## 2.2 Anthropogenic and Natural Sources of Sulfur Dioxide

3 This section briefly describes the main U.S. anthropogenic and natural sources of SO<sub>2</sub>  
4 emissions. Emissions estimates for natural and anthropogenic sulfide emissions for the  
5 U.S. alone are not available in the literature. Therefore, a brief discussion of the sulfur  
6 cycle and estimates of the contribution of sulfides at the global scale, all of which can be  
7 found in the literature, are provided. [Section 2.2.1](#) describes the main categories of  
8 anthropogenic SO<sub>2</sub> emissions, while [Section 2.2.2](#) presents the geographic distribution of  
9 SO<sub>2</sub> sources across the U.S. The declining trend in anthropogenic SO<sub>2</sub> emissions is  
10 discussed in [Section 2.2.3](#). Natural sources of SO<sub>2</sub> are discussed in [Section 2.2.4](#). Indirect  
11 production of SO<sub>2</sub> through oxidation of reduced sulfur compounds emitted from geologic  
12 and biological sources is discussed in [Section 2.2.5](#).

13 Sulfur is present to some degree in all fossil fuels, especially coal, and occurs as reduced  
14 organosulfur compounds. Coal also contains sulfur in mineral form (pyrite or other  
15 metallo-sulfur minerals) and in elemental form ([Calkins, 1994](#)). Of the most common  
16 types of coal (anthracite, bituminous, subbituminous, and lignite), sulfur content varies  
17 between 0.4 and 4% by mass. Fuel sulfur is almost entirely converted to SO<sub>2</sub> (or SO<sub>3</sub>)  
18 during combustion, making accurate estimates of SO<sub>2</sub> combustion emissions possible  
19 based on fuel composition and combustion rates.

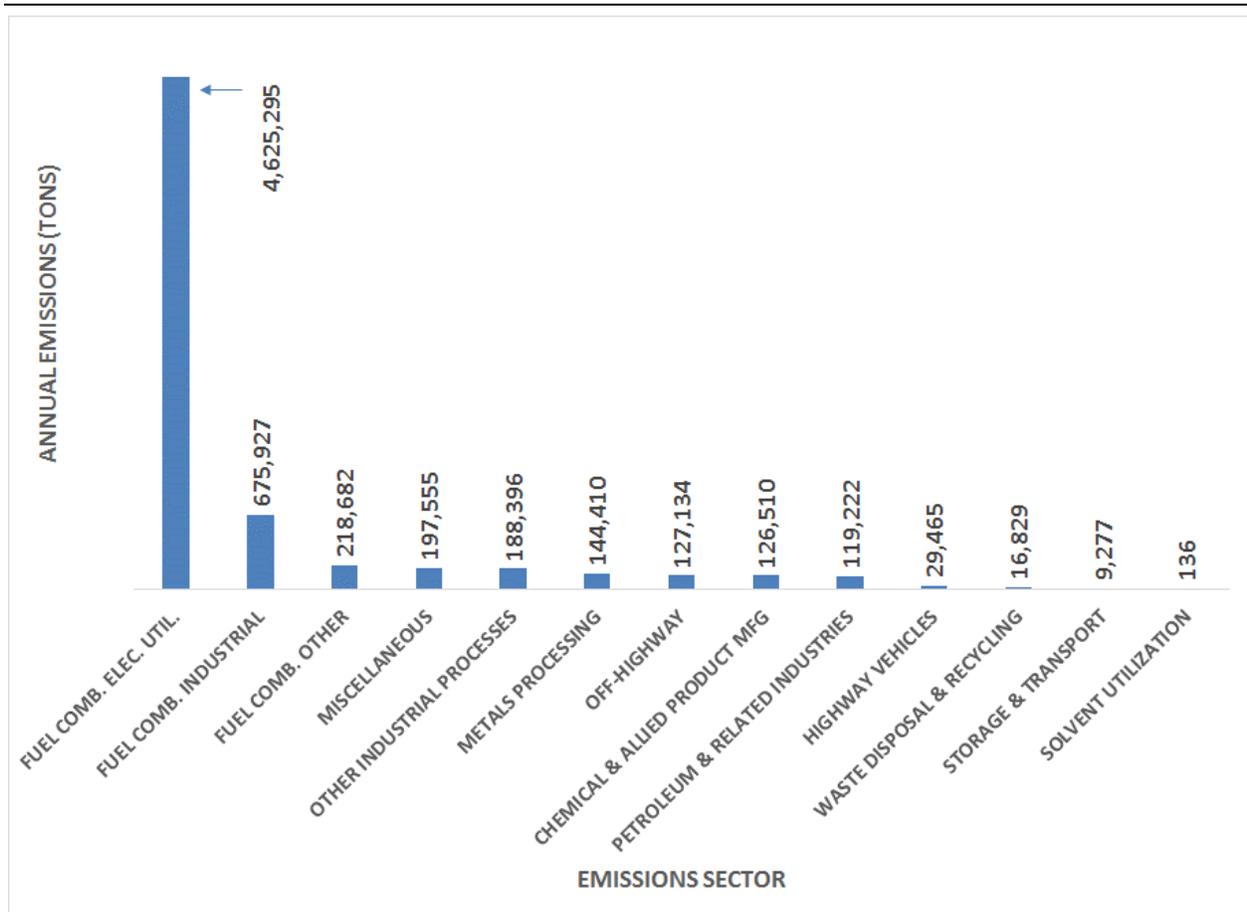
20 The mass of sulfur released into the environment by anthropogenic sources is comparable  
21 to natural sources ([Brimblecombe, 2003](#)). In addition to volcanic and other geologic SO<sub>2</sub>  
22 emissions, naturally occurring SO<sub>2</sub> is derived from the oxidation of sulfides emitted by  
23 low flux “area” sources, such as the oceans and moist soils. Anthropogenic emissions of  
24 sulfur are primarily in the form of SO<sub>2</sub>, emerging from point sources in quantities that  
25 may substantially affect local and regional air quality.

---

### 2.2.1 U.S. Anthropogenic Sources

26 The largest SO<sub>2</sub>-emitting sector within the U.S. is electricity generation based on coal  
27 combustion (4,625,295 tons). The mass of emissions produced by the Fuel Combustion in  
28 Electrical Utilities sector [i.e., coal-fired electric generating units (EGUs)] exceeds those  
29 produced by the next largest sector [the Fuel Combustion—Industrial sector  
30 (i.e., coal-fired boilers)] by nearly a factor of 7, and EGUs emit approximately 2.5 times

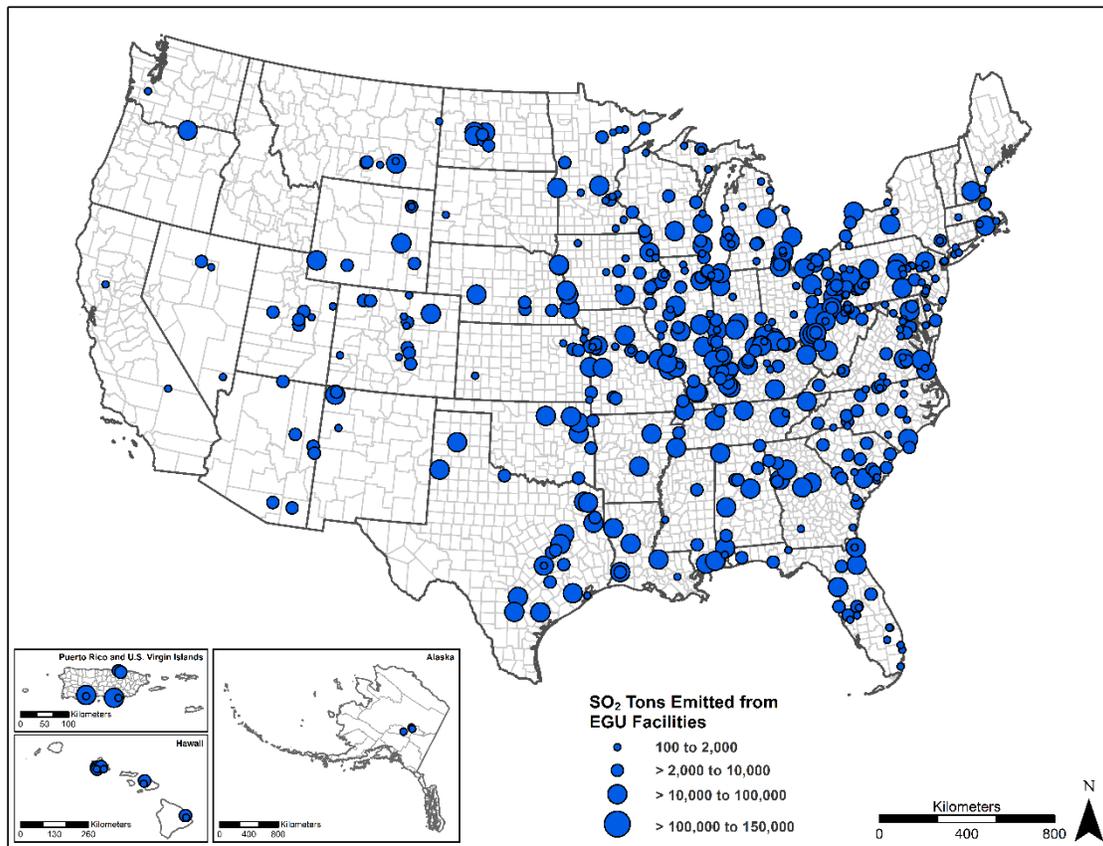
1 as much SO<sub>2</sub> as all other sources combined. [Figure 2-1](#) provides a sector comparison of  
2 annual emissions [in tons] found in the U.S. EPA 2011 National Emissions Inventory  
3 (NEI) ([U.S. EPA, 2013a](#)).



COMB = combustion; ELEC = electric; MFG = manufacturing; UTIL = utilities.  
Note: "Fuel combustion—Other" includes commercial, institutional, and residential sources.  
Source: <https://www.epa.gov/air-emissions-inventories/air-pollutant-emissions-trends-data>.

**Figure 2-1 Sulfur dioxide emissions by sector in tons, 2011.**

4 Because EGUs comprise the largest NEI source category, the spatial distribution of  
5 SO<sub>2</sub>-emitting EGUs is presented here ([U.S. EPA, 2013a](#)). Most EGU sources are located  
6 in the eastern half of the continental U.S., as indicated in [Figure 2-2](#). There is a  
7 particularly high concentration of EGUs in the Ohio River valley, upper Midwest, and  
8 along the Atlantic coast. Many of the monitoring sites with elevated SO<sub>2</sub> concentrations  
9 are located in these same areas ([Figure 2-11](#)).



Note: EGU = electric power generating unit; SO<sub>2</sub> = sulfur dioxide.  
 Source: <https://www.epa.gov/air-emissions-inventories>; U.S. EPA (2013a).

**Figure 2-2 Distribution of electric power generating unit-derived sulfur dioxide emissions across the U.S., based on the 2011 National Emissions Inventory.**

1 Industrial fuel combustion is the second largest source nationwide, emitting 675,927 tons  
 2 per year (tpy), followed by other fuel combustion (218,682 tpy). Miscellaneous (197,555  
 3 tpy) is the fourth-largest source and includes SO<sub>2</sub> emissions by fire used in landscape  
 4 management and agriculture as well as wildfires (U.S. EPA, 2013a). Wildfires, as a  
 5 natural source of SO<sub>2</sub> emissions, are discussed in Section 2.2.4.3.

6 The commercial marine sector falls within the off-highway category (127,134 tpy), after  
 7 EGUs and Industrial Fuel Combustion U.S. EPA (2013a). Wang et al. (2007) modeled  
 8 SO<sub>2</sub> emissions from commercial marine activity based on a combination of historical  
 9 shipping data and marine traffic predictions based on port sizes and probable routes using  
 10 data from 2002. A 200 nautical mile boundary was imposed around the marine, lake, and

1 river international borders of the U.S. Thirty-eight percent of emissions were estimated  
2 for the East Coast of the U.S. related to commercial marine shipping. Twenty percent  
3 were estimated for the West Coast, and 26% of emissions were estimated for the Gulf  
4 Coast. Smaller quantities were estimated elsewhere (10% for Alaska, 3% for Hawaii, and  
5 2% for the Great Lakes). Interior waterway activity was not included in the [Wang et al.  
6 \(2007\)](#) paper. In 2010, the International Maritime Organization introduced Emissions  
7 Control Areas (ECA) around U.S., Canadian, and French waters under the International  
8 Convention for the Prevention of Pollution from Ships ([Office of Transportation and Air  
9 Quality, 2010](#)). The ECA is a 200 nautical mile buffer around the maritime borders, in  
10 which fuels cannot contain more than 1,000 ppm sulfur as of 2015. The fuel sulfur  
11 regulation was first lowered from 15,000 to 10,000 ppm in 2010. These reductions are  
12 expected to be accomplished by maritime vessels switching fuel sources when they cross  
13 the 200 nautical mile buffer to approach their port. [Office of Transportation and Air  
14 Quality \(2010\)](#) estimates that this reduction in the amount of sulfur in marine fuels used  
15 within the 200 nautical mile buffer results in an 85% reduction in SO<sub>2</sub> emissions from the  
16 commercial marine sector.

17 Monitoring data that can indicate the effects of the ECA on air quality near ports is very  
18 limited. The SLAMS monitoring network used to implement the SO<sub>2</sub> NAAQS (discussed  
19 in [Section 2.4.1.1](#)) does not include any monitors located at ports. However, as part of its  
20 Clean Air Action effort, the San Pedro Bay Ports in California, operate a network of  
21 ambient monitors at the ports of Los Angeles and Long Beach (the two busiest ports in  
22 the U.S.). The network includes six monitors, four sites in located at the Port of Los  
23 Angeles and two sites located at the Port of Long Beach. A map of the network is  
24 available at <http://caap.airsis.com/MapView.aspx>. The latest reports from these two ports  
25 show SO<sub>2</sub> concentration well below the NAAQS. At the Port of Los Angeles, the 3 year  
26 average of the 99th percentile 1-h daily max for the latest reported period (May  
27 2013–April 2016) ranged from 17 ppb to 23 ppb at the four Port of Los Angeles sites  
28 ([Leidos Inc, 2016](#)). At the Port of Long Beach, the 3 year average of the 99th percentile  
29 1-h daily max for the latest reported period (January 2013–December 2015) ranged from  
30 13 ppb to 20 ppb at the two Port of Long Beach sites ([Leidos Inc, 2016](#)).

31 National SO<sub>2</sub> emissions sector summaries cannot offer insight concerning the local  
32 influence of individual SO<sub>2</sub>-emitting facilities. In addition to fossil fuel-fired steam  
33 electricity plants, other types of large emissions facilities that may be few in number  
34 include copper smelters, coal cleaning plants, kraft pulp mills, Portland Cement plants,  
35 iron and steel mill plants, sulfuric acid plants, petroleum refineries, and chemical  
36 processing plants. For example, the Metals Processing sector represents less than 2.2% of  
37 total emissions from the 2011 NEI ([U.S. EPA, 2013a](#)), but monitoring sites that have

1 recorded some of the highest 1-h daily max SO<sub>2</sub> concentrations in the U.S. are located  
2 near copper smelters in Arizona ([Section 2.5.2](#) and [Section 2.5.4; Figure 2-11](#)).

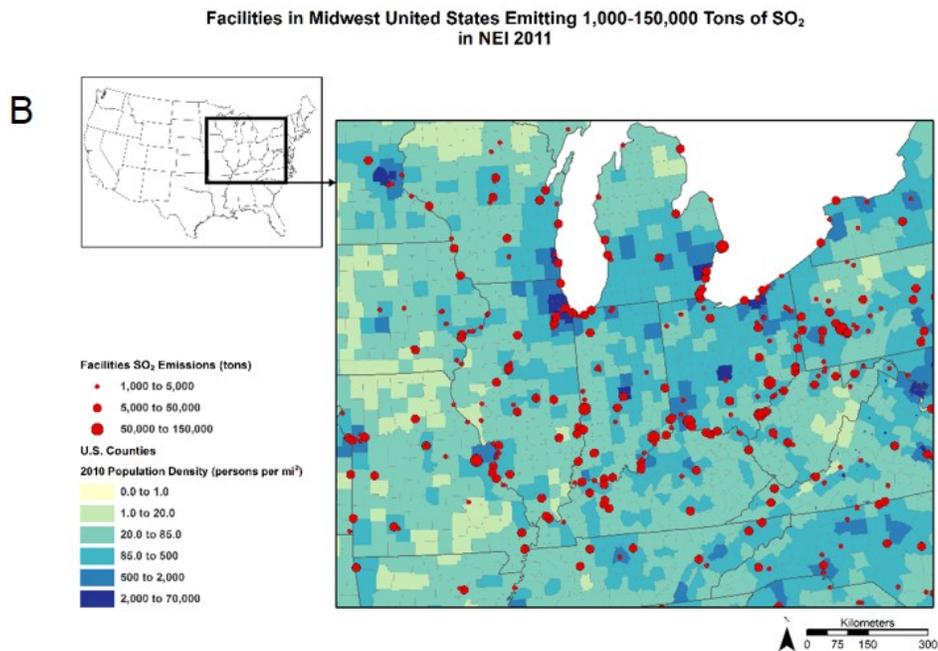
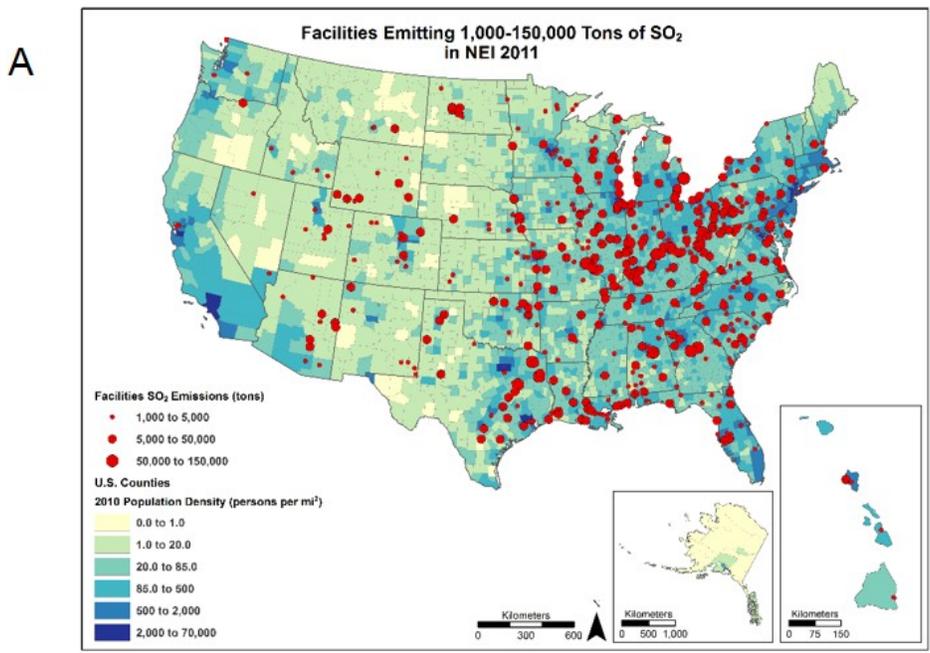
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## 2.2.2 National Geographic Distribution of Large Sources

3 [Figure 2-3](#) shows the geographic distribution of continental U.S. facilities emitting more  
4 than 1,000 tpy SO<sub>2</sub>, with an enlargement of the Midwest states including the Ohio River  
5 Valley, where a large number of these SO<sub>2</sub>-emitting sources are located.

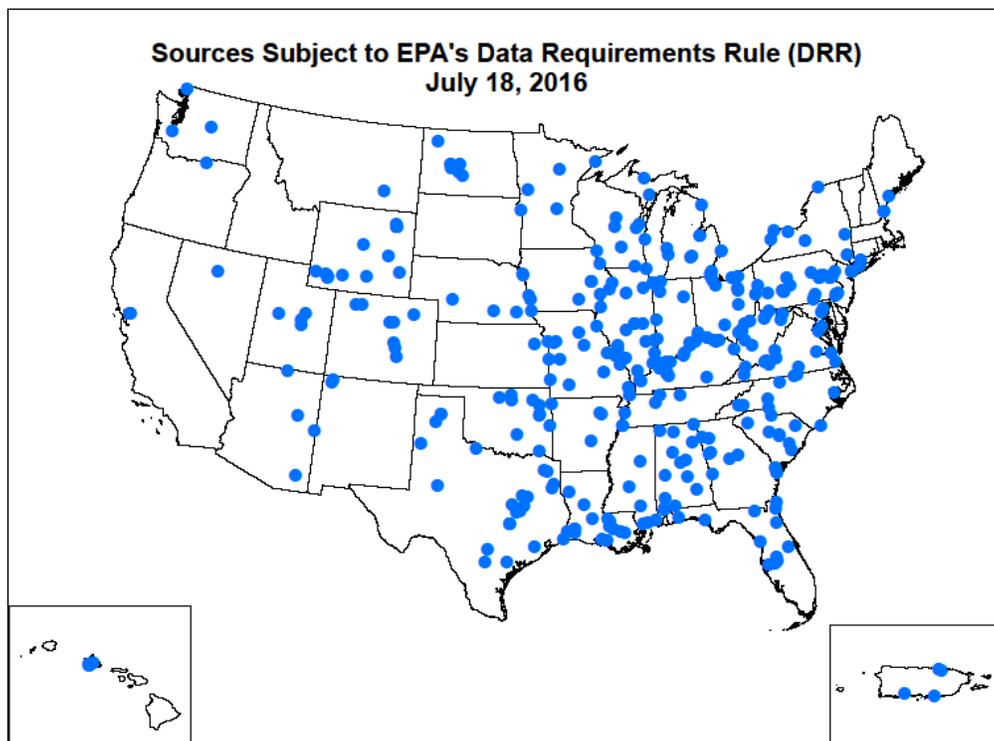
### ***U.S. EPA Sulfur Dioxide Data Requirements Rule***

6 Another source of information of large sources of SO<sub>2</sub> emissions is air agency  
7 submissions in response to a regulatory requirement concerning characterization of  
8 ambient SO<sub>2</sub> concentrations in areas with large sources of SO<sub>2</sub> emissions to help  
9 implement the 1-hour SO<sub>2</sub> NAAQS (CFR, 51.1202–51.1203; 80 FR50152, August 21,  
10 2015). This regulation requires that, at a minimum, air agencies must characterize air  
11 quality around sources that emit 2,000 tons per year or more of SO<sub>2</sub>. An air agency may  
12 avoid the requirement for air quality characterization near a source by adopting  
13 enforceable emission limits that ensure that the source will not emit more than 2,000 tpy.  
14 This final rule gives air agencies the flexibility to characterize air quality using either  
15 modeling of actual source emissions or using appropriately sited ambient air quality  
16 monitors. Under this requirement, air agencies submitted to the relevant EPA Regional  
17 Administrator a final list identifying the sources in the state around which SO<sub>2</sub> air quality  
18 is to be characterized. The list included sources with emissions above 2,000 tpy SO<sub>2</sub>.  
19 The EPA Regional Offices or air agencies included additional sources on this list that  
20 they deemed necessary. The final list included 377 sources ([https://www.epa.gov/so2-  
21 pollution/so2-data-requirements-rule-source-list](https://www.epa.gov/so2-pollution/so2-data-requirements-rule-source-list)). [Figure 2-4](#) shows the locations of those  
22 sources.



Note: NAAQS = national ambient air quality standards; NEI = National Emissions Inventory; SO<sub>2</sub> = sulfur dioxide.  
 Source: <https://www.epa.gov/air-emissions-inventories>; U.S. EPA (2013a).

**Figure 2-3** Geographic distribution of (A) continental U.S. facilities emitting more than 1,000 tpy sulfur dioxide, with (B) an enlargement of the midwestern states, including the Ohio River Valley, where a large number of these sources are concentrated.



DRR = Data Requirements Rule; EPA = U.S. Environmental Protection Agency.  
Source: U.S. EPA Office of Air Quality Planning and Standards.

**Figure 2-4 Sulfur dioxide sources identified by state/local air agencies under the U.S. Environmental Protection Agency's Data Requirements Rule, as of July 18, 2016.**

### 2.2.3 U.S. Anthropogenic Emission Trends

1 Anthropogenic emissions of SO<sub>2</sub> in the U.S. have shown dramatic declines since the  
 2 1970s, and emissions reductions have accelerated since the 1990 amendments to the  
 3 Clean Air Act were enacted (USC Title 42 Chapter 85). [Table 2-1](#) gives the annual SO<sub>2</sub>  
 4 emissions, percentage of the U.S. SO<sub>2</sub> total emissions, and change in emissions rate from  
 5 2004 to 2011. [Figure 2-5](#) illustrates the emissions trends by sector from 1970 to 2011 in  
 6 relation to the timeline over which the NAAQS for SO<sub>2</sub> and the Clean Air Act control  
 7 programs [Acid Rain Program (ARP), NO<sub>x</sub> Budget Program (NBP), and Clean Air  
 8 Interstate Rule (CAIR)] have been implemented. Exceptions to the steep decline in SO<sub>2</sub>  
 9 emissions in the listed sectors are the marked increases in emissions from the commercial  
 10 storage and transport sectors and from miscellaneous, i.e. landscape fires. However,

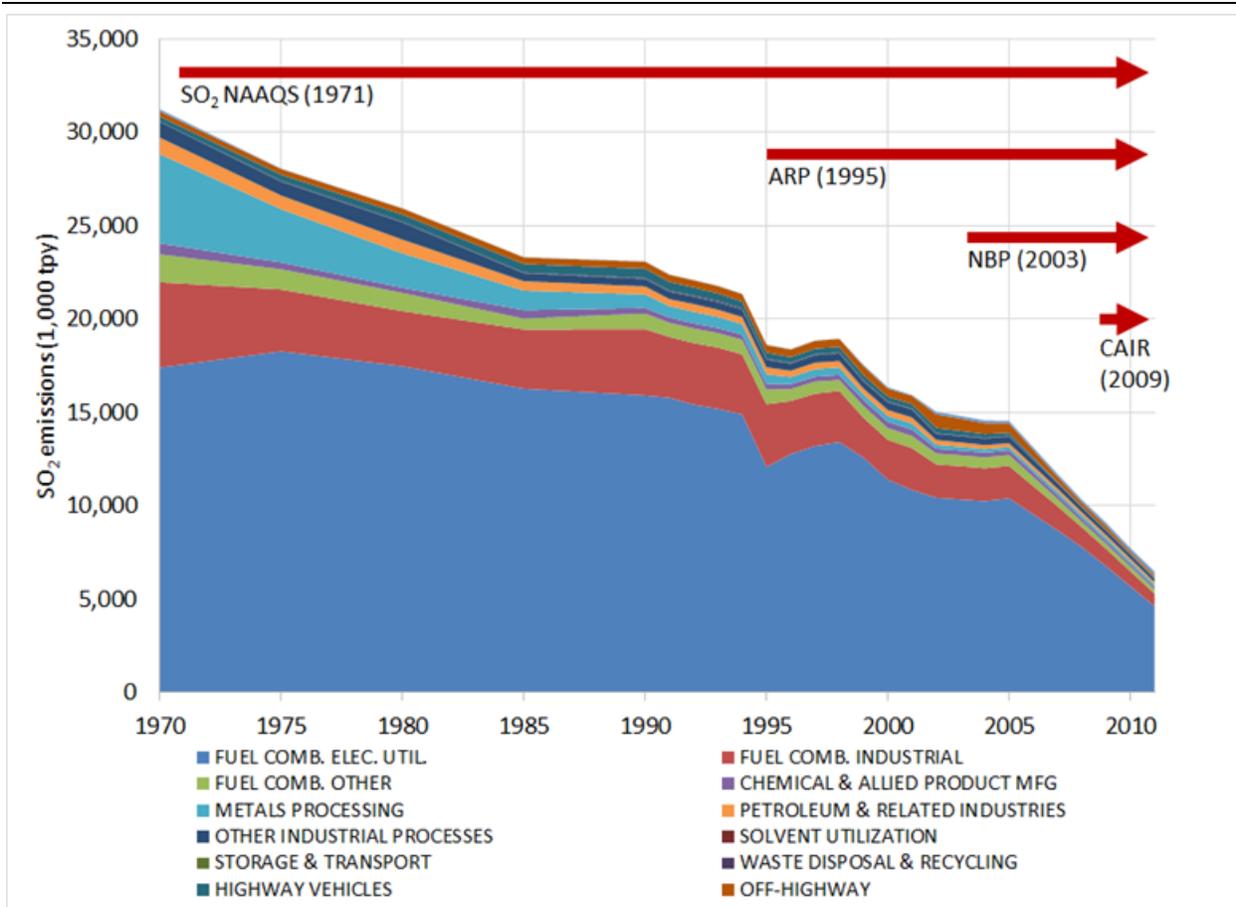
1 commercial storage and transport contributes only 0.1% of total 2011 SO<sub>2</sub> emissions.  
 2 Landscape fires are a larger contributor to the NEI (3%) and are discussed further in  
 3 [Section 2.2.4.3](#).  
 4 [Hand et al. \(2012\)](#) studied reductions in EGU-related annual SO<sub>2</sub> emissions during the  
 5 period 2001–2010. They found that emissions decreased throughout the U.S. by 6.2% per  
 6 year, with the largest reductions in the western U.S. at 20.1% per year. The smallest  
 7 reduction (1.3% per year) occurred in the Great Plains states.

**Table 2-1 Summary of 2011 U.S. Environmental Protection Agency sulfur dioxide trends data by emissions sector. Values shown in bold indicate increased emissions, 2001–2011.**

Source Type	Tons (2011)	Percentage of Total	Percent Change Since 2001
Fuel combustion—electric utilities	4,625,295	71.4	-57
Fuel combustion—industrial	675,927	10.4	-70
Fuel combustion—other	218,682	3.4	-66
Miscellaneous (landscape fire)	197,555	3.0	+346
Other industrial processes	188,396	2.9	-56
Metal processing	144,410	2.2	-56
Off-highway vehicles	127,134	2.0	-71
Chemical and allied product manufacturing	126,510	2.0	-63
Petroleum and related industries	119,222	1.8	-63
Highway vehicles	29,465	0.5	-88
Waste disposal and recycling	16,829	0.3	-51
Storage and transport	9,277	0.1	+40

Note: “Fuel combustion—other” includes commercial, institutional and residential sources. “Petroleum and related industries” include petroleum refineries, and oil and gas production. “Other industrial processes” include cement manufacturing, pulp and paper production, and other industrial emissions that are NEC. “Off-highway” includes commercial marine. “Miscellaneous” includes prescribed, agricultural and wild fires.

Source: <https://www.epa.gov/air-emissions-inventories/air-pollutant-emissions-trends-data>.



ARP = Acid Rain Program; CAIR = Clean Air Interstate Rule; COMB = combustion; ELEC = electric; MFG = manufacturing; NAAQS = National Ambient Air Quality Standards; NBP = NO<sub>x</sub> Budget Program; SO<sub>2</sub> = sulfur dioxide; tpy = tons per year; UTIL = utilities.

Source: <https://www.epa.gov/air-emissions-inventories/air-pollutant-emissions-trends-data>.

**Figure 2-5 National sulfur dioxide emissions trends by sector, 1970–2011.**

## 2.2.4 Natural Sources

1 This section provides an overview of the major natural sources of SO<sub>2</sub> and reduced sulfur  
 2 compounds that are oxidized in the atmosphere to form SO<sub>2</sub>. [Section 2.2.4.1](#) briefly  
 3 describes the elements of the global sulfur cycle. [Section 2.2.4.2](#) briefly discusses  
 4 volcanic sources of SO<sub>2</sub> within the U.S. [Section 2.2.4.3](#) discusses SO<sub>2</sub> emissions by U.S.  
 5 wildfires. [Section 2.2.4](#) concludes with a brief summary of both anthropogenic and  
 6 natural emissions of reduced sulfur gases that can serve as precursors to SO<sub>2</sub>.  
 7

---

### 2.2.4.1 The Global Sulfur Cycle

1 The total budget for sulfur, in all its forms, at Earth's surface is on the order of  $1.1 \times 10^{16}$   
2 tons S ([Schlesinger, 1997](#)). The sulfur cycle comprises the many chemical and biological  
3 processes that continuously interconvert the element between its four main oxidation  
4 states (-2, 0, +4, +6). The reduced form of sulfur is present in the environment in  
5 hydrogen sulfide, hydrogen disulfide, and a number of organic compounds. Oxidized  
6 sulfur is present primarily as SO<sub>2</sub> and sulfate (SO<sub>4</sub><sup>2-</sup>).

7 Volcanoes and wildfires are nonbiological natural sources that directly emit SO<sub>2</sub> to the  
8 atmosphere. Biological natural sources, together with volcanoes, emit reduced sulfur  
9 compounds that subsequently oxidize in the atmosphere to form SO<sub>2</sub>. Under anaerobic  
10 conditions, various species of plants, fungi, and prokaryotes convert oxidized sulfur into  
11 its reduced forms ([Madigan et al., 2006](#)). Photosynthetic green and purple bacteria and  
12 some chemolithotrophs oxidize sulfides to form elemental sulfur. Some species oxidize  
13 elemental sulfur to form SO<sub>4</sub><sup>2-</sup> and SO<sub>2</sub>; others reduce elemental sulfur to sulfides  
14 (*dissimilative sulfur reduction*), while others are capable of reducing SO<sub>4</sub><sup>2-</sup> all the way  
15 down to sulfide (*dissimilative SO<sub>4</sub><sup>2-</sup> reduction*).

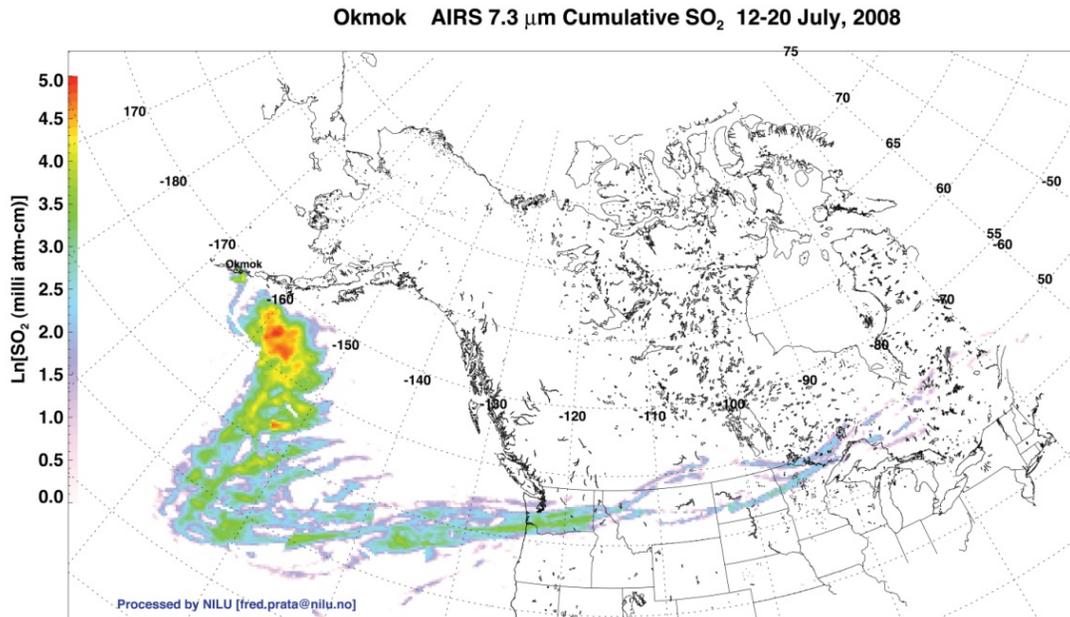
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### 2.2.4.2 Volcanoes as a Natural Source of Sulfur Dioxide

16 Geologic activity, including fumaroles, geysers, and metamorphic degassing, emits a  
17 number of gases, including SO<sub>2</sub>, carbon dioxide (CO<sub>2</sub>), hydrogen sulfide (H<sub>2</sub>S),  
18 hydrochloric acid, chlorine, and others ([Simpson et al., 1999](#)). Eruptive and noneruptive  
19 volcanoes are the most important sources of geologic SO<sub>2</sub> emissions. Noneruptive  
20 volcanoes outgas at relatively constant rates and appear to be more important than  
21 eruptive volcanoes as a source of SO<sub>2</sub>. The emissions of eruptive volcanoes are sporadic,  
22 and therefore, vary from year to year ([Simpson et al., 1999](#)).

23 The western U.S. borders the North American tectonic plate, which is subject to ongoing  
24 volcanic activity due to subduction of the Pacific plate. The Aleutian volcanic arc, part of  
25 the state of Alaska, comprises 75 volcanic centers. Volcanoes in this chain have erupted  
26 once or twice per year on average over the past 100 years with impacts on local  
27 communities ([Power, 2013](#)). [Figure 2-6](#) shows an image derived from data collected by  
28 the Atmospheric Infrared Sounder (AIRS) instrument aboard NASA's Aqua satellite  
29 during the July 12–20, 2008 eruption of the Okmok Volcano in Alaska's Aleutian  
30 Islands. The image shows sulfur dioxide at altitudes around 16 km (10 miles) released by  
31 the volcano over that time span, with red indicating the highest concentrations, and pale  
32 pink indicating the lowest ([Prata et al., 2010](#)). Sulfur dioxide has infrared absorption

1 features at 4 and 7.3  $\mu\text{m}$ , which allowed [Prata et al. \(2010\)](#) to calculate the total mass of  
2  $\text{SO}_2$  emitted during the eruption as  $319,670 \pm 11,023$  tons.



AIRS = Atmospheric Infrared Sounder;  $\text{SO}_2$  = sulfur dioxide.

Source: Image courtesy of Fred Prata of the Norwegian Institute for Air Research (NILU); [NASA \(2008a\)](#).

**Figure 2-6 Sulfur dioxide released during the July 12–20, 2008 eruption of the Okmok Volcano in Alaska’s Aleutian Islands (image derived from data collected by the Atmospheric Infrared Sounder instrument aboard the National Aeronautics and Space Administration Aqua satellite).**

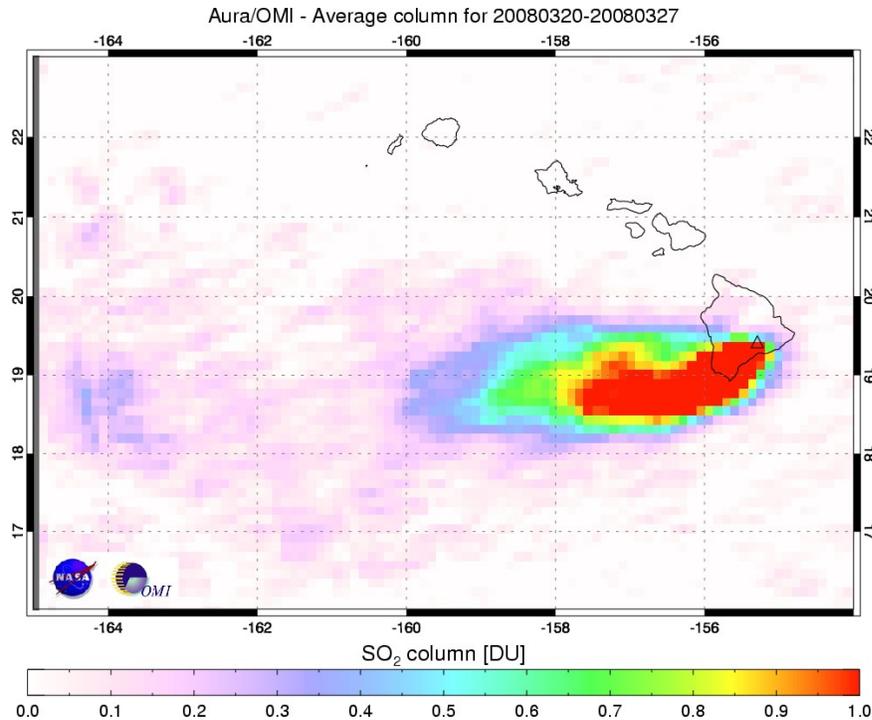
3 The line of volcanoes begins with the Aleutian Islands in Alaska and extends south and  
4 east through the states of Washington, Oregon, California, Arizona, and New Mexico,  
5 with outlying geologically active sites in Idaho (Craters of the Moon) and Wyoming  
6 (Yellowstone). [Figure 2-7](#) shows the geographic location and activity potential for these  
7 sites within the continental U.S.



Source: [USGS \(1999\)](#). Map courtesy of Lyn Topinka (1999, USGS / CVO), Modified from Steve Brantley (USGS 1994), Volcanoes of the United States, USGS General Interest Publication.

**Figure 2-7 Geographic location of volcanoes and other potentially active volcanic areas within the continental U.S.**

1 The state of Hawaii, located over a “hot spot” in the north-central portion of the Pacific  
 2 tectonic plate, is a series of volcanic islands with one of the world’s most active  
 3 volcanoes, Kīlauea, located on the Big Island of Hawaii. Kīlauea might typically be  
 4 described as a noneruptive volcano, emitting SO<sub>2</sub> at a steady rate. In mid-March of 2008,  
 5 the volcano experienced a small explosion followed by a two- to fourfold increase in SO<sub>2</sub>  
 6 emissions. The Ozone Monitoring Instrument (OMI) aboard the NASA Aura satellite  
 7 detected this increase in SO<sub>2</sub> emissions. [Figure 2-8](#) shows the average concentration of  
 8 SO<sub>2</sub> in the evolving plume for the March 20–27, 2008 period. Persistent easterly trade  
 9 winds moved the plume westward, away from populated areas.



DU = Dobson units; OMI = Ozone Monitoring Instrument; SO<sub>2</sub> = sulfur dioxide.

Note: A DU is approximately equivalent to a total column concentration of 1 ppbv of SO<sub>2</sub>. Horizontal axis is longitude with respect to Greenwich, U.K. Vertical axis is latitude with respect to the equator.

Source: [NASA \(2008b\)](#).

**Figure 2-8 National Aeronautics and Space Administration/Ozone Monitoring Instrument image of the Kilauea sulfur dioxide plume during its March 20–27, 2008 eruption.**

1 In another study using SO<sub>2</sub> column densities derived from GOME-2 satellite  
 2 measurements for the period 2007–2012, [Beirle et al. \(2013\)](#) determined Kilauea’s  
 3 monthly mean SO<sub>2</sub> emission rates and effective SO<sub>2</sub> lifetimes. For the March through  
 4 November, 2008 period, the authors reported Kilauea’s SO<sub>2</sub> emission rates as  
 5 8,818–20,943 tons/day and the effective SO<sub>2</sub> lifetime as 1–2 days. Several studies have  
 6 estimated the global SO<sub>2</sub> emissions of sulfur by volcanoes to be in the range of 7.7 x  
 7 10<sup>6</sup>–2.0 x 10<sup>7</sup> tpy ([Chin et al., 2000](#); [Feichter et al., 1996](#); [Pham et al., 1996](#); [Langner and](#)  
 8 [Rodhe, 1991](#)).

### 2.2.4.3 Wildfires as a Natural Source of Sulfur Dioxide

9 Sulfur is a component of amino acids in vegetation and is released during combustion,  
 10 mainly in the form of SO<sub>2</sub>. Using satellite data from various sources, including the

1 Moderate Resolution Imaging Spectroradiometer (MODIS) Thermal Anomalies Product,  
2 the Global Land Cover Characteristics 2000 data set, and the MODIS Vegetation  
3 Continuous Fields Product in conjunction with the literature to determine fire location  
4 and timing, fuel loadings, and emission factors, [Wiedinmyer et al. \(2006\)](#) estimated SO<sub>2</sub>  
5 emissions from fires for the U.S. at 176,370 tons in the year 2004. Canadian fires emitted  
6 121,254 tons, and Mexican fires emitted 55,116 tons of SO<sub>2</sub> for the same period.  
7 However, wildfire emissions do vary from year to year. Emissions estimates for SO<sub>2</sub>  
8 derived from global modeling studies of wildfire range between 5.1 x 10<sup>6</sup>–6.3 x 10<sup>6</sup> tpy  
9 SO<sub>2</sub> ([Chin et al., 2000](#); [Feichter et al., 1996](#); [Pham et al., 1996](#); [Langner and Rodhe,](#)  
10 [1991](#)).

11 Projected increases in wildfire frequency and intensity under warming climate conditions  
12 imply increasing wildfire-related SO<sub>2</sub> emissions. However, these estimates are highly  
13 uncertain due to the lack of data on the sensitivity of emissions composition with respect  
14 to the effects of climate change on landscape species composition and burning  
15 conditions. For comparison, the 2011 NEI also includes an estimate for agricultural and  
16 prescribed burning emissions at 99,208 tpy, which is about half of the estimated SO<sub>2</sub>  
17 emissions from wildfires ([U.S. EPA, 2013a](#)).

---

## 2.2.5 Reduced Sulfur Compounds as Indirect Sources of Sulfur Dioxide

18 Sulfides, including H<sub>2</sub>S, carbonyl sulfide (OCS), carbon disulfide (CS<sub>2</sub>),  
19 methylmercaptan (CH<sub>3</sub>SH), dimethyl sulfide (DMS), and dimethyl disulfide (DMDS), are  
20 emitted from energy production, industrial activities, agriculture, and various ecosystems,  
21 especially coastal wetland systems, inland soils, and oceans. In addition to SO<sub>2</sub>,  
22 volcanoes release sulfides, specifically H<sub>2</sub>S, OCS, and CS<sub>2</sub>. As described in [Section 2.3](#),  
23 all of these gases, with the exception of OCS, have short atmospheric lifetimes, given  
24 their high rates of reaction with hydroxyl radicals and given the high rates of reaction of  
25 nitrate radicals (NO<sub>3</sub>) with SO<sub>2</sub> as a reaction product. [Table 2-2](#) provides a list of the  
26 natural and anthropogenic sources of the five main organosulfides. Dimethyl sulfide is  
27 particularly important, both for the large role it plays as a source of atmospheric sulfur  
28 and for its role in initiating the formation of marine clouds.

**Table 2-2 Global sulfide emissions in tpy sulfur.**

Sources	OCS	CS <sub>2</sub>	CH <sub>3</sub> SH	DMS	DMDS
Seawater and marshes	3.4 x 10 <sup>5</sup>	2.68 x 10 <sup>5</sup>	5.22 x 10 <sup>6</sup>	3.11 x 10 <sup>7</sup>	2.35 x 10 <sup>5</sup>
Vegetation and soils		7.72 x 10 <sup>4</sup>	1.91 x 10 <sup>6</sup>	3.83 x 10 <sup>6</sup>	9.57 x 10 <sup>5</sup>
Volcanoes	1.21 x 10 <sup>4</sup>	1.87 x 10 <sup>4</sup>			
Atmospheric oxidation	5.10 x 10 <sup>5</sup>				
Biomass burning (all types)	5.07 x 10 <sup>4</sup>	2.03 x 10 <sup>3</sup>		6.61 x 10 <sup>3</sup>	1.31 x 10 <sup>5</sup>
Pulp and paper industry	1.07 x 10 <sup>5</sup>	8.65 x 10 <sup>4</sup>	1.85 x 10 <sup>6</sup>	1.61 x 10 <sup>6</sup>	3.01 x 10 <sup>5</sup>
Rayon/cellulosics manufacture		1.17 x 10 <sup>6</sup>	1.52 x 10 <sup>5</sup>	1.05 x 10 <sup>5</sup>	
Manure			3.64 x 10 <sup>5</sup>	7.28 x 10 <sup>5</sup>	7.28 x 10 <sup>5</sup>
Paddy fields	4.19 x 10 <sup>2</sup>	2.97 x 10 <sup>4</sup>	8.38 x 10 <sup>2</sup>	2.76 x 10 <sup>4</sup>	6.28 x 10 <sup>2</sup>
Pigment industry	8.16 x 10 <sup>4</sup>	2.26 x 10 <sup>5</sup>			
Food processing and waste	6.94 x 10 <sup>2</sup>			4.38 x 10 <sup>3</sup>	3.19 x 10 <sup>4</sup>
Gas industry	7.72 x 10 <sup>2</sup>		5.29 x 10 <sup>3</sup>	9.26 x 10 <sup>2</sup>	1.10 x 10 <sup>2</sup>
Wastewater	3.75 x 10 <sup>1</sup>	1.14 x 10 <sup>3</sup>	7.17 x 10 <sup>4</sup>	6.17 x 10 <sup>3</sup>	2.98 x 10 <sup>4</sup>
Aluminum industry	9.70 x 10 <sup>4</sup>	4.41 x 10 <sup>3</sup>			
Coal combustion	1.80 x 10 <sup>4</sup>	3.64 x 10 <sup>2</sup>			
Coke production	9.92 x 10 <sup>3</sup>	1.54 x 10 <sup>4</sup>			
Biofuel combustion	5.16 x 10 <sup>4</sup>	2.09 x 10 <sup>3</sup>			
Vehicles	6.61 x 10 <sup>3</sup>	3.31 x 10 <sup>2</sup>			
Shipping	3.31 x 10 <sup>4</sup>	1.65 x 10 <sup>3</sup>			
Tire wear	1.87 x 10 <sup>3</sup>	2.54 x 10 <sup>3</sup>			
Tire combustion	3.31	6.61 x 10 <sup>-2</sup>			
Landfill	8.71 x 10 <sup>1</sup>	2.09 x 10 <sup>2</sup>	3.75 x 10 <sup>2</sup>	2.87 x 10 <sup>2</sup>	8.82
Brick making		3.31 x 10 <sup>2</sup>			
<b>Total global sources</b>	<b>1.33 x 10<sup>6</sup></b>	<b>1.90 x 10<sup>6</sup></b>	<b>9.58 x 10<sup>6</sup></b>	<b>3.74 x 10<sup>7</sup></b>	<b>2.41 x 10<sup>6</sup></b>

CH<sub>3</sub>SH = methylmercaptan; CS<sub>2</sub> = carbon disulfide; DMDS = dimethyl disulfide; DMS = dimethylsulfide; OCS = carbonyl sulfide. Adapted from ([Lee and Brimblecombe, 2016](#)).

1 Dimethyl sulfide (DMS) is the most abundant reduced sulfur gas. It has appreciable  
2 anthropogenic sources (pulp and paper production, agricultural operations), but these are  
3 dwarfed by the quantity emitted by natural biological activity. Natural emissions of  
4 dimethyl sulfide originate with the breakdown of dimethyl sulfoniopropionate, a  
5 metabolite of the amino acid, methionine, produced by marine organisms living in  
6 upwelling or coastal zones and by anaerobic bacteria in marshes and estuaries.  
7 The oxidation of dimethyl sulfide contributes to low-level background SO<sub>2</sub>  
8 concentrations in coastal environments. [Lee and Brimblecombe \(2016\)](#) provide a  
9 literature-derived global estimate of DMS emissions from seawater and marshland of 3.1  
10 x 10<sup>7</sup> tpy S. Earlier estimates for seawater DMS emissions range widely from 6.1 x 10<sup>6</sup> to  
11 2.4 x 10<sup>7</sup> tpy ([Liu et al., 2005](#); [Chin et al., 2000](#); [Feichter et al., 1996](#); [Pham et al., 1996](#);  
12 [Langner and Rodhe, 1991](#)). A warming climate may have a complex feedback effect on  
13 DMS emissions, influencing both ocean surface temperatures and currents controlling  
14 nutrient dispersion that impact the population and location of DMS producing  
15 phytoplankton ([Kloster et al., 2007](#)).

---

## 2.3 Atmospheric Chemistry and Fate

16 Known sulfur oxides in the troposphere include SO<sub>2</sub> and SO<sub>3</sub> ([U.S. EPA, 2008d](#)). SO<sub>3</sub>  
17 can be emitted by power plants and factories, but it reacts within seconds with water in  
18 the stacks or immediately after release into the atmosphere to form H<sub>2</sub>SO<sub>4</sub>. Gas-phase  
19 sulfuric acid quickly condenses onto existing particles or participates in new particle  
20 formation ([Finlayson-Pitts and Pitts, 2000](#)). Of those species, only SO<sub>2</sub> is present at  
21 concentrations relevant for chemistry in the troposphere, boundary layer, and for human  
22 exposures.

23 This section provides an overview of the primary atmospheric chemistry and removal  
24 processes for SO<sub>2</sub> of relevance to atmospheric concentrations at urban scales.

25 [Section 2.3.1](#) describes the photochemical reactions that remove SO<sub>2</sub> from the  
26 atmosphere by converting it into compounds that condense into the particle or cloud  
27 water phase. [Section 2.3.2](#) describes the aqueous-phase oxidation of SO<sub>2</sub>, the major  
28 oxidation mechanism in the atmosphere, as well as dry and wet deposition of SO<sub>2</sub>.  
29

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### 2.3.1 Photochemical Removal of Atmospheric SO<sub>2</sub>

30 The atmospheric lifetime ( $\tau$ ) of SO<sub>2</sub> with respect to reactions with the OH radical in the  
31 troposphere is 7.2 days. The rate constant for the reaction between SO<sub>2</sub> and NO<sub>3</sub> radical is

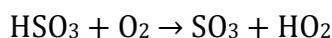
1 too small to be of any importance in the reduction of SO<sub>2</sub> concentrations at urban or  
2 regional scales. The same is true for the reaction between SO<sub>2</sub> and the hydroperoxyl  
3 (HO<sub>2</sub>) radical ([Sander et al., 2011](#)).

4 In the stepwise oxidation of SO<sub>2</sub> by OH, SO<sub>2</sub> is oxidized to form SO<sub>3</sub>, taking the sulfur  
5 atom from the S(IV) to S(VI) oxidation state, producing the bisulfite radical (HSO<sub>3</sub>):



**Equation 2-1**

6 where M is an unreactive gas molecule that absorbs excess, destabilizing energy from the  
7 SO<sub>2</sub>-OH transition state. This reaction is followed by



**Equation 2-2**

8 An alternative route involves a stabilized Criegee intermediate (sCI):



**Equation 2-3**

9 The unspecified “products” of this reaction are other organic radicals derived from the  
10 degradation of the Criegee intermediate ([Berndt et al., 2012](#); [Mauldin et al., 2012](#); [Welz  
11 et al., 2012](#)). Rate coefficients for the reaction of sCIs with SO<sub>2</sub> have been reported as  
12  $4 \times 10^{-15}$  cm<sup>3</sup>/sec ([Johnson et al., 2001](#)), approximately  $3.5 \times 10^{-11}$  cm<sup>3</sup>/sec ([Liu et al.,  
13 2014b](#)), and  $3.9 \times 10^{-11}$  cm<sup>3</sup>/sec ([Welz et al., 2012](#)). Recent studies report rate  
14 coefficients greater than  $3 \times 10^{-11}$  cm<sup>3</sup>/sec ([Friedman et al., 2016](#); [Lee, 2015](#); [Berndt et  
15 al., 2012](#)). These reaction rate coefficients far exceed those of the reactions between these  
16 intermediates and H<sub>2</sub>O. However, hydrolysis of SO<sub>2</sub> could be limited if sCIs that are  
17 potential SO<sub>2</sub> oxidants are hydrolyzed via competing reactions ([Kim et al., 2015](#)).  
18 The efficiency of Criegee radical hydrolysis is sensitive to the molecular structure of the  
19 alkene. Bimolecular hydrolysis rates constants vary by a factor of 1,000 between syn-  
20 versus anti-substituted low molecular weight alkenes ([Lin and Takahashi, 2016](#)).

21 Criegee radicals are produced by the reaction of alkenes with O<sub>3</sub> during both night and  
22 day. The relative importance of the OH and sCI pathways depends in large measure on  
23 the local concentration of alkenes, such as low molecular weight alkenes emitted by  
24 motor vehicles and industrial processes as well terpenoids emitted by trees.

25 The importance of this mechanism as a sink for SO<sub>2</sub> is supported by observations that  
26 areas adjacent to SO<sub>2</sub> sources, with high biogenic or industrial VOC concentrations, have  
27 elevated organic PM concentrations ([Friedman et al., 2016](#)). However, limited  
28 information on the identity and concentrations of alkenes at urban scales prevents  
29 estimates of the impact of this reaction pathway on urban SO<sub>2</sub> concentrations.

1 The SO<sub>3</sub> that is generated by either oxidation mechanism (i.e., reaction with OH or via  
2 the Criegee reaction mechanism) is a highly reactive species. Water vapor is sufficiently  
3 abundant in the troposphere to ensure that SO<sub>3</sub> is quickly converted to gas-phase sulfuric  
4 acid, as shown in the equation below ([Loerting and Liedl, 2000](#)).



**Equation 2-4**

5 Because H<sub>2</sub>SO<sub>4</sub> is extremely water soluble, gaseous H<sub>2</sub>SO<sub>4</sub> will be removed rapidly by  
6 dissolution into the aqueous phase of aerosol particles and cloud droplets. In a study of  
7 SO<sub>2</sub> plume transport in and out of foggy conditions, [Eatough et al. \(1984\)](#) observed that  
8 roughly 30% of the SO<sub>2</sub> converts to H<sub>2</sub>SO<sub>4</sub> particulate each hour when inside a fog bank  
9 and roughly 3.1% per hour outside a fog bank. [Khoder \(2002\)](#) observed that conversion  
10 from SO<sub>2</sub> to H<sub>2</sub>SO<sub>4</sub> increases with increasing relative humidity and increasing O<sub>3</sub>, based  
11 on a sampling campaign in an urban area of Egypt. Pearson correlation of SO<sub>2</sub>-to-H<sub>2</sub>SO<sub>4</sub>  
12 conversion ratio with relative humidity was 0.81 in the winter and 0.89 in the summer.  
13 [Hung and Hoffmann \(2015\)](#) recently conducted spray chamber experiments of SO<sub>2</sub> to  
14 H<sub>2</sub>SO<sub>4</sub> conversion. They observed that SO<sub>2</sub> deposited to the surfaces of water  
15 microdroplets and then underwent rapid oxidation, first to HSO<sub>3</sub><sup>-</sup> and HSO<sub>4</sub><sup>-</sup>, and then to  
16 SO<sub>4</sub><sup>2-</sup>. Acidic conditions promoted more rapid oxidation of SO<sub>2</sub>.

---

### 2.3.2 Heterogeneous Oxidation of Sulfur Dioxide

17 The major sulfur-containing species in clouds are the HSO<sub>3</sub><sup>-</sup> and SO<sub>3</sub><sup>2-</sup> (sulfite) ions that  
18 form when SO<sub>2</sub> dissolves in cloud droplets and subsequently undergoes acid dissociation.  
19 Both exist in the S(IV) oxidation state, which readily oxidizes in the presence of  
20 aqueous-phase oxidizing agents to form the S(VI) anions, HSO<sub>4</sub><sup>-</sup> (bisulfate), and SO<sub>4</sub><sup>2-</sup>.  
21 The major species capable of oxidizing S(IV) to S(VI) in cloud water are O<sub>3</sub>, peroxides  
22 [either hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>) or organic peroxides], OH radicals, and transition metal  
23 ions such as Fe and Cu that catalyze the oxidation of S(IV) to S(VI) by O<sub>2</sub>.

24 The basic mechanism of the aqueous-phase oxidation of SO<sub>2</sub> can be found in numerous  
25 texts on atmospheric chemistry [e.g., ([Seinfeld and Pandis, 2006](#); [Jacobson, 2002](#);  
26 [Finlayson-Pitts and Pitts, 2000](#); [Jacob, 1999](#))]. Similar initial steps occur in the fluids  
27 lining the airways ([Section 4.2.1](#)). The steps involved in the aqueous phase oxidation of  
28 SO<sub>2</sub> are summarized below ([Jacobson, 2002](#)).

29 Dissolution of SO<sub>2</sub> occurs first,



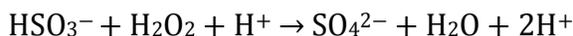
**Equation 2-5**

1 followed by the formation and dissociation of sulfurous acid (H<sub>2</sub>SO<sub>3</sub>).



Equation 2-6

2 In the pH range commonly found in rainwater (2 to 6), H<sub>2</sub>O<sub>2</sub> will oxidize HSO<sub>3</sub><sup>-</sup> to SO<sub>4</sub><sup>2-</sup>.



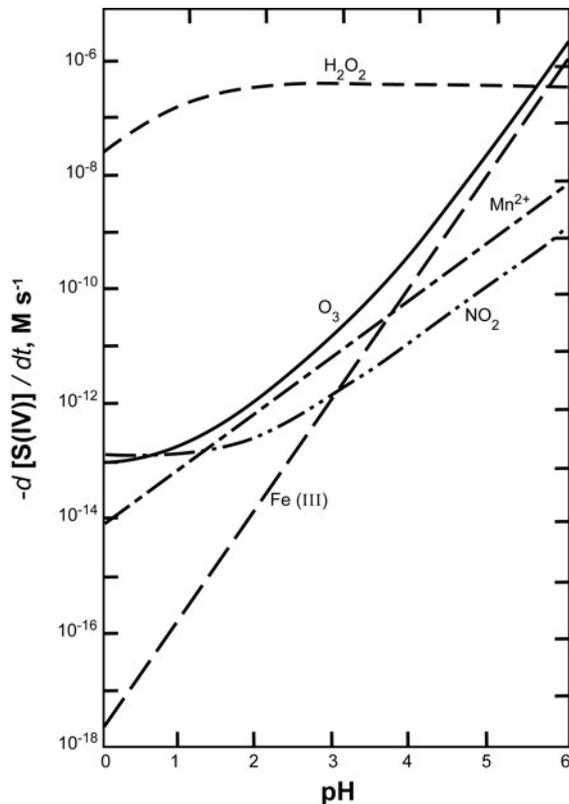
Equation 2-7

3 The rates of aqueous-phase oxidation of S(IV) to S(VI) as a function of pH are shown in  
4 [Figure 2-9](#). For pH values up to about 5.3, H<sub>2</sub>O<sub>2</sub> is the predominant oxidant; above pH  
5 5.3, O<sub>3</sub>, followed by Fe(III), becomes predominant.

6 Ambient ammonia (NH<sub>3</sub>) vapor readily dissolves in acidic cloud drops to form  
7 ammonium (NH<sub>4</sub><sup>+</sup>). Because NH<sub>4</sub><sup>+</sup> is very effective in controlling acidity, it amplifies the  
8 rate of oxidation of S(IV) to S(VI) and the rate of dissolution of SO<sub>2</sub> in particles and  
9 cloud droplets. Therefore, in environments where NH<sub>3</sub> is abundant, SO<sub>2</sub> is subject to fast  
10 removal by cloud and fog droplets and ultimately forms ammonium sulfate [(NH<sub>4</sub>)<sub>2</sub>SO<sub>4</sub>].

11 Higher pH levels are expected to be found mainly in marine aerosols. In marine aerosols,  
12 the chlorine radical-catalyzed oxidation of S(IV) may be more important ([Hoppel and](#)  
13 [Caffrey, 2005](#); [Zhang and Millero, 1991](#)).

14 In the same way that it is removed from the gas phase by dissolution into cloud droplets,  
15 SO<sub>2</sub> can be removed by dry deposition onto wet surfaces ([Shadwick and Sickles, 2004](#);  
16 [Clarke et al., 1997](#)). For example, in the eastern U.S., SO<sub>2</sub> is responsible for more than  
17 85% of dry sulfur deposition ([Sickles and Shadwick, 2007](#)). However, aqueous SO<sub>4</sub><sup>2-</sup>  
18 may be removed through occult deposition of large fog or cloud droplets ([Lillis et al.,](#)  
19 [1999](#); [Pandis and Seinfeld, 1989](#); [Dollard et al., 1983](#)). Scavenging by rain (wet  
20 deposition) serves as another removal route. Modeling studies have shown that slightly  
21 more than half of SO<sub>2</sub> in both models is lost by gas- and aqueous-phase oxidation, with  
22 the remainder of SO<sub>2</sub> loss accounted for by wet and dry deposition ([Long et al., 2013](#); [Liu](#)  
23 [et al., 2012a](#)).



Fe = iron; H<sub>2</sub>O<sub>2</sub> = hydrogen peroxide; Mn<sup>2+</sup> = manganese ion; NO<sub>2</sub> = nitrogen dioxide; O<sub>3</sub> = ozone; S = sulfur.

Note: The rate of conversion of aqueous (droplet)-phase S(IV) to S(VI) is shown as a function of pH. Conditions assumed are: [SO<sub>2</sub>(g)] = 5 ppb; [NO<sub>2</sub>(g)] = 1 ppb; [H<sub>2</sub>O<sub>2</sub>(g)] = 1 ppb; [O<sub>3</sub>(g)] = 50 ppb; [Fe(III)(aq)] = 0.3 μM; [Mn(II)(aq)] = 0.3 μM.

Source: [Seinfeld and Pandis \(2006\)](#).

**Figure 2-9 The effect of pH on the rates of aqueous-phase sulfur (IV) oxidation by various oxidants.**

1  
 2 Sulfur dioxide is known to adhere to and then react on dust particles. Very recent  
 3 investigations have shown that, for some mineral compositions, SO<sub>2</sub> uptake on dust  
 4 particles is sensitive to relative humidity, the mineral composition of the particle, and the  
 5 availability of H<sub>2</sub>O<sub>2</sub>, the relevant oxidant ([Huang et al., 2015b](#)). Once SO<sub>2</sub> is oxidized to  
 6 H<sub>2</sub>SO<sub>4</sub> on the particle surface, glyoxyl, one of the most prevalent organic compounds in  
 7 the atmosphere, will adhere to the surface and react to form oligomers and organosulfate  
 8 compounds. This process is enhanced under high humidity conditions ([Shen et al., 2016](#)).

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## 2.4 Measurement Methods

1 This section discusses the federal reference method (FRM) and federal equivalent method  
2 (FEM) used for NAAQS compliance as well as the state, local, and tribal monitoring  
3 networks across the U.S. used for NAAQS compliance monitoring. Detailed information  
4 about monitoring methods, including accuracy, precision, limits of detection, and other  
5 operational parameters was published in the 1982 Air Quality Criteria for Particulate  
6 Matter and Sulfur Oxides Volume II ([U.S. EPA, 1982a](#)) and then updated in  
7 Appendix B.6 of the 2008 ISA for Sulfur Oxides—Health Criteria ([U.S. EPA, 2008d](#)).  
8 The List of Designated Reference and Equivalent Methods ([U.S. EPA, 2016f](#)) lists all  
9 monitors approved as FRMs or FEMs and provides monitor specifications. A brief  
10 summary of that information, along with a discussion of more recent studies evaluating  
11 FRMs and FEMs for monitoring SO<sub>2</sub> concentration ([Section 2.4.1](#)) or alternative SO<sub>2</sub>  
12 monitoring methods ([Section 2.4.2](#)), is provided. [Section 2.4.3](#) describes the sampling  
13 network.

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### 2.4.1 Federal Reference and Equivalent Methods

14 Currently, there are two FRMs for the measurement of SO<sub>2</sub>—the manual pararosaniline  
15 wet-chemistry method and the automated pulsed ultraviolet fluorescence (UVF) method.  
16 The manual method was approved as an FRM in the 1970s and was quickly replaced by  
17 the flame photometric detection (FPD) method, an FEM because the manual method was  
18 too complex and had a slow response even in automated form. The UVF method was  
19 designated as an FEM in the late 1970s and ultimately replaced the FPD method.  
20 The UVF method is inherently linear and relatively safe whereas the FPD method  
21 requires highly flammable hydrogen gas. The UVF method has been the most commonly  
22 used method by state and local monitoring agencies since the 1980s. It was added as an  
23 FRM as a result of the new 1-hour SO<sub>2</sub> primary NAAQS established in 2010 (75 FR  
24 35520). The UVF method supports the need for a continuous monitoring method, as it  
25 can easily provide 1-hour SO<sub>2</sub> measurements. The existing pararosaniline manual method  
26 was retained as a FRM, and although cumbersome, the method can provide hourly  
27 measurements to support the 1-hour NAAQS.

28 In the UVF method, SO<sub>2</sub> molecules absorb UV light at one wavelength and emit UV light  
29 at longer wavelengths through excitation of the SO<sub>2</sub> molecule to a higher energy  
30 electronic state. Once excited, the molecule loses a portion of its energy by collision with  
31 another gas molecule and, then by emitting a photon of light at a longer wavelength  
32 which returns to its electronic ground state. The intensity of the emitted light is, therefore,  
33 proportional to the number of SO<sub>2</sub> molecules in the sample gas. In commercial analyzers,

1 light from a high-intensity UV lamp passes through a bandwidth filter that allows only  
2 photons with wavelengths around the SO<sub>2</sub> absorption peak (near 214 nm) to enter the  
3 optical chamber. The light passing through the source bandwidth filter is collimated using  
4 a UV lens and passes through the optical chamber, where it is detected on the opposite  
5 side of the chamber by the reference detector. A detector is offset from and placed  
6 perpendicular to the light path to detect the SO<sub>2</sub> fluorescence. Because the SO<sub>2</sub>  
7 fluorescence at about 330 nm is different from its excitation wavelength, an optical  
8 bandwidth filter is placed in front of the detector to filter out any stray light from the UV  
9 lamp. A lens is located between the filter and the detector to focus the fluorescence onto  
10 the active area of the detector and optimize the fluorescence signal. A particulate filter is  
11 also placed after the sample inlet to prevent damage, malfunction, and interference from  
12 particles in the sampled air.

13 Studies have compared UVF to sampled SO<sub>2</sub> from impregnated filters for quality  
14 assurance. Comparison of 24-h avg concentration measurements obtained with the UVF  
15 method and with impregnated filters showed annual-average differences within  
16  $\pm 0.07$  ppb, based on data obtained between 1993 and 2001 from four Finnish cities  
17 ([Leppänen et al., 2005](#)). [Ferek et al. \(1997\)](#) evaluated the Teco model UVF (developed at  
18 the University of Washington) against carbonate-impregnated filters for measurement of  
19 SO<sub>2</sub> concentration in laboratory studies. The Teco UVF measured SO<sub>2</sub> concentrations  
20 down to 16 ppt and, on average, produced a positive difference of 7% compared with the  
21 filter. The Teco UVF analyzed data at a frequency as high as 1 Hz, but noise was  
22 curtailed by averaging up to 10 minutes. The [Ferek et al. \(1997\)](#) study highlighted the  
23 Teco UVF but also included other SO<sub>2</sub> measurement techniques in the SO<sub>2</sub> monitor  
24 comparison, including gas spectrometry/mass spectrometry, high performance liquid  
25 chromatography, and a mist chamber, which produced a maximum of 30% differences  
26 for filter-measured SO<sub>2</sub> concentrations of 3–4 ppb averaged over 90 minutes.

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#### 2.4.1.1 Minimum Performance Specifications

27 Minimum performance specifications [in accordance with 40 Code of Federal  
28 Regulations (CFR) Part 53] were made more stringent for any new FRM and FEM  
29 automated method with the addition of the UVF method as an FRM. The new  
30 specifications are provided in [Table 2-3](#). The previous specifications were based on the  
31 older, manual, wet-chemistry FRM and were updated to reflect current technology and  
32 improved performance in SO<sub>2</sub> instrumentation. The lower detection limit (LDL) for a  
33 routine, automated SO<sub>2</sub> analyzer is required to be 2 ppb. As part of the National Core  
34 (NCore) monitoring network, new trace-level SO<sub>2</sub> instruments have been developed and  
35 added to State and Local Air Monitoring Sites (SLAMS). These new trace-level (i.e., low

1 LDL) instruments have LDLs of 0.2 ppb or lower. Note that FRMs and FEMs may have  
 2 more stringent performance characteristics than the minimum performance specifications  
 3 presented in [Table 2-3](#).

**Table 2-3 Minimum performance specifications for sulfur dioxide based in 40 Code of Federal Regulations Part 53, Subpart B.**

Performance Parameter	Specification
Range	0–0.5 ppm (500 ppb)
Noise	0.001 ppm (1 ppb)
Lower detectable limit ( <i>two times the noise</i> )	0.002 ppm (2 ppb)
Interference equivalent	
• Each interferent	±0.005 ppm (5 ppb)
• Total, all interferents	—
Zero drift (12 and 24 h)	±0.004 ppm (4 ppb)
Span drift (24 h)	
• 20% of upper range limit	—
• 80% of upper range limit	±3.0%
Lag time	2 min
Rise time	2 min
Fall time	2 min
Precision	
• 20% of upper range limit	2.0%
• 80% of upper range limit	2.0%

#### 2.4.1.2 Positive and Negative Interferences

4 The UVF method has a number of positive and negative interferences. The most frequent  
 5 source of positive interference is other gases that fluoresce at the same wavelength as  
 6 SO<sub>2</sub>. The most common gases include volatile organic compounds (e.g., xylenes,  
 7 benzene, toluene) and polycyclic aromatic hydrocarbons (PAHs; e.g., naphthalene).  
 8 To reduce this source of positive interference, high-sensitivity SO<sub>2</sub> analyzers are  
 9 equipped with scrubbers or “kickers” to remove these compounds from the air stream

1 prior to entering the optical chamber. [Luke \(1997\)](#) evaluated a modified pulsed  
2 fluorescence SO<sub>2</sub> detector and found positive interference from nitric oxide (NO), CS<sub>2</sub>,  
3 and several highly fluorescent aromatic hydrocarbons such as benzene, toluene, *o*-xylene,  
4 *m*-xylene, *p*-xylene, *m*-ethyltoluene, ethylbenzene, and 1,2,4-trimethylbenzene.  
5 The positive artifacts could be virtually eliminated by using a hydrocarbon “kicker”  
6 membrane. At a flow rate of 300 standard cm<sup>3</sup>/minute and a pressure drop of 645 torr  
7 across the membrane, the interference from ppm levels of many aromatic hydrocarbons  
8 can be eliminated.

9 Another source of positive interference is NO, which fluoresces in a region close to that  
10 of SO<sub>2</sub>. However, in high-sensitivity SO<sub>2</sub> analyzers, the bandpass filter in front of the  
11 detector is specifically designed to prevent detection of NO fluorescence at the detector.  
12 Care must be exercised when using multicomponent calibration gases containing both  
13 NO and SO<sub>2</sub>, so that the NO rejection ratio of the SO<sub>2</sub> analyzer is sufficient to prevent  
14 NO interference.

15 The most common source of positive bias in high-sensitivity SO<sub>2</sub> analyzers is stray light  
16 in the optical chamber. Because SO<sub>2</sub> can be excited by a broad range of UV wavelengths,  
17 any stray light entering the optical chamber with an appropriate wavelength can excite  
18 SO<sub>2</sub> in the air stream and increase the fluorescence signal. Additionally, stray light  
19 entering the optical chamber with a similar wavelength of SO<sub>2</sub> fluorescence may impinge  
20 on the detector and increase the fluorescence signal. Stray light is also minimized with  
21 changes in instrument design such as use of light filters, dark surfaces, and opaque  
22 tubing.

23 H<sub>2</sub>O is a common source of negative interference in high-sensitivity SO<sub>2</sub> monitors. When  
24 excited SO<sub>2</sub> molecules collide with water vapor as well as other common molecules in air  
25 (e.g., nitrogen and oxygen), nonradiative deactivation (quenching) can occur. During  
26 collisional quenching, the excited SO<sub>2</sub> molecule transfers energy, kinetically allowing the  
27 SO<sub>2</sub> molecule to return to a lower energy state without emitting a photon. Collisional  
28 quenching decreases the SO<sub>2</sub> fluorescence and results in an underestimation of SO<sub>2</sub>  
29 concentration in the air sample. Of particular concern is the variable water vapor content  
30 of air. [Luke \(1997\)](#) reported that the response of the detector could be reduced by an  
31 amount of approximately 7 to 15% at water vapor mixing ratios of 1 to 1.5 mole percent  
32 [relative humidity (RH) = 35 to 50% at 20 to 25°C and 1 atmosphere for a modified  
33 pulsed fluorescence detector (Thermo Environmental Instruments, Model 43s)].  
34 Condensation of water vapor in sampling lines must be avoided, as water on the inlet  
35 surfaces can absorb SO<sub>2</sub> from the sample air. Condensation is normally prevented by  
36 heating sampling lines to a temperature above the expected dew point and to within a few  
37 degrees of the controlled optical bench temperature. Some monitors are equipped with a

1 dryer system to remove moisture from the sample gas before it reaches the particulate  
2 filter.

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## 2.4.2 Alternative Sulfur Dioxide Measurements

3 A number of optical methods for measuring SO<sub>2</sub> are available. They include laser  
4 induced fluorescence (LIF), cavity ring-down spectroscopy (CRDS), differential optical  
5 absorption spectrometry (DOAS), and UV absorption. There are also methods based on  
6 mass spectroscopy or mass spectrometry [e.g., chemical ionization mass spectroscopy  
7 (CIMS) and atmospheric pressure ionization mass spectrometry (APIMS)]. These  
8 methods are often too expensive and complex for routine monitoring applications and are  
9 more suitable for source monitoring. However, approaches to reduce interferences and  
10 increase SO<sub>2</sub> selectivity could be extended to FRM and FEM instrumentation. The LIF,  
11 CRDS, and DOAS methods will be discussed below as they have the potential to provide  
12 trace-level SO<sub>2</sub> measurements or have shown good agreement with UVF instrumentation.

13 LIF is a technique that can provide high sensitivity for ambient SO<sub>2</sub> measurements and  
14 reduces interferences with species that fluoresce at the same wavelength as SO<sub>2</sub>. Both  
15 tunable and nontunable laser sources have been evaluated. [Matsumi et al. \(2005\)](#)  
16 evaluated a LIF method using a tunable laser at an SO<sub>2</sub> absorption peak at 220.6 nm and  
17 trough at 220.2 nm. The difference between the signals at the two wavelengths is used to  
18 estimate the SO<sub>2</sub> concentration. This technique has a sensitivity of 5 ppt in 60 sec.  
19 [Simeonsson et al. \(2012\)](#) evaluated a direct LIF technique using a nontunable laser source  
20 at an absorption wavelength of 223 nm, which coincides with the SO<sub>2</sub> absorption peak.  
21 This technique has a high sensitivity with LDL of 0.5 ppb. Both the tunable and  
22 nontunable instruments have low LDL ( $\leq 0.5$  ppb); therefore, they can provide trace-level  
23 SO<sub>2</sub> measurements.

24 CRDS is an optical absorption method based on measurement of the rate of light  
25 absorption through a sample. CRDS has successfully been used to measure ambient NO<sub>2</sub>  
26 and NO with high sensitivity. [Medina et al. \(2011\)](#) compared a CRDS-tunable laser  
27 method to the routinely used pulsed ultraviolet fluorescence (UVF) method for measuring  
28 SO<sub>2</sub>. At an absorption wavelength of 308 nm, the CRDS had an LDL of 3.5 ppb, which  
29 was higher than those for routine and trace-level UVF SO<sub>2</sub> monitors (e.g., Thermo  
30 Scientific 43i and Thermo Scientific 43i-TLE). However, the response time was faster  
31 compared to the UVF methods (a few seconds vs. 80 sec). To reduce interferences, a  
32 ferrous sulfate scrubber was used to remove NO<sub>2</sub> and O<sub>3</sub>, and a denuder was used to zero  
33 SO<sub>2</sub> levels. Improvements could be made to increase the sensitivity to about 1 ppb by  
34 changing the placement of the mirrors to optimize laser light reaching the cavity or using

1 a better detection system. Additionally, improving the mirror reflectivity could improve  
2 the sensitivity to about 0.1 ppb, similar to the detection levels of trace-level SO<sub>2</sub>  
3 monitors.

4 DOAS is an optical remote sensing method based on the absorption of light in the  
5 UV-visible wavelength region to measure atmospheric pollutants. [Kim and Kim \(2001\)](#)  
6 compared SO<sub>2</sub> concentrations measured using a DOAS system with daily mean SO<sub>2</sub>  
7 concentrations measured by an in situ monitor in Seoul, Korea during a 13-month period.  
8 In this study, the DOAS typically reported SO<sub>2</sub> concentrations around 10–40% above the  
9 in situ technique, but SO<sub>2</sub> concentrations measured by the DOAS were sometimes  
10 100–200% below those measured with the in situ monitor. Across all measurements, the  
11 daily mean SO<sub>2</sub> concentration was 36% higher from the DOAS compared with the in situ  
12 monitor. Discrepancies between the two methods were attributed to ability to respond to  
13 meteorological factors. The DOAS was reported to have an LDL of 0.07 ppb, compared  
14 with 1 ppb reported for the in situ method. A newer technique called multiaxis  
15 differential optical absorption spectroscopy (MAX-DOAS) has been developed that  
16 offers increased sensitivity in measuring SO<sub>2</sub> ([Honninger et al., 2004](#)). MAX-DOAS is  
17 based on the measurement of scattered sunlight at multiple viewing directions and can  
18 obtain both surface concentrations and vertical column density of SO<sub>2</sub>. [Wang et al.](#)  
19 [\(2014b\)](#) compared MAX-DOAS SO<sub>2</sub> column measurements in the 305 to 317.5 nm  
20 absorption wavelength to surface SO<sub>2</sub> measurements from a modified UVF SO<sub>2</sub> monitor  
21 (Thermo Environmental Instruments Model 43C) and found good agreement ( $r = 0.81$ ,  
22 slope = 0.90).

23 Remote sensing by satellites (e.g., OMI, infrared atmospheric sounding interferometer,  
24 etc.) is an emerging technique for measuring SO<sub>2</sub> as well as other pollutants. This  
25 technique can be used for a variety of applications, including air quality management  
26 (e.g., augmenting ground-based monitors, assessing emissions inventories), studying  
27 pollutant transport, assessing emissions reductions, and evaluating air quality models.  
28 Remote sensing methods employ a retrieval system using a combination of solar  
29 backscatter or thermal infrared emission spectra and mathematical algorithms to estimate  
30 pollutant concentrations. Remote sensing from space is particularly challenging for SO<sub>2</sub>  
31 measurements for two reasons: (1) air scattering causes SO<sub>2</sub> to have a low optical  
32 thickness (three orders of magnitude lower than O<sub>3</sub>), so that only large SO<sub>2</sub> sources can  
33 be observed ([Bogumil et al., 2003](#)) and (2) emissions reductions programs have led to  
34 lower SO<sub>2</sub> emissions from stationary sources, making it more difficult to see  
35 anthropogenic SO<sub>2</sub> emissions ([Streets et al., 2014](#)). The majority of remote sensing  
36 studies have focused on large natural sources (e.g., volcanoes), large anthropogenic  
37 sources (e.g., coal-burning power plants, smelters), fuel extraction from oil sands, and  
38 newly constructed coal-burning facilities with high, uncontrolled SO<sub>2</sub> emissions

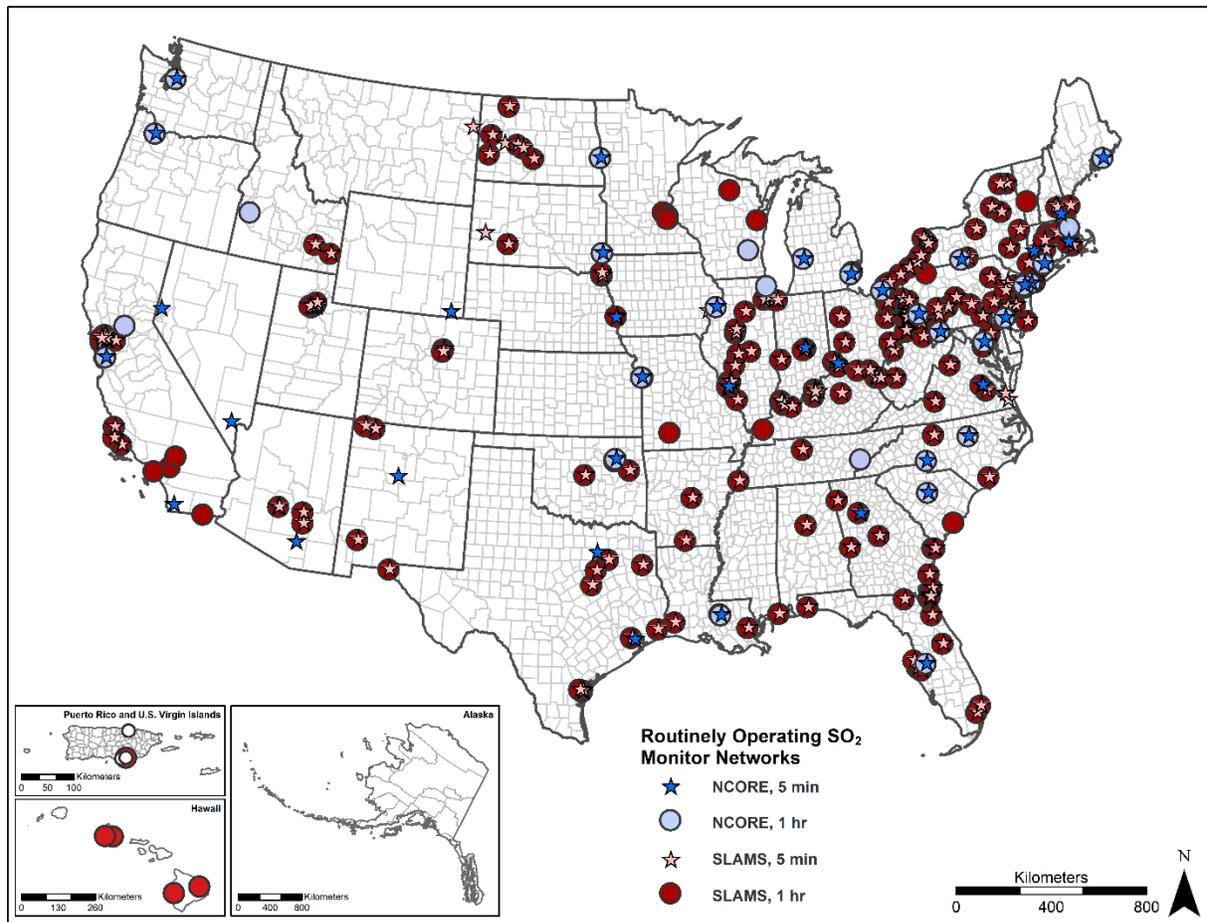
1 [\(Boynard et al., 2014; McCormick et al., 2014; Streets et al., 2014; Clarisse et al., 2012;](#)  
2 [McLinden et al., 2012; Fioletov et al., 2011; Nowlan et al., 2011; Bobrowski et al., 2010;](#)  
3 [Li et al., 2010; Khokhar et al., 2008; Carn et al., 2007\).](#)

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### 2.4.3 Ambient Sampling Network Design

4 Compliance with NAAQS is primarily carried out through the SLAMS network, although  
5 modeling may also be used to characterize air quality for implementation purposes (75  
6 FR 35520). There are 438 SLAMS sites reporting 1-hour SO<sub>2</sub> concentrations to the Air  
7 Quality System (AQS), U.S. EPA's repository for detailed air pollution data that is  
8 subject to quality control and assurance procedures. In addition to their use in compliance  
9 evaluations, some of these sites function as central monitoring sites for use in  
10 epidemiological studies. The SLAMS network also reports either the maximum 5-minute  
11 concentration in the hour (one of twelve 5-minute periods within an hour) or all twelve  
12 5-minute average SO<sub>2</sub> concentrations within the hour. Siting requirements for monitors in  
13 the SLAMS network can be found in 40 CFR Part 58, Appendix E.

14 The SLAMS network includes the NCore monitoring network, which began January 1,  
15 2011 and consists of 80 sites (63 urban and 17 rural). NCore is a multipollutant  
16 measurement network and includes SO<sub>2</sub> measurements as well as measurements for other  
17 gaseous pollutants (O<sub>3</sub>, CO, NO<sub>x</sub>, oxides of nitrogen), PM<sub>2.5</sub>, PM<sub>10-2.5</sub>, and meteorology.  
18 NCore is focused on characterizing trends in pollutants, understanding pollutant transport  
19 in urban and rural areas, and evaluating data with respect to the NAAQS. [Figure 2-10](#)  
20 shows the locations of these monitoring networks across the U.S. The Clean Air Status  
21 and Trends Network (CASTNet) also measures ambient SO<sub>2</sub>. However, these data are not  
22 used for NAAQS compliance purposes and are obtained predominantly in National Parks  
23 or other ecologically sensitive sites. Because CASTNet monitors are not deployed in  
24 populated areas, they are not useful in evaluating the health effects of SO<sub>2</sub>. This network  
25 provides weekly averages of total sulfur (dry SO<sub>2</sub>, dry SO<sub>4</sub><sup>2-</sup>, and wet SO<sub>4</sub><sup>2-</sup>) in about  
26 90 sites located in or near rural locations to assess long-term trends in acidic deposition  
27 due to emission reduction programs. CASTNet data are presented in the Integrated  
28 Science Assessment for Oxides of Nitrogen and Sulfur—Ecological Criteria ([U.S. EPA,](#)  
29 [2008b](#)).



NCORE = National Core; SLAMS = State and Local Air Monitoring Sites; SO<sub>2</sub> = sulfur dioxide.

**Figure 2-10** Routinely operating sulfur dioxide monitoring networks: National Core and State and Local Air Monitoring Sites, reporting 1 hour and 5 minute sulfur dioxide concentration data.

1 The minimum monitoring requirements for the SLAMS network are outlined in 40 CFR  
 2 Part 58, Appendix D. SO<sub>2</sub> monitors at SLAMS sites represent four main spatial scales:  
 3 (1) microscale—areas in close proximity, up to 100 m from a SO<sub>2</sub> point or area source,  
 4 (2) middle scale—areas up to several city blocks, with linear dimensions of about 100 to  
 5 500 m, (3) neighborhood scale—areas with linear dimensions of 0.5 to 4 km, and  
 6 (4) urban scale—urban areas with linear dimensions of 4 to 50 km. Microscale,  
 7 middle-scale, and neighborhood-scale sites are used to determine maximum hourly SO<sub>2</sub>  
 8 concentrations because these sites are close to stationary point and area sources, whereas  
 9 neighborhood- and urban-scale sites are used as central monitoring sites to characterize  
 10 population exposures and trends, such as in epidemiologic studies ([Section 3.2.1](#)).

1 Urban-scale sites can also be used to determine background concentrations in areas where  
2 monitors are located upwind of a local source. There are also a number of regional-scale  
3 monitoring sites, representing length scales of tens to hundreds of kilometers, typically in  
4 rural areas of uniform geography without large SO<sub>2</sub> sources. These sites can be used to  
5 determine the amount of regional pollution transport and to support secondary NAAQS.

6 Stationary sources are the primary emission sources of SO<sub>2</sub>. Prior to the revised SO<sub>2</sub>  
7 primary NAAQS in 2010, U.S. EPA evaluated about 488 SO<sub>2</sub> monitoring sites in  
8 operation during 2008 and found that the network was not adequately focused to support  
9 the revised NAAQS ([U.S. EPA, 2009d](#)). To address this deficiency, U.S. EPA  
10 promulgated minimum monitoring requirements based on a near-source monitoring  
11 approach. The Population Weighted Emissions Index (PWEI), which is based on  
12 population and emissions inventory data at the core-based statistical area (CBSA) level,  
13 was introduced to assign the appropriate number of monitoring sites in a given CBSA (75  
14 FR 35520). The PWEI accounts for SO<sub>2</sub> exposure by requiring monitor placement in  
15 urban areas where population and emissions may lead to higher potential for population  
16 exposure to maximum hourly SO<sub>2</sub> concentrations. The PWEI value is calculated by  
17 multiplying the population of each CBSA by the total amount of SO<sub>2</sub> emissions (in tons  
18 per year) in a given CBSA, using the most recent census data (or estimates) and  
19 combining the most recent county-level emissions data (from the National Emissions  
20 Inventory) for each county in each CBSA, respectively. This value is then divided by  
21 1 million, resulting in a PWEI value with units of million person-tons per year.

22 A minimum of three SO<sub>2</sub> monitoring sites is required for any CBSA with a PWEI value  
23 greater than or equal to 1,000,000. For any CBSA with a PWEI value greater than or  
24 equal to 100,000 but less than 1,000,000, a minimum of two SO<sub>2</sub> monitoring sites is  
25 required. Lastly, a minimum of one SO<sub>2</sub> monitoring site is required for any CBSA with a  
26 PWEI value greater than or equal to 5,000 but less than 100,000. The monitors sited  
27 within a CBSA based on the PWEI criterion should also be, at minimum, one of the  
28 following monitoring site types: population exposure, highest concentration, source  
29 impacted, general background, or regional transport.

30 Another minimum monitoring requirement for the revised NAAQS involves the quantity  
31 of monitoring sites in a given state, which is based on the state's contribution to the NEI  
32 for SO<sub>2</sub>. This requirement was designed to offer some flexibility in monitoring site  
33 placement, either inside or outside of a CBSA, independent of the PWEI criteria.

34 Additionally, all monitoring sites in the network must be placed at locations where  
35 maximum peak hourly SO<sub>2</sub> concentrations are expected. Monitoring sites in the NCore  
36 network are not source oriented, and therefore, do not necessarily count towards the  
37 minimum monitoring requirements for SO<sub>2</sub>. However, if an NCore SO<sub>2</sub> monitoring site is

1 located in a CBSA that meets the aforementioned requirements based on the PWEI  
2 criteria, that monitoring site can count towards the minimum monitoring requirements.

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## 2.5 Environmental Concentrations

3 This section provides an overview of SO<sub>2</sub> ambient and background concentrations. SO<sub>2</sub>  
4 data discussed in this section were obtained from the AQS. [Section 2.5.1](#) introduces  
5 different SO<sub>2</sub> metrics used for NAAQS compliance and epidemiologic applications.  
6 Ambient concentrations of SO<sub>2</sub> are then discussed on various spatial and temporal scales.  
7 Spatial variability is discussed in [Section 2.5.2](#), which is divided into two sections  
8 discussing large-scale variability (i.e., nationwide) and small-scale variability (i.e., urban  
9 areas). Temporal variability is then discussed in [Section 2.5.3](#), extending from multiyear  
10 trends to subhourly variations. The relationships between 5-minute hourly max and  
11 1-hour concentrations are described in [Section 2.5.4](#). Background SO<sub>2</sub> concentrations  
12 from natural sources are subsequently discussed in [Section 2.5.5](#).

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### 2.5.1 Sulfur Dioxide Metrics and Averaging Time

13 Different metrics are used to represent ambient SO<sub>2</sub> concentrations for epidemiologic  
14 analysis and NAAQS compliance. As discussed in [Section 2.5.4](#), hourly and 5-minute  
15 concentration data are routinely reported to U.S. EPA's AQS data repository by state,  
16 local, and tribal agencies. Metrics can be derived from these hourly and 5-minute data to  
17 represent concentration and exposure levels on different time scales. [Table 2-4](#) provides  
18 information on how different SO<sub>2</sub> metrics are derived. Daily metrics include the 24-h avg  
19 SO<sub>2</sub> concentration and the 1-h daily max SO<sub>2</sub> concentration. Hourly metrics include the  
20 5-minute hourly max concentration reported during a given hour and the 1-h avg  
21 concentration. Metrics derived using maximum concentration statistics  
22 (i.e., 1-h daily max or 5-minute hourly max) provide insight about peak ambient  
23 concentrations occurring over a given hour or day.

24 The following sections include national and urban statistics on daily and hourly metrics.  
25 When interpreting the statistics, it is important to consider the aggregation time when  
26 comparing the magnitude and range of ambient concentrations related to different  
27 metrics.

---

**Table 2-4 Summary of sulfur dioxide metrics and averaging times.**

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<b>Metric</b>	<b>Aggregation Time</b>	<b>Averaging Time Description</b>
24-h avg	Daily	Daily mean of 1-h avg SO <sub>2</sub> concentrations
1-h daily max	Daily	Maximum 1-h SO <sub>2</sub> concentration reported during the day
1-h avg	Hourly	Hourly mean SO <sub>2</sub> concentrations reported during the day
5-min hourly max	Hourly	Maximum 5-min SO <sub>2</sub> concentration reported during 1 h

avg = average; max = maximum; SO<sub>2</sub> = sulfur dioxide.

1 AQS SO<sub>2</sub> data used to compute national statistics meet the data quality and completeness  
2 criteria listed in [Table 2-5](#). Three additional criteria were applied for the 5-minute data to  
3 reduce the influence of outliers. The 5-minute data had to correspond to an hourly data  
4 concentration, the mean of the 5-minute data could be no more than 120% of the hourly  
5 mean, and the 5-minute hourly max concentration had to fall within 1 to 12 times the  
6 1-h avg concentration. Although negative values may be entered into the AQS database,  
7 they were excluded from this analysis. Concentrations below the monitor detection limit  
8 were included as they likely represent true low values. Based on these criteria, statistics  
9 were computed for data from a total of 380 sites across the U.S. for 5-minute hourly max  
10 SO<sub>2</sub> concentrations and for data from a total of 438 sites for the 1-h daily max, 24-h avg,  
11 and 1-h avg SO<sub>2</sub> metrics. 13% of sites did not have 5-minute data for comparison with  
12 1-hour data.

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## **2.5.2 Spatial Variability**

13 This section provides a brief overview of national- and urban-scale SO<sub>2</sub> spatial variability  
14 and discusses how variations in ambient SO<sub>2</sub> concentrations influence human exposure in  
15 different geographical regions.

**Table 2-5 Summary of sulfur dioxide data sets originating from the Air Quality System database.**

<b>AQS SO<sub>2</sub> data used to compute national statistics (to meet the data quality and completeness criteria)</b>	
Years	2013–2015
Months	January–December
Completeness criteria	75% of 5-min periods in an hour (where 5-min data are available)
	75% of hours in day
	75% of days in calendar quarter
	3 of 4 quarters of the year
Number of monitoring sites meeting completeness criteria	380 sites reporting 5-minute data (2013–2015)
	438 sites reporting 1-hour data (2013–2015)

### 2.5.2.1 Nationwide Spatial Variability

In the previous ISA for Sulfur Oxides ([U.S. EPA, 2008d](#)), 24-h avg, 1-h daily max, 1-h avg, and 5-minute hourly max SO<sub>2</sub> concentrations measured at AQS monitoring sites during 2003–2005 were reported. Nationwide statistics of 5-minute hourly max SO<sub>2</sub> data were limited in the previous assessment due to a scarcity of monitoring sites reporting such data. From 2003–2005 nationwide, central statistics (mean and median) of 1-h daily max and 24-h avg SO<sub>2</sub> concentrations were generally low (less than 15 ppb), while concentrations in the upper range of the distribution (e.g., 99th percentile) were substantially higher (23–116 ppb), particularly for 1-h daily max concentrations (99th percentile: 116 ppb). In addition, 1-h avg SO<sub>2</sub> concentrations exhibited low mean concentrations (4 ppb), with 99th percentile concentrations near 34 ppb. Relatively high concentrations were typically observed at sites near stationary anthropogenic sources (e.g., EGUs).

SO<sub>2</sub> summary data provide a snapshot of recent concentrations and, compared with those presented in the 2008 SO<sub>x</sub> ISA ([U.S. EPA, 2008d](#)), allow for ascertainment of trends. As shown by [Table 2-6](#), nationwide concentrations for 2013–2015 were slightly lower than concentrations reported in the 2008 SO<sub>x</sub> ISA. For all 24-h avg, 1-h daily max, 1-h avg, and 5-minute hourly max data pooled nationwide, mean statistics were below 6 ppb, median statistics (50th percentile) were 2 ppb or below, and SO<sub>2</sub> concentrations in the upper range of the distribution (99th percentile) covered a wide range of concentrations

1 but were never greater than the primary NAAQS level of 75 ppb. Across all metrics,  
2 large differences were observed between mean and 99th percentile concentrations,  
3 particularly for the SO<sub>2</sub> 1-h daily max and 5-minute hourly max data. Such large  
4 differences between mean and 99th percentile concentrations are consistent with the  
5 highly variable nature of SO<sub>2</sub>, which is characterized by periodic peak concentrations  
6 superimposed on a relatively low background concentration. Higher concentrations in the  
7 1-h daily max distribution compared with the 5-minute hourly max distribution were  
8 likely attributable to the omission of high 5-minute concentrations from the  
9 58 monitoring sites without 5-minute data.

10 The absolute highest 1-h daily max SO<sub>2</sub> concentration in 2013–2015 was 2,071 ppb. 99th  
11 percentile 1-h daily max concentrations over 200 ppb were reported at this site and other  
12 sites near active volcanoes in Hawaii [Table 2-6](#)), which are discussed further in  
13 [Section 2.5.5](#). Other reports of 99th percentile, 1-h daily max concentrations greater than  
14 200 ppb occurred at three monitoring sites near a copper smelter in Gila County, AZ, as  
15 mentioned in [Section 2.2.2](#). In addition, sites where the 99th percentile 1-h daily max  
16 concentration was greater than 75 ppb were located in North Dakota, Illinois, Iowa,  
17 Wisconsin, Arizona, Missouri, Indiana, Tennessee, Ohio, Kentucky, Louisiana, and  
18 Pennsylvania, often near coal-fired EGUs. As shown in the nationwide map in  
19 [Figure 2-11](#), the majority of monitoring sites across the U.S. report 99th percentile,  
20 1-h daily max concentrations below the primary NAAQS level of 75 ppb. The 99th  
21 percentile of 24-h avg concentrations, which are often used as exposure metrics in  
22 epidemiologic studies, followed a similar pattern, with most elevated values located in  
23 the industrial Midwest ([Figure 2-12](#)).

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### 2.5.2.2 Urban Spatial Variability

24 Air quality measurements from centrally located, urban monitoring sites are often used to  
25 represent community-scale exposure in epidemiologic analyses. However, central site  
26 exposure estimates may not fully capture variations in pollutant concentrations over  
27 urban scales. SO<sub>2</sub> spatial variability was characterized in six focus areas: Cleveland, OH;  
28 Pittsburgh, PA; New York City, NY; St. Louis, MO; Houston, TX; and Gila County, AZ.  
29 These focus areas were selected based on (1) their relevance to current health studies  
30 (i.e., areas with peer-reviewed, epidemiologic analysis), (2) the existence of four or more  
31 monitoring sites located within the area boundaries, and (3) the presence of several  
32 diverse SO<sub>2</sub> sources within a given focus area boundary.

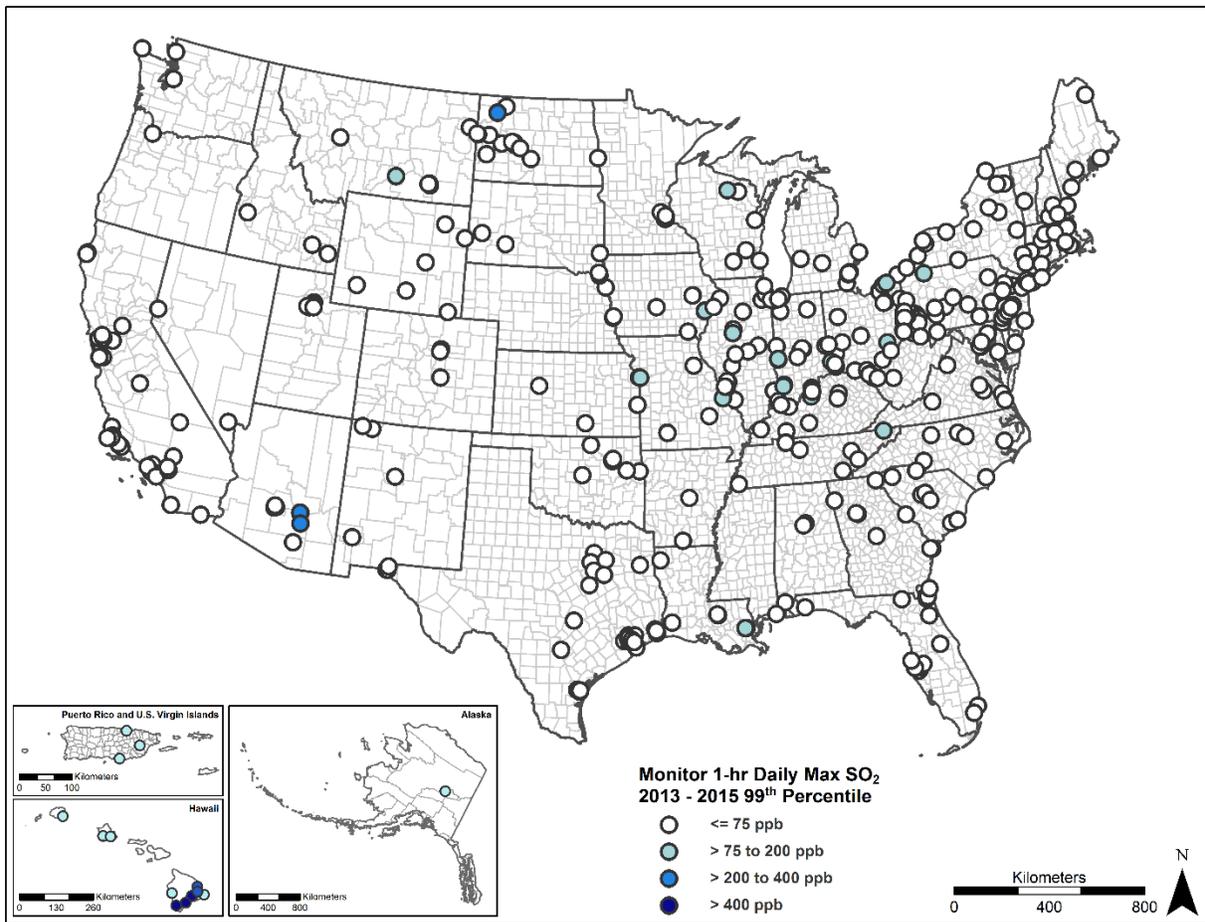
**Table 2-6 National statistics of sulfur dioxide concentrations (parts per billion) from Air Quality System monitoring sites, 2013–2015.<sup>a</sup>**

Year	N of Obs	Mean	5%	10%	25%	50%	75%	90%	95%	98%	99%	Max	AQS Max ID <sup>b</sup>
<b>5-min hourly max</b>													
2013	3,105,078	2.3	0.0	0.0	0.2	1.0	2.0	4.2	7.0	15.0	26.0	1,441.4	160050004
2014	3,047,302	2.2	0.0	0.0	0.2	1.0	2.0	4.0	7.0	15.0	25.4	4,208.0	160050004
2015	2,997,344	1.8	0.0	0.0	0.2	0.8	1.6	3.0	5.4	12.0	20.3	1,678.0	160050004
2013–2015	9,149,724	2.1	0.0	0.0	0.2	1.0	2.0	4.0	6.7	14.0	24.0	4,208.0	160050004
<b>1-h avg</b>													
2013	3,105,078	1.7	0.0	0.0	0.0	0.8	1.8	3.2	5.0	9.3	15.8	2,071.0	150010007
2014	3,047,302	1.6	0.0	0.0	0.0	0.8	1.5	3.0	5.0	9.6	16.0	1,830.0	150010007
2015	2,997,344	1.3	0.0	0.0	0.0	0.6	1.1	2.5	4.0	8.0	13.3	1,779.0	150010007
2013–2015	9,149,724	1.5	0.0	0.0	0.0	0.7	1.4	3.0	5.0	9.0	15.0	2,071.0	150010007
<b>1-h daily max</b>													
2013	133,925	5.6	0.0	0.0	0.9	2.0	4.5	10.5	19.0	37.3	62.5	2,071.0	150010007
2014	131,553	5.7	0.0	0.0	0.8	2.0	4.4	11.0	19.8	41.0	68.0	1,830.0	150010007
2015	128,991	4.7	0.0	0.0	0.6	1.4	3.3	8.2	15.9	34.4	60.0	1,779.0	150010007
2013–2015	394,469	5.4	0.0	0.0	0.8	1.8	4.0	10.0	18.0	37.7	64.0	2,071.0	150010007
<b>24-h avg</b>													
2013	133,925	1.6	0.0	0.0	0.3	0.9	1.8	3.5	5.2	8.6	13.1	366.5	150010007
2014	131,553	1.6	0.0	0.0	0.3	0.8	1.7	3.3	5.0	8.6	13.1	317.2	150010007
2015	128,991	1.3	0.0	0.0	0.2	0.7	1.4	2.7	4.0	7.4	12.1	393.0	150010007
2013–2015	394,469	1.5	0.0	0.0	0.2	0.8	1.7	3.2	4.8	8.3	12.8	393.0	150010007

AQS = Air Quality System; avg = average; ID = identification; mean = arithmetic average; max = maximum; N = population number; Obs = observations.

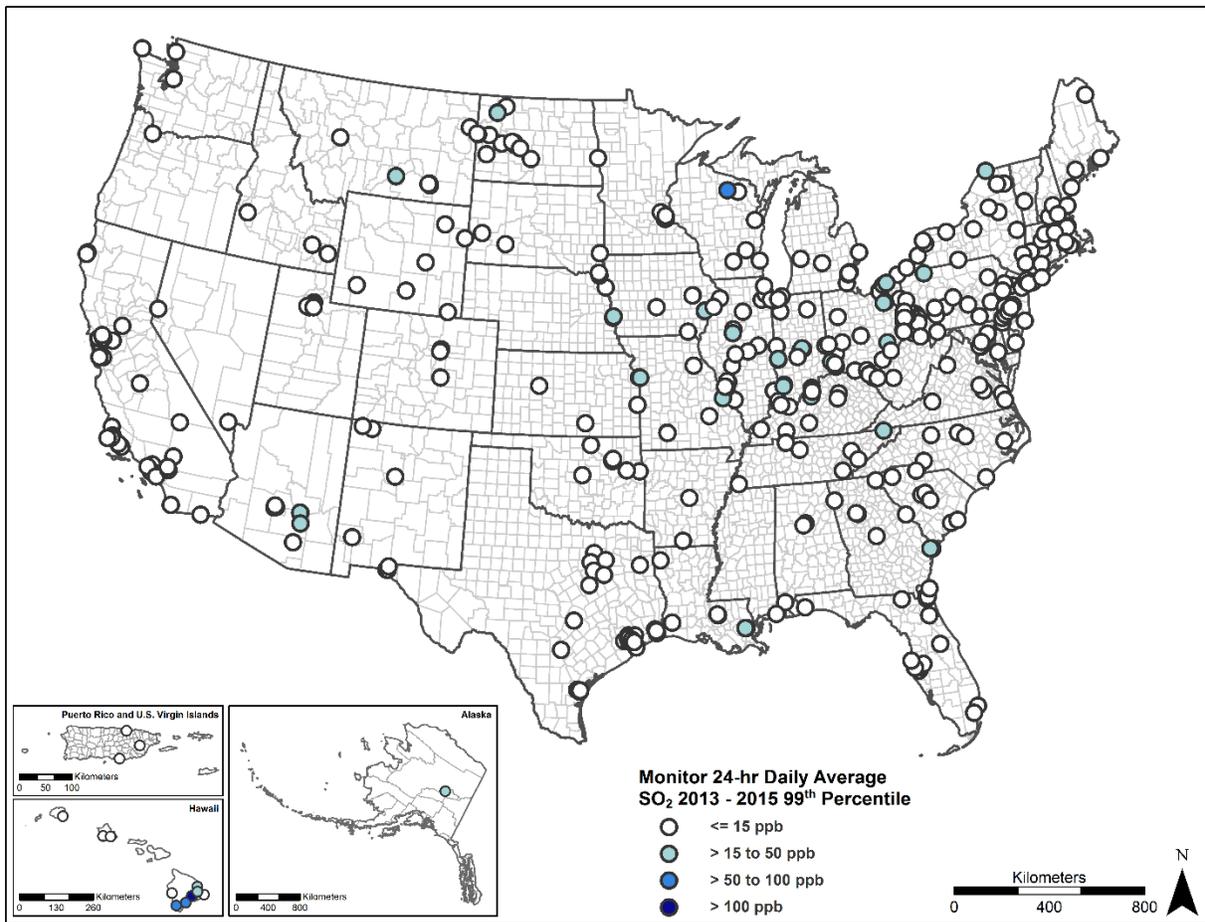
<sup>a</sup>Data below 0 ppb have been trimmed from the data set.

<sup>b</sup>AQS site ID number reporting the highest 3-yr concentration across the U.S.



Max = maximum; SO<sub>2</sub> = sulfur dioxide.

**Figure 2-11** Map of 99th percentile of 1-h daily max sulfur dioxide concentration reported at Air Quality System monitoring sites, 2013–2015.

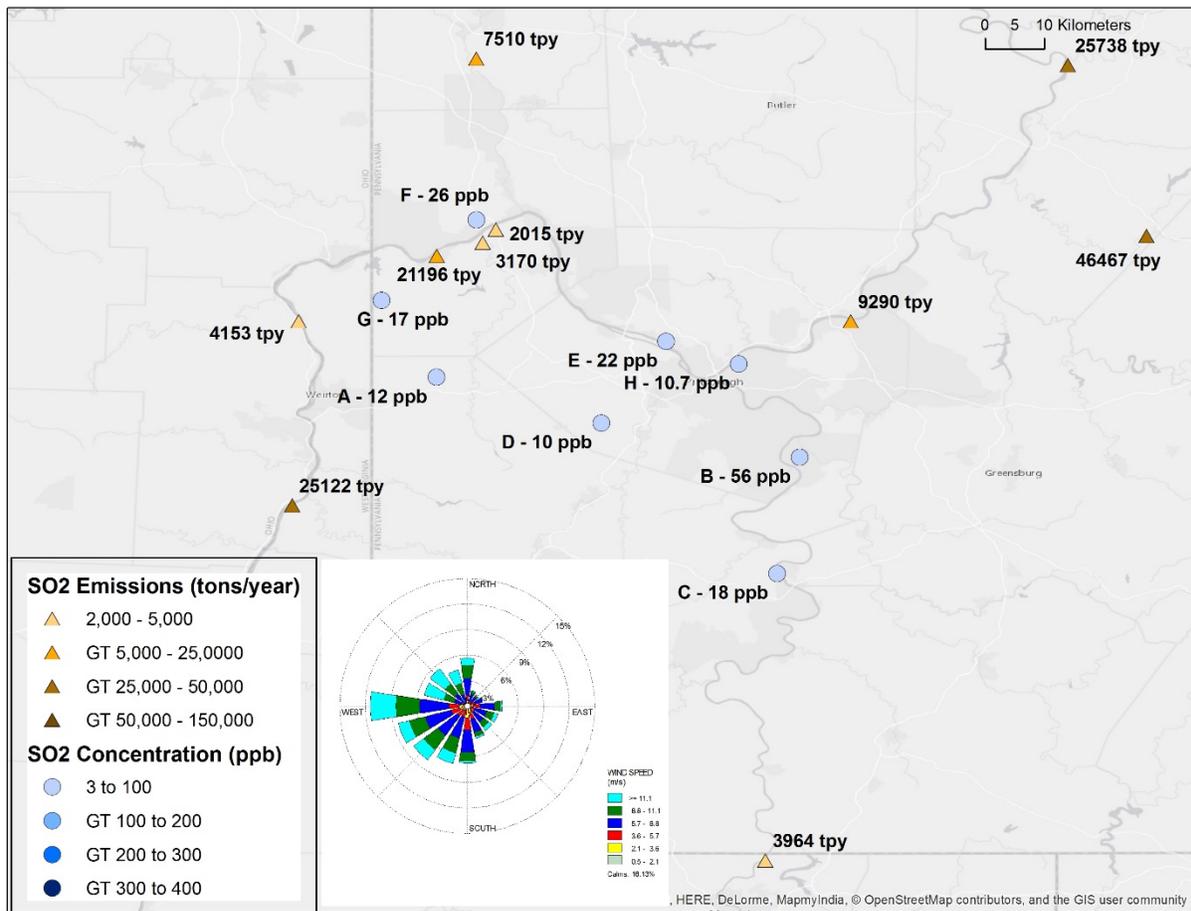


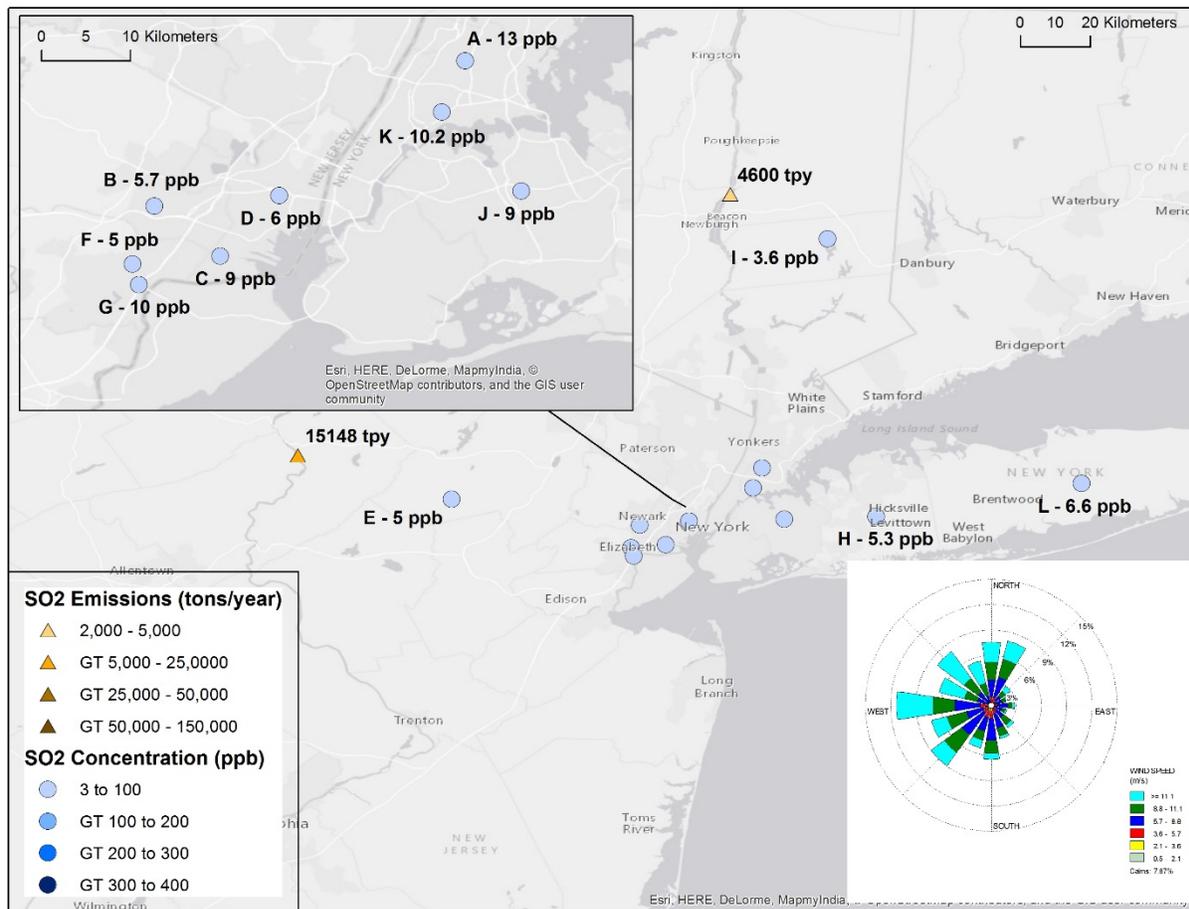
Note: The 24-h avg concentration is a metric often used in epidemiologic studies.  
SO<sub>2</sub> = sulfur dioxide.

**Figure 2-12 Map of 99th percentile of 24-h avg sulfur dioxide concentration reported at Air Quality System monitoring sites, 2013–2015.**

1 Maps of individual focus areas indicating 99th percentile 5-minute hourly max  
 2 concentrations at monitoring sites and emissions from large point sources and their  
 3 locations are presented in [Figure 2-13](#) through [Figure 2-18](#). As shown by the maps, up to  
 4 12 SO<sub>2</sub> monitoring sites are located in individual focus areas. Monitoring sites in each  
 5 focus area are located at various distances from SO<sub>2</sub> sources. Due to the relatively short  
 6 atmospheric lifetime of SO<sub>2</sub>, monitoring sites within close proximity of large point  
 7 sources (e.g., electric generating units, industrial sources, copper smelting facilities,  
 8 shipping ports) are expected to detect higher SO<sub>2</sub> concentrations than those further  
 9 downwind. However, other variables, particularly stack height and wind speed and  
 10 direction, influence concentrations observed near sources. For example, Sites C and E in

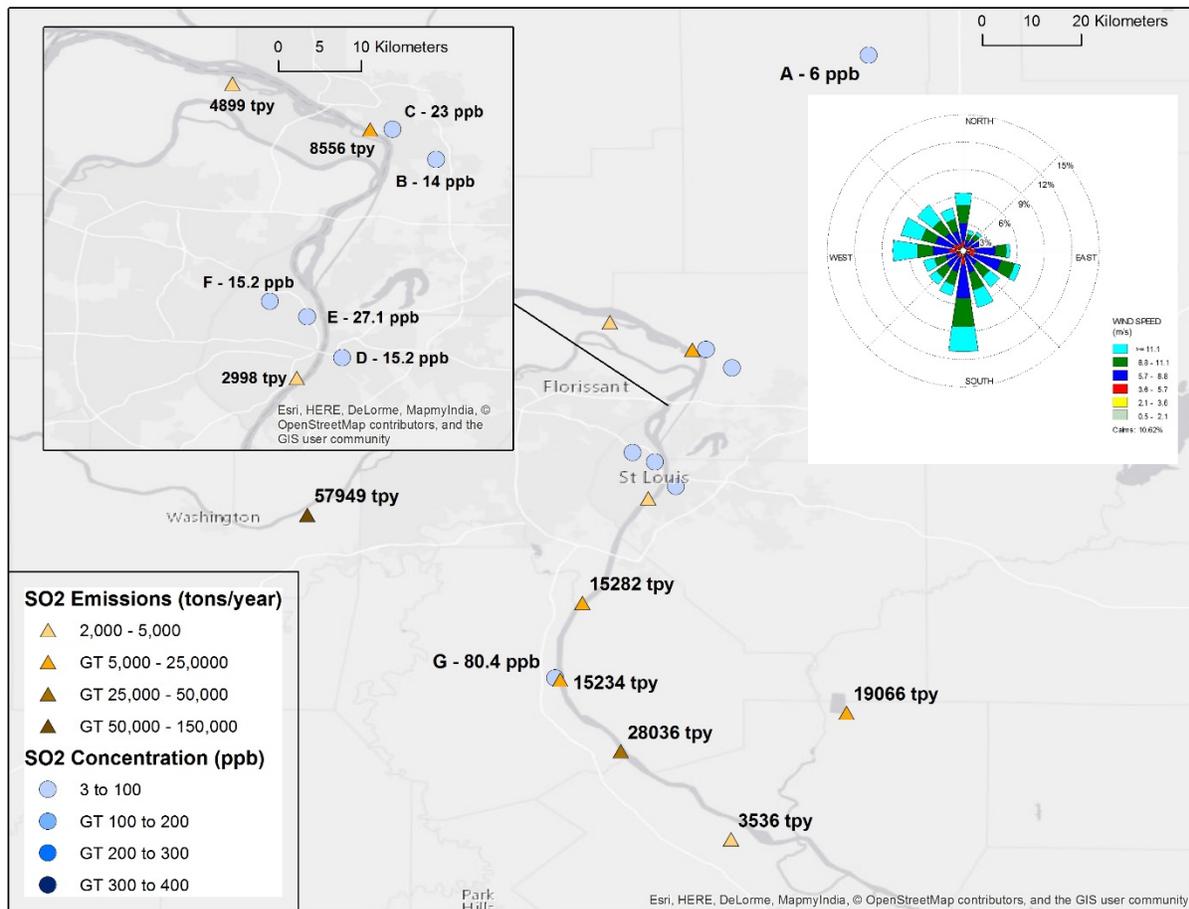






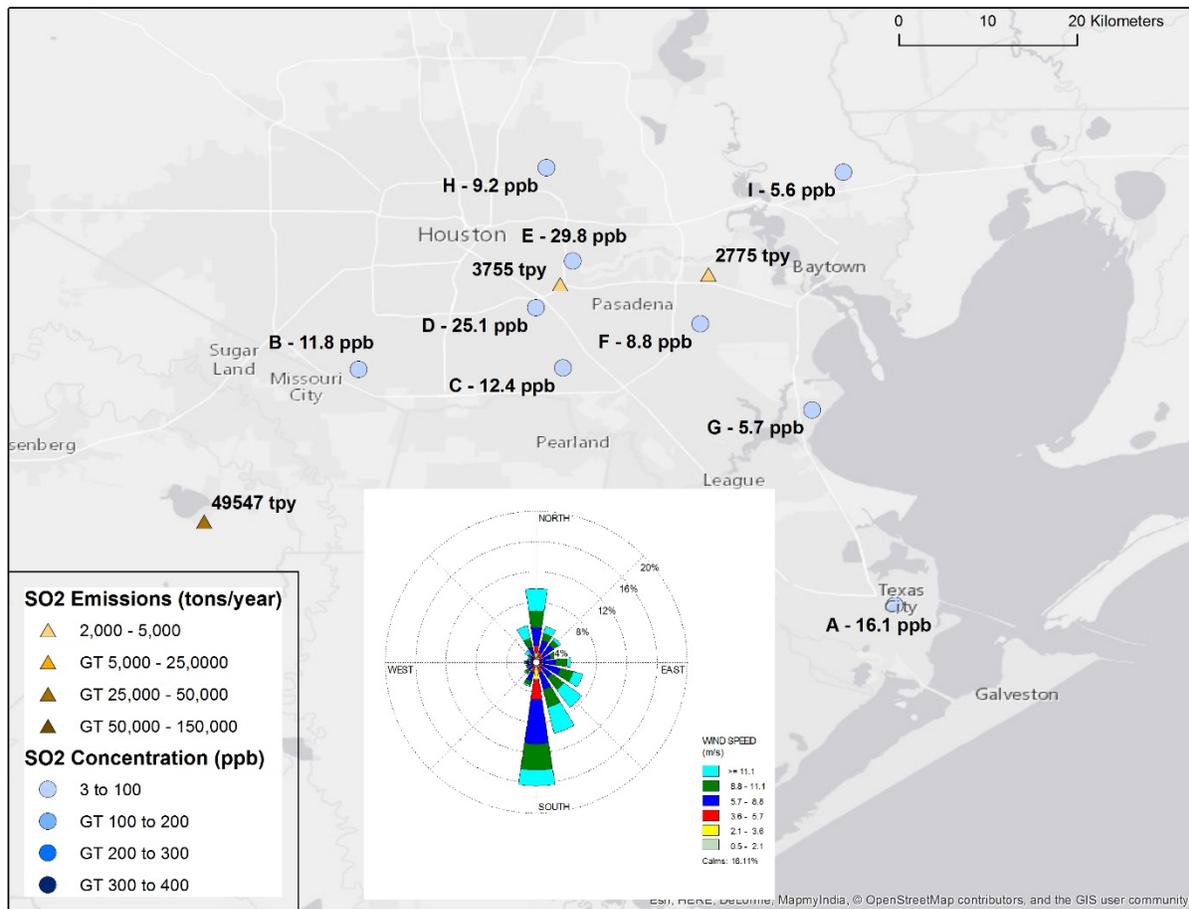
Note: Blue circles denote monitoring sites included in the U.S. Air Quality Monitoring System. Yellow triangles denote sources emitting 2,000 tons/yr or more according to the 2011 U.S. National Emissions Inventory. inset, upper right, displays a wind rose of average wind speed and direction for data acquired at Newark International Airport over the 3-yr period 2013-2015.

**Figure 2-15 Map of the New York City, NY focus area showing emissions from large sources and the 99th percentile 5-minute hourly max concentration at ambient monitors during 2013-2015.**



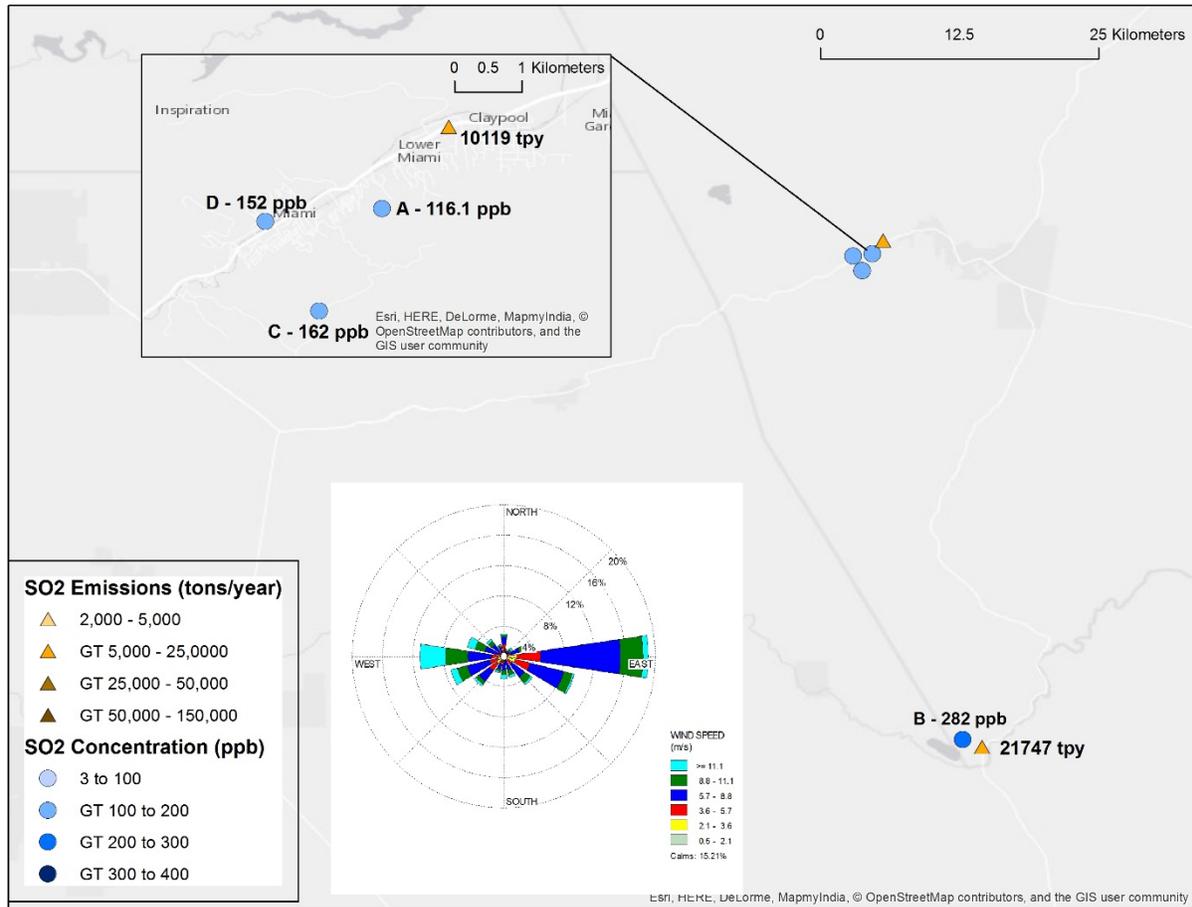
Note: Blue circles denote monitoring sites included in the U.S. Air Quality Monitoring System. Yellow triangles denote sources emitting 2,000 tons/yr or more according to the 2011 U.S. National Emissions Inventory. The inset, upper left, displays a wind rose of average wind speed and direction for data acquired at Lambert-St. Louis International Airport over the 3-yr period 2013-2015.

**Figure 2-16 Map of the St. Louis, MO-IL focus area showing emissions from large sources and the 99th percentile 5-minute hourly max concentration at ambient monitors during 2013-2015.**



Note: Blue circles denote monitoring sites included in the U.S. Air Quality Monitoring System. Yellow triangles denote sources emitting 2,000 tons/yr or more according to the 2011 U.S. National Emissions Inventory. The inset, upper left, displays a wind rose of average wind speed and direction for data acquired at George Bush Intercontinental Airport over the 3-yr period 2013-2015.

**Figure 2-17 Map of the Houston, TX focus area showing emissions from large sources and the 99th percentile 5-minute hourly max concentration at ambient monitors during 2013-2015.**



Note: Blue circles denote monitoring sites included in the U.S. Air Quality Monitoring System. Yellow triangles denote sources emitting 2,000 tons/yr or more according to the 2011 U.S. National Emissions Inventory. The inset, lower center, displays a wind rose of average wind speed and direction for data acquired at the Phoenix Sky Harbor Intercontinental Airport over the 3-yr period 2013–2015.

**Figure 2-18 Map of the Gila County, AZ focus area showing emissions from large sources and the 99th percentile 5-minute hourly max concentration at ambient monitors during 2013–2015.**

1 [Table 2-7](#) provides the distribution of 1-h daily max SO<sub>2</sub> concentrations and monitor type  
 2 (standard vs. trace level monitor) reported at individual AQS sites in the six focus areas.  
 3 Concentrations reported at these sites were similar to nationwide SO<sub>2</sub> concentrations  
 4 discussed earlier in this section ([Section 2.5.2.1](#)). For all but one individual monitoring  
 5 site, median concentrations were below 15 ppb. The one exception was the monitoring  
 6 site in the Gila County, AZ focus area, for which the median concentration was 39 ppb.  
 7 This particular monitoring site (Site B) is located within 1 km of a copper smelting plant

1  
2

with markedly high annual SO<sub>2</sub> emissions [greater than 20,000 tpy SO<sub>2</sub> ([U.S. EPA, 2013a](#))].

**Table 2-7 1-h daily max sulfur dioxide concentration distribution by Air Quality System monitoring site in six focus areas, 2013–2015.<sup>a</sup>**

Site Label	AQS Monitoring Site ID	N of Obs	Mean	Min	10%	25%	50%	75%	90%	99%	Max	Monitor Type
<b>Cleveland-Elyria-Mentor, OH</b>												
A	390350065	709	6.4	0.0	0.0	1.0	3.0	7.0	13.2	55.9	125.0	Standard
B	390350060	887	11.5	0.0	0.0	2.0	6.0	16.0	32.0	62.1	92.0	Standard
C	390850003	758	7.6	0.0	2.0	3.0	6.0	10.0	15.0	37.4	95.0	Standard
D	390350038	786	14.0	0.0	1.0	4.0	10.0	20.0	32.5	61.3	105.0	Standard
E	390850007	901	11.2	0.0	2.0	3.0	6.0	11.0	22.0	117.0	201.0	Standard
F	390350045	630	3.9	0.0	0.0	0.0	2.0	5.0	9.0	30.0	51.0	Standard
<b>Pittsburgh, PA</b>												
A	421255001	1,020	3.6	0.0	0.0	0.0	3.0	5.0	9.0	17.0	53.0	Standard
B	420030064	1,076	16.6	0.0	2.0	4.0	11.0	21.0	39.5	90.8	244.0	Standard
C	421250005	1,044	6.1	0.0	2.0	3.0	4.0	7.0	11.0	33.6	61.0	Standard
D	420030067	1,069	3.4	0.0	0.0	1.0	2.0	4.0	7.0	19.0	55.0	Standard
E	420030002	1,090	5.9	0.0	1.0	2.0	4.0	7.0	12.0	41.0	75.0	Standard
F	420070005	1,014	7.0	0.0	0.0	1.0	4.0	10.0	17.0	40.0	80.0	Standard
G	420070002	1,028	5.6	0.0	1.0	2.0	4.0	8.0	12.0	24.7	45.0	Standard
H	420030008	706	4.0	0.0	0.9	1.7	2.8	4.5	7.7	20.2	100.3	Trace
<b>New York-Northern New Jersey-Long Island, NY-NJ-PA</b>												
A	360050133	1,089	4.0	0.2	0.9	1.5	2.8	5.3	8.9	16.5	26.5	Standard
B	340130003	1,089	1.8	0.0	0.3	0.6	1.3	2.4	3.9	7.8	13.0	Trace
C	340170006	725	1.4	0.0	0.0	0.0	1.0	2.0	4.0	9.0	11.0	Standard
D	340171002	1,090	1.4	0.0	0.0	0.0	1.0	2.0	4.0	8.0	11.0	Standard
E	340273001	1,065	1.4	0.0	0.0	0.0	1.0	2.0	3.0	9.0	20.0	Standard

**Table 2-7 (Continued): 1 h daily max sulfur dioxide concentration distribution by Air Quality System monitoring site in six focus areas, 2013–2015.<sup>a</sup>**

Site Label	AQS Monitoring Site ID	N of Obs	Mean	Min	10%	25%	50%	75%	90%	99%	Max	Monitor Type
F	340390003	1,089	1.3	0.0	0.0	0.0	1.0	2.0	3.0	6.0	12.0	Standard
G	340390004	1,081	2.3	0.0	0.0	1.0	1.0	3.0	5.0	13.2	109.0	Standard
H	360590005	1,001	2.0	0.2	0.8	1.1	1.5	2.3	3.6	8.3	14.6	Standard
I	360790005	1,083	1.2	0.1	0.4	0.6	0.8	1.3	2.2	5.8	10.3	Standard
J	360810124	1,086	2.5	0.0	0.5	0.9	1.7	3.3	5.4	11.0	18.5	Trace
K	360050110	1,075	3.1	0.0	0.8	1.2	2.2	4.1	6.8	14.3	32.1	Standard
L	361030009	898	1.7	0.0	0.2	0.4	1.0	2.3	4.1	8.7	15.8	Standard
<b>St. Louis, MO-IL</b>												
A	171170002	646	2.2	0.0	0.8	1.0	2.0	3.0	4.0	8.5	21.0	Standard
B	171191010	1,023	4.1	0.0	0.9	1.3	3.0	5.0	9.0	18.0	40.0	Standard
C	171193007	1,041	5.6	0.0	1.0	2.0	4.0	7.0	11.6	24.4	42.0	Standard
D	171630010	1,018	4.7	0.0	1.0	2.0	3.6	6.0	10.0	20.8	30.0	Standard
E	295100085	921	7.2	0.0	1.3	2.4	4.2	9.1	16.5	40.2	51.4	Trace
F	295100086	1,077	4.5	0.5	1.2	1.8	3.3	5.6	9.5	19.6	31.8	Standard
G	290990027	1,089	11.6	0.3	1.1	2.2	4.2	8.8	36.3	94.5	252.7	Standard
<b>Houston-Sugar Land-Baytown, TX</b>												
A	481670005	736	3.6	0.3	1.0	1.5	2.4	3.8	6.8	26.5	50.6	Standard
B	482010051	214	3.1	0.0	0.7	1.0	1.9	3.4	6.1	22.2	44.4	Standard
C	482010062	160	3.7	0.4	1.0	1.7	2.4	4.4	7.9	18.0	19.3	Standard
D	482010416	313	5.5	0.3	0.9	1.6	3.4	6.9	12.1	33.6	54.0	Standard
E	482011035	71	4.9	0.3	0.5	1.5	2.4	5.4	13.1	25.9	29.8	Standard
F	482011039	590	2.2	0.0	0.2	0.7	1.6	2.9	5.2	11.0	16.0	Trace
G	482011050	885	1.9	0.2	0.5	0.7	1.4	2.4	3.8	9.0	16.4	Standard
H	482010046	15	3.5	1.8	1.9	2.3	2.8	3.2	4.7	12.0	13.1	Standard
I	482011017	415	1.5	0.0	0.4	0.6	1.0	1.9	3.3	8.3	10.6	Standard

**Table 2-7 (Continued): 1 h daily max sulfur dioxide concentration distribution by Air Quality System monitoring site in six focus areas, 2013–2015.<sup>a</sup>**

Site Label	AQS Monitoring Site ID	N of Obs	Mean	Min	10%	25%	50%	75%	90%	99%	Max	Monitor Type
<b>Gila County, AZ</b>												
A	40070009	1,080	24.9	0.0	2.0	3.0	12.0	34.3	64.0	153.2	259.0	Standard
B	40071001	889	50.8	0.0	1.0	13.0	39.0	71.0	114.2	247.2	368.0	Trace
C	40070011	739	28.5	0.0	1.0	2.0	9.0	36.0	84.0	204.9	380.0	Trace
D	40070012	630	31.3	0.0	1.0	2.0	8.0	39.8	95.0	230.7	324.0	Trace

AQS = Air Quality System; ID = identification; max = maximum; mean = arithmetic average; min = minimum.

<sup>a</sup>Monitor values below 0 ppb have been trimmed from the data set.

1 More substantial site-to-site differences were observed in the 99th percentile of SO<sub>2</sub>  
2 concentrations. Across these monitoring sites, 99th percentile concentrations ranged from  
3 5.8 to 247.2 ppb, with the majority of sites exhibiting 99th percentile concentrations at or  
4 below 37.5 ppb. Relatively high 99th percentile concentrations were reported at  
5 monitoring sites within 5 km of a large SO<sub>2</sub> point source, particularly in Gila County, AZ.  
6 Relatively high 99th percentile concentrations were also observed in the Cleveland, OH  
7 and Pittsburgh, PA focus areas. These data were in agreement with previous studies,  
8 which generally observed higher urban SO<sub>2</sub> concentrations near local  
9 industrial/combustion sources related to oil-burning units, diesel truck traffic, and EGUs  
10 ([Clougherty et al., 2013](#); [Wheeler et al., 2008](#)).

11 Over the past decade, the number of AQS monitoring sites reporting 5-minute SO<sub>2</sub>  
12 concentrations has substantially increased. At the time of the 2008 SO<sub>x</sub> ISA ([U.S. EPA,](#)  
13 [2008d](#)), a total of 98 monitoring sites periodically reported 5-minute hourly max  
14 concentrations. To date, approximately 380 sites report 5-minute data, including urban  
15 sites within focus areas, sites near city centers, and sites near SO<sub>2</sub> sources (see  
16 [Figure 2-10](#) in [Section 2.4.3](#)).

17 Similar analyses of 5-minute hourly max concentrations were performed on more recent  
18 data reported at individual monitoring sites in the six focus areas. [Table 2-8](#) shows the  
19 range in 5-minute hourly max SO<sub>2</sub> concentrations reported at individual monitors, within  
20 the six focus areas in the 2013–2015 time frame. Median 5-minute hourly max  
21 concentrations are below 5 ppb, while maximum concentrations range from 15 to  
22 1,241 ppb.

**Table 2-8 5-minute sulfur dioxide concentrations by Air Quality System monitoring sites in select focus areas, 2013–2015.<sup>a</sup>**

Site Label	AQS Monitoring Site ID	N of Obs	Mean	Min	10%	25%	50%	75%	90%	99%	Max	Monitor Type
<b>Cleveland-Elyria-Mentor, OH</b>												
A	390350065	16,201	3.7	0.0	0.0	0.0	2.0	5.0	8.0	27.0	397.0	Standard
B	390350060	18,585	4.9	0.0	0.0	0.0	1.0	4.0	13.0	53.0	159.0	Standard
C	390850003	15,966	3.6	0.0	0.0	1.0	2.0	5.0	8.0	26.0	241.0	Standard
D	390350038	17,321	6.0	0.0	0.0	0.0	2.0	7.0	16.0	49.0	180.0	Standard
E	390850007	19,297	5.6	0.0	0.0	1.0	3.0	5.0	9.0	69.0	428.0	Standard
F	390350045	13,720	1.5	0.0	0.0	0.0	0.0	2.0	4.0	15.0	131.0	Standard
<b>Pittsburgh, PA</b>												
A	421255001	24,367	1.5	0.0	0.0	0.0	0.0	2.0	4.0	12.0	73.0	Standard
B	420030064	25,602	6.1	0.0	0.0	1.0	2.0	7.0	16.0	56.0	493.0	Standard
C	421250005	24,930	3.3	0.0	1.0	1.0	2.0	4.0	6.0	18.0	137.0	Standard
D	420030067	25,480	1.4	0.0	0.0	0.0	1.0	2.0	4.0	10.0	89.0	Standard
E	420030002	26,001	2.4	0.0	0.0	0.0	1.0	3.0	6.0	22.0	112.0	Standard
F	420070005	24,264	3.1	0.0	0.0	0.0	1.0	3.0	8.0	26.0	155.0	Standard
G	420070002	24,572	2.2	0.0	0.0	0.0	1.0	3.0	6.0	17.0	64.0	Standard
H	420030008	16,095	1.7	0.0	0.1	0.4	1.0	2.2	3.8	10.7	158.3	Trace
<b>New York-Northern New Jersey-Long Island, NY-NJ-PA</b>												
A	360050133	25,699	2.5	0.0	0.4	0.8	1.5	3.2	5.8	13.0	32.3	Standard
B	340130003	25,928	0.9	0.0	0.1	0.2	0.5	1.2	2.3	5.7	23.1	Trace
C	340170006	17,200	0.8	0.0	0.0	0.0	0.0	1.0	3.0	9.0	29.0	Standard
D	340171002	25,826	1.0	0.0	0.0	0.0	1.0	1.0	2.0	6.0	34.0	Standard
E	340273001	24,451	1.2	0.0	0.0	1.0	1.0	1.0	2.0	5.0	58.0	Standard
F	340390003	25,887	1.2	0.0	0.0	0.0	1.0	2.0	3.0	5.0	47.0	Standard
G	340390004	25,748	1.4	0.0	0.0	0.0	1.0	2.0	3.0	10.0	317.0	Standard
H	360590005	23,683	1.4	0.1	0.6	0.8	1.1	1.6	2.3	5.3	21.5	Standard

**Table 2-8 (Continued): 5-minute sulfur dioxide concentrations by Air Quality System monitoring sites in select focus areas, 2013–2015.<sup>a</sup>**

Site Label	AQS Monitoring Site ID	N of Obs	Mean	Min	10%	25%	50%	75%	90%	99%	Max	Monitor Type
I	360790005	25,630	0.9	0.0	0.4	0.5	0.7	1.0	1.4	3.6	16.1	Standard
J	360810124	25,557	1.5	0.0	0.1	0.3	0.8	1.9	3.8	9.0	26.8	Trace
K	360050110	25,333	2.1	0.0	0.4	0.8	1.5	2.7	4.5	10.2	46.6	Standard
L	361030009	22,128	1.4	0.0	0.3	0.5	1.0	1.8	3.0	6.6	30.5	Standard
<b>St. Louis, MO-IL</b>												
A	171170002	14,260	1.5	0.0	0.5	1.0	1.2	2.0	2.7	6.0	56.0	Standard
B	171191010	22,801	1.7	0.0	0.0	0.0	0.9	2.0	4.0	15.0	240.0	Standard
C	171193007	23,684	2.7	0.0	0.0	0.8	1.3	3.0	6.0	24.0	94.0	Standard
D	171630010	22,691	1.9	0.0	0.0	0.0	1.0	2.0	4.2	15.0	87.4	Standard
E	295100085	20,653	3.3	0.0	0.6	1.2	2.0	3.3	6.3	26.5	93.7	Trace
F	295100086	25,720	2.4	0.2	0.8	1.1	1.5	2.5	4.5	15.2	53.0	Standard
G	290990027	26,002	5.7	0.2	0.5	0.9	2.1	3.6	8.0	80.4	657.1	Standard
<b>Houston-Sugar Land-Baytown, TX</b>												
A	481670005	16,307	1.9	0.0	0.4	0.6	1.1	2.1	3.6	15.8	84.9	Standard
B	482010051	4,523	1.1	0.0	0.2	0.3	0.6	1.2	2.3	10.3	65.9	Standard
C	482010062	3,399	1.6	0.0	0.3	0.5	1.0	1.8	3.1	12.5	33.4	Standard
D	482010416	6,982	2.4	0.0	0.3	0.6	1.0	2.3	5.2	24.1	90.9	Standard
E	482011035	1,482	2.4	0.0	0.3	0.5	1.0	2.3	4.4	26.3	75.8	Standard
F	482011039	12,547	0.9	0.0	0.0	0.0	0.5	1.1	2.2	6.8	25.7	Trace
G	482011050	19,894	1.0	0.0	0.3	0.4	0.6	1.1	2.1	5.7	21.3	Standard
H	482010046	313	1.8	0.0	0.3	0.5	1.5	2.6	3.3	7.2	15.2	Standard
I	482011017	8,728	0.7	0.0	0.0	0.2	0.4	0.8	1.5	5.0	25.3	Standard

**Table 2-8 (Continued): 5-minute sulfur dioxide concentrations by Air Quality System monitoring sites in select focus areas, 2013–2015.<sup>a</sup>**

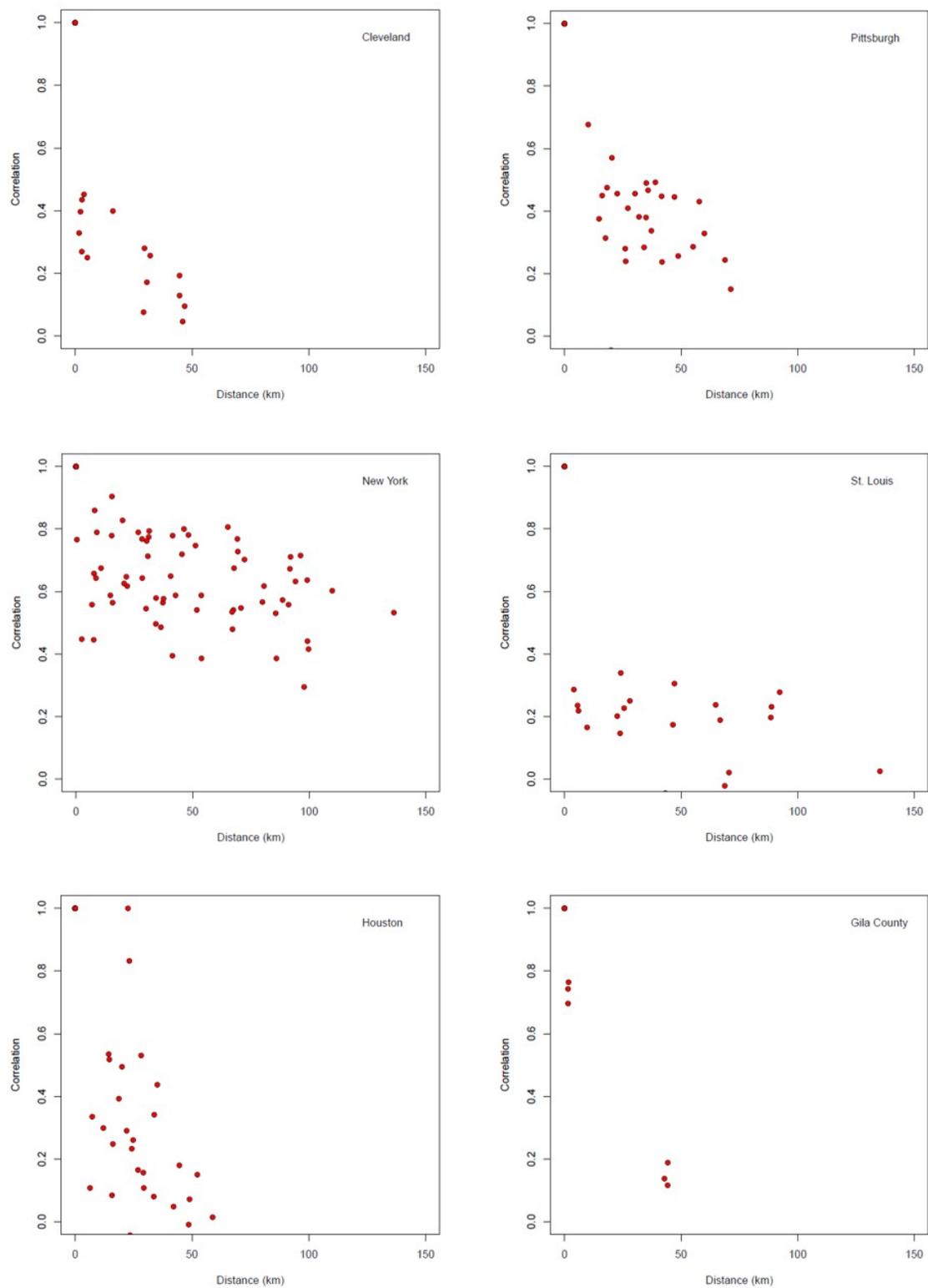
Site Label	AQS Monitoring Site ID	N of Obs	Mean	Min	10%	25%	50%	75%	90%	99%	Max	Monitor Type
<b>Gila County, AZ</b>												
A	40070009	25,732	9.2	0.0	1.0	1.0	3.1	4.5	21.6	115.5	461.0	Standard
B	40071001	20,222	19.6	0.0	0.0	1.0	2.0	10.6	55.0	252.2	1,241.2	Trace
C	40070011	16,630	9.1	0.0	0.0	0.0	1.0	3.0	22.0	142.1	694.0	Trace
D	40070012	14,156	7.6	0.0	0.0	1.0	1.0	2.0	11.0	148.0	993.0	Trace

AQS = Air Quality System; ID = identification; max = maximum; mean = arithmetic average; min = minimum.

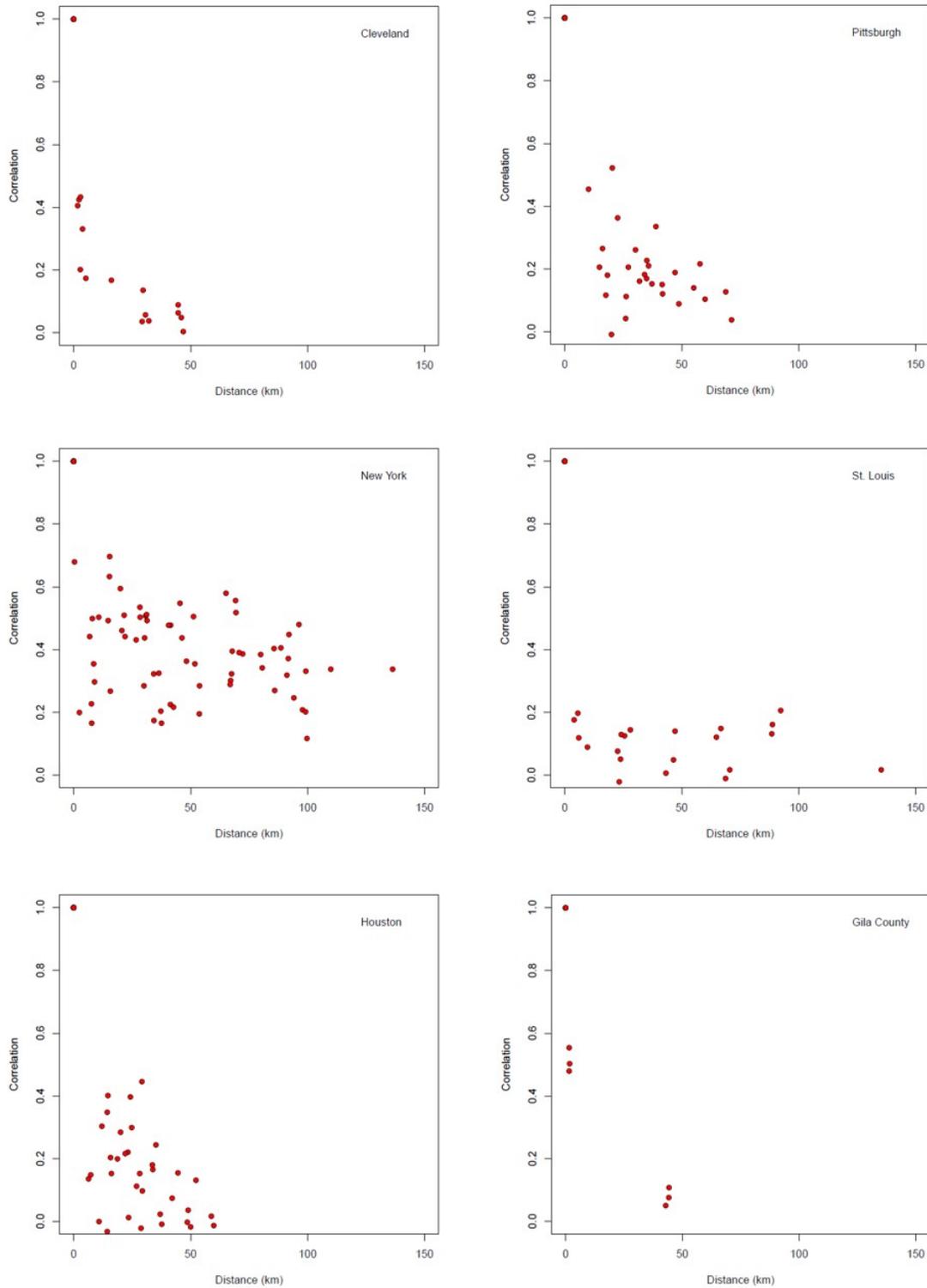
<sup>a</sup>Monitor values below 0 ppb have been trimmed from the data set.

1  
2 To evaluate the extent of SO<sub>2</sub> spatial variability over urban geographical scales,  
3 concentration correlations between monitoring site pairs were calculated in each of the  
4 six focus areas. To estimate the degree to which concentrations at two different  
5 monitoring sites followed similar temporal trends, pairwise comparisons were evaluated  
6 using Pearson correlations. Across the six focus areas, Pearson correlations ranged from 0  
7 to 1.0 for 24-h avg data. Correlations close to 1 represent strong correspondence over  
8 time between pairwise monitoring site concentrations, while values close to 0 represent  
9 poor correspondence between concentrations. [Figure 2-19](#) and [Figure 2-20](#) respectively  
10 show scatterplots of pairwise correlations of 24-h avg and 5-minute hourly max SO<sub>2</sub>  
11 concentrations versus distance between monitoring site pairs. 24-h avg concentrations are  
12 presented due to their frequent use in epidemiologic studies, while 5-minute hourly max  
13 concentrations are a metric of interest for short-duration exposures. Given the  
14 meandering nature of SO<sub>2</sub> plumes and potential for plume touchdown several kilometers  
15 from the stack ([Turner, 1970](#)), low correlation among monitoring sites would be expected  
16 in most cases for the 5-minute hourly max data.

17 Inter-site pairwise comparisons in [Figure 2-19](#) suggest high spatial variability of the  
18 24-h avg SO<sub>2</sub> concentration time series. In every focus area except for New York  
19 (discussed below), low to moderate inter-site pairwise correlations of 24-h avg SO<sub>2</sub>  
20 concentration data were observed, with the majority of Pearson correlations below 0.6.  
21 Inter-site pairwise correlations tended to decrease with distance. Even within relatively  
22 short distances (up to 15 km), most inter-site pairwise correlations were low, reflecting  
23 the variable nature of ambient SO<sub>2</sub> across urban spatial scales, possibly due to short  
24 atmospheric residence time, variable meteorology, and the episodic nature of the  
25 emissions as discussed in [Section 2.2](#).



**Figure 2-19** Pairwise correlations of 24-h avg sulfur dioxide versus distance between monitoring site pairs in six focus areas, 2013–2015.



**Figure 2-20** Pairwise correlations of 5-minute hourly max data versus distance between monitoring sites in six focus areas, 2013–2015.

1 In comparison, 5-minute hourly max SO<sub>2</sub> concentrations had somewhat higher spatial  
2 variability across urban spatial scales ([Figure 2-20](#)). In most cases, inter-site pairwise  
3 correlations of 5-minute hourly max concentrations are lower (less than 0.4) and decline  
4 more dramatically with distance than inter-site pairwise correlations of 24-h avg  
5 concentrations. Greater spatial variability in 5-minute hourly max concentrations may be  
6 explained by the fact that maximum metrics tend to capture peak SO<sub>2</sub> events that are  
7 likely more variable across urban areas than 24-h avg concentrations.

8 While spatial variability is evident to some degree in all urban areas, the extent of this  
9 variability is location dependent. For example, pairwise correlations in Cleveland, OH  
10 and St Louis, MO indicate strong SO<sub>2</sub> spatial heterogeneity. In comparison, pairwise  
11 correlations in New York City, NY are generally high and uniform across more than  
12 100 km despite sometimes large distances between monitoring sites. Stronger pairwise  
13 correlations in New York City, NY may be related to similar temporal source patterns,  
14 given that the focus area's smaller power plants (<2,000 tpy SO<sub>2</sub> emissions), including  
15 gas-coal cogeneration facilities in Brooklyn, NY and Sayreville, NJ; an oil-burning  
16 facility in Queens, NY; a coal-fired power plant in Jersey City, NJ; and numerous homes  
17 using oil-burning heat likely have similar periods of high operation across the  
18 metropolitan area. This is analogous to observations about similarities in traffic patterns  
19 across large distances that promote higher correlation despite distance between the  
20 sources ([Sarnat et al., 2010](#)). Conversely, high spatial variations in Cleveland, OH and St.  
21 Louis, MO may be explained by the presence of a limited number of sources (>2,000 tpy)  
22 located at unevenly distributed sites across the metropolitan area.

23 In summary, SO<sub>2</sub> concentrations vary substantially across urban spatial scales as  
24 evidenced by poor to moderate inter-site pairwise correlations observed in SO<sub>2</sub> data in six  
25 focus areas. Spatial heterogeneity in urban-scale SO<sub>2</sub> concentrations and their temporal  
26 patterns may be explained by the presence of multiple, unevenly distributed SO<sub>2</sub> sources,  
27 meteorological factors that lead to varying degrees of SO<sub>2</sub> dilution, or removal through  
28 cloud/fog chemistry and deposition. Additionally, in this analysis, metrics representing  
29 maximum SO<sub>2</sub> concentrations generally exhibited more spatial heterogeneity than  
30 24-h avg metrics.

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### 2.5.3 Temporal Variability

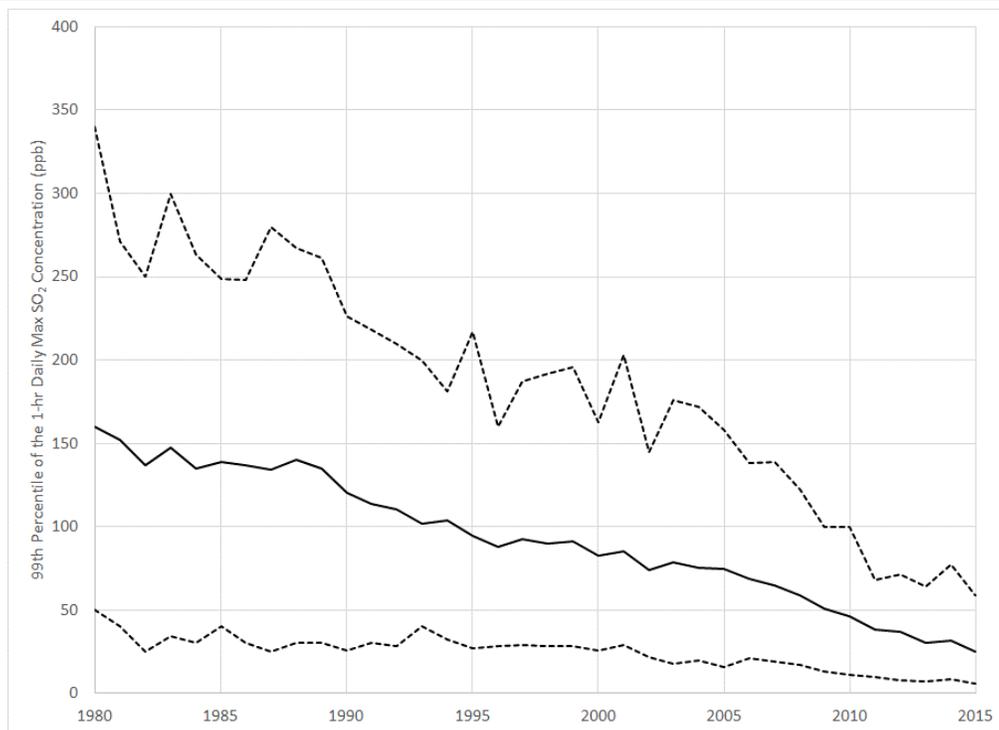
31 Temporal variations in outdoor SO<sub>2</sub> concentrations affect the magnitude, duration, and  
32 frequency in which humans are exposed to SO<sub>2</sub>. In this section, different types of

1 temporal trends are discussed, spanning long-term temporal trends on an annual basis to  
2 short-term trends on a subhourly basis.

---

### 2.5.3.1 Long-Term Trends

3 Trends in SO<sub>2</sub> concentrations reported at AQS monitoring sites across the U.S. from 1980  
4 to 2015 are shown in [Figure 2-21](#) for the annual 99th percentile of the 1-h daily max SO<sub>2</sub>  
5 concentration. Information on SO<sub>2</sub> concentration trends at individual, local air monitoring  
6 sites can be found at <https://www.epa.gov/air-trends/sulfur-dioxide-trends> (U.S. EPA,  
7 [2012b](#)).



SO<sub>2</sub> = sulfur dioxide.

Note: The solid line shows the mean concentrations and the upper and lower dashed lines represent the 10th and 90th percentile concentrations, respectively.

Source: <https://www.epa.gov/air-trends/sulfur-dioxide-trends>.

**Figure 2-21 National sulfur dioxide air quality trend, based on the 99th percentile of the 1-h daily max concentration for 163 sites, 1980–2015. A 76% decrease in the national average was observed from 1980–2015.**

1 The steady decline in SO<sub>2</sub> concentrations over the past 25 years is largely attributed to  
2 emissions reductions at EGUs due to the Acid Rain and NO<sub>x</sub> Budget Programs, and the  
3 Clean Air Interstate Rule (CAIR) implemented under the Clean Air Act Amendments of  
4 1990 (USC Title 42 Chapter 85). The goal of the Acid Rain Program was to reduce  
5 power plant SO<sub>2</sub> emissions by 8.95 x 10<sup>6</sup> tons from 1980 levels. Reductions in SO<sub>2</sub>  
6 emissions commenced in 1996 and continued into the 2000s, resulting in dramatic  
7 decreases in total, nationwide SO<sub>2</sub> emissions and concentrations ([Figure 2-5](#)). The NO<sub>x</sub>  
8 Budget Program and CAIR led to further reductions in SO<sub>2</sub> emissions. From 1990–2014,  
9 the annual 99th percentile average of 1-h daily max SO<sub>2</sub> concentration has decreased by  
10 76% nationally.

11 Substantial declines in SO<sub>2</sub> concentration over the past decades have also been observed  
12 on regional scales. [Blanchard et al. \(2013\)](#) reported an average decline of 7.6% per year  
13 (±1.6%) in SO<sub>2</sub> emissions from 1999–2010 across four southeastern U.S. states  
14 (Alabama, Florida, Georgia, Mississippi), primarily due to reductions in power plant  
15 emissions, which account for approximately 75% of total SO<sub>2</sub> emissions in the  
16 southeastern U.S. region. This decline corresponded to large reductions in annual SO<sub>2</sub>  
17 concentrations (between 5.1 and 9.7% per year) reported at monitoring sites across these  
18 four states.

---

### 2.5.3.2 Seasonal Trends

19 In the 2008 SO<sub>x</sub> ISA ([U.S. EPA, 2008d](#)), month-to-month trends for SO<sub>2</sub> were observed  
20 across a number of metropolitan areas, and these seasonal profiles varied by location.  
21 Some cities, such as Steubenville, OH and Phoenix, AZ showed clear wintertime  
22 maxima, while other urban areas (Philadelphia, PA; Los Angeles, CA; Riverside, CA)  
23 exhibited higher SO<sub>2</sub> concentrations during summer months. Differences in seasonal  
24 profiles were attributed to variations in source emissions, topography, and meteorological  
25 conditions among different areas.

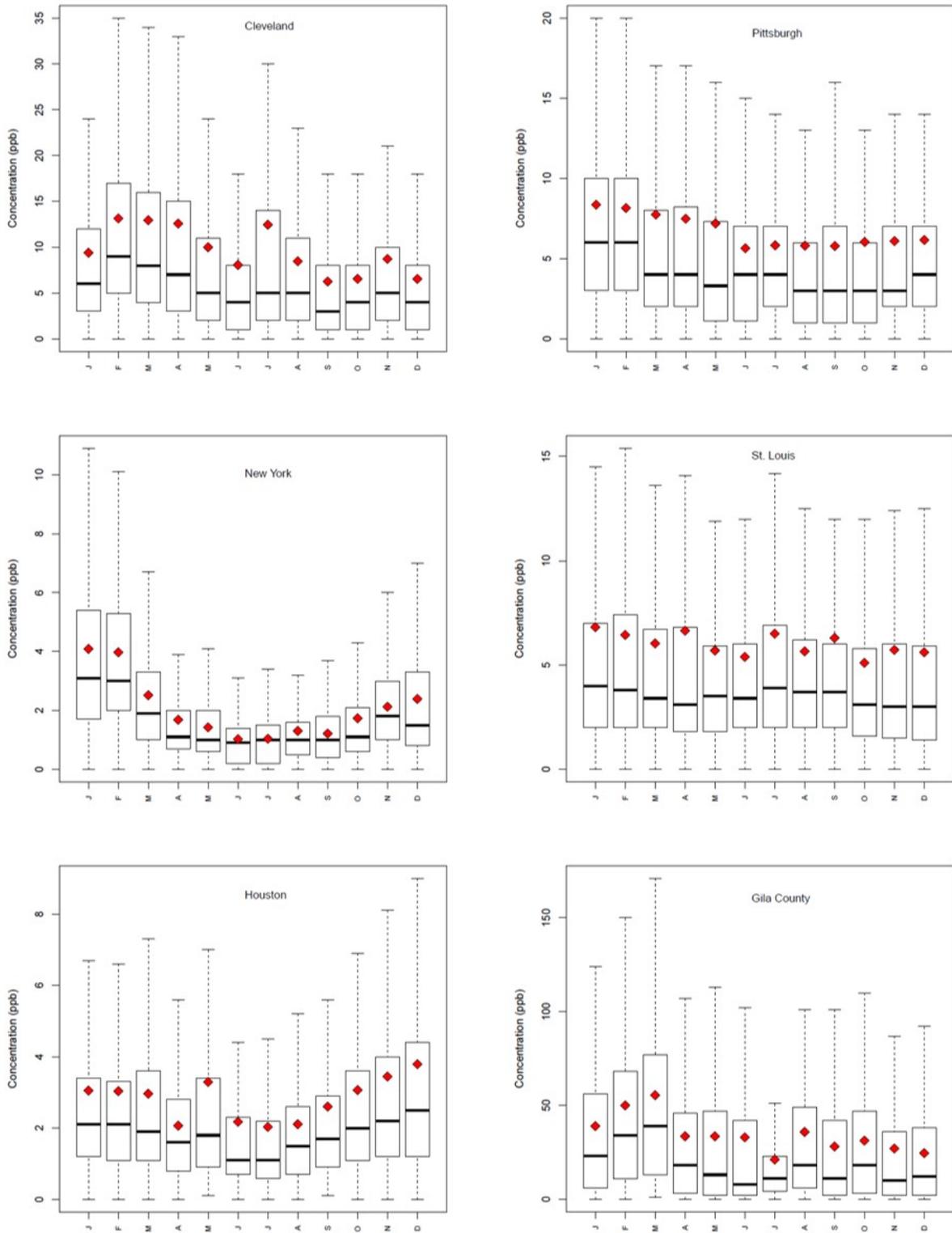
26 Month-to-month variability based on more recent 1-h daily max concentrations  
27 (2013–2015) is shown for the six focus areas introduced earlier in this chapter  
28 ([Section 2.5.2.2](#)). [Figure 2-22](#) displays the range of SO<sub>2</sub> concentrations reported at all  
29 monitoring sites within each focus area.

30 The data indicate that 1-h daily max SO<sub>2</sub> concentrations vary across seasons, especially in  
31 the higher concentrations within monthly SO<sub>2</sub> concentration distributions. Among the  
32 five urban focus areas, median concentrations (50th percentile: black line) varied by no  
33 more than 6 ppb throughout the year, while the median concentration in the Gila County,  
34 AZ focus area varied by 30 ppb. Large variations across all focus areas are observed in

1 the upper end (greater than 75th percentile) of SO<sub>2</sub> concentrations. Notably, mean  
2 monthly SO<sub>2</sub> concentrations were higher and more variable than median values,  
3 indicating that the distribution is skewed by high, infrequent observations.

4 Recent data further demonstrate that seasonal profiles vary by location. While each focus  
5 area exhibits some degree of seasonal variation, no consistent seasonal profile was  
6 observed across the focus areas. For example, springtime maxima in 1-h daily max SO<sub>2</sub>  
7 are evident in Cleveland, OH and Gila County, AZ, corresponding to focus areas with the  
8 highest SO<sub>2</sub> concentrations. Alternatively, New York City, NY, Houston, TX, and  
9 Pittsburgh, PA show clear wintertime maxima.

10 Month-to-month variations in SO<sub>2</sub> concentrations are consistent with month-to-month  
11 emissions patterns ([Lee et al., 2011a](#)) and the atmospheric chemistry of SO<sub>2</sub>.  
12 Summertime minima, observed in the New York City, NY, and Houston, TX, focus  
13 areas, may correspond to enhanced oxidation of SO<sub>2</sub> to SO<sub>4</sub><sup>2-</sup> by photochemically derived  
14 atmospheric oxidants that are more prevalent during the humid summer ([Khoder, 2002](#)).  
15 The difference in seasonality among these cities suggest that SO<sub>2</sub> can be substantially  
16 variable across local and regional scales.



**Figure 2-22 Sulfur dioxide month-to-month variability based on 1-h daily max concentrations at Air Quality System sites in each core-based statistical area, 2013–2015.**

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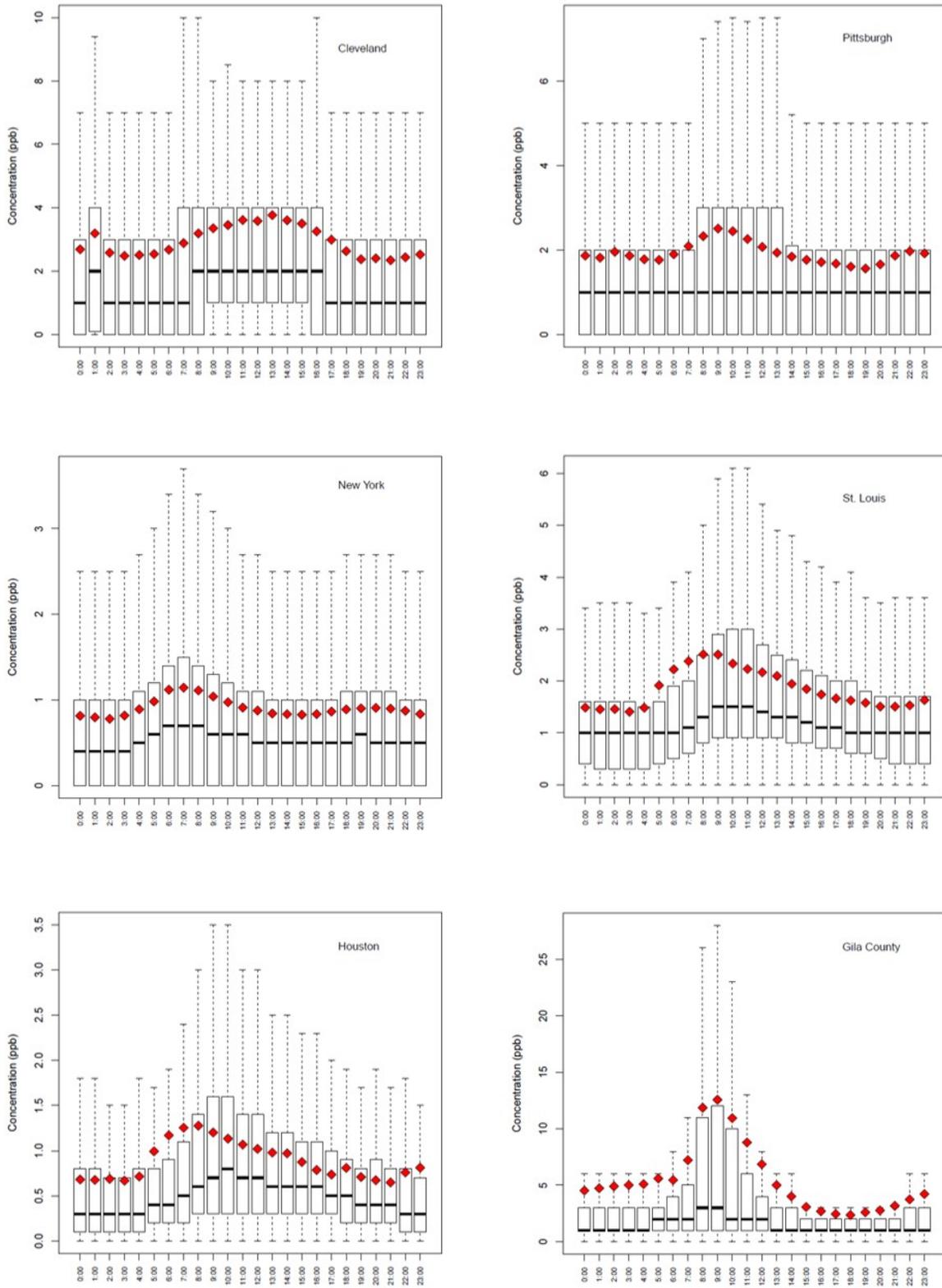
### 2.5.3.3 Diel Variability

1 The 2008 SO<sub>x</sub> ISA ([U.S. EPA, 2008d](#)) explored nationwide patterns in diel variability of  
2 SO<sub>2</sub> concentrations (i.e., variability of SO<sub>2</sub> concentrations across a 24-hour period), and  
3 found clear daytime maxima and nighttime minima, with larger day-night differences  
4 with increasing SO<sub>2</sub> concentrations. Daytime maxima were attributed to entrainment of  
5 SO<sub>2</sub> from elevated point sources (e.g., power plants and industrial sources) into the mixed  
6 boundary layer, which expands due to rising surface temperatures.

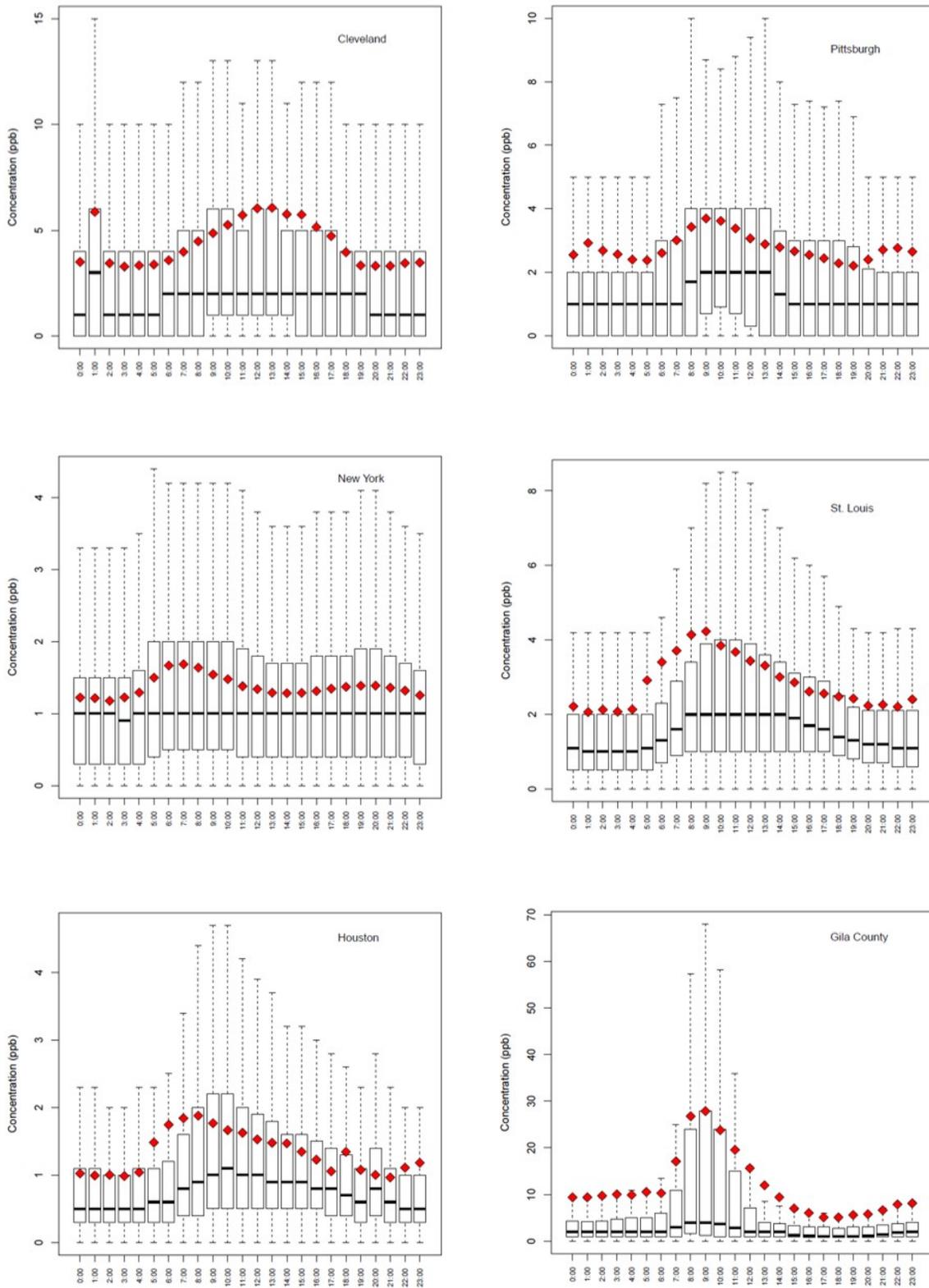
7 Diel patterns were investigated in the focus areas using 1-h avg and 5-minute hourly max  
8 SO<sub>2</sub> data for the 2013–2015 time frame. [Figure 2-23](#) and [Figure 2-24](#) show variations in  
9 1-h avg and 5-minute hourly max SO<sub>2</sub> concentrations in the six focus areas.

10 Consistent with the nationwide diel patterns reported in the 2008 SO<sub>x</sub> ISA ([U.S. EPA,](#)  
11 [2008d](#)), SO<sub>2</sub> concentrations in the six focus areas were generally low during nighttime  
12 and approach maxima values during daytime hours ([Figure 2-23](#) and [Figure 2-24](#)). In  
13 Pittsburgh, PA; New York City, NY; St. Louis, MO; Houston, TX; and Gila County, AZ,  
14 daytime maxima occurred during early morning hours (6:00 to 9:00 a.m. LST). In  
15 Cleveland, OH, SO<sub>2</sub> tended to peak later in the morning or in some cases early- to  
16 mid-afternoon.

17 The timing and duration of daytime SO<sub>2</sub> peaks in the six focus areas were likely a result  
18 of a combination of source emissions and meteorological parameters. The 2008 SO<sub>x</sub> ISA  
19 ([U.S. EPA, 2008d](#)) concluded that higher daytime SO<sub>2</sub> likely reflected an increase in  
20 power plant emissions coupled with an increase in entrainment of these elevated  
21 emissions into the lower atmosphere as the mixed layer expands throughout the day.  
22 Distinct morning peaks may have been related to stable atmospheric conditions, which  
23 tend to trap atmospheric pollution near the ground, resulting in an overall increase in  
24 ground-level pollution.



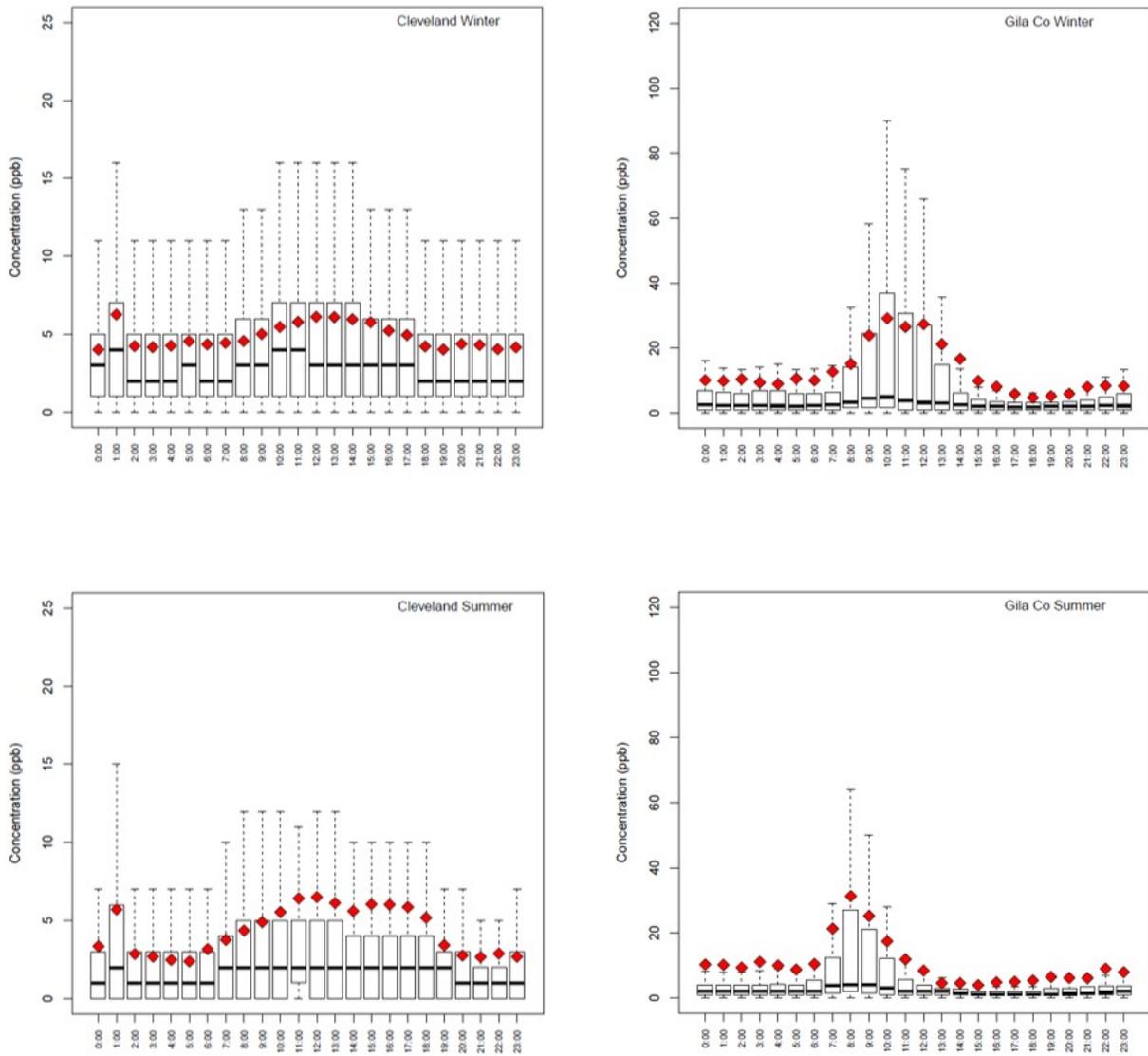
**Figure 2-23** Diel variability based on 1-h avg sulfur dioxide concentrations in the six focus areas, 2013–2015.



**Figure 2-24** Diel trend based on 5-minute hourly max data in the six focus areas, 2013–2015.

1 Notably, SO<sub>2</sub> concentrations were all well below the primary NAAQS level during all  
2 hours of the day in every focus area except Gila County, AZ. In all focus areas, median  
3 5-minute hourly max and 1-h avg concentrations were less than 5 ppb. SO<sub>2</sub>  
4 concentrations were for the most part below 15 ppb for all but Gila County, AZ, even  
5 when examining the upper end of the distribution of 5-minute hourly max concentrations.  
6 For Gila County, AZ, the 95th percentile of 5-minute hourly max and 1-h avg SO<sub>2</sub>  
7 concentrations exceeded 65 ppb and 25 ppb, respectively.

8 Diel SO<sub>2</sub> concentration patterns may be influenced by seasonal factors. Diel plots of  
9 5-minute hourly max for winter and summer are presented for Cleveland, OH and Gila  
10 County, AZ in [Figure 2-25](#). A clear contrast can be seen between the two locations.  
11 Cleveland, OH exhibited very little change in diel patterns between the cold and warm  
12 seasons. In contrast, the mode of the diel pattern occurred earlier in summer compared  
13 with winter for Gila County, AZ. Factors that may influence the mode of the diel pattern  
14 include peak smelter operation times and atmospheric mixing. For example, seasonal  
15 differences in solar radiation prolong nighttime inversion periods during the winter.  
16 Transport to downwind monitoring sites may be impeded by stable conditions. Moreover,  
17 increased solar radiation during the summer enhances mixing, increasing the probability  
18 of plume touchdown ([Slade, 1968b](#)). The median and average 5-minute hourly max SO<sub>2</sub>  
19 concentrations were also somewhat lower during the summer compared with winter in  
20 Gila County, AZ. O<sub>3</sub> production in the summer may have promoted oxidation of SO<sub>2</sub>  
21 ([Khoder, 2002](#)) to produce the observed losses.



Note: For every hour, median concentrations are displayed as black lines inside the box, and the mean concentrations are displayed as diamond-shaped red markers. The interquartile concentration range (25th to 75th percentile range) is outlined by the box, and 5th and 95th percentile concentrations are shown by the top and bottom whiskers, respectively.

**Figure 2-25** Diel trend based on 5-minute hourly max data in the Cleveland, OH and Gila County, AZ focus areas during winter and summer, 2013–2015.

---

## 2.5.4 Relationships between Hourly Mean and Peak Concentrations

1 Peak concentrations within an SO<sub>2</sub> plume can greatly exceed the mean concentration at  
2 the plume centerline, so that exposure to the peak may be much greater than an hourly or  
3 daily SO<sub>2</sub> measurement. Plume dispersion is a Gaussian process, but the plume meanders  
4 so that the peak at any instant in time exceeds the mean of the plume centerline found by  
5 averaging over some longer time period, such as 1 hour or 1 day ([Slade, 1968a](#); [Gifford,  
6 1960](#)). Several studies ([Dourado et al., 2012](#); [Schauburger et al., 2012](#); [Venkatram, 2002](#);  
7 [Turner, 1970](#)) have characterized the peak-to-mean ratio (PMR), showing that the ratio  
8 increases with longer averaging time. [Venkatram \(2002\)](#) used dispersion modeling to  
9 illustrate the stochasticity of the dispersion process, where the mean over a longer time  
10 period is determined by an ensemble average across simulations. At a fixed location, the  
11 results of [Venkatram \(2002\)](#) imply that exposure to the plume peak occurs with varying  
12 probabilities based on the time scale used to represent the instantaneous plume, the time  
13 scale over which the average is computed, the intermittency of atmospheric turbulence,  
14 and atmospheric stability.

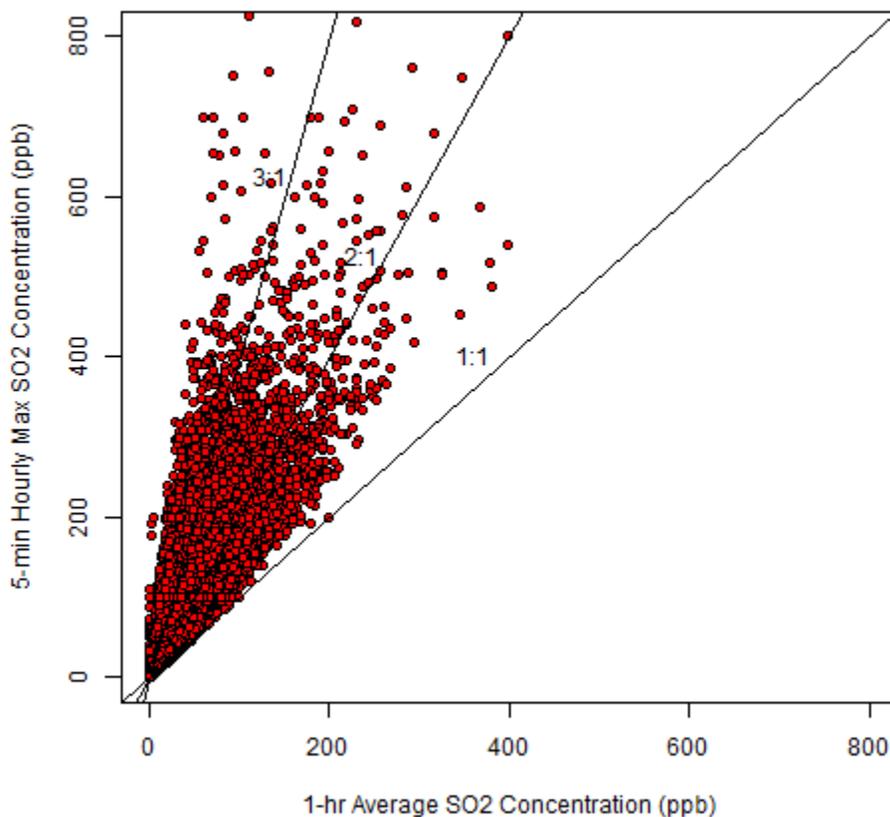
15 The PMR has been computed in the literature as a function of the ratio of the  
16 mean-to-peak concentration integration times raised to some power in the range of 0.2 to  
17 0.5 ([Venkatram, 2002](#)) or 0 to 0.68 ([Schauburger et al., 2012](#)), with the increasing  
18 exponent corresponding to increased atmospheric instability. When 5-minute hourly max  
19 data are compared with 1-h avg data, the mean-to-peak integration time ratio is  
20 60 minutes-to-5 minutes = 12. A peak-to-mean ratio of 1 to 5.4 would be expected using  
21 the wider range of exponents (i.e., 12<sup>0</sup> to 12<sup>0.68</sup>).

22 Scatterplots of collocated 5-minute hourly max and 1-h avg measurements are displayed  
23 for all monitors in [Figure 2-26](#) and by focus area in [Figure 2-27](#). Data for the PMR  
24 analyses were subject to the same completeness criteria outlined in [Table 2-5](#)  
25 ([Section 2.5.1](#)).

26 PMRs were used extensively in the previous SO<sub>2</sub> NAAQS review to evaluate the  
27 distribution of 5-minute hourly max concentrations corresponding to a given 1-h avg SO<sub>2</sub>  
28 concentration ([U.S. EPA, 2009b](#)). PMRs are determined by dividing the 5-minute hourly  
29 max concentration by the 1-h avg concentration. Using this approach, a PMR of 1  
30 demonstrates that 5-minute hourly max and 1-h avg concentrations are equivalent. A high  
31 PMR value (up to a maximum value of 12 in this case) indicates that the 5-minute hourly  
32 max concentration is higher than the 1-h avg concentration. For example, a PMR of 2  
33 (shown as 2:1 on [Figure 2-26](#) and [Figure 2-27](#)) indicates that 5-minute hourly max  
34 concentration is 2 times higher than the 1-h avg concentration. PMR values of 1 (1:1)  
35 through (3:1) are displayed as lines in [Figure 2-26](#) and [Figure 2-27](#). Median PMRs  
36 obtained from comparing the 5-minute hourly max with the 1-h avg AQS data at sites

1 where both measures were available simultaneously, and neglecting concentrations below  
2 0 ppb, had a range of 1 to 5.5 with a median of 1.3, in reasonable agreement with the  
3 predicted range of 1 to 5.4 for the PMR.

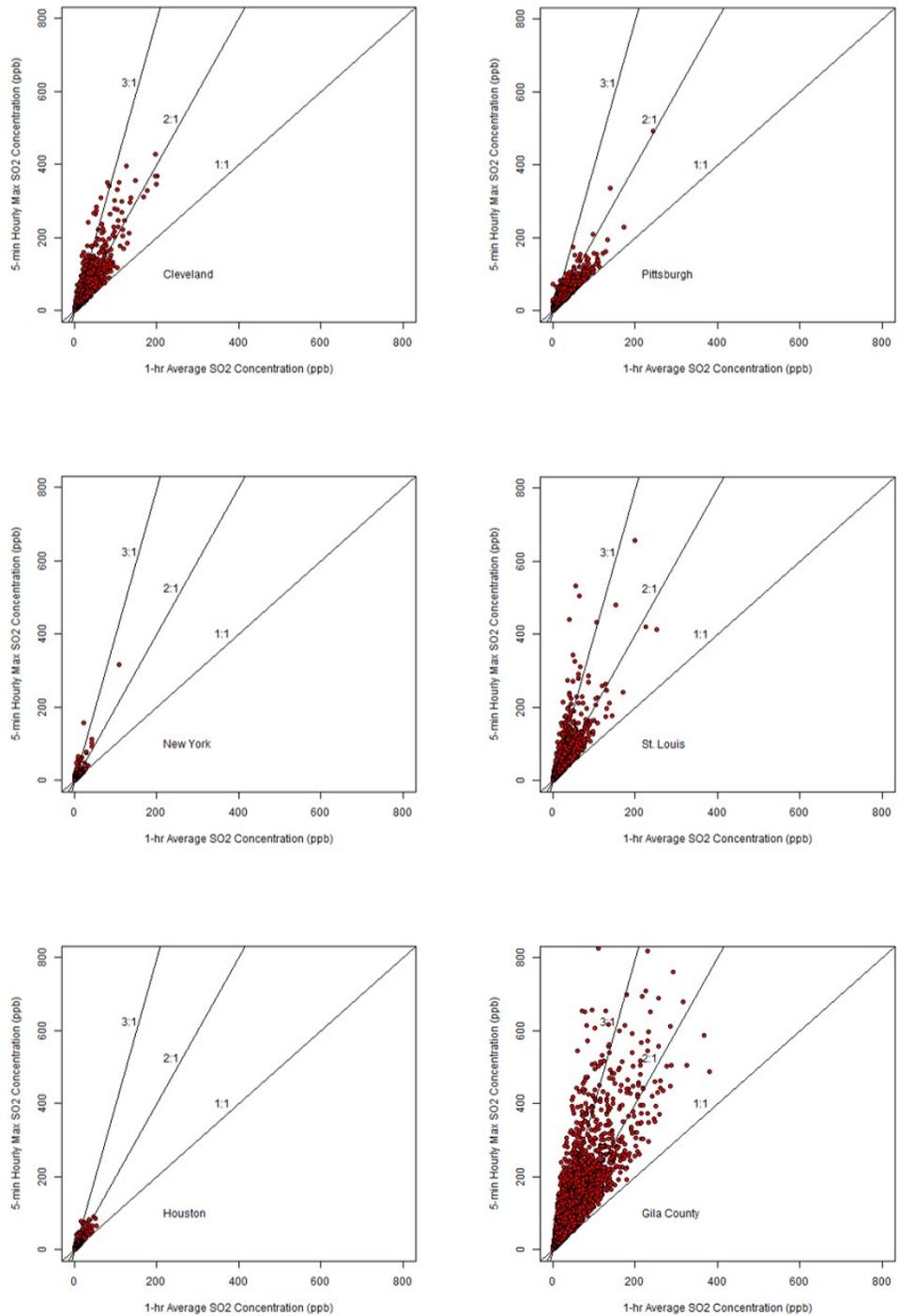
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SO<sub>2</sub> = sulfur dioxide.

Note: Peak-to-mean ratios are displayed on each scatter plot as 1:1 (5-min hourly max = 1-h avg), 2:1 (5-min hourly max is 2 times higher than 1-h avg), and 3:1 (5-min hourly max is 3 times higher than 1-h avg).

**Figure 2-26 Scatterplot of 5-minute hourly max versus 1-h avg sulfur dioxide concentrations, 2013–2015.**



SO<sub>2</sub> = sulfur dioxide.

Note: Peak-to-mean ratios are displayed on each scatter plot as 1:1 (5-min hourly max = 1-h avg), 2:1 (5-min hourly max is 2 times higher than 1-h avg), and 3:1 (5-min hourly max is 3 times higher than 1-h avg).

**Figure 2-27 Scatterplot of 5-minute hourly max versus 1-h avg sulfur dioxide concentrations by focus area, 2013–2015.**

1 [Table 2-9](#) displays the range of temporal correlations between corresponding 5-minute  
2 hourly max and 1-h avg concentrations and the range of PMRs computed from SO<sub>2</sub>  
3 measurements reported at these monitoring sites within the six focus areas shown in  
4 [Figure 2-27](#). Similar to results in the 2008 SO<sub>x</sub> ISA ([U.S. EPA, 2008d](#)), 5-minute hourly  
5 max concentrations tend to correlate well with 1-h avg metrics, suggesting that 1-h avg  
6 metrics, in most cases, adequately represent changes in 5-minute hourly max data over  
7 time. However, 5-minute hourly max concentrations tend to be higher than 1-h avg  
8 concentrations. PMRs were skewed higher for the Gila County focus area and slightly  
9 higher for the New York City focus area. However, overall 1-h daily max concentrations  
10 in New York were relatively low (highest 99th percentile 1-h daily max was 16.5 ppb), so  
11 a PMR of 2 or 3 would lead to a 5-minute hourly max of 33 or 49.5 ppb. In contrast, the  
12 1-h daily max concentrations in Gila County were much higher (highest 99th percentile  
13 1-h daily max was 247 ppb), which would lead to 5-minute hourly max concentrations of  
14 494 ppb if the PMR were 2 and of 741 ppb if the PMR were 3.

---

## 2.5.5 Background Concentrations

15 With the exception of periodic volcanic eruptions in Hawaii, natural and international  
16 transboundary sources of SO<sub>2</sub> make only minor contributions to the total atmospheric  
17 burden of SO<sub>2</sub> in the U.S. [Section 2.2.4](#) and [Section 2.2.5](#) describe those sources  
18 contributing to background SO<sub>2</sub>.

19 No new studies have appeared that attempt to estimate background SO<sub>2</sub> concentrations  
20 since the 2008 SO<sub>x</sub> ISA ([U.S. EPA, 2008d](#)). The 2008 SO<sub>x</sub> ISA discussed a global scale  
21 three-dimensional modeling study that estimated annual mean SO<sub>2</sub> concentrations in  
22 surface air including both anthropogenic and natural sources, using the MOZART-2  
23 (Model of Ozone and Related Chemical Tracers) [Horowitz et al. \(2003\)](#). Sources  
24 included in the study included emissions from fossil and biofuel combustion, biomass  
25 burning, biogenic and soil emissions, and oceanic emissions. Background SO<sub>2</sub>  
26 concentration estimates were below 0.01 ppb over much of the U.S. Maximum  
27 background concentrations of SO<sub>2</sub> are 0.03 ppb. In the U.S. Northwest, geothermal  
28 sources of SO<sub>2</sub> are responsible for 70 to 80% of the background SO<sub>2</sub> concentration; even  
29 so, total SO<sub>2</sub> concentrations are still on the order of ~2 ppb or less. In these simulations,  
30 background contributed less than 1% to SO<sub>2</sub> concentrations in surface air in 2001  
31 throughout much of the contiguous U.S.

**Table 2-9 Pearson correlation coefficient and peak-to-mean ratio for maximum sulfur dioxide concentrations in the six focus areas, 2013–2015.**

Focus Area	N Monitoring Sites	Correlation Coefficient	Median PMR <sup>a</sup>
Cleveland, OH	7	0.89–0.93	1.00–1.85
Pittsburgh, PA	9	0.91–0.97	1.00–1.40
New York City, NY	12	0.66–0.98	1.28–2.33
St Louis, MO	7	0.88–0.94	1.17–1.38
Houston, TX	9	0.91–0.95	1.33–1.69
Gila County, AZ	4	0.84–0.93	3.24–6.15

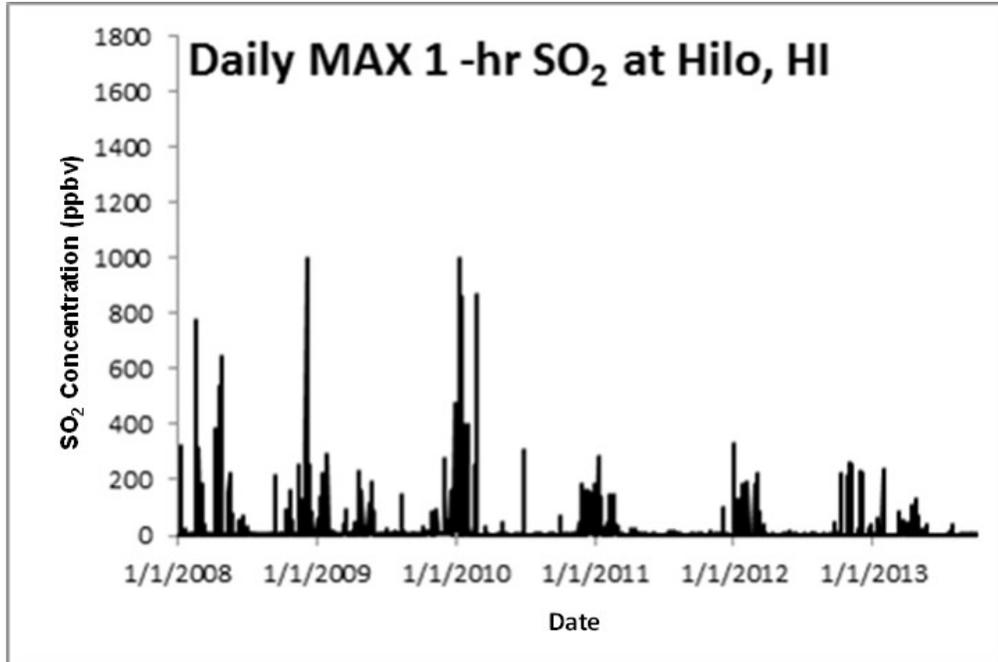
N = population number; PMR = peak-to-mean ratio.

<sup>a</sup>Median PMR = 5 min max/1-h avg. The range of data represents median PMR across each site within the focus area.

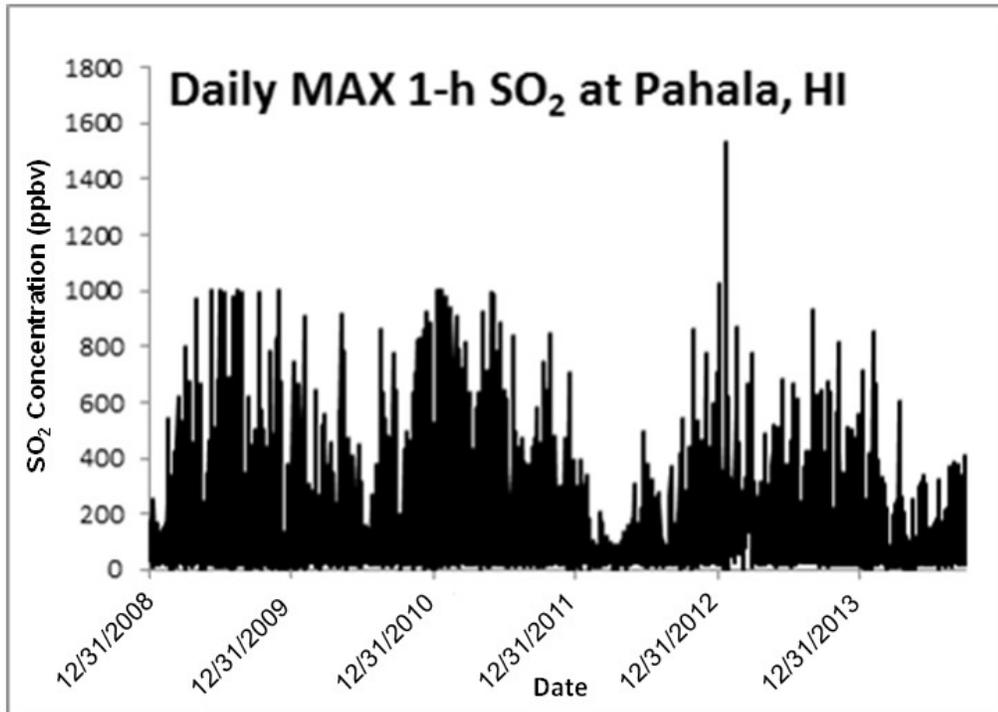
1 Satellite-borne instruments have mapped large SO<sub>2</sub> sources globally and have obtained  
 2 data showing intercontinental transport. [Fioletov et al. \(2013\)](#) identified a number of  
 3 “hotspots” for continuous SO<sub>2</sub> emissions, both anthropogenic and volcanic  
 4 (e.g., industrial sources in China, Russia, the U.S., the Gulf of Mexico and Saudi Arabia;  
 5 volcanic sources in Kīlauea, HI and Anahatan in the Marianas). [Clarisse et al. \(2011\)](#)  
 6 showed evidence for transport of SO<sub>2</sub> from Asia to Alaska and Canada. In one such  
 7 episode in November 2010, there was a clearly defined plume crossing the Pacific.

8 As described in [Section 2.2.4.2](#), volcanic sources of SO<sub>2</sub> in the U.S. are found in the  
 9 Pacific Northwest, Alaska, and Hawaii. The most important domestic effects from  
 10 volcanic SO<sub>2</sub> occur on the Hawaiian Islands. Nearly continuous venting of SO<sub>2</sub> from  
 11 Mauna Loa and Kīlauea produces SO<sub>2</sub> in high concentrations that can affect populated  
 12 areas on the Big Island of Hawaii (as well as others in the chain, depending on wind  
 13 conditions). [Figure 2-28A](#) shows the 2008–2013 time series for 1-h daily max SO<sub>2</sub>  
 14 concentrations at Hilo, HI, (population of approximately 40,000), which is located about  
 15 50 km northeast of Kīlauea. [Figure 2-28B](#) shows the same time series at Pahala  
 16 (population ~1,300) which is located about 30 km southeast of Kīlauea ([Longo et al.,](#)  
 17 [2010](#)). As demonstrated by these figures, 1-h daily max SO<sub>2</sub> concentrations can reach  
 18 levels greater than 1,000 ppb. [Figure 2-29](#) shows a 6-month concentration time series for  
 19 the Ka’u District, one of the other communities scattered throughout the southern half of  
 20 the island that are also exposed to high SO<sub>2</sub> concentrations ([Longo et al., 2010](#)).

A

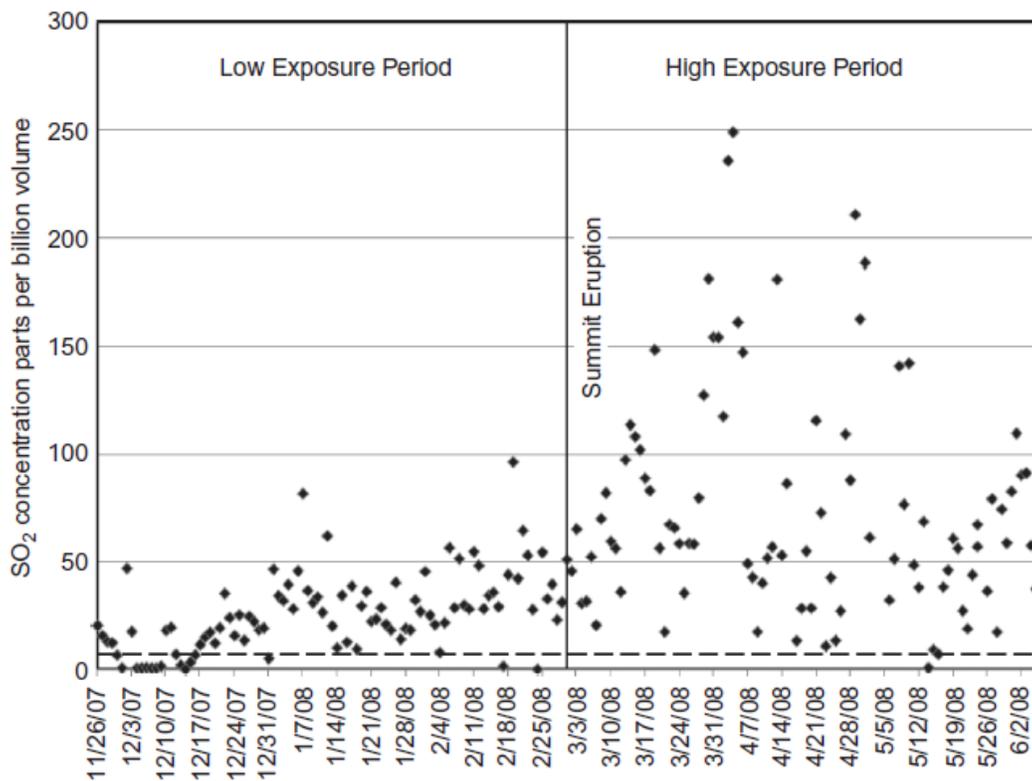


B



SO<sub>2</sub> = sulfur dioxide.

**Figure 2-28** 1-h daily max sulfur dioxide concentrations measured at (A) Hilo, HI and (B) Pahala, HI.



SO<sub>2</sub> = sulfur dioxide.

Note. The dashed line represents the World Health Organization 24-h avg SO<sub>2</sub> guideline = 7.5 ppbv (WHO, 2006).

Data source: SO<sub>2</sub> measured continuously by a TECO pulsed-fluorescence monitor, State of Hawaii Air Quality Division.

Source [Longo et al. \(2010\)](#).

**Figure 2-29 Average 24-hour ambient sulfur dioxide concentrations during low and high (volcanic gas) concentration study periods (November 26, 2007 to June 6, 2008) for Ka’u District, located downwind of Kīlauea Volcano.**

## 2.6 Atmospheric Modeling

1 This section discusses various modeling techniques to estimate ambient concentrations of  
 2 SO<sub>2</sub>. Different types of models are discussed in terms of their capabilities, strengths, and  
 3 limitations. [Section 2.6.1](#) focuses on dispersion models, which are the most widely used  
 4 and the most relevant for modeling the influence of large point sources on local-scale SO<sub>2</sub>  
 5 concentrations in the urban and other near-field environments. [Section 2.6.2](#) briefly  
 6 discusses chemical transport models (CTMs) that can be used to model SO<sub>2</sub>  
 7 concentrations at regional and national scales.

---

## 2.6.1 Dispersion Modeling

1 Atmospheric transport and dispersion (ATD) models are important mathematical tools for  
2 simulating the fate of air pollutants in support of a wide variety of environmental  
3 assessments. ATD models can be used to estimate SO<sub>2</sub> concentration for regulatory  
4 purposes if monitoring data are not available or sufficient (75 CFR 35520). Using  
5 equations that represent the physical and chemical atmospheric processes that govern  
6 dispersal and fate, ATD models provide an estimate of the concentration distribution,  
7 both temporally and spatially, of pollutants emitted from sources such as industrial  
8 facilities, roadways, and urban areas. The processes that are most important vary  
9 depending on the particular model application. The models must specifically account for  
10 the characteristics of the source or sources of the pollutant (e.g., buoyant releases), the  
11 meteorological conditions, the surrounding surfaces and complexities (e.g., buildings,  
12 terrain, and trees), the background concentrations from sources not considered directly in  
13 the modeling and the chemical transformations of the pollutant in the atmosphere.

14 Dispersion models are particularly important to pollutant studies where monitoring is not  
15 practical or sufficient. For pollutants such as SO<sub>2</sub> where spatial distributions of 1-h avg  
16 concentrations associated with large sources often contain extreme gradients, the siting of  
17 individual monitors to capture high ground-level concentrations over a wide variety of  
18 sources and meteorological conditions would be challenging at best. Extensive arrays of  
19 monitors are impractical. Thus, the implementation program for the 2010 primary SO<sub>2</sub>  
20 NAAQS allows for air quality modeling to be used in place of monitoring to characterize  
21 air quality, and for such air quality information to be used in the process for informing  
22 final designation decisions (75 FR 35520). The SO<sub>2</sub> NAAQS is currently the only criteria  
23 pollutant standard for which modeling may be used to characterize air quality for the  
24 purpose of the area designation process. In addition, modeling is critical to the  
25 assessment of the impact of future sources or proposed modifications where monitoring  
26 cannot inform. Also, modeling is helpful in the design and implementation of mitigation  
27 techniques for addressing existing pollution problems and for compliance evaluations.

28 ATD models take many forms. They include steady-state (emissions and meteorology),  
29 Gaussian-based formulations [e.g., AERMOD, ([Cimorelli et al., 2005](#))]; Lagrangian  
30 models [e.g., SCIPUFF, ([Sykes et al., 2007](#)); HYSPLIT, ([Draxler, 1999](#)); ([NOAA, 2014](#))],  
31 which are particularly useful when emissions and meteorological conditions are  
32 variable over the modeling increment, and Eulerian photochemical grid-based models  
33 [e.g., Community Multiscale Air Quality (CMAQ), ([Byun and Schere, 2006](#))], which  
34 explicitly model chemical processes and have modeling resolution ranges from about one  
35 to tens of kilometers. Additionally, there are stochastic or statistical approaches using, for  
36 example, Monte Carlo techniques ([Hanna et al., 1982](#)) or those using simple regression

1 approaches ([Banerjee et al., 2011](#)). For very complex flows such as a release within an  
2 urban canopy of a city, computational fluid dynamics models are considered. [Hanna et al.](#)  
3 [\(2006\)](#) demonstrated that these models are capable of reproducing the general flow and  
4 measured tracer dispersion patterns when very detailed source and three-dimensional  
5 building information are available.

6 In the U.S., steady-state Gaussian models are the most common dispersion models used  
7 for primary pollutants like SO<sub>2</sub> ([U.S. EPA, 2010a](#)). These models may be used to  
8 determine compliance with standards and primary pollutant impacts from new or  
9 proposed sources. The same is true for these types of analyses in other countries. For  
10 example, ADMS ([Carruthers et al., 1995](#)), HPDM ([Hanna and Chang, 1993](#)), OML  
11 ([Olesen et al., 1992](#)), and several other steady-state Gaussian-based models have been  
12 recommended by the European Environment Agency ([van Aalst et al., 1998](#)) for  
13 applications involving SO<sub>2</sub> from smoke stacks. Other examples in which Gaussian-type  
14 models are found to be applicable for near-field applications are by the U.K. Department  
15 of Environment, Food, and Rural Affairs ([Williams et al., 2011](#)) and by the New Zealand  
16 Ministry of the Environment ([Bluett et al., 2004](#)). The primary concerns for many of  
17 these compliance-type applications are the magnitude, location, and frequency of high  
18 concentrations and the strong gradients of concentrations found near sources. Often the  
19 highest concentrations are found within a few kilometers and sometimes within tens of  
20 meters of the source. Near-field or near-to-the-source dispersion is the real strength of  
21 steady-state modeling.

22 AERMOD is the preferred model for the vast majority of near-field applications with  
23 OCD being used for offshore emissions and alternative models used for unique situations  
24 (e.g. CALPUFF for Class I area screening application) where justified. AERMOD  
25 represents a modernization of applied Gaussian models with advances in areas such as:  
26 boundary layer scaling formulations; dispersion rates for both surface and elevated  
27 releases; plume interactions with buildings and complex terrain; and characteristics of  
28 point, area, and volume source types. In convective conditions, where dispersion  
29 produces a distinctly non-Gaussian vertical pollutant distribution, AERMOD provides a  
30 three-part formulation (each Gaussian) that when combined yield distributions  
31 representative of those observed ([Weil et al., 1997](#); [Briggs, 1993](#)). The challenges faced  
32 by Gaussian models in very light wind conditions are addressed in AERMOD by  
33 simulating a meandering plume, and providing turbulence-based lower limits on the  
34 transport wind speed and an empirically based correction for the surface friction velocity.  
35 In recent years, U.S. EPA has been working to improve AERMOD predictions under  
36 light wind conditions, including an adjustment of surface friction velocity under stable  
37 light wind conditions (80 FR 45340). For modeling applications where light and variable  
38 winds are dominant and reliable wind field estimates are available, models such as

1 SCIPUFF or HYSPLIT provide estimates of plume trajectories and more temporally  
2 resolved concentration distributions [e.g., [Wannberg et al. \(2010\)](#)].

3 AERMOD and models like it are designed to simulate concentrations on an hourly  
4 increment, and model evaluations are focused on averaging times of 1 hour or greater  
5 ([Perry et al., 2005](#)). Longer term concentrations are obtained by averaging the 1-hour  
6 concentrations. Spatial resolution is simply determined by the density of receptors  
7 included in the analysis (i.e., very high resolution possible). For each hour, emissions and  
8 other source characteristics, land surface characteristics, and meteorological conditions  
9 are provided to the model. Additionally, the model requires a description of buildings and  
10 complex terrain within the modeling domain that are expected to influence pollutant  
11 dispersion. The model can simulate hundreds of sources and receptors, providing for  
12 analyses in urbanized and industrialized areas.

13 One limitation of the Gaussian approach is the assumption of steady conditions over a  
14 1-hour modeling period and over the plume transport distance to the receptors. The model  
15 is recommended for receptors up to 50 km from a source when steady conditions are  
16 appropriate ([U.S. EPA, 2005b](#)). However, this can be challenging, especially for light  
17 winds. Under low wind conditions, there are concerns that AERMOD can overestimate  
18 measured SO<sub>2</sub> concentrations without adjustment for empirical relationships between  
19 wind and concentration ([Paine et al., 2015](#)). Recent updates to AERMOD have been  
20 made by the U.S. EPA to address those concerns (80 FR 45340). AERMOD is also  
21 limited in its treatment of SO<sub>2</sub> chemistry, using a method much simpler than the more  
22 rigorous simulation of atmospheric transformation of SO<sub>2</sub> found in models such as  
23 CMAQ or SCICHEM ([Chowdhury et al., 2012](#)). AERMOD uses a simple 4-hour half-life  
24 assumption for reducing SO<sub>2</sub> concentration in the plume with travel time ([Turner, 1964](#)).  
25 This approach yields results consistent with the SO<sub>2</sub> residence time estimates by [Hidy](#)  
26 ([1994](#)) and [Seinfeld and Pandis \(2006\)](#). Therefore, for conditions and sources where the  
27 highest hourly concentrations are expected to be relatively close to the source, chemistry  
28 is not expected to play a major role in determining compliance with primary standards.

29 Lagrangian puff dispersion models, such as CALPUFF, have been developed as an  
30 alternative to Gaussian dispersion models, such as AERMOD. CALPUFF models SO<sub>2</sub> as  
31 particles and then uses a Lagrangian step algorithm to model nonsteady-state dynamics,  
32 using time-varying winds specified by meteorological models, such as MM5 [e.g., [Atabi](#)  
33 [et al. \(2016\)](#), [Abdul-Wahab et al. \(2011\)](#), [Souto et al. \(2014\)](#), [Lee et al. \(2014\)](#), [Zhang et](#)  
34 [al. \(2015a\)](#)]. The nonsteady-state approach offered by Lagrangian puff dispersion models  
35 may be considered an alternative to Gaussian dispersion models that do not account for  
36 time dependence. Comparisons have been conducted between Lagrangian models such as  
37 CALPFUFF and Gaussian plume models such as AERMOD. CALPUFF predictions of

1 24-hour SO<sub>2</sub> concentrations at an oil refinery in Sohar, Oman compared within 36% of  
2 measurements ([Abdul-Wahab et al., 2011](#)). Comparison of CALPUFF and AERMOD to  
3 SO<sub>2</sub> measurements at a gas refinery in South Pars, Qatar showed that, while CALPUFF  
4 and AERMOD both typically underestimated SO<sub>2</sub> measurements, CALPUFF predictions  
5 were usually closer to measured SO<sub>2</sub> concentrations compared with AERMOD ([Atabi et  
6 al., 2016](#)). However, [Rood \(2014\)](#) observed that Lagrangian puff models and Gaussian  
7 dispersion models both underpredicted 1-h and 9-h avg concentrations, but the magnitude  
8 of bias was larger in the Lagrangian puff models applied at a field site in Colorado with  
9 variable winds and natural topography. [Holnicki et al. \(2016\)](#) noted that the model  
10 performance improved with longer averaging times and that the 1-h avg concentration  
11 predicted by CALPUFF was less accurate than predictions for annual average  
12 concentrations, when compared to SO<sub>2</sub> measurements. However, recent dispersion  
13 modeling results were compared between CALPUFF and AERMOD for the Section 126  
14 Petition from New Jersey for the Portland Generating Station (76 FR 69052) where  
15 CALPUFF overestimated 1-h daily max SO<sub>2</sub> observations taken in Columbia, NJ by  
16 226%, while AERMOD overestimated the same observations by 14%.

17 Uncertainty in the model predictions is influenced by the uncertainty in model input data  
18 (in particular emission or source characterization and meteorological conditions) as well  
19 as by inadequacies in model formulations. Uncertainty related to model input variables is  
20 generally estimated by propagating the expected errors in the individual input variables  
21 (e.g., wind speed, emission rate) through the model using Monte Carlo techniques  
22 ([Dabberdt and Miller, 2000](#)). In addition, there is uncertainty related to the fundamental  
23 difference between modeled and measured concentrations. Monitored data (within  
24 sampling error) represents actual realizations of events, while modeling estimates  
25 represent ensemble mean concentrations ([Rao, 2005](#)). Based on a study comparing a  
26 variety of models (including Gaussian) to a number of tracer field study results, [Hanna et  
27 al. \(1993\)](#) found that for continuous point releases and receptors within a kilometer of the  
28 source, uncertainty in model inputs in combination with the stochastic nature of the  
29 atmosphere result in typical mean biases on the order of 20 to 40% and normalized mean  
30 square errors up to 70%. The author points out that these levels of difference between  
31 model and monitor results would likely exist even for more sophisticated models. [Hanna  
32 \(2007\)](#) provided a comprehensive review of methods for determining sensitivity and  
33 uncertainty in ATD models.

34 Focusing on the uncertainties in model inputs, it is easy to see that an individual model  
35 estimate paired in time and space with a monitored concentration will likely differ,  
36 sometimes substantially, due to the propagation of errors through the model. [Weil \(1992\)](#)  
37 pointed out that wind direction uncertainties alone can cause disappointing results in  
38 space and time pairings from otherwise well-performing dispersion models. With wind

1 direction errors, the plume footprints from the model and that from the observations may  
2 not overlap. However, a model that is based on appropriate characterizations of the  
3 important physical processes should be able to reproduce the distribution of observed  
4 concentrations assuming that the distributions of model inputs is similar to that of the  
5 observed conditions ([Venkatram et al., 2001](#)). Meteorological inputs coupled with  
6 AERMOD can impact the results, and the output may depend on the use of recorded  
7 meteorological observations or meteorological models (e.g., Weather Research and  
8 Forecasting (WRF) model). Meteorological models may add error to the dispersion  
9 simulation, and that error is impacted by model selection and resolution ([Isakov et al.,  
10 2007](#)). Therefore, in evaluating a model's ability to predict concentrations within the  
11 modeling domain, it is important to include an analysis of modeled and monitored  
12 concentration distributions for any location studied. As part of the proposed update to the  
13 Guideline on Air Quality Models, U.S. EPA proposed to allow the use of prognostic  
14 meteorological data for regulatory applications of AERMOD (80 FR 45340). U.S. EPA  
15 conducted several assessments comparing observed meteorological data to prognostic  
16 meteorological data and found that the prognostic data performed adequately ([U.S. EPA,  
17 2015a](#)).

18 [Chang and Hanna \(2004\)](#) provided a comprehensive discussion of methods for evaluating  
19 the performance of air quality models. They discuss a series of performance measures  
20 that included statistical metrics such as fractional bias (FB), geometric mean bias,  
21 normalized mean squared error and the fraction of estimates within a factor of two  
22 observations. These and other measures are included in the commonly used BOOT  
23 software ([Chang and Hanna, 2005](#)), which also allows for estimation of confidence limits  
24 on the concentrations computed and provides insight about the sources of bias in the  
25 model ([Irwin, 2014](#)). [Chang and Hanna \(2004\)](#) also discussed exploratory analysis  
26 methods of plotting and analyzing the modeled and measured concentrations. They  
27 pointed out that the most useful model evaluation studies are those that examine a  
28 number of models and compare them with a number of field studies.

29 For models intended for application to compliance assessments (e.g., related to the  
30 1-h daily max SO<sub>2</sub> standard), the model's ability to capture the high end of the  
31 concentration distribution is important. Measures such as robust highest concentration  
32 (RHC) ([Cox and Tikvart, 1990](#)), and exploratory examinations of quantile-quantile plots  
33 ([Chambers et al., 1983](#)) are useful. The RHC represents a smoothed estimate of the top  
34 values in the distribution of hourly concentrations. In contrast, for dispersion modeling in  
35 support of health studies where the model must capture concentrations at specified  
36 locations and time periods, additional measures of bias and scatter are important.

1 The intended use of a model and the objective of a model evaluation guide the selection  
2 of evaluation criteria. [Frost \(2014\)](#) considered model performance for AERMOD, applied  
3 to the study of 1 year of SO<sub>2</sub> emissions from three coal-fired EGUs. The authors found  
4 good agreement (judged to be within a factor of two of the 99th percentile SO<sub>2</sub> design  
5 value) for the majority of the data but noted performance outside a factor of two for the  
6 top 5% of measured 1-h avg concentrations. However, [Rehbein et al. \(2014\)](#) found that  
7 the model fell within a factor of two of the monitoring data even at high concentrations  
8 for a model validation outside a nickel smelting facility in Sudbury, Ontario, Canada.  
9 U.S. EPA also conducted evaluations of prognostic meteorological data in AERMOD  
10 ([U.S. EPA, 2015a](#)), including the facility modeled by [Frost \(2014\)](#). These evaluations  
11 included data analysis adhering to the U.S. EPA Protocol for Best Performing Models,  
12 which includes a scientific and operational component of model performance ([U.S. EPA,](#)  
13 [1992](#)). SO<sub>2</sub> concentrations modeled by AERMOD were within a factor of two of  
14 observations in all but one simulation when using the metrics of the protocol.  
15 Meteorological parameters were modeled with FB within 20% of observations ([U.S.](#)  
16 [EPA, 2015a](#)).

17 At the time of its inclusion into the U.S. EPA Guideline on Air Quality Models ([U.S.](#)  
18 [EPA, 2005b](#)), the performance of AERMOD was evaluated against seventeen field-study  
19 databases over averaging times from 1 hour to 1 year ([Perry et al., 2005](#)). In each case,  
20 the emissions characteristics and background concentrations were well known;  
21 meteorological data were available on site; and tracer concentrations were measured at  
22 multiple locations where high plume impacts were expected. Four of the studies involved  
23 very dense sampler arrays. For the four intensive studies, [Perry et al. \(2005\)](#) found the  
24 ratio of modeled 1-h avg RHC to monitored RHC ranged from 0.77 to 1.18  
25 [i.e., relatively unbiased in estimating extreme (high) values]. For studies involving tall  
26 buoyant stacks with more limited monitoring locations, 1-hour ratios were not reported,  
27 but the 3-h avg ratios ranged from 1.0 to 1.35 (i.e., a slight tendency to overpredict the  
28 high concentrations). Examination of quantile-quantile plots supported the findings that  
29 the model was capturing the upper end of the 1- and 3-h avg concentration distribution.  
30 [Hanna et al. \(2001\)](#) evaluated the AERMOD and ADMS Gaussian dispersion models  
31 with five field study databases including area sources, low releases and tall power plant  
32 stacks in rural, flat, and complex terrain. Among the median performance measures they  
33 reported, the ratio of maximum modeled to maximum observed concentrations was 0.77  
34 for AERMOD and 0.80 for ADMS, each a small underprediction. The median value over  
35 the five databases of the geometric mean (MG, a measure of the ratio of averaged  
36 modeled to monitored concentration) was 1.7 for AERMOD and 1.22 for ADMS. With  
37 1.0 as the ideal value, both models were found to overpredict (with ADMS less biased).  
38 Unlike the ratio of maximum values, MG is a measure of performance over the entire  
39 distribution of concentrations. [Hurley \(2006\)](#) also evaluated AERMOD and two

1 Australian models against seven field studies and found no database against which  
2 AERMOD performed poorly.

3 With the adoption of the 2010 1-h daily max SO<sub>2</sub> standard, there is renewed interest in  
4 AERMOD's abilities to simulate near-field maximum short-term concentrations.  
5 A number of specific areas for model improvement were discussed at the 10th and 11th  
6 Modeling Conference on Air Quality in 2012 ([U.S. EPA, 2012a](#)) and 2015 ([U.S. EPA,  
7 2016a](#)). Among them were concerns about simulations in stable conditions with light and  
8 meandering winds, use of prognostic meteorological data, modeling of emissions from  
9 haul roads, plume chemistry, and building downwash. Proposed improvements include an  
10 adjusted friction velocity model for stable/low wind conditions in AERMET, a new  
11 model for dispersion options in AERMOD, and an option for buoyant line sources in  
12 AERMOD ([U.S. EPA, 2016a](#)). Research in many of these areas is underway, and  
13 improvements to AERMOD have been made based on the outcomes of those  
14 conferences, largely as part of EPA rulemaking to revise the *Guideline*. While the  
15 stochastic nature of the atmosphere will always preclude the development of a perfect  
16 model, improvements to the model formulations will continue with the goal of estimating  
17 hourly average concentrations while reducing model uncertainty and expanding  
18 applicability.

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## 2.6.2 Chemical Transport Models

19 Chemical transport models are an important tool for characterizing regional- and  
20 national-scale air quality. The scales at which they typically operate are too large to  
21 satisfactorily capture meteorological and chemical processes involving SO<sub>2</sub> at the local or  
22 near-source scale. The dispersion models discussed previously are thus preferable for  
23 characterizing SO<sub>2</sub> concentrations at these scales.

24 Chemical transport models such as the Community Multiscale Air Quality (CMAQ)  
25 model, are deterministic models of chemical transport that account for physical and  
26 chemical processes, including advection, turbulence, diffusion, deposition, gas-phase and  
27 heterogeneous chemistry, and convective cloud transport, while following the constraint  
28 of mass conservation ([Byun and Schere, 2006](#)). CTMs provide regional concentration  
29 estimates and are typically run with horizontal grid resolutions of 4, 12, or 36 km.  
30 Temporal resolutions are typically 1 hour, although larger temporal aggregation often  
31 occurs for the purpose of maintaining reasonable data file size. CTMs are used to  
32 compute interactions among primary atmospheric pollutants and their transformation  
33 products, the production of secondary aerosols, the evolution of particle size distribution,  
34 and transport and deposition of pollutants. CTMs are driven by emissions inventories for

1 primary species such as SO<sub>2</sub>, NO<sub>2</sub>, NH<sub>3</sub>, VOCs, and primary PM, and by meteorological  
2 fields produced by other numerical weather prediction models. Values for meteorological  
3 variables such as winds and temperatures are taken from a meteorological model that is  
4 nudged by operational analyses, re-analyses, or general circulation models. In most cases,  
5 these are off-line meteorological predictions, thus they are not modified by radiatively  
6 active species generated by the air quality model. Work to integrate meteorology and  
7 chemistry was initiated in the mid-1990s [by [Lu et al. \(1997a\)](#) and [Lu et al. \(1997b\)](#) and  
8 references therein], although limits to computing power prevented widespread  
9 application. More recently, new integrated models of meteorology and chemistry are  
10 available; see, for example, the Weather Research and Forecast model with chemistry  
11 (WRF-Chem; <http://ruc.noaa.gov/wrf/wrf-chem/>) and WRF-CMAQ ([Wong et al., 2012](#)).

12 Biases in SO<sub>2</sub> concentrations predicted by CTMs can occur as a result of error in model  
13 representation of atmospheric processes converting SO<sub>2</sub> to H<sub>2</sub>SO<sub>4</sub> and in removal  
14 processes. For example, overestimates of cloud-based reactions converting SO<sub>2</sub> to H<sub>2</sub>SO<sub>4</sub>  
15 have been shown to negatively bias SO<sub>2</sub> concentration estimates in CMAQ v4.6 ([Mueller  
16 et al., 2011](#)). Improvements to modeling these processes, such as capturing metal  
17 catalysis of the SO<sub>2</sub> → H<sub>2</sub>SO<sub>4</sub> conversion process, have been included in CMAQ v5.0.2  
18 to improve model estimates of SO<sub>2</sub> and SO<sub>4</sub><sup>2-</sup> ([Alexander et al., 2009](#)). Therefore, when  
19 using CMAQ to estimate exposure to SO<sub>2</sub>, attention must be given to the version of the  
20 model so that any inherent biases are understood.

21 The Air Quality Model Evaluation International Initiative (AQMEII) was developed by  
22 scientists in Europe and North America to evaluate several CTMs against each other  
23 using common input data sets ([Rao et al., 2011](#)). [Pouliot et al. \(2015\)](#) assembled  
24 emissions input data for European and North American simulations performed over two  
25 phases of the AQMEII study and found a 12% reduction in SO<sub>2</sub> emission estimates for  
26 2006 in both Europe and North America. These differences were attributed to differences  
27 in methodologies used to estimate emissions and to differences in input data that  
28 influence the CTM output. In a comparison of CTM models of SO<sub>2</sub> with surface  
29 measurements in Europe, the Modeling Atmospheric Composition and Climate (MACC)  
30 model reanalysis overestimated surface SO<sub>2</sub> concentrations by 40% in winter and  
31 underestimated surface SO<sub>2</sub> levels by 63% in summer ([Giordano et al., 2015](#)). In North  
32 America, MACC underestimated SO<sub>2</sub> in summer by 81%. MACC results were higher  
33 than regional CTMs in the winter for North America, and seasonal variability was not  
34 well captured ( $r = 0.16$  in summer and  $r = 0.19$  in winter). These errors were thought to  
35 relate to the differences in the lifetime of SO<sub>2</sub> transported from the domain borders to the  
36 domain center being shorter than the timescale of the model bias.

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## 2.7 Summary

1 Of the sulfur oxides, SO<sub>2</sub> is the most abundant in the atmosphere, the most important in  
2 atmospheric chemistry, and the one most clearly linked to human health effects. Thus, the  
3 NAAQS are currently set using SO<sub>2</sub> as the indicator species. As a consequence of several  
4 U.S. air quality regulatory programs, emissions of SO<sub>2</sub> have declined by approximately  
5 72% for all NEI source categories during the time period 1990–2011 ([Section 2.2](#)).  
6 Coal-fired EGUs remain the dominant anthropogenic source by nearly an order of  
7 magnitude above the next highest source (coal-fired boilers), emitting 4.6 x 10<sup>6</sup> tons SO<sub>2</sub>  
8 annually, according to the 2011 NEI. Natural sources include volcanoes, wildfires, and  
9 biogenic sulfides that are intermittent and of limited spatial extent.

10 Beyond the size of the emissions source, the important variables that determine the  
11 concentration of SO<sub>2</sub> downwind of a source are the photochemical removal processes  
12 occurring in the emissions plume ([Section 2.3](#)) and local meteorology. The gas-phase  
13 oxidation of SO<sub>2</sub> by hydroxyl radical is slow in comparison to aqueous-phase oxidation  
14 in cloud and fog droplets. Clouds and fog can reduce local SO<sub>2</sub> concentrations by  
15 converting it to H<sub>2</sub>SO<sub>4</sub> in the droplet phase. Another gas-phase oxidation mechanism  
16 involves a Criegee intermediate biradical that participates in converting SO<sub>2</sub> to SO<sub>3</sub>.  
17 The Criegee-based SO<sub>2</sub> oxidation mechanism may amplify the rate of SO<sub>2</sub> removal in  
18 areas with high concentrations of Criegee precursors (i.e., low molecular weight organic  
19 gases, such as biogenic compounds, and unsaturated hydrocarbons) present downwind of  
20 industrial sites and refineries. The atmospheric SO<sub>2</sub> oxidation processes, coupled with  
21 variable meteorological conditions, including wind, atmospheric stability, humidity, and  
22 cloud/fog cover, influence the observed SO<sub>2</sub> concentrations at urban monitoring sites.

23 Changes were undertaken to the existing U.S. EPA monitoring network as a result of the  
24 new 1-h daily max primary NAAQS standard promulgated in 2010 ([Section 2.4](#)). First,  
25 the automated pulsed ultraviolet fluorescence (UVF) method, the method most  
26 commonly used by state and local monitoring agencies for NAAQS compliance, was  
27 designated as a FRM. Second, new SO<sub>2</sub> monitoring guidelines require states to report  
28 5-minute data in light of health effects evidence on lung function decrements among  
29 exercising individuals with asthma following a 5–10 minute exposure of SO<sub>2</sub> above  
30 200 ppb ([Section 5.2.1.2](#)). There are 380 monitoring sites across the U.S. reporting  
31 5-minute data. Analysis of environmental concentrations of SO<sub>2</sub> data reported in this  
32 chapter reflect the monitoring network changes, particularly the analysis of the recent  
33 5-minute data.

34 On a nationwide basis, the average 1-h daily max SO<sub>2</sub> concentration reported during  
35 2013–2015 is 5.4 ppb ([Section 2.5.2.1](#)). However, peak concentrations (99th percentile)

1 of the 1-h daily max SO<sub>2</sub> concentrations can be greater than 75 ppb at some monitoring  
2 sites located near large anthropogenic or natural sources (e.g., volcanoes). SO<sub>2</sub>  
3 concentration is highly variable across urban spatial scales ([Section 2.5.2.2](#)), exhibiting  
4 moderate to poor correlations between SO<sub>2</sub> concentrations measured at different  
5 monitoring sites across a metropolitan area. This high degree of urban spatial variability  
6 may not be fully captured by central site monitoring estimates.

7 Long-term concentration trends show a steady decline in the mean, 10th, and 90th  
8 percentile of the site-specific 99th percentile of the 1-h daily max SO<sub>2</sub> concentrations  
9 ([Section 2.5.3](#)). The data show a 76% decline in 99th percentile 1-h daily max SO<sub>2</sub>  
10 concentration over the period 1990–2015. Seasonal trends were examined for six focus  
11 areas, and only New York and, to a lesser extent, Houston, exhibited strong intra-annual  
12 trend in which cool season 1-h daily max SO<sub>2</sub> concentrations were higher than warm  
13 season 1-h daily max SO<sub>2</sub> concentrations. Diel patterns in 1-h avg SO<sub>2</sub> concentration  
14 mostly shows daytime concentrations peak in the morning or midday, and the time of the  
15 peak can vary by location and may be influenced by seasonal conditions.

16 Peak concentrations within an SO<sub>2</sub> plume can greatly exceed the mean concentration at  
17 the plume centerline, so that exposure to the peak may greatly exceed an hourly or daily  
18 SO<sub>2</sub> measurement ([Section 2.5.4](#)). PMRs obtained from comparing the 5-minute hourly  
19 max with the 1-h avg AQS data at sites where both measures were available  
20 simultaneously had a range of 1 to 5.5 with a median of 1.3. In a city with low SO<sub>2</sub>  
21 concentrations, a high PMR may still be related to elevated 5-minute hourly max SO<sub>2</sub>  
22 concentration. For example, overall 1-h daily max concentrations in the New York focus  
23 area were relatively low (highest 99th percentile 1-h daily max was 16.5 ppb), so a PMR  
24 of 2 or 3 would lead to a 5-minute hourly max of 33 or 49.5 ppb. In contrast, the  
25 1-h daily max concentrations in Gila County were much higher (highest 99th percentile  
26 1-h daily max was 247 ppb), which would suggest 5-minute hourly max concentrations of  
27 504 ppb if the PMR were 2 and of 741 ppb if the PMR were 3.

28 Contributions to background concentrations include natural emissions of SO<sub>2</sub> and  
29 photochemical reactions involving reduced sulfur compounds of natural origin, as well as  
30 the transport of sulfur compounds from outside of the U.S. ([Section 2.5.5](#)). In the U.S.  
31 Northwest, geothermal sources of SO<sub>2</sub> are responsible for 70 to 80% of the background  
32 SO<sub>2</sub> concentration; even so, total SO<sub>2</sub> concentrations are still on the order of ~2 ppb or  
33 less. In model simulations, background contributed less than 1% to SO<sub>2</sub> concentrations in  
34 surface air in 2001 throughout much of the contiguous U.S. Even with ambient  
35 concentrations for 2013–2015 that were roughly half the magnitude of those measured  
36 around 2001, the estimated background SO<sub>2</sub> would contribute only 2% to ambient SO<sub>2</sub>  
37 concentrations in most of the contiguous U.S.

1 Atmospheric modeling includes dispersion and chemical transport models to estimate  
2 SO<sub>2</sub> concentrations in locations where monitoring is not practical or sufficient  
3 ([Section 2.6](#)). Because existing ambient SO<sub>2</sub> monitors may not be sited in locations to  
4 capture peak 1-h daily max concentrations, the implementation program for the 2010  
5 primary SO<sub>2</sub> NAAQS allows for air quality modeling to be used to characterize air  
6 quality for informing designation decisions (75 FR 35520). Modeling is critical to  
7 assessing the impact of future sources or proposed modifications when monitoring cannot  
8 be informative, and for designing and implementing mitigation techniques.

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## Chapter 3 Exposure to Ambient Sulfur Dioxide

---

### 3.1 Introduction

1 The 2008 SO<sub>x</sub> ISA ([U.S. EPA, 2008d](#)) evaluated ambient SO<sub>2</sub> concentrations and  
2 exposure assessment in multiple microenvironments, presented methods for estimating  
3 personal and population exposure via monitoring and modeling, analyzed relationships  
4 between personal SO<sub>2</sub> exposure and ambient SO<sub>2</sub> concentrations, and discussed the  
5 implications of using ambient SO<sub>2</sub> concentrations to estimate exposure in epidemiologic  
6 studies. This chapter summarizes that information and presents new information  
7 regarding exposure to ambient SO<sub>2</sub>. The chapter will focus on the inhalation exposure  
8 route for SO<sub>2</sub> from the key sources described in [Chapter 2](#) because the presence of other  
9 SO<sub>x</sub> species in the atmosphere has not been demonstrated, as discussed previously.  
10 Exposure to particulate sulfate formed by oxidation of SO<sub>2</sub> is considered in the PM ISA  
11 ([U.S. EPA, 2009a](#)). Sections within the chapter are organized to first present broad  
12 exposure concepts applicable to air pollution in general, followed by SO<sub>2</sub>-specific  
13 material. Topics addressed in the chapter include methodological considerations for use  
14 of exposure data, and exposure assessment and epidemiologic inference. Many new  
15 studies are included in this chapter to better characterize exposure and understand  
16 exposure error. This material provides context for interpreting the epidemiologic studies  
17 described in [Chapter 5](#).

---

### 3.2 Conceptual Overview of Human Exposure

#### 3.2.1 Exposure Metrics

18  
19 A variety of metrics and terms are used to characterize air pollution exposure. They are  
20 described here at the beginning of the chapter to provide clarity for the subsequent  
21 discussion.

22 The *concentration* of an air pollutant is defined as the mass or volume of the pollutant in  
23 a given volume of air (e.g., µg/m<sup>3</sup> or ppb). Concentrations observed in outdoor locations  
24 are referred to as ambient concentrations. The term *exposure* refers to contact with a  
25 specific pollutant concentration over a certain period of time ([Zartarian et al., 2005](#)), in  
26 single or multiple locations. For example, contact with a concentration of 10 ppb SO<sub>2</sub> for  
27 1 hour would be referred to as a 1-hour exposure to 10 ppb SO<sub>2</sub>, and 10 ppb is referred to

1 as the *exposure concentration*. As discussed in [Chapter 4](#), dose incorporates the concept  
2 of intake into the body (via inhalation). Exposure concentrations are particularly relevant  
3 for interpreting controlled human exposure studies, where participants are exposed to a  
4 well-defined pollutant concentration, or panel epidemiologic studies that use personal  
5 exposure monitors. Ambient concentrations are more relevant to epidemiologic studies  
6 using measured or modeled concentrations.

7 A location where exposure occurs is referred to as a *microenvironment*, and an  
8 individual's daily exposure consists of the time-integrated concentrations in each of the  
9 microenvironments visited during the day. Ambient air pollution may penetrate indoors  
10 (see [Section 3.4.1.1](#) on infiltration), where it combines with air pollution from indoor  
11 sources (*nonambient air pollution*) to produce the total measured indoor concentration.  
12 Exposure to the ambient fraction of this concentration, together with exposure to ambient  
13 concentrations in outdoor microenvironments, is referred to as *ambient exposure* ([Wilson  
14 et al., 2000](#)).

15 Because personal exposures are not routinely measured, the term *surrogate* is used in this  
16 chapter to describe a quantity meant to estimate or represent exposure, such as an SO<sub>2</sub>  
17 concentration measured at a central site monitor ([Sarnat et al., 2000](#)). When surrogates  
18 are used for exposure assignment in epidemiologic studies, exposure misclassification or  
19 exposure error can result. *Exposure misclassification* refers to exposure error for  
20 categorical variables, such as diseased and nondiseased individuals. Exposure  
21 misclassification due to exposure assignment methods and spatial and temporal  
22 variability in pollutant concentrations may be either differential (i.e., systematic), or  
23 nondifferential (i.e., random). An example of differential misclassification is the use of  
24 geocoding to estimate air pollution exposure by proximity to roadways, because  
25 concentrations are different upwind and downwind of a major roadway ([Lane et al.,  
26 2013](#); [Singer et al., 2004](#)). Nondifferential misclassification refers to the situation where  
27 exposure characterization is similarly accurate across all groups.

28 Exposure misclassification and exposure error can result in bias and reduced precision of  
29 the effect estimate. *Bias* refers to the difference between the population-average  
30 measured and true exposure, while precision is a measure of the variation of  
31 measurement error in the population ([Armstrong et al., 1992](#)). Bias toward the null, or  
32 attenuation of the effect estimate, indicates an underestimate of the magnitude of the  
33 effect, and is characteristic of nondifferential measurement error. Bias away from the null  
34 can occur through differential exposure measurement error or under certain exposure  
35 scenarios ([Armstrong et al., 1992](#)).

36 *Exposure error* refers to the bias and uncertainty associated with using concentration  
37 metrics to represent the actual exposure of an individual or population ([Lipfert and](#)

1 [Wyzga, 1996](#)). Exposure error has two components: (1) exposure measurement error  
2 derived from uncertainty in the metric being used to represent exposure, and (2) use of a  
3 surrogate target parameter of interest in the epidemiologic study in lieu of the true  
4 exposure, which may be unobservable. Classical error is defined as error scattered around  
5 the true personal exposure and independent of the true exposure. Berkson error is defined  
6 as error scattered around the measured exposure surrogate (in most cases, the central site  
7 monitor measurement) and independent of the measured value ([Goldman et al., 2011](#);  
8 [Reeves et al., 1998](#)). [Section 3.4.4](#) provides additional definitions for specific types of  
9 exposure error and discusses the potential impact of such errors on epidemiologic study  
10 results.

---

### 3.2.2 Conceptual Model of Personal Exposure

11 A theoretical model of personal exposure is presented in this section to highlight  
12 measurable quantities and uncertainties. This model has been developed and presented in  
13 previous ISAs, most recently in the 2016 ISA for Oxides of Nitrogen ([U.S. EPA, 2016e](#)),  
14 and it is reproduced here to provide context for the current document.

15 An individual's time-integrated total exposure to SO<sub>2</sub> can be described based on a  
16 compartmentalization of the person's activities throughout a given time period:

$$E_T = \int C_j dt$$

Equation 3-1

17 where  $E_T$  = total exposure over a time period of interest,  $C_j$  = airborne SO<sub>2</sub> concentration  
18 at microenvironment  $j$ , and  $dt$  = portion of the time period spent in microenvironment  $j$ .  
19 Total exposure can be decomposed into a model that accounts for exposure to SO<sub>2</sub> of  
20 ambient ( $E_a$ ) and nonambient ( $E_{na}$ ) origin of the form:

$$E_T = E_a + E_{na}$$

Equation 3-2

21 Although indoor combustion of sulfur-containing fuels, particularly kerosene, is a  
22 nonambient source of SO<sub>2</sub> (see [Section 3.4.1](#)), these sources are specific to individuals  
23 and may not be important sources of population exposure. This ISA focuses on the  
24 ambient component of exposure because this is more relevant to the NAAQS review.  
25 Assuming steady-state outdoor conditions,  $E_a$  can be expressed in terms of the fraction of  
26 time spent in various outdoor and indoor (including enclosed microenvironments such as  
27 vehicles) microenvironments ([U.S. EPA, 2006](#); [Wilson et al., 2000](#)):

$$E_a = \sum f_o C_o + \sum f_i F_{inf,i} C_{o,i}$$

**Equation 3-3**

1 where  $f$  = fraction of the relevant time period (equivalent to  $dt$  in [Equation 3-1](#)); subscript  
 2  $o$  denotes outdoor microenvironments; subscript  $i$  denotes indoor microenvironments;  
 3 subscript  $o,i$  denotes outdoor microenvironments adjacent to a given indoor  
 4 microenvironment; and  $F_{inf,i}$  = infiltration factor for indoor microenvironment  $i$ .  
 5 [Equation 3-3](#) is subject to the constraint  $\sum f_o + \sum f_i = 1$  to reflect the total exposure over a  
 6 specified time period, and each term on the right-hand side of the equation has a  
 7 summation because it reflects various microenvironmental exposures. Here, “indoors”  
 8 refers to being inside any aspect of the built environment, [e.g., home, office buildings,  
 9 enclosed vehicles (automobiles, trains, buses), and/or recreational facilities (movie  
 10 theaters, restaurants, bars)]. “Outdoor” exposure can occur in parks or yards, on  
 11 sidewalks, and on bicycles or motorcycles. Assuming steady-state ventilation conditions,  
 12 the infiltration factor ( $F_{inf}$ ) is a function of the penetration ( $P$ ) of  $SO_2$  into the  
 13 microenvironment, the air exchange rate ( $a$ ) of the microenvironment, and the rate of  $SO_2$   
 14 loss ( $k$ ) in the microenvironment:

$$F_{inf} = \frac{Pa}{(a + k)}$$

**Equation 3-4**

15 In epidemiologic studies, the central site ambient  $SO_2$  concentration,  $C_a$ , is often used in  
 16 lieu of outdoor microenvironmental data to represent these exposures based on the  
 17 availability of data. Thus, it is often assumed that the local outdoor concentration  $C_o = C_a$   
 18 and that the fraction of time spent outdoors can be expressed cumulatively as  $f_o$ ; the  
 19 indoor terms still retain a summation because infiltration differs for different  
 20 microenvironments. If an epidemiologic study employs only  $C_a$ , then the assumed model  
 21 of an individual’s exposure to ambient  $SO_2$ , given in [Equation 3-3](#), is re-expressed solely  
 22 as a function of  $C_a$ :

$$E_a = (f_o + \sum f_i F_{inf,i}) C_a$$

**Equation 3-5**

23 The spatial variability of outdoor  $SO_2$  concentrations due to meteorology, topography,  
 24 and oxidation rates; the design of the epidemiologic study; and other factors determine  
 25 whether [Equation 3-5](#) is a reasonable approximation for [Equation 3-3](#). These equations  
 26 also assume steady-state microenvironmental concentrations. Errors and uncertainties  
 27 inherent in using [Equation 3-5](#) in lieu of [Equation 3-3](#) are described in [Section 3.4.4](#) with  
 28 respect to implications for interpreting epidemiologic studies. Epidemiologic studies may

1 use concentration measured at a central site monitor to represent ambient concentration;  
2 thus  $\alpha$ , the ratio between personal exposure to ambient SO<sub>2</sub> and the ambient concentration  
3 of SO<sub>2</sub>, is defined as:

$$\alpha = \frac{E_a}{C_a}$$

Equation 3-6

4 Combining [Equation 3-5](#) and [Equation 3-6](#) yields:

$$\alpha = f_o + \sum f_i F_{inf,i}$$

Equation 3-7

5 where  $\alpha$  varies between 0 and 1. Estimates of  $\alpha$  for SO<sub>2</sub> are provided in [Section 3.4.1.3](#). If  
6 a person's exposure occurs in a single microenvironment, the ambient component of a  
7 microenvironmental SO<sub>2</sub> concentration can be represented as the product of the ambient  
8 concentration and  $F_{inf}$ . Time-activity data and corresponding estimates of  $F_{inf}$  for each  
9 microenvironmental exposure are needed to compute an individual's  $\alpha$  with accuracy  
10 ([U.S. EPA, 2006](#)). In epidemiologic studies,  $\alpha$  is assumed to be constant in lieu of  
11 time-activity data and estimates of  $F_{inf}$ , which varies with building- and  
12 meteorology-related air exchange characteristics ([Section 3.4.1.1](#)). If important local  
13 outdoor sources and sinks exist that are not captured by central site monitors, then the  
14 ambient component of the local outdoor concentration may be estimated using dispersion  
15 models, land use regression (LUR) models, receptor models, fine-scale chemical  
16 transport models (CTMs), or some combination of these techniques. These techniques are  
17 described in [Section 3.3.2](#).

---

### 3.2.3 Exposure Considerations Specific to Sulfur Dioxide

18 The inhalation exposure pathway relevant for SO<sub>2</sub> is influenced by sources, chemistry,  
19 meteorology, and ambient concentrations, described in detail in [Chapter 2](#) and  
20 summarized briefly here. The vast majority of SO<sub>2</sub> is emitted by coal-fired EGUs  
21 ([Section 2.2](#)); the point source nature of these emissions contributes to the relatively high  
22 spatial variability of SO<sub>2</sub> concentrations (both ambient and exposure) compared with  
23 pollutants such as PM and O<sub>3</sub> ([Section 2.5](#); [Section 3.4.2.2](#)). Another contributing factor  
24 to spatial variability is the dispersion and oxidation of SO<sub>2</sub> in the atmosphere  
25 ([Section 2.3](#)), resulting in decreasing ambient SO<sub>2</sub> concentrations with increasing  
26 distance from the source. SO<sub>2</sub> travels as a plume, which may or may not impact portions  
27 of an urban area depending on meteorological conditions. Ambient SO<sub>2</sub> concentrations do  
28 not exhibit consistently strong temporal variability over daily or seasonal time scales

1 (Section 2.5); however, in some areas, concentrations are low during nighttime and show  
2 a daytime maximum, affecting temporal exposure patterns. Due to the relative lack of  
3 indoor SO<sub>2</sub> sources, personal SO<sub>2</sub> exposure is expected to be dominated by ambient  
4 exposure (Section 3.4.1.3).

---

### 3.3 Methodological Considerations for Use of Exposure Data

5 This section describes techniques that have been used to measure microenvironmental  
6 concentrations of SO<sub>2</sub> that serve as surrogates for personal SO<sub>2</sub> exposures in  
7 epidemiologic studies. Previous studies from the 2008 SO<sub>x</sub> ISA (U.S. EPA, 2008d) are  
8 described along with newer studies.

---

#### 3.3.1 Measurements

##### 3.3.1.1 Central Site Monitoring

9 Central site monitors are sited for the purpose of determining whether attainment goals  
10 are met under the Clean Air Act. However, central site monitoring ambient SO<sub>2</sub>  
11 concentration data are also often used in epidemiologic studies as a surrogate for  
12 exposure to SO<sub>2</sub>, as discussed in Section 3.4.4. Methods, errors, and uncertainties  
13 regarding measurements made by central site monitors are described in Section 2.4.  
14 The effect of errors and uncertainties due to instrumentation issues depends on  
15 epidemiologic study design, as described further in Section 3.4.4. Various uses of these  
16 data are possible depending on the design of the epidemiologic study. Short-term  
17 (e.g., daily, hourly) data can be used for time-series studies and long-term (e.g., annual  
18 average) data for longer term studies. For a given CBSA, central site monitors are sited at  
19 a fixed location based on the number of people living in the CBSA and the sources of  
20 SO<sub>2</sub> emissions (40 CFR 58, Appendix D). Even in CBSAs with multiple monitors, the  
21 monitors do not fully capture spatial variability in SO<sub>2</sub> concentration across the study  
22 area.

---

##### 3.3.1.2 Personal Monitoring Techniques

23 Personal SO<sub>2</sub> monitors have been used in studies characterizing relationships between  
24 indoor and outdoor SO<sub>2</sub> concentrations and relationships between personal exposure to  
25 SO<sub>2</sub> and ambient SO<sub>2</sub> concentrations (Section 3.4.1.3). Additionally, personal monitoring

1 is used infrequently in the epidemiologic studies described in [Chapter 5](#). As described in  
2 the 2008 SO<sub>x</sub> ISA ([U.S. EPA, 2008d](#)), both active and passive samplers have been used  
3 to measure personal SO<sub>2</sub> exposures. The Harvard-EPA annular denuder system is an  
4 active sampler initially developed to measure particles and acidic gases simultaneously  
5 ([Brauer et al., 1989](#); [Koutrakis et al., 1988](#)). The system draws air at 4 L/minute past an  
6 impactor to remove particles and then through an annular denuder coated with sodium  
7 carbonate to trap SO<sub>2</sub> and other acidic gases. Gases collected within the denuder are  
8 extracted with ultrapure water and analyzed by ion chromatography. The detection limit  
9 depends on the sensitivity of the ion chromatography analysis as well as the volume of air  
10 sampled, and is typically below 1 ppb ([Brauer et al., 1989](#)), with a collection efficiency of  
11 99.3% ([Koutrakis et al., 1988](#)). Another active sampler, developed for a study in  
12 Baltimore, MD, used a hollow glass denuder coated with triethanolamine, with SO<sub>2</sub>  
13 detection by ion chromatography ([Chang et al., 2000](#)). At a sampling rate of  
14 100 mL/minute for 1 hour, the detection limit was 62 ppb, resulting in many of the 1-hour  
15 SO<sub>2</sub> samples being below the detection limit; see [Section 2.5](#) for a summary of typical  
16 ambient SO<sub>2</sub> concentrations.

17 Passive badge-type samplers have also been developed to eliminate the need for a  
18 powered sampling pump. A common version is manufactured by Ogawa USA, Inc. and  
19 consists of a cellulose fiber filter coated with triethanolamine ([Ogawa & Co, 2007](#)). SO<sub>2</sub>  
20 is detected via ion chromatography with a reported detection limit for a 24-hour sample  
21 of 2–6 ppb ([Sarnat et al., 2006](#); [Sarnat et al., 2005](#); [Sarnat et al., 2000](#)). Passive badge  
22 samplers can also be combined with active particle samplers to create a multipollutant  
23 sampler [e.g., [Demokritou et al. \(2001\)](#)]. Passive badges for measuring SO<sub>2</sub>  
24 concentrations are not very sensitive to ambient concentration level, temperature, relative  
25 humidity, or exposure duration, unlike passive badges for measuring NO<sub>2</sub> ([Swaans et al.,  
26 2007](#)). The cumulative sampling approach and the relatively high detection limit of the  
27 passive badges makes them mainly suitable for monitoring periods of 24 hours or greater,  
28 which limits their ability to measure short-term daily fluctuations in personal SO<sub>2</sub>  
29 exposures.

---

### 3.3.2 Modeling

30 Models can be used to predict the outdoor concentration of SO<sub>2</sub> across geographic  
31 regions or at specific locations of interest where people spend time (e.g., outdoors at  
32 homes, schools, workplaces, roadways). The modeled concentration can be used as a  
33 surrogate for human exposure to SO<sub>2</sub>. Models do not estimate exposures to ambient SO<sub>2</sub>  
34 directly, because time-activity patterns and indoor concentrations of ambient SO<sub>2</sub> in  
35 various microenvironments are not considered. Approaches described below include

1 source proximity models (SPM), LUR, inverse distance weighting (IDW) models,  
2 dispersion models, CTM, and microenvironmental models. These models can be  
3 employed at urban, regional, or national scales to estimate daily, or longer, average  
4 ambient SO<sub>2</sub> concentrations as an exposure surrogate. Short-term (e.g., daily) ambient  
5 SO<sub>2</sub> concentration estimates are needed for ambient SO<sub>2</sub> exposure surrogates in acute  
6 exposure assessments, whereas long-term (e.g., annual) ambient SO<sub>2</sub> concentration  
7 estimates can be used for ambient SO<sub>2</sub> exposure surrogates in chronic exposure  
8 assessments.

---

### 3.3.2.1 Source Proximity Models

9 SPMs provide a simple method to estimate ambient SO<sub>2</sub> concentration as a surrogate for  
10 ambient SO<sub>2</sub> exposure. These models calculate the distance from receptors (e.g., homes,  
11 schools) to a source of SO<sub>2</sub> emissions (e.g., industrial facilities). It is assumed that  
12 ambient SO<sub>2</sub> concentration is some function of distance from the source. SO<sub>2</sub> emitted  
13 from a point source is thought to disperse as a meandering plume, such that average  
14 ambient SO<sub>2</sub> concentration decreases with distance from the source ([Section 2.6.1](#)). These  
15 models do not necessarily account for the effect of stack height to limit ambient SO<sub>2</sub>  
16 concentrations in the immediate vicinity of the point source. [Burstyn et al. \(2008\)](#)  
17 avoided the stack height issue by modeling ambient SO<sub>2</sub> concentration as a function of  
18 the inverse distance within 2- and 50-km buffers of each gas plant and oil well. In another  
19 study, proximity to source was treated as a Boolean variable as a surrogate for high and  
20 moderate ambient SO<sub>2</sub> exposure ([Cambra et al., 2011](#)). Likewise, [Liu et al. \(2012b\)](#)  
21 computed relative risk of respiratory disease using ZIP codes with fuel-fired power plants  
22 compared with the reference of ZIP codes without fuel-fired power plants. One study  
23 specifically examined near-road proximity and ambient SO<sub>2</sub> concentration and found no  
24 statistically significant decrease in ambient SO<sub>2</sub> concentration near a highway ([McAdam  
25 et al., 2011](#)).

26 SPMs are widely applied for exposure assessments because few input data are required.  
27 The main limitation of an SPM is the potential for exposure error because none of the  
28 factors affecting emission rates, dispersion, and photochemical activity of pollutants  
29 (e.g., emission rates, atmospheric physics, chemistry, meteorology) are considered [e.g.,  
30 [Zou et al. \(2009a\)](#)].

31 To improve the accuracy of SPMs in providing a surrogate for exposure, an  
32 emission-weighted proximity model (EWPM) was developed that considers the emission  
33 rate and duration of each ambient SO<sub>2</sub> point source, in addition to the distance from  
34 source. [Zou et al. \(2009b\)](#) evaluated the SPM and EWPM to estimate ambient SO<sub>2</sub>

1 concentrations in Dallas and Ellis counties, TX. Normalized ambient SO<sub>2</sub> concentration  
2 estimates based on SPM and EWPM were compared to normalized ambient SO<sub>2</sub>  
3 concentration measurements at three monitoring sites and found that EWPM-based  
4 ambient SO<sub>2</sub> concentration estimates agreed more closely to the observed ambient SO<sub>2</sub>  
5 concentrations than SPM-based ambient SO<sub>2</sub> concentration estimates. Epidemiologic  
6 estimates of risk also were in closer agreement between EWPM and AERMOD compared  
7 with the comparison of results using SPM and AERMOD ([Zou et al., 2011](#)). In addition,  
8 surface maps of EWPM- and SPM-predicted ambient SO<sub>2</sub> concentrations across two  
9 counties showed that with SPM risk of exposure is usually overestimated in the region of  
10 dense emission sources and underestimated where emission sources were sparse ([Zou et  
11 al., 2009b](#)). As compared to SPM, EWPM more accurately predicted ambient SO<sub>2</sub>  
12 concentrations that individuals were exposed to across these regions.

---

### 3.3.2.2 Land Use Regression Models

13 LUR models are used to estimate ambient SO<sub>2</sub> concentration as a surrogate for exposure  
14 in some large health studies, because they provide spatial variability in estimates of  
15 ambient SO<sub>2</sub> concentration across the geographic area of the study population. A detailed  
16 description of LUR models is provided in Chapter 3 of the 2016 ISA for Oxides of  
17 Nitrogen ([U.S. EPA, 2016e](#)). Briefly, LUR fits a multiple linear regression model of  
18 concentration based on local data (e.g., proximity to SO<sub>2</sub> emissions sources, road length,  
19 land use, population density) and then applies that model to locations without monitors as  
20 an attempt to increase heterogeneity in the spatial resolution of the ambient SO<sub>2</sub>  
21 concentration field compared with other methods, such as central site monitoring  
22 ([Marshall et al., 2008](#)). A structured framework for comparing modeling approaches  
23 could occur with reporting of metrics such as spatial scale, averaging time, out-of-sample  
24 coefficient of variation (i.e., goodness of fit of the model with data not used to fit it to  
25 cross-validate the model), in-sample coefficient of variation (i.e., goodness of fit of the  
26 model with data used to fit it), and root mean squared error (RMSE). However, studies in  
27 the literature of LUR model results do not consistently report all of these parameters.  
28 The discussion of LUR models below includes the metrics provided in specific papers.

29 Models are typically calibrated using ambient SO<sub>2</sub> concentration data from passive  
30 sampler measurements and several local predictor variables. Given that most passive  
31 ambient SO<sub>2</sub> concentration measurement methods are not designed for short-term  
32 sampling, LUR models are typically based on several days, weeks, or years of data and  
33 thus do not account well for short-term temporal variability in the ambient SO<sub>2</sub>  
34 concentration estimates. Hence, LUR is commonly used to estimate air pollution  
35 exposure in long-term epidemiologic studies. Although LUR is usually employed for

1 NO<sub>2</sub>, it has also been used to study spatial variability in ambient SO<sub>2</sub> concentration in a  
2 small number of studies [e.g., [Atari et al. \(2008\)](#)]. Several methodological issues must be  
3 considered when interpreting LUR model results. These issues include number of  
4 measurement sites used to fit the statistical model, predictor variable selection, and  
5 comparison of LUR performance among LUR model formulations and with other  
6 models. These issues affect how well the spatial variability of ambient SO<sub>2</sub> concentration  
7 in a city is represented by the LUR. For example, in a study incorporating aerosol optical  
8 density from satellite measurements and three-dimensional building data with land use  
9 variables in predicting variation in SO<sub>2</sub> concentration across space, the LUR model fit  
10 improved from adjusted  $R^2 = 0.52$  to  $0.71$  ([Gong et al., 2016](#)).

11 LUR models have been applied to estimate ambient SO<sub>2</sub> concentrations in close  
12 proximity to industrial SO<sub>2</sub> sources. [Atari et al. \(2008\)](#) developed an LUR model to  
13 predict ambient SO<sub>2</sub> concentrations in Sarnia, Ontario, Canada, an area known as  
14 “Chemical Valley” for its high density of chemical industries. Ambient SO<sub>2</sub>  
15 concentrations measured by passive badge monitors were used to “train” the model, and  
16 the explanatory variables for the LUR model were distance to an industrial zone, location  
17 within 1,200 m of industrial areas, and location within 100 m of major roads.  
18 Measurements of ambient SO<sub>2</sub> concentration for model training were collected with  
19 passive samplers at 37 locations across the city for 2 weeks in the fall of 2005, with an  
20 average concentration of 3.4 ppb. The in-sample coefficient of determination was  
21  $R^2 = 0.66$ . An out-of-sample coefficient of determination was calculated to cross-validate  
22 the model. The out-of-sample coefficient ranged from  $R^2 = 0.62$  to  $R^2 = 0.73$ , and the  
23 RMSE of the out-of-sample predictions were 0.3 to 1 ppb. The ambient SO<sub>2</sub>  
24 concentration validation produced a wider range of errors and lower out-of-sample  $R^2$   
25 compared with LUR simulations for ambient NO<sub>2</sub> concentration; [Atari et al. \(2008\)](#)  
26 attributed this moderate validation to a skewed ambient SO<sub>2</sub> concentration distribution  
27 compared with the concentration distribution of ambient NO<sub>2</sub>, although skewness metrics  
28 were not provided.

29 Spatial variability in ambient SO<sub>2</sub> concentrations offered by LUR has been used to  
30 estimate inter-individual variability in exposure by assuming the ambient SO<sub>2</sub>  
31 concentration modeled at the study participants’ homes matched their exposure. Ambient  
32 SO<sub>2</sub> concentrations computed using LUR by [Atari et al. \(2008\)](#) were used by [Atari et al.](#)  
33 [\(2009\)](#) to correlate modeled ambient SO<sub>2</sub> concentrations with individual and community  
34 perceptions of odor, by [Oiamo and Luginaah \(2013\)](#) to study whether males and females  
35 are affected differently by ambient SO<sub>2</sub> exposure, and by [Oiamo et al. \(2011\)](#) to  
36 investigate the relationship between estimated ambient SO<sub>2</sub> exposure and access to a  
37 general practitioner. [Kanaroglou et al. \(2013\)](#) used a spatial autocorrelation LUR model  
38 to estimate ambient SO<sub>2</sub> concentrations, in which the spatial autocorrelation component

1 of the model's residuals was removed. [Kanaroglou et al. \(2013\)](#) applied the spatial  
2 autocorrelation LUR model in the vicinity of an industrial area in Hamilton, Ontario,  
3 Canada and observed that location and difference between wind direction and direction of  
4 the industrial area to the receptor were each statistically significant predictors of ambient  
5 SO<sub>2</sub> concentration ( $p < 0.001$ , RMSE = 1.24).

6 LUR has also been applied to predict ambient SO<sub>2</sub> concentrations in the vicinity of urban  
7 sources. [Clougherty et al. \(2013\)](#) modeled concentrations of ambient SO<sub>2</sub>, NO<sub>2</sub>, PM<sub>2.5</sub>,  
8 and black carbon (BC) across New York City, NY. Ambient SO<sub>2</sub> concentration was  
9 predicted by the reference site mean (partial  $R^2 = 0.35$ ), number of oil-burning units  
10 (partial  $R^2 = 0.36$ ), and nighttime population within 1 km (partial  $R^2 = 0.06$ ) to give an  
11 overall out-of-sample model fit of  $R^2 = 0.77$ , where  $R^2$  was based on the comparison  
12 between raw ambient SO<sub>2</sub> concentrations and model predictions. Traffic covariates were  
13 not included in the model. The study authors thought these findings reflected the presence  
14 of large combustion boilers in Manhattan and western Bronx, where ambient SO<sub>2</sub>  
15 concentrations were predicted to be highest because sulfur content in residential heating  
16 fuel is high. Ambient SO<sub>2</sub> concentration was not influenced by vehicle traffic, unlike the  
17 other air pollutants studied. [Beelen et al. \(2007\)](#) modeled ambient SO<sub>2</sub>, NO<sub>2</sub>, NO, and  
18 black smoke (BS) concentrations as the sum of regional, urban, and local components.  
19 LUR was applied at the urban level to indicate land use (as location in a nonrural, urban,  
20 or industrial area) and at the local level to indicate traffic intensity with the combined  
21 spatial scale model in-sample  $R^2 = 0.56$ . The analysis used data from 1999–2000, when  
22 diesel fuel contained higher concentrations of sulfur, prior to 2006 and 2007 when the  
23 fuel standards promulgated in 2001 (66 FR 5002) reducing sulfur concentrations in diesel  
24 fuel took effect for highway vehicles and heavy-duty vehicles, respectively.

25 The out-of-sample RMSE was 1.6 ppb for the background model and 1.2 ppb for the  
26 urban model; RMSE was not reported for the local model. Ambient SO<sub>2</sub> concentrations  
27 modeled in the [Beelen et al. \(2007\)](#) study were used as exposure estimates in a  
28 longitudinal cohort study of vascular damage among young adults [see [Section 5.3.2.5](#)  
29 and [Lenters et al. \(2010\)](#)]. [Wheeler et al. \(2008\)](#) applied LUR for a study of ambient SO<sub>2</sub>  
30 concentration to estimate exposure in Windsor, Ontario and found that distance to the  
31 Ambassador Bridge, housing density, and SO<sub>2</sub> emission sources from Detroit within 3 km  
32 were all significant predictors of ambient SO<sub>2</sub> concentration with in-sample  $R^2 = 0.69$  and  
33 out-of-sample  $R^2 = 0.65$ . [Wheeler et al. \(2008\)](#) also evaluated LUR performance for  
34 predicting ambient SO<sub>2</sub> concentration across seasons by comparing the LUR results with  
35 measurements to estimate air pollutant exposure in Windsor, Ontario. They found that  
36 correlation of summer predictions of ambient SO<sub>2</sub> concentrations with those from other  
37 seasons was lower, suggesting that photochemistry might not be well represented in the  
38 LUR model.

---

### 3.3.2.3 Inverse Distance Weighting

1 IDW, in which ambient SO<sub>2</sub> concentration at a receptor point is calculated as the  
2 weighted average of ambient SO<sub>2</sub> concentration measured at monitoring locations, has  
3 been used to estimate exposure based on ambient SO<sub>2</sub> concentration surfaces. Several  
4 recent studies using IDW have been published. The weighting factor is an inverse  
5 function of distance between the receptor and the monitor. For example, [Brauer et al.  
6 \(2008\)](#) and [MacIntyre et al. \(2011\)](#) estimated exposure to ambient SO<sub>2</sub> and other  
7 industrial pollutants within 10 km of point sources using an IDW sum of ambient SO<sub>2</sub>  
8 concentration and the three closest monitors within 50 km for application in  
9 epidemiologic models ([Clark et al., 2010](#)). Often, the weighting factor is the inverse  
10 distance raised to some power, and a higher power is applied to increase the weight on  
11 monitors that are closer to the receptor. [Rivera-González et al. \(2015\)](#) applied an  
12 inverse-distance-squared weighting and compared the results with a citywide average,  
13 use of the nearest monitor, or kriging to develop an ambient SO<sub>2</sub> concentration surface.  
14 The results from IDW were correlated with the other three methods ( $r = 0.88\text{--}0.97$ ), and  
15 the mean ambient SO<sub>2</sub> concentration estimated with IDW was within 10% of the mean  
16 computed with the other methods. However, [Neupane et al. \(2010\)](#) estimated the ambient  
17 SO<sub>2</sub> concentration surface using both bicubic spline interpolation and IDW for a study of  
18 long-term exposure to air pollutants and risk of hospitalization for pneumonia in  
19 Hamilton, Ontario, Canada in a case-control study design. Bicubic spline interpolation  
20 produced a lower mean ambient SO<sub>2</sub> concentration and larger IQR compared with IDW;  
21 the odds ratio (OR) was higher for the cubic splines model [OR: 0.23, 95% confidence  
22 interval (CI): 0.02–0.45] compared with the IDW model (OR: 0.06, 95% CI:  
23 –0.06–0.18), probably due to greater variability in the ambient SO<sub>2</sub> concentration data.

---

### 3.3.2.4 Dispersion Models

24 Gaussian dispersion models have been applied to estimate ambient SO<sub>2</sub> concentration as  
25 a surrogate for human exposure to SO<sub>2</sub>. A detailed description of Gaussian dispersion  
26 modeling, along with its strengths and limitations for modeling ambient SO<sub>2</sub>  
27 concentrations, can be found in [Section 2.6](#). This section highlights examples of using  
28 dispersion models to estimate ambient SO<sub>2</sub> concentration as a surrogate for exposure.

29 [Zou et al. \(2009c\)](#) developed a hybrid modeling system to estimate source-specific  
30 ambient SO<sub>2</sub> concentration across space as a surrogate for population exposure to  
31 ambient SO<sub>2</sub> in Dallas County, TX. First, an AERMOD dispersion model was run for  
32 three source scenarios (vehicle only, industrial only, and combined vehicle and  
33 industrial), and kriging interpolation was applied to the modeling results to produce a

1 monthly average ambient SO<sub>2</sub> concentration grid map (100 m × 100 m). The population  
2 exposure was next estimated by multiplying the ambient SO<sub>2</sub> concentration value and the  
3 corresponding population density value for each grid cell (100 m × 100 m) and for the  
4 three source classifications. The results showed that monthly population SO<sub>2</sub> exposure  
5 concentrations were moderately correlated with simulated ambient SO<sub>2</sub> concentrations  
6 from vehicle sources ( $r = 0.440$ ) and weakly correlated with ambient SO<sub>2</sub> concentrations  
7 from industrial sources ( $r = 0.069$ ); this study used emissions data from the year 2000,  
8 before the ultra-low sulfur diesel fuel regulations were enacted.

9 Lagrangian particle modeling has also been used to estimate ambient SO<sub>x</sub> concentration  
10 as a surrogate for ambient SO<sub>x</sub> exposure from specific sources ([Ancona et al., 2015](#)) to  
11 study the relationship of long-term exposure to SO<sub>x</sub> with mortality for all-causes  
12 ([Section 5.5.2.2](#)), cardiovascular disease ([Section 5.3.2.2](#)), and cancer ([Section 5.6.1](#)).  
13 The Lagrangian particle model tracks the movement of SO<sub>x</sub> as nonreactive parcels  
14 (i.e., massless particles), considering SO<sub>x</sub> to be a marker of the emission source  
15 representing some combination of directly emitted SO<sub>2</sub> and sulfate formed in the  
16 atmosphere ([Section 2.3](#)). [Gariazzo et al. \(2004\)](#) compared this type of Lagrangian  
17 particle model against ambient SO<sub>2</sub> concentration measurements and observed reasonable  
18 agreement, although the observations seemed to lag the modeled ambient SO<sub>2</sub>  
19 concentration at times. The results suggest that the model would have provided a  
20 reasonable estimate of exposure in the [Ancona et al. \(2015\)](#) study, especially given the  
21 long-term nature of the study.

---

### 3.3.2.5 Chemical Transport Models

22 Ambient SO<sub>2</sub> concentrations calculated with CTMs, such as the CMAQ model, are  
23 sometimes used to estimate human exposure to ambient SO<sub>2</sub> ([Section 2.6](#)). For example,  
24 [Lipfert et al. \(2009\)](#) estimated ambient SO<sub>2</sub> concentration based on the CMAQ model for  
25 use as an exposure surrogate. Annual average ambient SO<sub>2</sub> concentrations were estimated  
26 with a 36-km by 36-km grid across the contiguous U.S. The modeled ambient SO<sub>2</sub>  
27 concentrations were used as exposure surrogates to determine their association with  
28 county-level mortality data for the Washington University-Electric Power Research  
29 Institute Veterans Cohort Mortality Study. To assign exposures at the county level, the  
30 CMAQ grid that included the largest city within each county was determined, and the  
31 associated CMAQ ambient SO<sub>2</sub> concentration was used as the exposure metric for the  
32 entire county.

33 CTMs can be applied in epidemiologic studies of either short- or long-term exposure to  
34 ambient SO<sub>2</sub> but are more commonly used in long-term ambient SO<sub>2</sub> exposure studies.

1 Given observed biases in the CTMs [e.g., [U.S. EPA \(2008c\)](#)], much attention has been  
2 given to bias correction of these models for application in exposure assessment. [Chen et  
3 al. \(2014a\)](#) evaluated CMAQ v4.7.1 results for several pollutants and found that ambient  
4 SO<sub>2</sub> concentration was underpredicted by roughly a factor of two, but this problem was  
5 largely ameliorated through bias correction techniques. Improvements to modeling  
6 ambient SO<sub>2</sub>-related reactions have been corrected in CMAQ v5.0.2, so that ambient SO<sub>2</sub>  
7 concentrations used for exposure surrogates from this or later versions would have  
8 smaller exposure errors.

9 One major limitation of CTMs for estimating ambient SO<sub>2</sub> concentrations as exposure  
10 surrogates is that the grid resolution, typically between 4 and 36 km, can be much larger  
11 than the length scale of the meandering plume upon touch-down. This limitation presents  
12 the possibility that ambient SO<sub>2</sub> concentrations can be underestimated along the plume  
13 path when localized peaks are averaged over space. [Baldasano et al. \(2014\)](#) recognized  
14 this limitation and merged HYSPLIT with a CTM simulation of ambient SO<sub>2</sub> and PM<sub>10</sub>  
15 transport in the vicinity of a refinery. HYSPLIT models dispersion of pollutants, such as  
16 ambient SO<sub>2</sub>, as particle trajectories; the WRF meteorological model is coupled with the  
17 particle trajectory model to account for wind speed, wind direction, and atmospheric  
18 turbulence. [Ching et al. \(2006\)](#) nested smaller grids (1, 4, 12 km) within larger grids  
19 (36 km) to improve spatial variability of the simulation. Similarly, [Karamchandani et al.  
20 \(2010\)](#) coupled a plume-in-grid model with CTM that treats dispersion as a Gaussian  
21 process with parameters that are set using micrometeorological conditions. Inclusion of  
22 subgrid-scale modeling enables calculation of the ambient SO<sub>2</sub> plume at finer spatial  
23 scales so that maximum ambient SO<sub>2</sub> concentration, and potentially maximum exposures,  
24 can be estimated by the model suite ([Baldasano et al., 2014](#)).

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### 3.3.2.6 Microenvironmental Exposure Models

25 Microenvironmental exposure models are designed to account for variations in the  
26 amount of time people spend in different locations by using time-weighted SO<sub>2</sub>  
27 concentrations in each microenvironment (e.g., outdoors; indoors at home, school,  
28 workplace; in-vehicle) for the exposure surrogate. Models such as SHEDS and APEX are  
29 used occasionally for exposure assessment in epidemiologic studies ([Dionisio et al.,  
30 2014](#); [Mannshardt et al., 2013](#); [Chang et al., 2012a](#)), and they are also used for the risk  
31 assessment performed as part of the NAAQS review process, as was done for the risk and  
32 exposure assessment during the last review of the SO<sub>2</sub> NAAQS ([U.S. EPA, 2009b](#)).

33 The fundamental principles of stochastic population exposure models are described in  
34 detail in the 2008 NO<sub>x</sub> ISA Annex 3.6 ([U.S. EPA, 2008a](#)). Briefly, the models combine

1 ambient concentration data with information on infiltration into enclosed  
2 microenvironments, such as buildings and vehicles (see [Section 3.4.1.1](#)), to estimate  
3 microenvironmental concentrations. The models then use demographic variables such as  
4 age and sex to select appropriate activity patterns from a database. For the risk  
5 assessment done during the last review of the SO<sub>2</sub> NAAQS, the U.S. EPA used CHAD,  
6 which is described in [Section 3.4.2.1](#) and in the 2016 NO<sub>x</sub> ISA ([U.S. EPA, 2016e](#)).  
7 Inhalation rates are determined from the level of effort associated with each activity  
8 (e.g., sitting, walking, or running). Inhalation rates and microenvironmental  
9 concentrations are combined to estimate dose. Depending on the availability of controlled  
10 human exposure data, response functions based either on microenvironmental exposure  
11 concentrations or inhaled dose are used to characterize expected health effects. For  
12 population-level exposure assessments, exposure models such as SHEDS and APEX  
13 estimate the distribution of exposures across the population of interest ([U.S. EPA, 2012c](#);  
14 [Burke et al., 2001](#)).

15 To improve the characterization of activity patterns, mobile electronic devices, such as  
16 smartphones with embedded GPS receivers and dedicated GPS data loggers, are  
17 increasingly used to collect time-location information. However, manual processing of  
18 GPS data to determine time spent in different microenvironments is limited due to large  
19 (potentially thousands of samples per person per day) and multidimensional (location,  
20 speed, time, signal quality) data sets, missing data due to loss of GPS signal reception  
21 while inside certain buildings, and difficulty discriminating among certain  
22 microenvironments (e.g., wooden structures have no substantial indoor/outdoor  
23 differences in satellite signal strength). To address these limitations, automated  
24 microenvironmental classification models have been developed ([Breen et al., 2014a](#); [Kim  
25 et al., 2012](#); [Wu et al., 2011a](#); [Adams et al., 2009](#); [Elgethun et al., 2007](#)). For example,  
26 [Breen et al. \(2014a\)](#) recently developed a classification model called MicroTrac to  
27 estimate time of day and duration spent in eight microenvironments (indoors and  
28 outdoors at home, work, school; inside vehicles; other locations) from GPS data and  
29 geocoded building boundaries. MicroTrac estimates were compared with diary data and  
30 correctly classified the microenvironment for 99.5% of the daily time spent by the  
31 participants. In conjunction with accelerometers, air pollutant monitors, and health  
32 monitors, GPS-based time-activity data and related monitors have the potential to reduce  
33 error in exposure assessment ([NRC, 2012](#)). Although these techniques are promising,  
34 researchers to date have not applied them to estimate exposures to SO<sub>2</sub> or to large field  
35 studies that could provide activity patterns suitable for inclusion in CHAD.

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### 3.3.3 Choice of Exposure Metrics in Epidemiologic Studies

1 Epidemiologic studies use a variety of methods to assign a surrogate for ambient SO<sub>2</sub>  
2 exposure. Study design, data availability, and research objectives are all important factors  
3 when selecting an exposure assessment method. Common methods for assigning an  
4 exposure surrogate from monitoring data include using ambient SO<sub>2</sub> concentration  
5 measured at a single monitor to represent population exposure and averaging ambient  
6 SO<sub>2</sub> concentrations from multiple monitors. Investigators may also use statistical  
7 adjustment methods, such as trimming extreme values, to prepare the ambient SO<sub>2</sub>  
8 exposure concentration data. Epidemiologic study design influences the relevance and  
9 utility of exposure metrics. [Table 3-1](#) summarizes various metrics used in epidemiologic  
10 studies of ambient SO<sub>2</sub> exposure, appropriate applications for the metrics, and errors and  
11 uncertainties that may be associated with the metrics.

---

## 3.4 Exposure Assessment, Error, and Epidemiologic Inference

12 This section describes exposure assessment issues related to the use of surrogates for  
13 ambient SO<sub>2</sub> exposure in epidemiologic studies that may influence or introduce error into  
14 the observed health effect estimate.

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### 3.4.1 Relationships between Personal Exposure and Ambient Concentration

15 Several factors influence the relationship between personal SO<sub>2</sub> exposure and ambient  
16 SO<sub>2</sub> concentration. Indoor SO<sub>2</sub> concentrations are highly dependent on air exchange rate  
17 (AER) due to the lack of indoor SO<sub>2</sub> sources and the rapid deposition of ambient SO<sub>2</sub>  
18 after it penetrates into enclosed microenvironments ([Section 3.4.1.1](#)). Generally, indoor  
19 SO<sub>2</sub> concentrations are lower than ambient SO<sub>2</sub> concentrations measured outdoors.  
20 Because people spend the bulk of their time indoors ([Section 3.4.2.1](#)), personal SO<sub>2</sub>  
21 exposures are often much lower than ambient SO<sub>2</sub> concentrations. For example, [Brown et](#)  
22 [al. \(2009\)](#) reported the mean winter personal SO<sub>2</sub> exposure concentrations in Boston to be  
23 1.8 ppb, while the ambient SO<sub>2</sub> concentration was 11.3 ppb. Both personal SO<sub>2</sub> exposure  
24 concentration and ambient SO<sub>2</sub> concentration were even lower in summer, with mean  
25 values of near zero and 3.6 ppb, respectively. The following sections describe studies  
26 evaluating AER, relationships between indoor and outdoor SO<sub>2</sub> concentrations, and  
27 personal-ambient relationships for SO<sub>2</sub>.

**Table 3-1 Summary of exposure assignment methods, their typical use in sulfur dioxide epidemiologic studies, strengths, limitations, and related errors and uncertainties.**

Exposure Assignment Method	Description	Epidemiologic Application	Strengths	Limitations	Errors and Uncertainties
Central site monitors (Section 3.3.1.1)	A FRM or FEM monitor located at a fixed location to measure ambient SO <sub>2</sub> concentration	Short-term community time-series studies: surrogate for ambient SO <sub>2</sub> exposure of a population within a city	Ambient SO <sub>2</sub> concentration measurements undergo rigorous quality assurance	Measurements of ambient SO <sub>2</sub> concentration made at a fixed location may differ from an exposed individual's true exposure, and no spatial variation is assumed	Correlation between outdoor SO <sub>2</sub> concentrations proximal to the receptors and ambient SO <sub>2</sub> concentration measurements typically decreases with increasing distance from the monitor, potentially leading to decreased precision and bias towards the null
		Long-term epidemiologic studies: surrogate for ambient SO <sub>2</sub> exposure to compare populations among multiple cities			Potential for bias and reduced precision if the monitor site does not correspond to the location of the exposed population
Active personal exposure monitors (Section 3.3.1.2)	Air is pulled through a pump and sampled for ambient SO <sub>2</sub> concentration using ion chromatography to measure personal SO <sub>2</sub> exposure	Short-term panel epidemiologic studies: SO <sub>2</sub> exposure (e.g., personal or residential samples) within a geographic area	SO <sub>2</sub> concentrations are obtained at the site of the exposed person	High detection limit	High detection limit and potential for nonambient SO <sub>2</sub> exposure sampling may lead to reduced precision
		Long-term epidemiologic studies: SO <sub>2</sub> exposure within a city or among multiple cities			Potential for nonambient SO <sub>2</sub> exposure sampling may lead to bias and reduced precision

**Table 3-1 (Continued): Summary of exposure assignment methods, their typical use in sulfur dioxide epidemiologic studies, strengths, limitations, and related errors and uncertainties.**

<b>Exposure Assignment Method</b>	<b>Description</b>	<b>Epidemiologic Application</b>	<b>Strengths</b>	<b>Limitations</b>	<b>Errors and Uncertainties</b>
Passive personal exposure monitors (Section 3.3.1.2)	SO <sub>2</sub> is captured on a coated filter via passive exposure for a time period to measure a personal or area sample	Long-term epidemiologic studies: ambient SO <sub>2</sub> exposure within a city or among multiple cities	SO <sub>2</sub> concentrations are obtained at the site of the exposed person	Integrated sample does not allow for time-series analysis; high detection limit	High detection limit and potential for nonambient SO <sub>2</sub> exposure sampling may lead to bias and reduced precision
Source proximity model (Section 3.3.2.1)	Ambient SO <sub>2</sub> concentrations are estimated from distance of receptor from source	Long-term epidemiologic studies: surrogate for ambient SO <sub>2</sub> exposure within a city or among multiple cities or regions	Few input data required	Does not consider emission rate and duration, atmospheric chemistry, or physics	Potential for bias and reduced precision if ambient SO <sub>2</sub> concentration at a receptor location is higher or lower than the average ambient SO <sub>2</sub> concentration over the area of the circle formed around the source with radius equal to the distance between the source and receptor
Emission weighted proximity model (Section 3.3.2.1)	Ambient SO <sub>2</sub> concentrations are estimated from distance of receptor to pollution source, emission rate, and duration	Long-term epidemiologic studies: surrogate for ambient SO <sub>2</sub> exposure within a city or among multiple cities or regions	Considers emission rate and duration	Does not consider atmospheric chemistry or physics	Potential for bias and reduced precision if ambient SO <sub>2</sub> concentration at a receptor location is higher or lower than the average ambient SO <sub>2</sub> concentration over the area of the circle formed around the source with radius equal to the distance between the source and receptor

**Table 3-1 (Continued): Summary of exposure assignment methods, their typical use in sulfur dioxide epidemiologic studies, strengths, limitations, and related errors and uncertainties.**

Exposure Assignment Method	Description	Epidemiologic Application	Strengths	Limitations	Errors and Uncertainties
Land use regression model (Section 3.3.2.2)	Measured ambient SO <sub>2</sub> concentrations are regressed on local variables (e.g., land use factors), and the resulting model is used to estimate ambient SO <sub>2</sub> concentrations at specific locations	Long-term epidemiologic studies: surrogate for ambient SO <sub>2</sub> exposure, usually across a city but sometimes among multiple cities	High spatial resolution	Does not account for atmospheric chemistry and physics, has limited generalizability, and moderate resources are needed	Potential for bias and reduced precision if grid is not finely resolved Potential for bias and reduced precision if the model is misspecified or applied to a location different from where the model was fit
Inverse distance weighting and kriging (Section 3.3.2.3)	Measured ambient SO <sub>2</sub> concentrations are interpolated to estimate ambient SO <sub>2</sub> concentration surfaces across regions. IDW uses an inverse function of distance to monitors, and kriging uses a statistical algorithm for interpolation	Long-term epidemiologic studies: surrogate for ambient SO <sub>2</sub> exposure, usually within a city or geographic region	High spatial resolution, few input data needed	Does not fully capture spatial variability of ambient SO <sub>2</sub> concentration among monitors	Potential for negative bias and reduced precision if ambient SO <sub>2</sub> sources are not captured or overly smoothed
Dispersion modeling (Section 3.3.2.4)	Ambient SO <sub>2</sub> concentrations at specific locations are estimated from emissions, meteorology, and atmospheric physics	Long-term epidemiologic studies: surrogate for ambient SO <sub>2</sub> exposure within a city or geographic region	High spatial and temporal resolution, accounts for atmospheric physics from local emission sources	Resource intensive, very limited representation of atmospheric chemistry or background SO <sub>2</sub> concentrations	Potential for bias where the dispersion model does not capture boundary conditions and resulting fluid dynamics well (e.g., in large cities with urban topography affecting dispersion)

**Table 3-1 (Continued): Summary of exposure assignment methods, their typical use in sulfur dioxide epidemiologic studies, strengths, limitations, and related errors and uncertainties.**

Exposure Assignment Method	Description	Epidemiologic Application	Strengths	Limitations	Errors and Uncertainties
Chemical transport model (Section 3.3.2.5)	Grid-based ambient SO <sub>2</sub> concentrations are estimated from emissions, meteorology, and atmospheric chemistry and physics	Long-term epidemiologic studies: surrogate for ambient SO <sub>2</sub> exposure, sometimes within a city but more typically across a larger region	Accounts for atmospheric chemistry and physics	Limited grid cell resolution (i.e., grid cell length scale is typically 4–36 km and much larger than plume width), resource-intensive, does not account for local SO <sub>2</sub> emissions sources	Potential for bias and reduced precision when grid cells are too large to capture spatial variability of ambient SO <sub>2</sub> exposures
Microenvironmental model (e.g., APEX, SHEDS) (Section 3.3.2.6)	Estimates distributions of micro-environmental SO <sub>2</sub> concentrations, exposures, and doses for populations (e.g., census tracts) based on air quality data, demographic variables, and activity patterns	Panel epidemiologic studies; no epidemiologic studies cited here use micro-environmental models	Accounts for variability of SO <sub>2</sub> exposures across large populations, accounts for different concentrations in different microenvironments, accounts for location-activity information	Input data from ambient SO <sub>2</sub> concentrations are required, does not estimate exposures for individuals	Potential for bias and reduced precision when the modeled distributions of ambient SO <sub>2</sub> concentration, indoor:outdoor pollutant ratios, and time-activity patterns differ from the true distributions

APEX = air pollutants exposure model; FEM = federal equivalent method; FRM = federal reference method; IDW = inverse distance weighting; SHEDS = stochastic human exposure and dose simulation; SO<sub>2</sub> = sulfur dioxide.

### 3.4.1.1 Air Exchange Rate

1 AER, which is the airflow into and out of a building and is represented by  $a$  in the  
2 conceptual model presented in Section 3.2.2, influences the rate of entry of ambient SO<sub>2</sub>  
3 and hence personal exposure to SO<sub>2</sub>, because people spend an average of 87% of their  
4 time indoors (Klepeis et al., 2001). Several factors affect the AER, including the physical  
5 driving forces of the airflows (e.g., pressure differences across the building envelope  
6 from wind, indoor-outdoor temperature differences, and mechanical ventilation), building  
7 characteristics (e.g., local wind sheltering, tightness of the building envelope), and  
8 occupant behavior (e.g., opening windows, operating outdoor-vented fans, thermostat  
9 temperature setting during heating and cooling seasons). Therefore, substantial spatial  
10 and temporal AER variations can occur due to temporal and geographical differences in

1 weather conditions, building characteristics, and occupant behavior. The resulting  
2 spatial-temporal variations in ambient SO<sub>2</sub> exposure may help explain possible  
3 differences in epidemiologic associations between ambient SO<sub>2</sub> concentrations and health  
4 effects in different U.S. communities ([Baxter and Sacks, 2014](#)).

5 Field studies indicate that the AER of U.S. residences varies by season and region, with  
6 substantial variability among different residences. [Yamamoto et al. \(2010\)](#) reported AER  
7 measured at residences in Los Angeles, CA, Elizabeth, NJ, and Houston, TX as part of  
8 the Relationship Among Indoor, Outdoor, and Personal Air (RIOPA) Study conducted  
9 between 1999 and 2001. Among the three cities and across seasons, AER was 0.71/hour.  
10 Regional differences can be seen when breaking the data down by season and location.  
11 Median AERs in Los Angeles, Elizabeth, and Houston were 0.87/hour, 0.88/hour, and  
12 0.47/hour. Differences between AER for Houston and AER for Los Angeles and  
13 Elizabeth may in part be related to larger home sizes (average home volume was 304 m<sup>3</sup>  
14 for Houston, compared with 163 m<sup>3</sup> in Los Angeles and 252 m<sup>3</sup> in Elizabeth). Seasonally,  
15 median AER was higher in summer compared to winter in Los Angeles (summer:  
16 1.14/hour; winter: 0.61/hour). However, the opposite pattern occurred in Elizabeth  
17 (summer: 0.88/hour; winter: 1.07/hour) and Houston (summer: 0.37/hour; winter:  
18 0.63/hour). More prevalent use of open windows in Los Angeles, where summertime  
19 tends to be less humid than in Elizabeth or Houston, may promote greater air exchange.  
20 This difference may grow smaller with the increased prevalence of air conditioning,  
21 because air conditioning usage is an important factor in infiltration ([Allen et al., 2012](#)).  
22 Low AER values in autumn may be due to a diminished “stack effect” resulting from  
23 indoor-outdoor temperature differential ([Breen et al., 2014b](#)).

24 Intra- and inter-home variability in AER was also tested in the RIOPA Study [Yamamoto](#)  
25 [et al. \(2010\)](#). Intra-home variability in AER indicated that individual homes’ AER  
26 changed considerably between seasons (32, 37, and 37% for Los Angeles, Elizabeth, and  
27 Houston, respectively). Inter-home variability also differed substantially for all three  
28 cities, with the interquartile range of AER exceeding the median AER consistently across  
29 seasons and cities.

30 AER is a critical parameter for estimating indoor SO<sub>2</sub> concentrations, because indoor  
31 sources of SO<sub>2</sub> are relatively scarce and SO<sub>2</sub> rapidly reacts with indoor surfaces [see  
32 [Grontoft and Raychaudhuri \(2004\)](#) and references cited therein] or oxidizes rapidly via  
33 indoor Criegee intermediates [see [Section 2.3](#) for a description of Criegee chemistry or  
34 [Shallcross et al. \(2014\)](#) for the role of indoor Criegee intermediates in SO<sub>2</sub> losses].  
35 The main indoor source of SO<sub>2</sub> is combustion of sulfur-containing fuels, such as  
36 kerosene, which is generally considered an emergency or supplemental source of heat in  
37 the U.S. Kerosene heaters, but not fireplaces, woodstoves, or gas space heaters, caused

1 elevated SO<sub>2</sub> concentrations indoors in a study conducted in Connecticut and Virginia  
2 ([Triche et al., 2005](#)). The median indoor SO<sub>2</sub> concentration measured by passive sampler  
3 over two weeks in homes using kerosene heat was 6.4 ppb, compared with 0.22 ppb for  
4 homes that did not use kerosene heat in the two-week period. This relatively low  
5 concentration when the kerosene heater was not in use is consistent with the rapid  
6 removal rate of infiltrated ambient SO<sub>2</sub>. As discussed in [Section 2.3](#), SO<sub>2</sub> is removed  
7 from the atmosphere by both dry and wet deposition to surfaces, represented by  $k$  in the  
8 conceptual model presented in [Section 3.2.2](#). The deposition rate of SO<sub>2</sub> in apartments in  
9 Athens, Greece was found to range from 0.76–4.3 /hour, similar to the rate observed for  
10 O<sub>3</sub>, but an order of magnitude higher than the deposition rate measured for NO<sub>2</sub> ([Halios  
11 et al., 2009](#)).

12 Limited information was identified regarding the penetration factor  $P$  ([Equation 3-4](#)).  
13 [López-Aparicio et al. \(2011\)](#) measured SO<sub>2</sub> concentrations indoors and outdoors at the  
14 National Library in Prague, Czech Republic from July 2009 to March 2010 and observed  
15 SO<sub>2</sub> penetration values ranging from  $P = 0.25$  to 0.74. Measured outdoor SO<sub>2</sub>  
16 concentrations were higher for the cold months of January, February, and March  
17 compared with the remainder of the sampling campaign, and penetration was lower  
18 during that period ( $P = 0.25$  to 0.48). The literature search only produced this one recent  
19 study of SO<sub>2</sub> infiltration.

20 Vehicle AERs can be substantially higher than residential AERs, leading to rapid  
21 infiltration of on-road pollutants. While on-road SO<sub>2</sub> emissions have declined due to  
22 reductions in fuel sulfur content ([Section 2.2.3](#)), high vehicle AER would increase  
23 exposure in areas with high ambient SO<sub>2</sub> concentrations. Many factors affect vehicle  
24 AER, including vehicle make and model, vehicle age, driving speed, and  
25 fan/recirculation setting on the vehicle ventilation system. The combined effect of these  
26 factors result in AERs that vary by more than two orders of magnitude, from less than  
27 1/hour (approximately equivalent to a typical residential AER) to more than 100/hour  
28 ([Hudda et al., 2011](#)). In a model fit to AER measurements on 59 vehicles driven at three  
29 different speeds under recirculation conditions, the most important variables were vehicle  
30 age, mileage, and speed, plus an adjustment for manufacturer ([Fruin et al., 2011](#)). Fan  
31 speed and vehicle shape were not influential variables.

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### 3.4.1.2 Indoor-Outdoor Relationships

32 A number of studies from the U.S., Canada, Europe, and Asia summarized in the 2008  
33 SO<sub>x</sub> ISA ([U.S. EPA, 2008d](#)), as well as a few new studies conducted outside the U.S.,  
34 have characterized the relationship between outdoor and indoor SO<sub>2</sub> concentrations.

1 Ratios and slopes of the indoor SO<sub>2</sub> concentration versus the SO<sub>2</sub> concentration  
2 immediately outside the indoor microenvironment had an extremely wide range in the  
3 studies described in the 2008 SO<sub>x</sub> ISA, from near zero to near unity. One of the most  
4 detailed older studies of SO<sub>2</sub> in a school was able to detect an indoor-outdoor slope of  
5 0.02–0.03, with near-zero intercept and a correlation of 0.79–0.91, while measuring  
6 indoor concentrations < 1 ppb, obtained over 10-hour periods when school was in session  
7 and 14-hour periods when the school was vacant ([Patterson and Eatough, 2000](#)). Studies  
8 conducted since the 2008 SO<sub>x</sub> ISA have focused on public buildings and show generally  
9 similar results to older studies. A historic library in Prague without heating or air  
10 conditioning had indoor:outdoor ratios of 0.25–0.74 (mean = 0.49) for monthly average  
11 outdoor SO<sub>2</sub> concentrations of 1–7 ppb obtained with passive samplers ([López-Aparicio  
12 et al., 2011](#)). In Brazil, ratios of average indoor and outdoor SO<sub>2</sub> concentrations from  
13 2-week passive samples were 0.7 and 1.0 for urban and suburban schools, respectively  
14 ([Godoi et al., 2013](#)).

15 Several factors could contribute to the differences observed among studies, including  
16 building characteristics (e.g., forced ventilation, building age, and building type such as  
17 residences or public buildings), behaviors affecting air exchange rates such as opening  
18 windows, indoor deposition of SO<sub>2</sub>, and analytical capabilities. When reported,  
19 correlations between indoor and outdoor ambient SO<sub>2</sub> concentrations were relatively high  
20 (>0.75), suggesting that variations in outdoor ambient SO<sub>2</sub> concentration are driving  
21 indoor SO<sub>2</sub> concentrations. These high correlations were observed across seasons and  
22 geographic locations. This is consistent with the relative lack of indoor sources of SO<sub>2</sub>  
23 ([Section 3.4.1.1](#)). For other criteria pollutants, nonambient sources can be an important  
24 contributor to total personal exposure, but personal SO<sub>2</sub> exposure is expected to be  
25 dominated by ambient SO<sub>2</sub> in outdoor microenvironments and in enclosed  
26 microenvironments with high air exchange rates (e.g., buildings with open windows and  
27 vehicles).

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### 3.4.1.3 Personal-Ambient Relationships

28 As discussed in the 2008 SO<sub>x</sub> ISA ([U.S. EPA, 2008d](#)), personal monitoring studies for  
29 SO<sub>2</sub> exposure assessment have frequently found that most SO<sub>2</sub> exposure concentrations  
30 are below the detection limit of the personal samplers used in the study. Several studies  
31 using passive samplers ([Section 3.3.1.2](#)) found that 95% or more of the personal SO<sub>2</sub>  
32 exposure concentrations were less than the field detection limit of 2–6 ppb for 24-h avg  
33 samples ([Sarnat et al., 2006](#); [Sarnat et al., 2005](#); [Sarnat et al., 2001](#); [Sarnat et al., 2000](#)).  
34 Thus, these data are not suitable for evaluating the relationship between personal  
35 exposure and ambient concentration for SO<sub>2</sub>.

1 A study in Boston using a different type of sampler, a personal annular denuder  
2 ([Section 3.3.1.2](#)) with a detection limit of 0.19 ppb, found that the slope between 24-hour  
3 personal SO<sub>2</sub> exposure concentration and ambient SO<sub>2</sub> concentration was 0.13, with a  
4 standard error of 0.02 and zero intercept ([Brauer et al., 1989](#)). The 2008 SO<sub>x</sub> ISA  
5 reported slopes of 0.03–0.13. Assuming that there are no nonambient sources of SO<sub>2</sub>, the  
6 slope can be considered an estimate of  $\alpha$ . The  $R^2$  value was 0.43 ( $r = 0.66$ ) in this  
7 analysis, which excluded values below the detection limit, indicating that personal SO<sub>2</sub>  
8 exposure concentration was moderately correlated with ambient SO<sub>2</sub> concentration.

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### 3.4.2 Factors Contributing to Error in Estimating Exposure to Ambient Sulfur Dioxide

9 Ambient SO<sub>2</sub> concentrations measured at central monitoring sites are commonly used for  
10 exposure surrogates in epidemiologic studies. As noted in [Section 3.3.1.1](#), use of a central  
11 site SO<sub>2</sub> monitor to capture a surrogate for true, likely unobserved ambient SO<sub>2</sub> exposure  
12 may lead to exposure error. Factors that may influence this type of error include human  
13 activity patterns, spatial and temporal variation in ambient SO<sub>2</sub> concentration, and indoor  
14 exposure to ambient SO<sub>2</sub> ([Brown et al., 2009](#); [Zeger et al., 2000](#)). Additionally,  
15 uncertainty in the metric used to represent exposure is a source of exposure error. This  
16 type of error may be influenced by method detection limit, accuracy, and precision of the  
17 instrument. These factors are discussed in the following section.

---

#### 3.4.2.1 Activity Patterns

18 The activity pattern of individuals is an important determinant of their exposure.  
19 Variation in SO<sub>2</sub> exposure concentrations among microenvironments means that the  
20 amount of time spent in each location will influence an individual's exposure to ambient  
21 SO<sub>2</sub>. The effect of activity pattern on exposure is explicitly accounted for in [Equation 3-3](#)  
22 by the fraction of time spent in different microenvironments. As discussed in the 2008  
23 SO<sub>x</sub> ISA ([U.S. EPA, 2008d](#)), although activity patterns vary both among and within  
24 individuals, resulting in corresponding variations in exposure across a population and  
25 over time, people generally spend more than 80% of their time indoors ([Spalt et al., 2015](#);  
26 [Klepeis et al., 2001](#)).

27 Time spent in different locations has been found to vary by age. [Table 3-2](#) summarizes  
28 National Human Activity Pattern Survey (NHAPS) data reported for four age groups,  
29 termed very young (0–4 years), school age (5–17 years), working (18–64 years), and  
30 retired (65+ years) ([Klepeis et al., 1996](#)). The working population spent the least time

1 outdoors, while the school age population spent the most time outdoors. NHAPS  
 2 respondents aged 65 years and over spent somewhat more time outdoors than adults aged  
 3 18–64 years, with a greater fraction of time spent outdoors at a residence. Children aged  
 4 0–4 years also spent most of their outdoor time in a residential outdoor location. On  
 5 average, the fraction of time spent outdoors by school age respondents was 2.62  
 6 percentage points higher than working respondents, corresponding to approximately  
 7 38 minutes more time outdoors per day. Moreover, in a survey comparing children  
 8 (mostly less than age 8 years), their parents who were mostly under age 55 years, and  
 9 adults older than age 55 years, a larger proportion of children reported spending over  
 10 30 minutes performing vigorous outdoor physical activity ([Wu et al., 2011b](#)).

**Table 3-2 Mean fraction of time spent in outdoor locations by various age groups in the National Human Activity Pattern Survey study.**

Age Group (yr)	Residential-Outdoor (%)	Other Outdoor (%)	Total Outdoors (%)
0–4	5.38	0.96	6.34
5–17	5.05	2.83	7.88
18–64	2.93	2.33	5.26
65+	4.48	1.27	5.75

Source: Data from [Klepeis et al. \(1996\)](#).

11 Longitudinal activity pattern information is also an important determinant of exposure, as  
 12 different people may exhibit different patterns of time spent outdoors over time due to  
 13 race/ethnicity, age, sex, employment, and lifestyle-dependent factors. [Spalt et al. \(2015\)](#)  
 14 analyzed the relationship between time-activity patterns and demographic patterns for the  
 15 MESA Air cohort. They found that time spent indoors was best predicted by employment  
 16 status, and participants of Chinese ethnicity were more likely to spend time indoors  
 17 compared with white, black, or Hispanic study participants. These differences may  
 18 manifest as higher mean SO<sub>2</sub> exposures or more frequent high-exposure episodes for  
 19 some individuals. The extent to which longitudinal variability in individuals contributes  
 20 to the population variability in activity and location can be quantified by the ratio of  
 21 between-person variance to total variance in time spent in different locations and  
 22 activities [the intraclass correlation coefficient (ICC)]. [Xue et al. \(2004\)](#) quantified ICC  
 23 values in time-activity data collected by Harvard University for 160 children aged  
 24 7–12 years in Southern California ([Geyh et al., 2000](#)). For time spent outdoors, the ICC  
 25 was approximately 0.15, indicating that 15% of the variance in outdoor time was due to

1 between-person differences. The ICC value might be different for other population  
2 groups.

3 Several methods are available for sampling diary information, and the method chosen can  
4 affect estimated personal SO<sub>2</sub> exposures and related exposure errors. [Che et al. \(2014\)](#)  
5 evaluated how diary sampling methods influenced estimates of children's exposure (in  
6 this case, to ambient PM<sub>2.5</sub>). Random resampling, diversity and autocorrelation, and  
7 Markov-chain cluster methods of diary sampling were tested. The three sampling  
8 methods provided similar results for total ambient exposure, outdoor ambient exposure,  
9 and ambient exposure at homes and indoor locations not including home, school, or  
10 vehicles.

11 The U.S. EPA's National Exposure Research Laboratory has consolidated many of the  
12 most important human activity databases into one comprehensive database called the  
13 Consolidated Human Activity Database (CHAD). The current version of CHAD contains  
14 data from 22 human activity pattern studies (including NHAPS), which were conducted  
15 between 1982 and 2010 and evaluated to obtain over 54,000 person-days of 24-hour  
16 human activities in CHAD ([Isaacs, 2014](#); [McCurdy et al., 2000](#)). Five studies conducted  
17 between 1997 and 2010 comprising over 30,000 person-days have been added to CHAD  
18 since the previous SO<sub>x</sub> ISA ([University of Michigan, 2016](#); [Isaacs et al., 2013](#); [Wu et al.,  
19 2012](#); [Hertz-Picciotto et al., 2010](#); [Knowledge Networks, 2009](#); [Williams et al., 2009](#)).

20 The surveys include probability-based recall studies conducted by U.S. EPA and the  
21 California Air Resources Board, as well as real-time diary studies, telephone interviews,  
22 and internet-based surveys conducted nationally and in individual U.S. metropolitan areas  
23 using both probability-based and volunteer subject panels. All ages of both sexes are  
24 represented in CHAD. The data for each subject consist of 1 or more days of sequential  
25 activities, in which each activity is defined by start time, duration, activity type, and  
26 microenvironmental classification (i.e., location). Activities vary from 1 minute to 1 hour  
27 in duration, with longer activities being subdivided into clock-hour durations to facilitate  
28 exposure modeling. CHAD also provides information on the level of exertion associated  
29 with each activity, which can be used by exposure models, including the APEX model, to  
30 estimate ventilation rate and pollutant dose ([Section 3.3.2.6](#)).

31 Recent studies have focused on the use of global positioning system (GPS) technologies,  
32 such as in smartphones, to develop detailed time-activity pattern data. GPS technology  
33 has the potential to provide increased resolution in recording activity patterns. For  
34 example, [Glasgow et al. \(2014\)](#) analyzed the frequency of Android-based smartphones in  
35 recording positional data among a panel of study participants and found that on average  
36 74% of the data were collected over intervals shorter than 5 minutes, which is a marked  
37 improvement over many time-activity studies using diaries.

1 Positional errors are a concern for GIS and GPS-based technologies. [Lane et al. \(2013\)](#)  
2 compared three geocoding techniques with aerial photography and observed median  
3 positional errors of 7–23 m. [Glasgow et al. \(2014\)](#) also compared smartphone positions  
4 with geocoded diary-based locations to test the positional accuracy of the phones. For all  
5 data combined, the smartphones had a median positional accuracy of 342.3 m. When  
6 broken down by network, the median positional accuracy varied from 98.0 to 1,168.8 m.  
7 [Wu et al. \(2010\)](#) compared several portable GPS devices to aerial photography. Median  
8 positional errors were 7.3–20.8 m for indoor measurements taken 3 m from a door or  
9 window. For outdoor measurements taken 6.1 m from a window or door, median  
10 positional errors were 4.1–16.3 m, and for on-road measurements, median positional  
11 errors were 3.5–5.5 m. [Ganguly et al. \(2015\)](#) compared two automated (GIS-based)  
12 geocoding techniques with GPS positional data in Detroit, MI. Median positional errors  
13 for two GIS methods were 26 m for both methods in comparison with GPS.

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#### 3.4.2.2 Spatial Variability

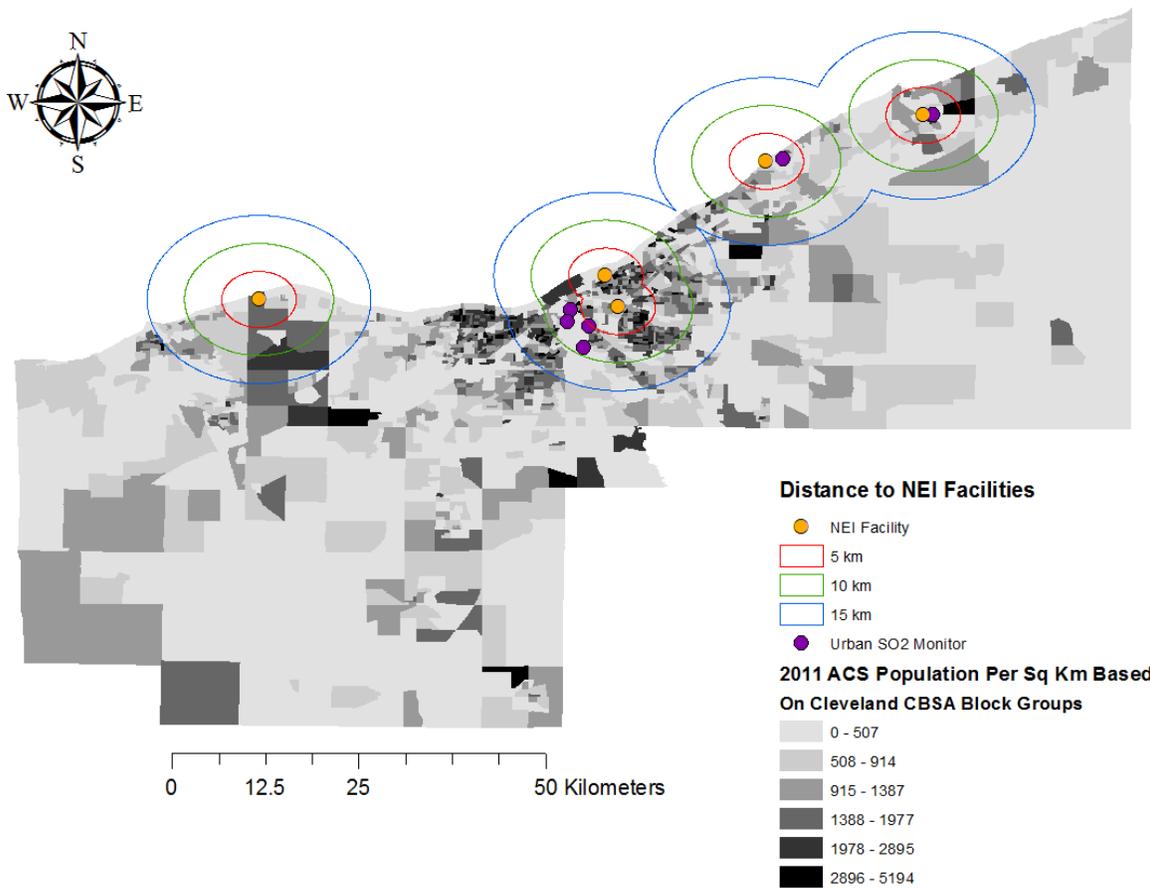
14 Spatial variability in ambient SO<sub>2</sub> concentrations can contribute to exposure error in  
15 epidemiologic studies, whether the studies rely on central site monitor data or model  
16 output as a surrogate for exposure concentration. Low correlations between the monitor  
17 used to measure concentration as an exposure surrogate and the true exposure  
18 concentrations at the locations of the study population contribute to exposure error in  
19 time-series studies [Goldman et al. \(2010\)](#).

20 The 2008 SO<sub>x</sub> ISA ([U.S. EPA, 2008d](#)) discussed spatial variability in ambient SO<sub>2</sub>  
21 concentrations and the impact of this variability on effect estimates from epidemiologic  
22 studies. Inter-monitor correlations within urban areas ranged from very low to very high  
23 values, suggesting that ambient SO<sub>2</sub> concentrations at some monitors may not be highly  
24 correlated with the community average SO<sub>2</sub> exposure concentration. Of particular  
25 concern for SO<sub>2</sub> is the predominance of point sources, resulting in an uneven distribution  
26 of ambient SO<sub>2</sub> concentrations across an urban area. Factors contributing to differences  
27 among monitors include the presence of point sources, proximity to point sources, terrain  
28 features, and uncertainty regarding the measurement of low ambient SO<sub>2</sub> concentrations.  
29 The 2008 SO<sub>x</sub> ISA ([U.S. EPA, 2008d](#)) concluded that low correlation between a specific  
30 monitor and the community average ambient SO<sub>2</sub> exposure concentration will tend to  
31 bias an effect estimate toward the null.

32 Because ambient SO<sub>2</sub> concentrations can have high spatial variability, average SO<sub>2</sub>  
33 exposure concentration estimates may have less error for populations living close to a  
34 monitor. [Figure 3-1](#) and [Figure 3-2](#) illustrate proximity of populations and SO<sub>2</sub> monitors

1 to multiple ambient SO<sub>2</sub> sources in the Cleveland and Pittsburgh CBSAs, respectively  
2 (discussed in [Chapter 2](#)). These CBSAs were chosen for further discussion here, because  
3 they have both high population density and numerous sources above 2,000 tpy.  
4 [Figure 3-1](#) shows the location of central site SO<sub>2</sub> monitors and sources with respect to  
5 population density for the Cleveland, OH CBSA. Four of the monitors are centrally  
6 located in the urban area, and are also within 10 km of SO<sub>2</sub> sources, while two other  
7 monitors are located much closer to point sources (<5 km). While some densely  
8 populated areas are near central site SO<sub>2</sub> monitors, some of the highest density census  
9 block groups are located more than 10–15 km from central site monitors despite  
10 proximity to the sources. [Table 3-3](#) indicates that approximately one-third of the  
11 population in various age groups lives more than 15 km from a central site SO<sub>2</sub> monitor.  
12 For the Pittsburgh CBSA ([Figure 3-2](#)), only two of the monitors are located near sources,  
13 with the other monitors distributed among population centers and less densely populated  
14 areas. Here, approximately 40% of the population lives more than 15 km from a central  
15 site SO<sub>2</sub> monitor ([Table 3-4](#)). Such variability in the proximity of populations to central  
16 site monitors suggests that some portions of an urban area may be subject to increased  
17 exposure error. While only minor differences were noted among age groups in the portion  
18 of the population living at specific distances from monitors, the potential exists for  
19 exposure error to differ among other potentially at-risk groups due to monitor proximity.

20 Several recent studies have evaluated the impact of spatial variability in ambient SO<sub>2</sub>  
21 concentration on epidemiologic effect estimates. [Strickland et al. \(2011\)](#) reported a  
22 relatively low chi-squared statistic for ambient 1-hour SO<sub>2</sub> exposure concentration (from  
23 a central site monitor, unweighted average across monitors, and population-weighted  
24 average) compared with other primary and secondary criteria pollutants in Atlanta, GA.  
25 The authors attributed this poor fit to spatial heterogeneity in ambient SO<sub>2</sub> exposure  
26 concentrations used as exposure surrogates and the inability of a central site monitor to  
27 capture ambient SO<sub>2</sub> plume touch-downs in other parts of the city. The chi-squared  
28 statistic moderately increased when average ambient SO<sub>2</sub> exposure concentrations (both  
29 population-weighted and unweighted) from monitors across the city were used. Effect  
30 estimates were higher for the monitor average metrics than for the central site monitor,  
31 and this difference was magnified when effect estimates were based on a standardized  
32 increment rather than the IQR. Because the IQR of the data covered the range of values  
33 observed across the monitors in Atlanta for the [Strickland et al. \(2011\)](#) study, spatial  
34 variability was partially accounted for in the IQR. The different exposure assignment  
35 approaches only altered the magnitude, not direction, of observed associations.



ACS = American Cancer Society; CBSA = core-based statistical area; NEI = National Emissions Inventory.

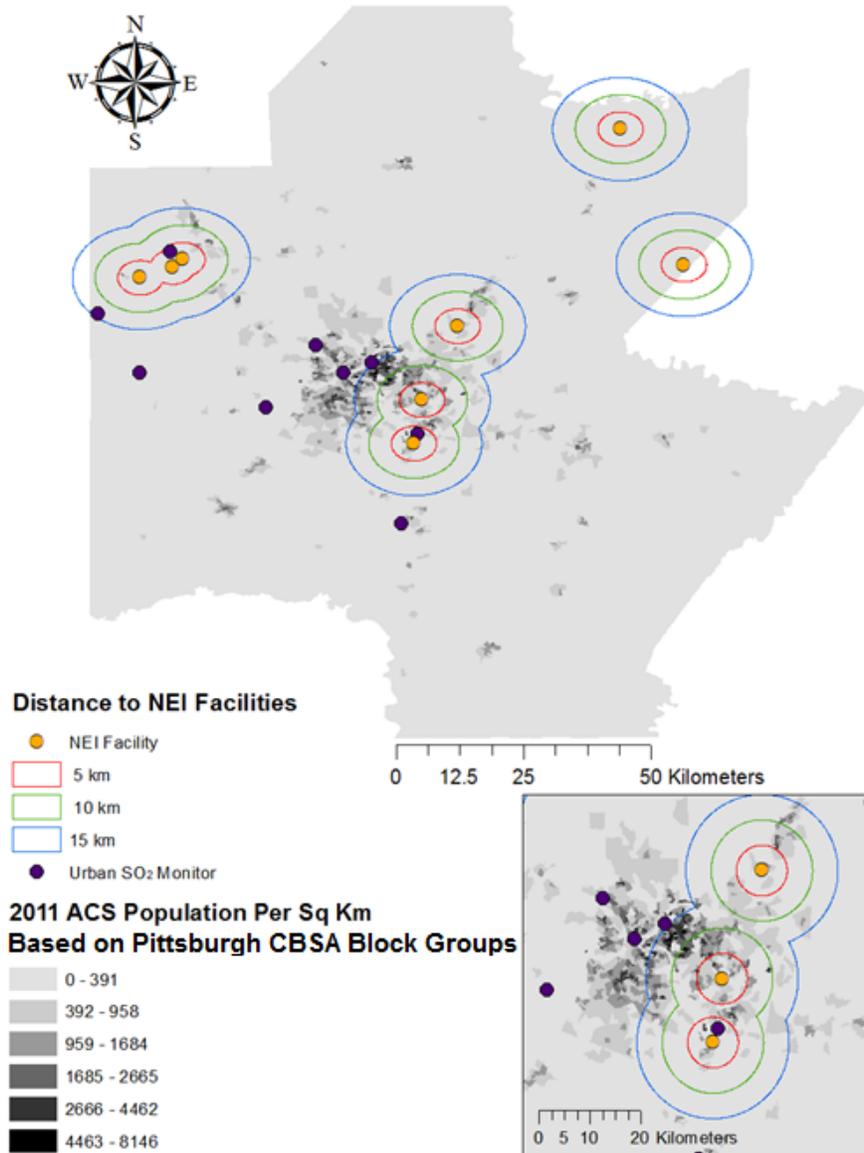
Note that the current map projection (GCS-WGS-1984) creates buffers that take on an elliptical shape instead of a circle. The map projection was chosen to preserve the projection integrity across the data files and reduce error associated with merging data projections.

**Figure 3-1 Map of the Cleveland, OH core-based statistical area including National Emissions Inventory facility locations, urban sulfur dioxide monitor locations, and distance to each facility with respect to core-based statistical area block group population density estimates for 2011. National Emissions Inventory facility emissions ranged from 1,942 tons/year to 48,300 tons/year.**

**Table 3-3 2011 American Community Survey population estimates of people living within a specified distance of an urban sulfur dioxide monitor in the Cleveland, OH core-based statistical area. Population estimates are based on census block group estimates.**

<b>Age Group</b>	<b>Total Population</b>	<b>Within 1 km</b>	<b>Within 5 km</b>	<b>Within 10 km</b>	<b>Within 15 km</b>
<b>Total</b>	2,080,318	11,816	266,777	759,078	1,310,309
≤4 yr	121,820	781	17,608	46,551	75,947
5–17 yr	364,740	1,872	44,719	129,432	222,401
18–64 yr	1,280,478	7,793	178,439	482,808	822,787
≥65 yr	313,280	1,370	26,011	100,287	189,174

Source: Data from the 2011 American Community Survey ([U.S. Census Bureau, 2011](http://www.census.gov)).



ACS = American Cancer Society; CBSA = core-based statistical area; NEI = National Emissions Inventory.

Note that the current map projection (GCS-WGS-1984) creates buffers that take on an elliptical shape instead of a circle. The map projection was chosen to preserve the projection integrity across the data files and reduce error associated with merging data projections.

The inset map shows National Emissions Inventory facilities located to the southeast of the highly urbanized areas.

**Figure 3-2 Map of the Pittsburgh, PA core-based statistical area including National Emissions Inventory facility locations, urban sulfur dioxide monitor locations, and distance to each facility with respect to core-based statistical area block group population density estimates for 2011. National Emissions Inventory facility emissions ranged from 1,279 tons/year to 46,467 tons/year.**

**Table 3-4 2011 American Community Survey population estimates of people living within a specified distance of an urban sulfur dioxide monitor in the Pittsburgh, PA core-based statistical area. Population estimates are based on census block group estimates.**

	Total Population	Within 1 km	Within 5 km	Within 10 km	Within 15 km
Population	2,357,769	64,224	494,382	1,076,465	1,428,871
≤4 yr	121,101	2,646	24,748	56,178	73,853
5–17 yr	358,500	8,641	65,882	152,858	211,204
18–64 yr	1,471,310	41,989	325,041	683,445	897,459
≥65 yr	406,858	10,948	78,711	183,984	246,355

Source: Data from the 2011 American Community Survey ([U.S. Census Bureau, 2011](http://www.census.gov)).

1 High spatial and temporal variability in ambient SO<sub>2</sub> concentration leading to a  
 2 null-biased effect estimate was also observed in Atlanta by [Goldman et al. \(2010\)](#) when  
 3 using 1-h daily max SO<sub>2</sub> concentration as an exposure surrogate. In this study, the authors  
 4 used a semivariance analysis incorporating both spatial and temporal variability to show  
 5 that secondary pollutants such as PM<sub>2.5</sub> and O<sub>3</sub> have lower exposure error (where ambient  
 6 concentration is a surrogate for exposure) than primary pollutants such as CO and SO<sub>2</sub>,  
 7 for which concentrations tend to have higher spatial variability than those of secondary  
 8 pollutants. [Goldman et al. \(2010\)](#) simulated exposure error as the difference between  
 9 concentration measured at the central site monitor and the concentration estimated at a  
 10 receptor’s location. The study authors computed a semivariance term over distance to the  
 11 central site monitor to concentration at a distance from the monitor. The estimated error  
 12 for SO<sub>2</sub> was then added to a base case scenario, in which the authors assumed that the  
 13 central site monitor would produce an accurate exposure. Both the central site monitor  
 14 estimate and the estimate at the receptor location were used in epidemiologic models to  
 15 estimate the risk ratio for cardiovascular emergency department visits. The authors  
 16 estimated that the risk ratio was biased towards the null by approximately 60% when  
 17 estimating exposure using the central site monitor in lieu of estimating exposure at the  
 18 receptors’ locations. In a related study, [Goldman et al. \(2012\)](#) used different methods to  
 19 obtain the surrogate for exposure: central site monitor, unweighted average across  
 20 monitors, population-weighted average across monitors, and area-weighted average  
 21 across monitors. The bias decreased for 1-h daily max SO<sub>2</sub> when using unweighted,  
 22 population-weighted, and area-weighted averages of concentrations from multiple  
 23 monitors for the exposure estimate compared with using concentration from a central site

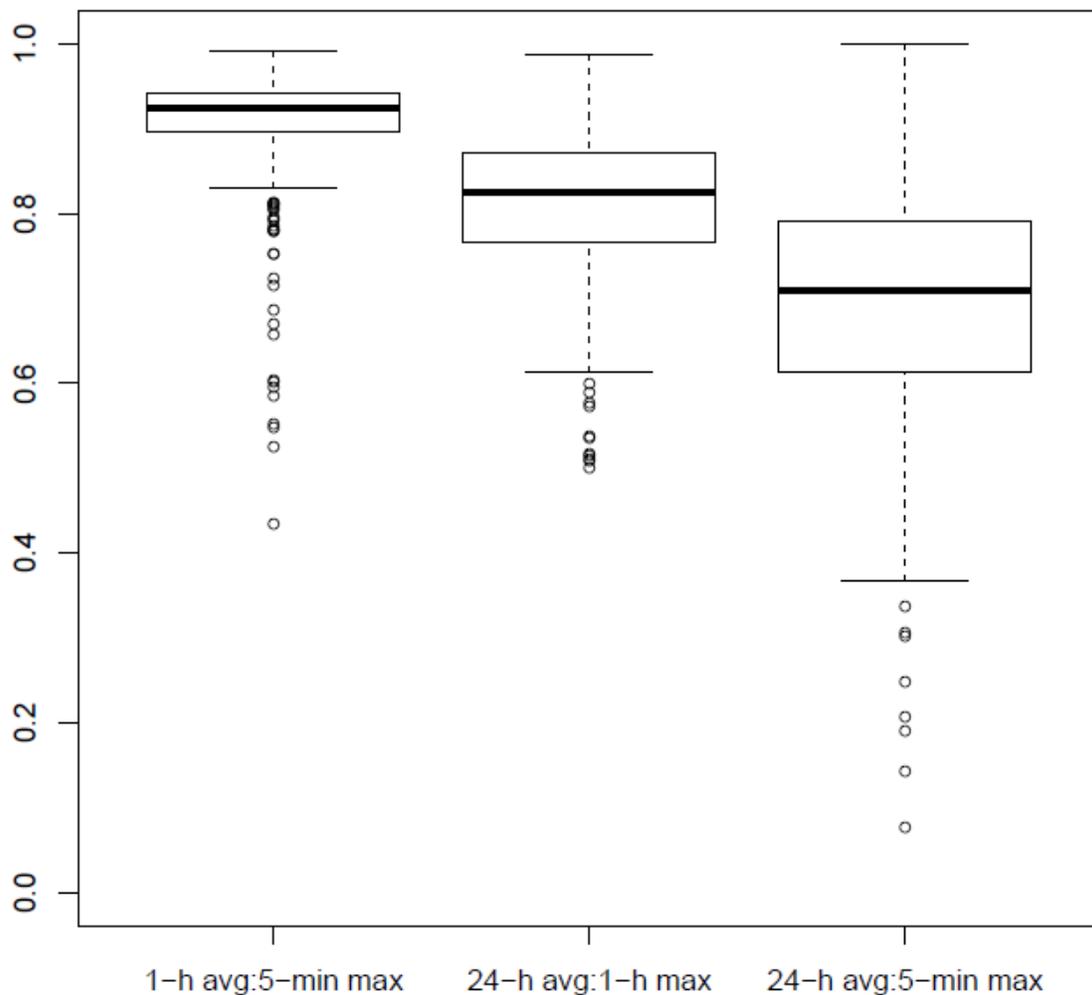
1 monitor for the exposure estimate. Similarly, epidemiologic studies in the U.S. ([Kumar, 2012](#); [Morello-Frosch et al., 2010](#)) and Australia [Jalaludin et al. \(2007\)](#) found higher  
2 associations between ambient SO<sub>2</sub> concentrations (used as exposure surrogates) and birth  
3 outcomes when the analysis was restricted to mothers matched with an ambient SO<sub>2</sub>  
4 monitor within 3–5 km of their residence, suggesting bias towards the null remained in  
5 the spatial averages used in the base case ([Section 5.4](#)).  
6

---

### 3.4.2.3 Temporal Variability

7 The influence of plume dynamics on human exposures is important for considering  
8 results of time-series studies of ambient SO<sub>2</sub> exposure. As described in [Section 2.5.4](#),  
9 peak concentrations within the ambient SO<sub>2</sub> plume can exceed concentrations averaged  
10 over an hour by up to a factor of five; for the observations made in this assessment, the  
11 peak was observed to exceed the mean by up to a factor of 5.5. Hence, SO<sub>2</sub> central site  
12 monitoring with averaging times of 1 hour or 1 day, commonly used in time-series  
13 epidemiologic studies as an exposure metric ([Chapter 5](#)), may fail to characterize the  
14 variability and peak SO<sub>2</sub> exposure concentrations associated with a meandering plume,  
15 resulting in exposure error. Moreover, controlled human exposure studies have  
16 demonstrated health effects at 5-minute time scales ([Chapter 5](#)). The longer averaging  
17 times used in epidemiologic studies may be misaligned with the critical time window of  
18 the health effect corresponding to peak SO<sub>2</sub> exposure.

19 Most of the community time-series epidemiologic studies on the health effects of ambient  
20 SO<sub>2</sub> exposure described in [Chapter 5](#) use 24-h avg concentration as a surrogate for  
21 exposure. Correlations among different temporal aggregations (1-h avg vs. 5-minute  
22 hourly max, 24-h avg vs. 1-h daily max, and 24-h avg vs. 5-minute daily max) were  
23 computed from the AQS data presented in [Section 2.5.4](#) to glean an indication of how  
24 well the 24-h avg represents the 1-h daily max and 5-minute daily max measures that  
25 correspond to peak SO<sub>2</sub> plume exposure ([Figure 3-3](#)). Approximately 75% of correlations  
26 between 1-h avg and 5-minute hourly max were above 0.9. Correlations between  
27 24-h avg and 1-h daily max were slightly lower, with roughly 75% of the data having  
28 correlations above 0.75. A larger range of data was observed for the correlations between  
29 24-h avg and 5-minute daily max, with 75% of the data having correlations above 0.60  
30 and more than 50% of the data having correlations above 0.70. These moderate-high  
31 correlations suggest that 24-h avg data used in many time-series epidemiologic studies  
32 capture the peak exposure reasonably well, but exceptions may be found for specific  
33 sites, as suggested by the lower outliers ( $r < 0.35$ ) and lower whisker ( $r < 0.6$ ) of the  
34 correlation between 24-h avg and 5-minute daily max data.



Data below 0 ppb trimmed from the data set.

**Figure 3-3** Pearson correlations between 1-h avg and 5-minute hourly max, 24-h avg and 1-h daily max, and 24-h avg and 5-minute daily max sulfur dioxide concentrations.

1 A study in Canada suggests that ambient SO<sub>2</sub> concentration measured over a single year  
 2 can represent ambient SO<sub>2</sub> exposure concentration over a multidecade period.  
 3 The authors compared measurement methods used to represent long-term SO<sub>2</sub> exposure  
 4 concentration and found that the annual average ambient SO<sub>2</sub> exposure concentration in  
 5 the census tract of a subject's residence during 1980 and 1994 was well correlated  
 6 (Pearson *R* = 0.83 and 0.85 for all subjects, respectively) with an ambient SO<sub>2</sub> exposure

1 concentration metric accounting for movement among census subdivisions during  
2 1980–2002 ([Guay et al., 2011](#)). This result may have been due in part to a relatively low  
3 rate of movement, with subjects residing on average for 71% of the 22-year period in the  
4 same census subdivision they were in during 1980. [Guay et al. \(2011\)](#) also found that  
5 coverage of the study population reduced from 40% for the fixed-time exposure  
6 assignments, to 31% when averaging fixed-time exposure assignments with exposure  
7 assignments based on census subdivision, to 29% when assigning exposures based only  
8 on census subdivision, suggesting that improved spatial and temporal resolution in  
9 long-term studies may come at the expense of data completeness.

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#### 3.4.2.4 Method Detection Limit, Instrument Accuracy, and Instrument Precision

10 Personal SO<sub>2</sub> exposure measurements with ambient SO<sub>2</sub> concentration typically have  
11 correlations of  $0.4 < r < 0.9$  when personal SO<sub>2</sub> exposure measurements are above the  
12 MDL. However, although the magnitude of personal SO<sub>2</sub> exposure measurements is often  
13 much lower than the magnitude of ambient SO<sub>2</sub> concentrations [[Section 3.4.1.3](#); [U.S.  
14 EPA \(2008d\)](#)]. Moderate to high correlation indicates that using ambient concentration as  
15 a surrogate for personal exposure captures the variability needed for epidemiologic  
16 studies, particularly for time-series and panel studies. Low personal-ambient correlations  
17 reported in the literature are strongly influenced by low personal exposures relative to the  
18 detection limits of personal samplers. When this happens, personal samplers are unable to  
19 provide a signal to correlate with variations in ambient concentration. Low correlations  
20 ( $r < 0.4$ ) in situations with a high proportion of samples below the detection limit should  
21 not be interpreted as evidence for the lack of a relationship between personal exposure  
22 and ambient SO<sub>2</sub> concentrations. Instead, a low personal sample value likely represents a  
23 true low exposure and thus appropriately leads to a low personal:ambient ratio. Low  
24 personal:ambient ratios may be due to low penetration and high deposition of SO<sub>2</sub> in  
25 indoor microenvironments where people spend most of their time. In a study of  
26 personal:ambient exposure ratios by [Brown et al. \(2009\)](#), the authors cited personal SO<sub>2</sub>  
27 samples below MDL and extremely low SO<sub>2</sub> levels to rationalize not pursuing further  
28 analysis.

29 Instrument error occurs when the measured SO<sub>2</sub> concentrations are subject to  
30 interferences that cause biases or noise leading to error in estimating exposure. Ambient  
31 SO<sub>2</sub> concentrations measured by FRM or FEM are subject to positive bias from the  
32 detection of interfering compounds. See [Section 2.4.1.2](#) for details on errors that affect  
33 FRMs and FEMs used for central site monitoring. Inter-monitor comparison is often used  
34 to estimate instrument precision. [Goldman et al. \(2010\)](#) used a simulation to investigate  
35 the influence of instrument precision error at locations where ambient SO<sub>2</sub> central site

1 monitors were collocated. Instrument precision error increased with increasing ambient  
2 concentration for the central site monitors. When instrument error and ambient SO<sub>2</sub>  
3 concentration were correlated, error was larger in locations with more prevalent or  
4 stronger sources or at times when SO<sub>2</sub> emissions were higher for a given location. For  
5 example, the magnitude of the instrument error was expected to be largest at times of day  
6 when SO<sub>2</sub> emissions were highest, such as during peak energy usage times. Instrument  
7 error was also observed to exhibit some autocorrelation at 1- and 2-day lags in the  
8 [Goldman et al. \(2010\)](#) simulation. Hence, the diurnal variability in relative SO<sub>2</sub>  
9 instrument error does not change substantially from day to day. For epidemiologic studies  
10 of short-term SO<sub>2</sub> exposure that use central site-monitored ambient SO<sub>2</sub> concentration as  
11 a surrogate for exposure, instrument error would not be expected to influence the  
12 exposure surrogate on a daily basis. When comparing health effect estimates among cities  
13 for an epidemiologic study of long-term SO<sub>2</sub> exposure, differences in instrument error  
14 among cities could lead to biased exposure surrogates, given the reliance on differences  
15 in magnitude of the exposure surrogate to study spatial contrasts. [Section 3.4.4](#) describes  
16 the influence of instrument error and high MDL on exposure error and health effect  
17 estimates for community time-series ([Section 3.4.4.1](#)), long-term average  
18 ([Section 3.4.4.2](#)), and panel ([Section 3.4.4.3](#)) epidemiologic studies.

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### 3.4.3 Copollutant Relationships

19 Simulations by [Zeger et al. \(2000\)](#) indicate that unaccounted correlation among exposure  
20 concentrations or exposure errors for copollutants may lead to bias and uncertainty in the  
21 health effect estimates in epidemiologic studies. Correlation among copollutant exposure  
22 concentrations may amplify the health effect estimates. In some cases, this could promote  
23 a false conclusion of an association between a health effect and the copollutant exposure  
24 concentration even if no relationship between the health effect and copollutant exposure  
25 actually exists. Correlation of the errors in measuring copollutant concentrations may  
26 cause bias in the health effect estimate, especially when one is measured with more error  
27 than the other ([Zeger et al., 2000](#)). Confounding is described in the [Preamble](#) to the ISAs  
28 ([U.S. EPA, 2015b](#)). Briefly, confounding occurs when the copollutant exposure  
29 concentrations are correlated with those of the pollutant of interest and the health effect.  
30 Confounding can cause misleading results for estimating the health effect of SO<sub>2</sub> if the  
31 copollutant is not accounted for ([Rothman and Greenland, 1998](#)). This differs from effect  
32 modification, where the health effect estimate for SO<sub>2</sub> is conditional upon the copollutant  
33 exposure concentration via interaction of the SO<sub>2</sub> and copollutant exposures.

34 To assess the independent health effects of ambient SO<sub>2</sub> exposure in an epidemiologic  
35 study, it is necessary to identify ([Bateson et al., 2007](#)) (1) measurement error for all

1 copollutants; (2) which copollutants (e.g., NO<sub>2</sub>, PM<sub>2.5</sub>, UFP, BC) are potential  
2 confounders of the health effect-SO<sub>2</sub> relationship so that their correlation and collinearity  
3 with SO<sub>2</sub> can be tested and, if needed, accounted for in the epidemiologic model; (3) the  
4 time period over which correlations might exist so that potential confounders are  
5 considered appropriately for the time period relevant for the epidemiologic study design  
6 (e.g., pollutants or other factors that are correlated over the long term might not be  
7 important for a short-term exposure epidemiologic study); and (4) the spatial correlation  
8 structure across multiple pollutants, if the epidemiologic study design is for long-term  
9 exposure [Paciorek \(2010\)](#). Additionally, confounding can also vary by the health  
10 endpoint studied.

11 When SO<sub>2</sub> and a copollutant are correlated, copollutant epidemiologic models may be  
12 used to adjust the SO<sub>2</sub> effect estimate for potential confounding by the copollutant  
13 ([Tolbert et al., 2007](#)). Two-pollutant models can help identify which is the better  
14 predictor of the effect, particularly if the etiologically linked pollutant is measured with  
15 more error than the other pollutant ([Zeger et al., 2000](#)). However, collinearity potentially  
16 affects the epidemiologic model's effect estimate when highly correlated pollutants are  
17 modeled simultaneously, and differences in the spatial distribution of ambient SO<sub>2</sub>  
18 concentration and the copollutants' ambient concentrations may also complicate model  
19 interpretation [[Section 5.1.2.1](#) and [Gryparis et al. \(2007\)](#)]. Because ambient SO<sub>2</sub> exhibits  
20 a relatively high degree of exposure error compared with other criteria pollutants  
21 [e.g., [Section 3.4.4.1](#); [Goldman et al. \(2010\)](#)], two-pollutant models in which the SO<sub>2</sub>  
22 effect estimate remains robust may provide additional support for a health effect to be  
23 associated with SO<sub>2</sub> exposure [e.g., [Ito et al. \(2007\)](#)].

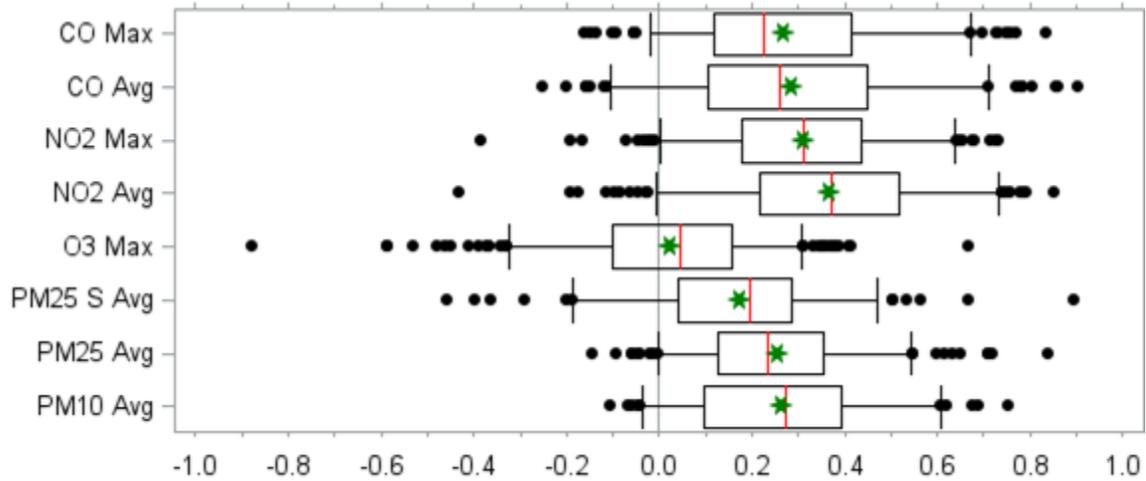
24 This section considers temporal copollutant correlations and how relationships among  
25 copollutants may change in space using AQS data and data reported in the epidemiologic  
26 literature ([Chapter 5](#)). Temporal copollutant correlations are computed from the time  
27 series of ambient concentrations for two copollutants measured with collocated AQS  
28 monitors. Spatial relationships are evaluated by comparing within-pollutant variation  
29 across space for different pollutants. The following sections review coexposures that can  
30 potentially confound the relationship between a health effect and ambient SO<sub>2</sub> exposure  
31 over different temporal and spatial resolutions.

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### 3.4.3.1 Temporal Relationships among Ambient Sulfur Dioxide and Copollutant Exposures

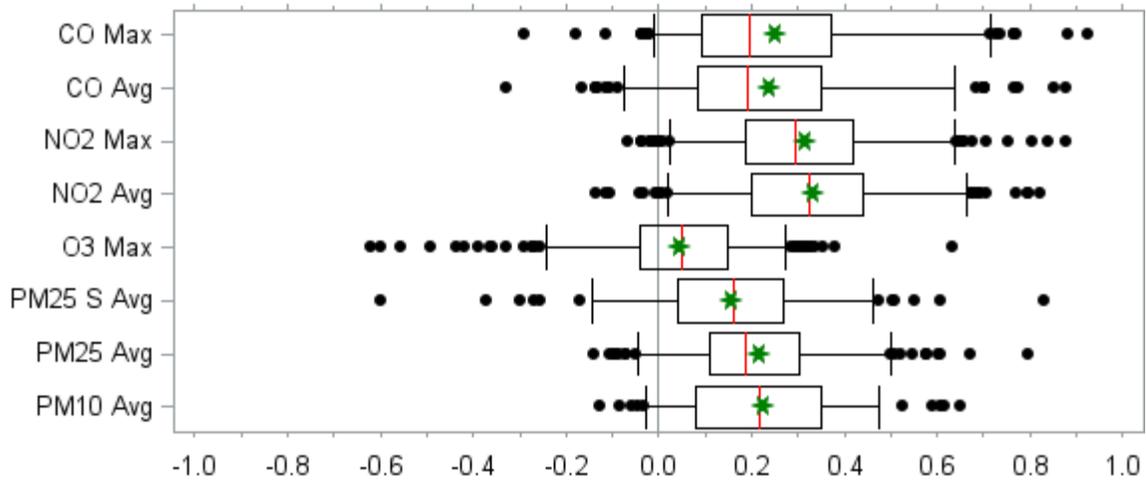
#### Short-Term Temporal Correlations

1 Short-term copollutant correlations were studied using collocated air quality data reported  
2 within the U.S. EPA AQS repository system during 2013–2015. 438 sites met the 75%  
3 data completeness criteria presented in [Section 2.5.1](#). Daily air quality metrics  
4 representing either 1-h daily max or 24-h avg ambient SO<sub>2</sub> concentration values were  
5 used. Pearson correlations were used to evaluate temporal correlations among ambient  
6 SO<sub>2</sub> concentrations and NAAQS copollutant concentrations. In addition, correlations  
7 between ambient SO<sub>2</sub> and PM<sub>2.5</sub>-sulfur were examined because PM<sub>2.5</sub>-sulfur serves as a  
8 surrogate for SO<sub>2</sub> oxidation products (i.e., sulfate) and may have confounding effects on  
9 health outcomes associated with ambient SO<sub>2</sub> exposure. [Figure 3-4](#) and [Figure 3-5](#)  
10 display the distribution of correlations between NAAQS copollutants and SO<sub>2</sub> daily  
11 metrics (24-h avg, 1-h daily max) for all data combined, and [Figure 3-6](#) and [Figure 3-7](#)  
12 display those copollutant correlations broken down by season. Because epidemiologic  
13 studies may use either daily average or daily maximum metrics, correlations are  
14 presented for both metrics, when available. For CO and NO<sub>2</sub>, 1-h daily max  
15 concentrations are used, while for O<sub>3</sub>, 8-h daily max concentrations are considered.



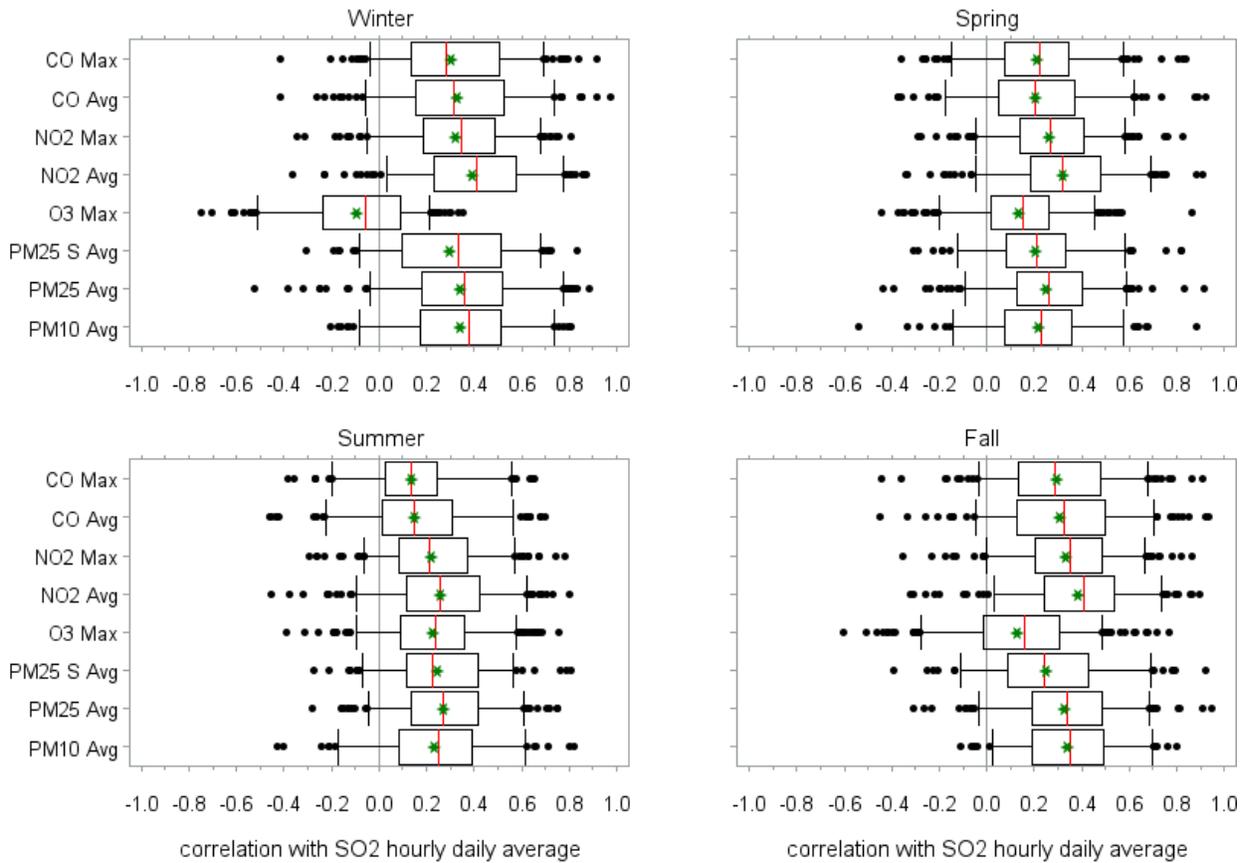
CO = carbon monoxide; NO<sub>2</sub> = nitrogen dioxide; O<sub>3</sub> = ozone; PM<sub>2.5</sub> = particulate matter with a nominal aerodynamic diameter less than or equal to 2.5 μm; PM<sub>10</sub> = particulate matter with a nominal aerodynamic diameter less than or equal to 10 μm; S = sulfur.  
 Note: Shown are the median (red line), mean (green star), and inner-quartile range (box), 5th and 95th percentile (whiskers) and extremes (black circles)

**Figure 3-4** Distribution of Pearson correlation coefficients for comparison of 24-h avg sulfur dioxide concentration from the year-round data set with collocated National Ambient Air Quality Standards pollutants (and sulfur in PM<sub>2.5</sub>) from Air Quality System during 2013–2015.



CO = carbon monoxide; NO<sub>2</sub> = nitrogen dioxide; O<sub>3</sub> = ozone; PM<sub>25</sub> = particulate matter with a nominal aerodynamic diameter less than or equal to 2.5 μm; PM<sub>10</sub> = particulate matter with a nominal aerodynamic diameter less than or equal to 10 μm; S = sulfur.  
 Note: Shown are the median (red line), mean (green star), and inner-quartile range (box), 5th and 95th percentile (whiskers) and extremes (black circles)

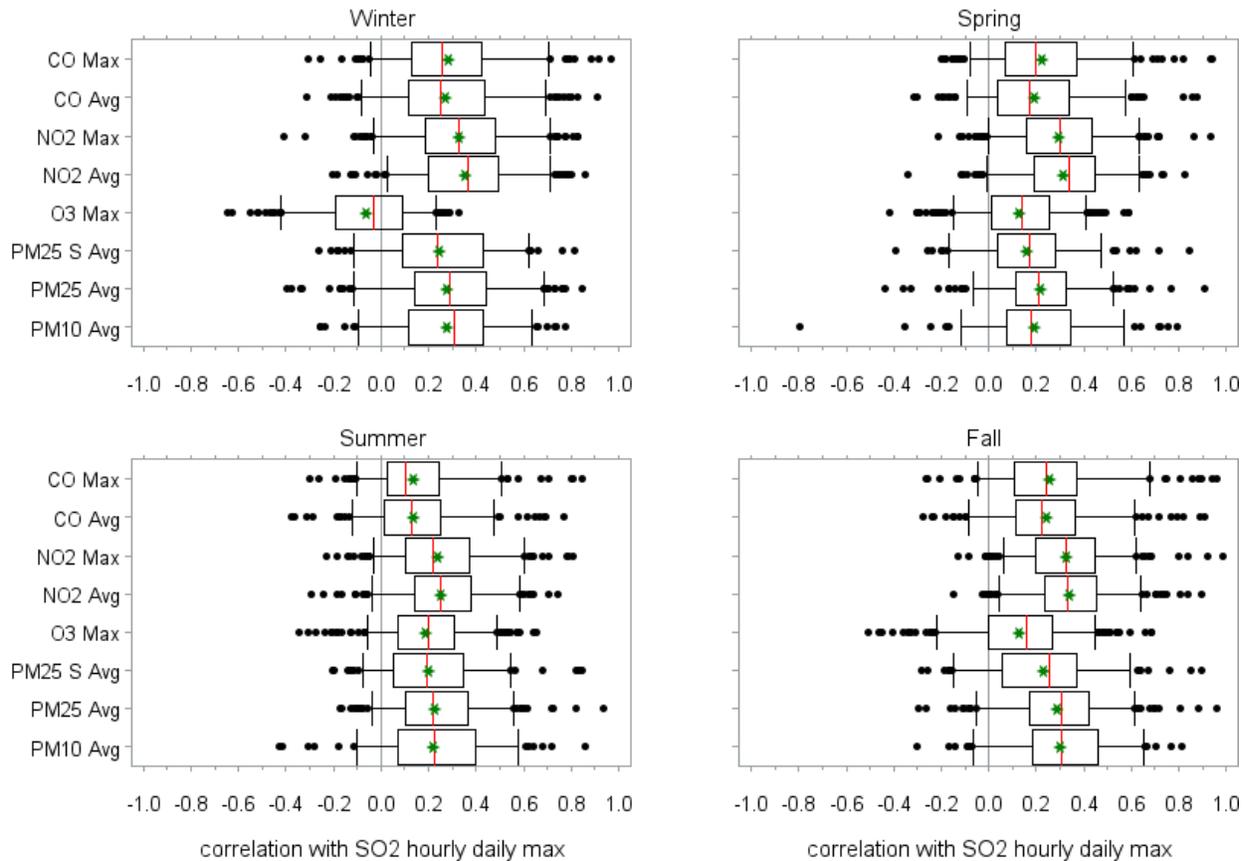
**Figure 3-5 Distribution of Pearson correlation coefficients for comparison of daily 1-h max sulfur dioxide concentration from the year-round data set with collocated National Ambient Air Quality Standards pollutants (and sulfur in PM<sub>2.5</sub>) from Air Quality System during 2013–2015.**



CO = carbon monoxide; NO<sub>2</sub> = nitrogen dioxide; O<sub>3</sub> = ozone; PM<sub>2.5</sub> = particulate matter with a nominal aerodynamic diameter less than or equal to 2.5 μm; PM<sub>10</sub> = particulate matter with a nominal aerodynamic diameter less than or equal to 10 μm; S = sulfur; SO<sub>2</sub> = sulfur dioxide.

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

**Figure 3-6 Distribution of Pearson correlation coefficients for comparison of daily 24-h avg sulfur dioxide ambient concentration stratified by season with collocated National Ambient Air Quality Standards pollutants (and PM<sub>2.5</sub>) from Air Quality System during 2013–2015.**



CO = carbon monoxide; NO<sub>2</sub> = nitrogen dioxide; O<sub>3</sub> = ozone; PM<sub>2.5</sub> = particulate matter with a nominal aerodynamic diameter less than or equal to 2.5 μm; PM<sub>10</sub> = particulate matter with a nominal aerodynamic diameter less than or equal to 10 μm; S = sulfur; SO<sub>2</sub> = sulfur dioxide.

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

**Figure 3-7 Distribution of Pearson correlation coefficients for comparison of daily 1-h max sulfur dioxide ambient concentration stratified by season with collocated National Ambient Air Quality Standards pollutants (and PM<sub>2.5</sub>) from Air Quality System during 2013–2015.**

1 While 24-h avg ambient SO<sub>2</sub> concentration exhibits a wide range of correlations with  
 2 NAAQS copollutants, median correlations are all below 0.4 (Figure 3-4). The lowest  
 3 correlations are observed between ambient SO<sub>2</sub> concentration and ambient O<sub>3</sub>  
 4 concentration, with median correlations below 0.1. Slightly higher correlations are  
 5 observed between ambient SO<sub>2</sub> concentration and other primary NAAQS pollutant  
 6 concentrations (NO<sub>2</sub> and CO), with median correlations between 0.3 and 0.4. Common  
 7 fuel combustion sources may be responsible for these correlations (Section 2.2). Lower  
 8 correlations with PM<sub>2.5</sub> sulfur than PM<sub>2.5</sub> mass may reflect the secondary formation of

1 sulfate by oxidation of SO<sub>2</sub>, while PM<sub>2.5</sub> mass also has a primary component.  
2 Correlations close to 1 or below 0 are sometimes observed but only occur at a few outlier  
3 monitoring sites. Comparatively, copollutant correlations of daily 1-h max ambient SO<sub>2</sub>  
4 in [Figure 3-5](#) are also slightly lower than the copollutant correlations based on ambient  
5 SO<sub>2</sub> 24-h avg values in [Figure 3-4](#). The medians of correlations between daily 1-h max  
6 ambient SO<sub>2</sub> concentrations and other NAAQS pollutants are below 0.3, with the  
7 exception of NO<sub>2</sub>, which exhibits median correlations slightly above 0.3. These results  
8 indicate that for short-term epidemiologic studies, the minority of sites with stronger  
9 correlations may introduce a greater degree of confounding into those epidemiologic  
10 results. It is notable that the nature of correlations between SO<sub>2</sub> and copollutants is  
11 changing given rulemaking on use of ultra-low sulfur diesel fuel that went into effect in  
12 2006 (66 FR 5002). Some of the epidemiologic studies cited in [Chapter 5](#) included data  
13 obtained prior to 2006 and 2007, when the new sulfur standards took effect for highway  
14 vehicles and heavy-duty vehicles, respectively. This change may have contributed to the  
15 wider variation observed in correlation between ambient SO<sub>2</sub> and copollutant  
16 concentrations. Note that potential for confounding also varies by health endpoint.

17 Correlations between ambient SO<sub>2</sub> and NAAQS copollutant concentrations demonstrate  
18 very little variability across seasons ([Figure 3-6](#) and [Figure 3-7](#)). All median and average  
19 copollutant correlations are below 0.4 across every season. The only substantial seasonal  
20 difference in correlations between ambient SO<sub>2</sub> and copollutant concentrations occurs  
21 during the winter, when ambient SO<sub>2</sub> concentration exhibits lower negative correlations  
22 with ambient O<sub>3</sub> concentration (median winter correlations = -0.1). SO<sub>2</sub>-O<sub>3</sub> correlations  
23 are generally low year-round, potentially because the regional nature of O<sub>3</sub> formation  
24 contrasts with the local nature of SO<sub>2</sub> plumes from point sources. In winter, the low  
25 correlations could be directly linked to relatively low ambient O<sub>3</sub> concentrations during  
26 this time of year due to less photochemical O<sub>3</sub> production and SO<sub>2</sub> oxidation.

27 Overall, daily and hourly ambient SO<sub>2</sub> concentrations generally exhibit median  
28 correlations around 0.2–0.4 with respect to other collocated NAAQS copollutants at AQS  
29 monitoring sites. However, given that a small subset of sites report relatively higher  
30 copollutant correlations, confounding may need to be considered on a study-by-study  
31 basis, preferably with correlations reported in the individual studies. High copollutant  
32 correlations in the national distribution could be due either to consistently low  
33 concentrations for both SO<sub>2</sub> and the copollutant or to consistent fluctuations in  
34 concentrations of both pollutants due to source behavior and meteorology.

35 Exposure studies have also examined correlations between ambient SO<sub>2</sub> concentration  
36 and ambient or personal copollutant exposure concentrations, generally reporting low or  
37 moderate correlations. For SO<sub>2</sub>, within-hourly concentrations have median correlations

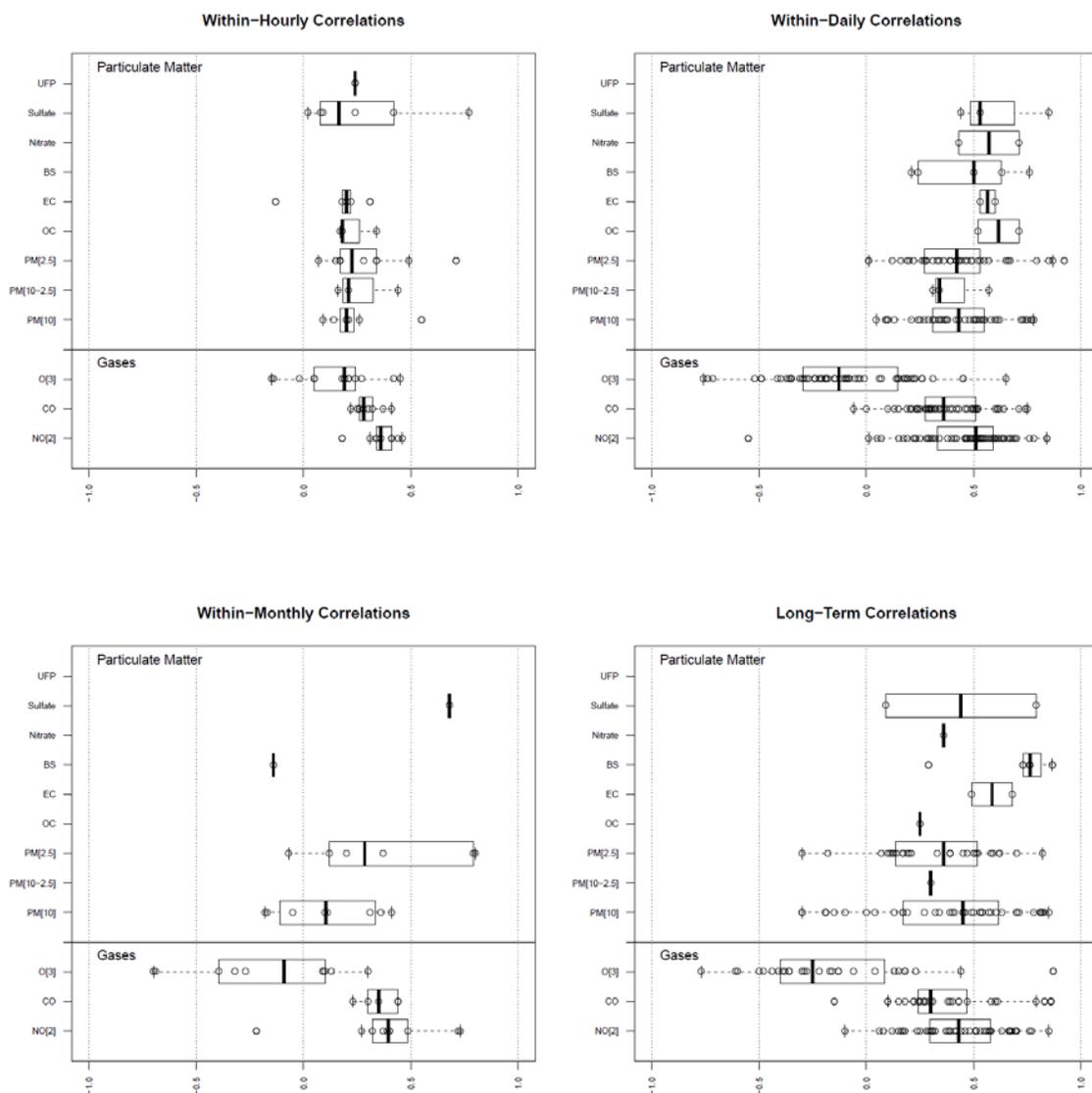
1 around 0.2 for most PM of different cut-points and species. For gases, median  
2 correlations of within-hourly data were lower for O<sub>3</sub> than for CO and NO<sub>2</sub>, respectively,  
3 but median correlations did not surpass 0.4. Correlations were mostly positive for all but  
4 O<sub>3</sub>, which exhibits both negative and positive correlations. See [Figure 3-8](#) and references  
5 cited therein for copollutant correlation data reported in the literature ([Liu et al. \(2016\)](#);  
6 [Mendola et al. \(2016a\)](#); [Michikawa et al. \(2016\)](#); [Neophytou et al. \(2016\)](#); [Smith et al.](#)  
7 [\(2016\)](#); [Wallace et al. \(2016\)](#); [Ancona et al. \(2015\)](#); [Assibey-Mensah et al. \(2015\)](#);  
8 [Bentayeb et al. \(2015\)](#); [Byers et al. \(2015\)](#); [Deng et al. \(2015a\)](#); [Dibben and Clemens](#)  
9 [\(2015\)](#); [Huang et al. \(2015a\)](#); [Hwang et al. \(2015b\)](#); [Ierodiakonou et al. \(2015\)](#);  
10 [Michikawa et al. \(2015\)](#); [Qian et al. \(2015\)](#); [Radwan et al. \(2015\)](#); [Ware et al. \(2015\)](#);  
11 [Yorifuji et al. \(2015b\)](#); [Zhu et al. \(2015\)](#); [Chen et al. \(2014b\)](#); [Gorai et al. \(2014\)](#); [Lin et](#)  
12 [al. \(2014\)](#); [Liu et al. \(2014a\)](#); [Winqvist et al. \(2014\)](#); [Xu et al. \(2014\)](#); [Altuğ et al. \(2013\)](#);  
13 [Carey et al. \(2013\)](#); [Clougherty et al. \(2013\)](#); [Dong et al. \(2013a\)](#); [Faiz et al. \(2013\)](#);  
14 [Greenwald et al. \(2013\)](#); [Mehta et al. \(2013\)](#); [Qiu et al. \(2013b\)](#); [Slama et al. \(2013\)](#); [Son](#)  
15 [et al. \(2013\)](#); [Zheng et al. \(2013\)](#); [Costa Nascimento et al. \(2012\)](#); [Ebisu and Bell \(2012\)](#);  
16 [Faiz et al. \(2012\)](#); [HEI \(2012\)](#); [Le et al. \(2012\)](#); [Lee et al. \(2012\)](#); [Portnov et al. \(2012\)](#);  
17 [Tsai et al. \(2012\)](#); [Turin et al. \(2012\)](#); [Bhaskaran et al. \(2011\)](#); [Darrow et al. \(2011\)](#);  
18 [Hwang et al. \(2011\)](#); [Ito et al. \(2011\)](#); [Lee et al. \(2011b\)](#); [Li et al. \(2011\)](#); [Liao et al.](#)  
19 [\(2011\)](#); [Peel et al. \(2011\)](#); [Samoli et al. \(2011\)](#); [Zhao et al. \(2011\)](#); [Akinbami et al.](#)  
20 [\(2010\)](#); [Chen et al. \(2010b\)](#); [Hsieh et al. \(2010\)](#); [Pan et al. \(2010\)](#); [Penard-Morand et al.](#)  
21 [\(2010\)](#); [Arbex et al. \(2009\)](#); [Arnedo-Pena et al. \(2009\)](#); [Cheng et al. \(2009\)](#); [Darrow et al.](#)  
22 [\(2009\)](#); [Forbes et al. \(2009c\)](#); [Guo et al. \(2009\)](#); [Lipfert et al. \(2009\)](#); [Rich et al. \(2009\)](#);  
23 [Sahsuvargolu et al. \(2009\)](#); [Stieb et al. \(2009\)](#); [Strickland et al. \(2009\)](#); [Dales et al.](#)  
24 [\(2008\)](#); [Hwang and Jaakkola \(2008\)](#); [Jalaludin et al. \(2008\)](#); [Ségala et al. \(2008\)](#);  
25 [Woodruff et al. \(2008\)](#); [Ko et al. \(2007a\)](#); [Liu et al. \(2007\)](#); [Tolbert et al. \(2007\)](#); [ATSDR](#)  
26 [\(2006\)](#); [Ballester et al. \(2006\)](#); [Cendon et al. \(2006\)](#); [Fung et al. \(2006\)](#); [Jalaludin et al.](#)  
27 [\(2006\)](#); [Leem et al. \(2006\)](#); [Lipfert et al. \(2006a\)](#); [Filleul et al. \(2005\)](#); [Llorca et al.](#)  
28 [\(2005\)](#); [Peel et al. \(2005\)](#); [Sagiv et al. \(2005\)](#); [Wilson et al. \(2005\)](#); [Metzger et al. \(2004\)](#);  
29 [Jaffe et al. \(2003\)](#); [Lee et al. \(2003\)](#); [Liu et al. \(2003\)](#); [Sheppard \(2003\)](#); [Yang et al.](#)  
30 [\(2003b\)](#); [Yang et al. \(2003a\)](#); [Anderson et al. \(2001\)](#); [Ballester et al. \(2001\)](#); [Ha et al.](#)  
31 [\(2001\)](#); [Krewski et al. \(2000\)](#); [Lipfert et al. \(2000b\)](#); [Abbey et al. \(1999\)](#); [Sheppard et al.](#)  
32 [\(1999\)](#); [Pereira et al. \(1998\)](#); [Burnett et al. \(1997\)](#); [Schwartz \(1997\)](#)).

33 More data were available for within-daily correlations of SO<sub>2</sub> and copollutant exposure  
34 concentrations. Median correlation around 0.5 were observed for SO<sub>4</sub><sup>2-</sup>, NO<sub>3</sub><sup>-</sup>, black  
35 smoke (BS), and organic carbon (OC) PM<sub>2.5</sub> species, PM<sub>10</sub>, and NO<sub>2</sub> for that time scale.  
36 Median correlation was around 0.3 for PM<sub>10-2.5</sub>, around 0.4 for CO and PM<sub>2.5</sub>, and around  
37 -0.2 for O<sub>3</sub>. Both data availability and inter-site variability were much greater for the  
38 gases, PM<sub>2.5</sub>, and PM<sub>10</sub> compared with the individual PM<sub>2.5</sub> species or PM<sub>10-2.5</sub>. Where  
39 data were available, a large degree of scatter was evident in the data. In studies where

1 within-daily correlations of SO<sub>2</sub> exposure concentrations with NO<sub>2</sub> and CO exposure  
2 concentrations were observed to be high, it is possible the data were collected before the  
3 rulemaking to reduce sulfur content in diesel fuel went into effect in 2006 (66 FR 5002)  
4 or when coal was in greater use in energy generation ([Section 2.2](#)). The minority of sites  
5 with stronger correlations may introduce a greater degree of confounding into the  
6 epidemiologic results. For this reason, copollutant correlations need to be reported in  
7 individual epidemiological studies to assess if confounding is a possibility.

8 Data for correlations between ambient SO<sub>2</sub> concentrations and personal copollutant  
9 exposures were reported in the 2008 SO<sub>x</sub> ISA ([U.S. EPA, 2008d](#)), and no studies have  
10 been produced to substantiate or revise the observations reported at that time.

11 Between-subject correlations of daily ambient SO<sub>2</sub> concentration with personal PM<sub>2.5</sub>  
12 exposures were found to vary widely with positive and negative correlations in the [Sarnat  
13 et al. \(2005\)](#) and [Sarnat et al. \(2001\)](#) studies. In the ([Sarnat et al., 2005](#)) study, 95–97% of  
14 the SO<sub>2</sub> data were below the MDL, indicating high uncertainty. This evidence suggests  
15 that correlations between personal copollutant exposures and ambient SO<sub>2</sub> concentration  
16 vary among individuals, and thus the potential for copollutant confounding cannot be  
17 ruled out.

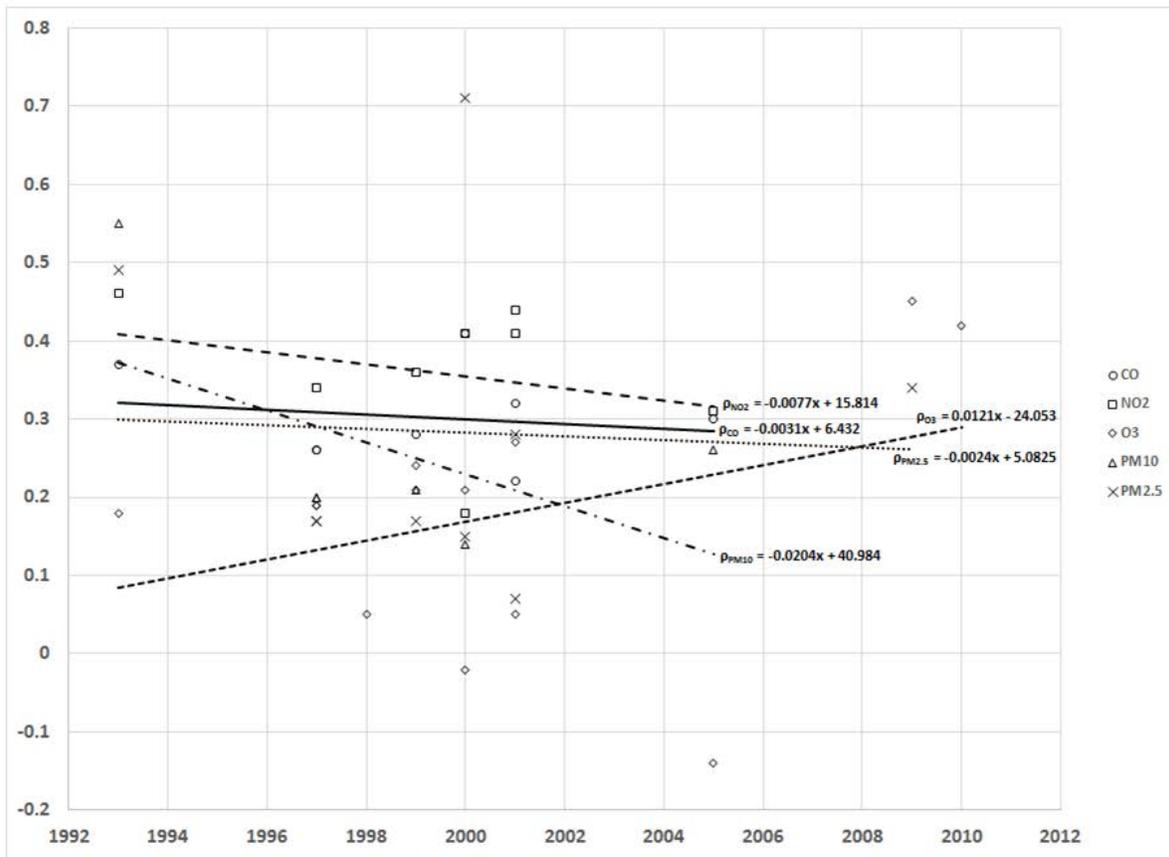


BS = black smoke; CO = carbon monoxide; EC = elemental carbon; LUR = land use regression; NO<sub>2</sub> = nitrogen dioxide; O<sub>3</sub> = ozone; OC = organic carbon; PM<sub>2.5</sub> = in general terms, particulate matter with a nominal aerodynamic diameter less than or equal to 2.5 μm, a measure of fine particles; PM<sub>10</sub> = in general terms, particulate matter with a nominal aerodynamic diameter less than or equal to 10 μm, a measure of thoracic particles (i.e., that subset of inhalable particles thought small enough to penetrate beyond the larynx into the thoracic region of the respiratory tract); PM<sub>10-2.5</sub> = in general terms, particulate matter with a nominal aerodynamic diameter less than or equal to 10 μm and greater than 2.5 μm, a measure of thoracic coarse particulate matter or the coarse fraction of PM<sub>10</sub>; SO<sub>2</sub> = sulfur dioxide; UFP = ultrafine particulate matter.

Notes: Boxes represent the interquartile range of the data with the median line plotted, and 90th and 10th percentile of the data are plotted as the whiskers. Correlation data computed from LUR studies are not included here. Correlations shown by closed red circles come from near-road studies, and correlations shown by open black circles either come from urban-regional scale studies or do not specify the study's spatial scale. Within-monthly correlations include correlations obtained over 5 weeks or less for SO<sub>2</sub>.

**Figure 3-8 Summary of temporal sulfur dioxide-copollutant correlation coefficients from measurements reported in the literature, sorted by temporal averaging period.**

1 Data from the studies cited in [Figure 3-8](#) suggest that the correlations between exposure  
2 concentrations of SO<sub>2</sub> and copollutants have changed over time for some cases  
3 ([Figure 3-9](#)). On average, copollutant correlations using 1-hour data have declined in  
4 magnitude over the last two decades for CO, NO<sub>2</sub>, PM<sub>10</sub>, and PM<sub>2.5</sub>, albeit with a lot of  
5 scatter in these relationships reflected in the mostly low correlation values. These trends  
6 may be related to the adoption of alternatives to coal in energy generation ([Section 2.2](#)).  
7 Most of the studies presented were performed during periods that precede 2006, when the  
8 ultra-low sulfur diesel rule went into effect (66 FR 5002). The amount of SO<sub>2</sub> co-emitted  
9 with CO and NO<sub>x</sub> during combustion processes has since been greatly reduced. Hence,  
10 copollutant confounding is less probable for newer studies of the health effects of SO<sub>2</sub>  
11 exposure compared with older studies. At the same time, scatter in the copollutant  
12 correlation trends suggests that copollutant correlations need to be checked for individual  
13 epidemiological studies to assess if confounding is a possibility.



CO = carbon monoxide; NO<sub>2</sub> = nitrogen dioxide; O<sub>3</sub> = ozone; PM<sub>2.5</sub> = particulate matter with a nominal aerodynamic diameter less than or equal to 2.5 μm; PM<sub>10</sub> = particulate matter with a nominal aerodynamic diameter less than or equal to 10 μm; ρ = correlation; x = year.

**Figure 3-9 Trends in copollutant correlations computed using hourly (1-h avg or 1-h daily max) concentration data.**

### Long-Term Correlations

1 Long-term epidemiologic studies that have reported copollutant correlations are also  
 2 displayed in [Figure 3-8](#) and references cited therein for within-monthly and longer term  
 3 correlations. Data were limited for many of the PM<sub>2.5</sub> components. For exposure  
 4 concentrations of PM<sub>2.5</sub>, PM<sub>10</sub>, O<sub>3</sub>, CO, and NO<sub>2</sub>, a wide range of correlations has been  
 5 reported. Median correlation was lower for PM<sub>2.5</sub> exposure concentration ( $r = 0.2$ )  
 6 compared with that of PM<sub>10</sub> ( $r = 0.4$ ), CO ( $r = 0.3$ ), and NO<sub>2</sub> ( $r = 0.3$ ). Median correlation  
 7 was negative ( $r = -0.3$ ) for O<sub>3</sub> exposure concentration. For correlations between exposure  
 8 concentrations of SO<sub>2</sub> and PM<sub>2.5</sub>, most of the data were clustered around the median,

1 while variability in the correlations was larger for the other copollutants. As for  
2 short-term copollutant relationships, no clear conclusion can be drawn regarding the  
3 potential for confounding of long-term SO<sub>2</sub> epidemiologic estimates by copollutants.  
4 Wide variability in copollutant correlations with the highest correlations around 0.7–0.8  
5 for PM<sub>2.5</sub>, PM<sub>10</sub>, CO, and NO<sub>2</sub> suggests that confounding may need to be considered on a  
6 study-by-study basis.

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### 3.4.3.2 Spatial Relationships among Ambient Sulfur Dioxide and Copollutants

7 Spatial confounding can potentially influence health effect estimates in epidemiologic  
8 studies of long-term SO<sub>2</sub> exposure. [Paciorek \(2010\)](#) performed simulations to test the  
9 effect of spatial confounding on health effect estimates in long-term exposure  
10 epidemiologic studies. He identified unmeasured spatial confounding as a key driver in  
11 biasing health effect estimates in a spatial regression. The study author maintained that  
12 bias can be reduced when variation in the exposure metric occurs at a smaller spatial  
13 scale than that of the unmeasured confounder.

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### 3.4.4 Implications for Epidemiologic Studies of Different Designs

14 Exposure error is defined in [Section 3.2.1](#). To summarize, exposure error refers to the  
15 bias and uncertainty associated with using concentration metrics to represent the actual  
16 exposure of an individual or population. Exposure error has two components:  
17 (1) uncertainty in the metric used to represent exposure concentration and (2) the  
18 difference between the surrogate parameter of interest in the epidemiologic study and the  
19 true exposure (which may not be observable) ([Zeger et al., 2000](#)). Classical error can be  
20 considered the component of exposure measurement error derived from uncertainty in the  
21 metric being used to represent exposure. Classical error is defined as error scattered  
22 around the true personal exposure and independent of the measured exposure  
23 concentration. Classical error results in bias of the epidemiologic health effect estimate  
24 that is typically towards the null (no effect of the exposure). Classical error can also cause  
25 inflation or reduction of the standard error of the health effect estimate. Berkson error can  
26 be considered the component of exposure error related to the use of a surrogate target  
27 parameter of interest in the epidemiologic study in lieu of the true exposure. Berkson  
28 error is defined as error scattered around the exposure surrogate (in most cases, the  
29 central site monitor measurement) and independent of the true value ([Goldman et al.,  
30 2011](#); [Reeves et al., 1998](#)). Pure Berkson error is not expected to bias the health effect  
31 estimate.

1 When investigators use statistical models to predict exposure concentrations, the  
2 exposure error is no longer purely classical or purely Berkson but may have  
3 characteristics of each error type. Measurement error for modeled exposure  
4 concentrations has been decomposed into Berkson-like and classical-like components,  
5 sharing some characteristics with Berkson and classical errors, respectively, but with key  
6 differences ([Szpiro et al., 2011](#)). Berkson-like errors occur when the modeled exposure  
7 concentration does not capture all of the variability in the true exposure. Under ideal  
8 conditions, Berkson-like errors increase the variability around the health effect estimate  
9 in a manner similar to pure Berkson error and does not induce bias, but Berkson-like  
10 error is spatially correlated and not independent of predicted exposure concentrations, so  
11 it results in underestimation of standard errors. [Szpiro and Paciorek \(2013\)](#) analyzed the  
12 impact of Berkson-like error under more general conditions and found that it can bias  
13 health effect estimates either toward the null or away from the null. For example, in one  
14 simulation study in which the spatial distributions of monitor and subject locations were  
15 dramatically different, the health effect estimates were biased away from the null. In  
16 another example, where spatially structured covariates were included in the health model  
17 but not in the exposure model, the health effect estimates were biased toward the null.  
18 Hence, Berkson-like error can lead to bias of the health effect estimate in either direction  
19 and should not be ignored. Classical-like errors result from uncertainty in estimating  
20 exposure model parameters. It can add variability to predicted exposure concentrations  
21 and can bias health effect estimates in a manner similar to pure classical error, but it  
22 differs from pure classical error in that the additional variability in estimated exposure  
23 concentrations is also not independent across space. Exposure error can bias  
24 epidemiologic associations between ambient pollutant concentrations and health  
25 outcomes, compared with the effect estimate obtained using the true exposure, and it  
26 tends to widen confidence intervals around those estimates beyond nominal coverage of  
27 the confidence intervals ([Sheppard et al., 2005](#); [Zeger et al., 2000](#)).

28 Exposure error can be an important contributor to uncertainty and variability in  
29 epidemiologic study results. Time-series studies assess the daily health status of a  
30 population of thousands or millions of people over the course of multiple years  
31 (i.e., thousands of days) across an urban area by estimating people's exposure  
32 concentrations using a short monitoring interval (hours to days). In these studies, the  
33 community-averaged concentration of an air pollutant measured at central site monitors is  
34 typically used as a surrogate for individual or population ambient exposure. In addition,  
35 panel studies, which consist of a relatively small sample (typically tens) of study  
36 participants followed over a period of days to months, have been used to examine the  
37 health effects associated with short-term exposure to ambient concentrations of air  
38 pollutants [e.g., [Delfino et al. \(1996\)](#)]. Panel studies may also apply a  
39 microenvironmental model to represent exposure concentrations for an air pollutant.

1 A longitudinal cohort epidemiologic study, such as the American Cancer Society (ACS)  
2 cohort study, typically involves hundreds or thousands of subjects followed over several  
3 years or decades [e.g., [Jerrett et al. \(2009\)](#)]. Concentrations are generally aggregated over  
4 time and by community to estimate exposures. The importance of exposure error varies  
5 with study design and is dependent on the spatial and temporal aspects of the design.  
6 Factors that could influence exposure estimates include topography of the natural and  
7 built environment, meteorology, instrument errors, use of ambient SO<sub>2</sub> concentration as a  
8 surrogate for exposure to ambient SO<sub>2</sub>, and the presence of SO<sub>2</sub> in a mixture of  
9 pollutants. The following sections will consider various sources of error and how they  
10 affect the interpretation of results from epidemiologic studies of different designs.

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#### 3.4.4.1 Community Time-Series Studies

11 In most short-term exposure epidemiologic studies of the health effects of SO<sub>2</sub>, the health  
12 effect endpoint is modeled as a function of ambient exposure,  $E_a$ , which is defined as the  
13 product of  $C_a$ , and  $\alpha$ , a term encompassing time-weighted averaging and infiltration of  
14 SO<sub>2</sub> ([Section 3.2.2](#)). Community time-series epidemiologic studies capturing the  
15 exposures and health outcomes of a large cohort frequently use the ambient concentration  
16 at a central site monitor ( $C_{a,csm}$ ) as a surrogate for  $E_a$  in an epidemiologic model ([Wilson  
17 et al., 2000](#)). At times, an average of central site-monitored concentrations is used for the  
18  $E_a$  surrogate. For studies involving thousands of participants, it is not feasible to measure  
19 personal exposure concentrations or time-activity patterns. Moreover, for community  
20 time-series epidemiology studies of short-term exposure, the temporal variability in  
21 ambient SO<sub>2</sub> concentration is of primary importance to relate to variability in the health  
22 effect estimate ([Zeger et al., 2000](#)).  $C_{a,csm}$  can be an acceptable surrogate if the central site  
23 monitor captures the temporal variability of the true air pollutant exposure. Spatial  
24 variability in ambient SO<sub>2</sub> concentrations across the study area could attenuate an  
25 epidemiologic health effect estimate if the exposures are not correlated in time with  $C_{a,csm}$   
26 when central site monitoring is used to represent exposure in the epidemiologic model. If  
27 exposure assessment methods that more accurately capture spatial variability in the  
28 concentration distribution over a study area are employed, then the confidence intervals  
29 around the health effect estimate may decrease.  $C_{a,csm}$  may be an acceptable surrogate for  
30  $E_a$  if the concentration time series at the central site monitor is correlated in time with the  
31 exposures.

32 In a time-series study of ED visits for cardiovascular disease, [Goldman et al. \(2011\)](#)  
33 simulated the effect of classical and Berkson errors due to spatiotemporal variability  
34 among ambient or outdoor (i.e., a noncentral site monitor situated outside the home) air  
35 pollutant concentrations over a large urban area. For 1-h daily max SO<sub>2</sub>, the relative risk

1 (RR) per ppm was negatively biased in the case of classical error (-1.3%) and negligibly  
2 positively biased in the case of Berkson error (0.0042%). The 95% confidence interval  
3 range for RR per ppm was wider for Berkson error (0.028) compared with classical error  
4 (0.0025).

5 Recent studies have explored the effect of spatial exposure error on health effect  
6 estimates to test the appropriateness of using central site monitoring for time-series  
7 studies. [Goldman et al. \(2010\)](#) simulated spatial exposure error based on a semivariogram  
8 function across monitor sites with and without temporal autocorrelation at 1- and 2-day  
9 lags to analyze the influence of spatiotemporal variability among ambient concentrations  
10 over a large urban area on a time-series study of ED visits for cardiovascular disease.  
11 A random term was calculated through Monte Carlo simulations based on the data  
12 distribution from the semivariogram, which estimated the change in spatial variability in  
13 exposure concentration with distance from the monitoring site. The average of the  
14 calculated random term was added to an ambient central site monitoring SO<sub>2</sub>  
15 concentration time series (considered in this study to be the base case) to estimate SO<sub>2</sub>  
16 population exposure concentration subject to spatial error. For the analysis with temporal  
17 autocorrelation considered, RR per ppm for 1-h daily max SO<sub>2</sub> dropped slightly to 1.0045  
18 (95% CI: 1.0023, 1.0065) when it was compared with the central site monitor RR per  
19 ppm = 1.0139 (for all air pollutants).<sup>1</sup> When temporal autocorrelation was not considered,  
20 RR per ppm dropped very slightly to 1.0042 for 1-h daily max SO<sub>2</sub>. The results of  
21 [Goldman et al. \(2010\)](#) suggest that spatial exposure error from the use of ambient central  
22 site SO<sub>2</sub> concentration monitoring data results in biasing the health effect estimate  
23 towards the null, but the magnitude of the change in effect was small.

24 In another simulation study analyzing the influence of spatiotemporal variability among  
25 ambient concentrations over a large urban area on health effect estimates, [Goldman et al.](#)  
26 [\(2012\)](#) evaluated the effect of different types of spatial averaging on bias in the health  
27 effect risk ratio and the effect of correlation between measured and reference ambient  
28 concentrations of SO<sub>2</sub> and other air pollutants. Ambient concentrations were simulated at  
29 alternate monitoring locations using the geostatistical approach described above  
30 ([Goldman et al., 2010](#)) for the 20-county Atlanta metropolitan area for comparison with  
31 ambient concentration measurements obtained directly from monitors at those sites.  
32 Geostatistical-simulated ambient exposure concentrations were designated as the  
33 reference in this study, and other exposure assessment methods were assumed to have  
34 some error. Five different exposure assessment approaches were tested: (1) using a single  
35 central site monitor, (2) averaging the simulated exposures across all monitoring sites,

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<sup>1</sup> Note that 95% CIs were not reported for the central site monitor RR or for the cases where temporal autocorrelation was not considered.

1 (3) performing a population-weighted average across all monitoring sites, (4) performing  
2 an area-weighted average across all monitoring sites, and (5) performing  
3 population-weighted averaging of the geostatistical simulation. [Goldman et al. \(2012\)](#)  
4 observed that the exposure error was somewhat correlated with both the measured  
5 exposure concentration and the reference ambient concentrations, reflecting both Berkson  
6 and classical error components. For the central site monitor, the exposure errors were  
7 somewhat inversely correlated with the exposure concentration reference value but had  
8 relatively higher positive correlation with the measured ambient concentration. For the  
9 other exposure estimation methods, the exposure errors were inversely correlated with the  
10 reference exposure concentration, while having positive but lower magnitude correlation  
11 with the measured ambient concentration. Additionally, the exposure bias, given by the  
12 ratio of the exposure error to the measured value, was much higher in magnitude at the  
13 central site monitor than for the spatial averaging techniques for SO<sub>2</sub>. Hence, compared  
14 with other exposure assessment methods, the health effect estimate would likely have  
15 greater bias towards the null with reduced precision when a central site monitor is used to  
16 measure ambient SO<sub>2</sub> concentration as a surrogate for exposure. However, exposure error  
17 is likely to cause some bias and imprecision for other exposure surrogate methods as  
18 well.

19 In addition to the effect of the correlations and ratios themselves, spatial variation across  
20 urban areas also impacts time-series epidemiologic results. The [Goldman et al. \(2010\)](#)  
21 and [Goldman et al. \(2012\)](#) findings suggest more Berkson error in the spatially resolved  
22 exposure concentration metrics compared with the central site monitor ambient  
23 concentration and more classical error for the central site monitor ambient concentration  
24 estimate compared with the other exposure concentration measurement techniques.  
25 Hence, more bias would be expected for the health effect estimate calculated from the  
26 central site monitor ambient concentration, and more variability would be expected for  
27 the health effect estimate calculated from exposure concentrations estimated by the more  
28 spatially resolved methods. Differences in the magnitude of exposure concentration  
29 estimates are not likely to cause substantial bias, but they tend more to widen confidence  
30 intervals and thus reduce the precision of the effect estimate beyond the nominal  
31 coverage of the confidence intervals that would be obtained if using the true exposure  
32 ([Zeger et al., 2000](#)). The more spatially variable air pollutants studied in [Goldman et al.](#)  
33 [\(2012\)](#) also had more bias in the health effect estimates. This occurred across exposure  
34 assignment methods but was more pronounced for the central site measurement ambient  
35 concentration data. Note that the [Goldman et al. \(2010\)](#), [Goldman et al. \(2011\)](#), and  
36 [Goldman et al. \(2012\)](#) studies were performed only in Atlanta, GA. These simulation  
37 studies are informative, but similar simulation studies in additional cities would aid  
38 generalization of these study results.

1 [Section 3.4.2.4](#) describes the influence of high MDL on the relationship between  
2 measured ambient SO<sub>2</sub> concentrations and personal SO<sub>2</sub> exposures. When measurements  
3 are above MDL, then the amount of correlation between personal SO<sub>2</sub> exposure and  
4 ambient SO<sub>2</sub> concentrations determines the extent of bias in a time-series study. If the  
5 reported values of personal exposure measurements are below MDL, correlation between  
6 personal SO<sub>2</sub> exposure measurements and ambient SO<sub>2</sub> concentrations will likely be low  
7 due to random noise in the signal. To the extent that true correlations are less than one,  
8 epidemiologic effect estimates based on ambient concentration will be biased toward the  
9 null, based on simulations by [Zeger et al. \(2000\)](#). Time-series epidemiologic studies  
10 employing data below MDL may demonstrate attenuated effect, but this scenario cannot  
11 be used to reject the hypothesis of a health effect.

12 [Section 3.4.2.4](#) also describes the influence of instrument accuracy and precision on the  
13 relationship between ambient SO<sub>2</sub> concentrations and personal SO<sub>2</sub> exposures. Exposure  
14 measurement error related to instrument precision has a smaller influence on health effect  
15 estimates in time-series studies compared with error related to spatial gradients in the  
16 ambient SO<sub>2</sub> concentration because instrument precision would not be expected to  
17 modify the ability of the instruments to respond to changes in ambient concentration over  
18 time. [Goldman et al. \(2010\)](#) investigated the influence of instrument error on health effect  
19 estimates in a time-series epidemiology study by studying differences in exposure  
20 concentration estimates and health effect estimates obtained using collocated monitors. In  
21 this study, a random error term based on observations from collocated monitors was  
22 added to a central site monitor's ambient concentration time series to simulate population  
23 estimates for ambient air concentrations subject to instrument precision error in  
24 1,000 Monte Carlo simulations. Very small changes in the risk ratios were observed for  
25 1-h daily max SO<sub>2</sub> ambient concentrations. For 1-h daily max SO<sub>2</sub> ambient concentration,  
26 the RR per ppm of SO<sub>2</sub> ambient concentration with simulated instrument precision error  
27 was 1.0132 compared with RR per ppm = 1.0139 for the central site monitor. The amount  
28 of bias in the health effect estimate related to instrument precision was very small.

29 As described in [Section 3.4.1](#) nonambient sources of SO<sub>2</sub> are rare. Even in  
30 microenvironments where nonambient SO<sub>2</sub> exposure is substantial, such as in a room  
31 with a kerosene heater, such nonambient exposure concentrations are unlikely to be  
32 temporally correlated with ambient SO<sub>2</sub> exposure concentrations ([Wilson and Suh, 1997](#)),  
33 and therefore would not affect epidemiologic associations between ambient SO<sub>2</sub> exposure  
34 concentrations and a health effect in a time-series study. [Sheppard et al. \(2005\)](#) concluded  
35 that nonambient exposure does not influence the health outcome effect estimate if  
36 ambient and nonambient exposure concentrations are independent. Personal exposure to  
37 ambient SO<sub>2</sub> is some fraction of the ambient concentration. Therefore, effect estimates  
38 based on personal SO<sub>2</sub> exposure rather than ambient SO<sub>2</sub> concentration will be positively

1 biased in proportion to the ratio of ambient SO<sub>2</sub> concentration to ambient SO<sub>2</sub> exposure  
2 concentration. Daily fluctuations in this ratio can widen the confidence intervals in the  
3 ambient SO<sub>2</sub> concentration effect estimate beyond the nominal coverage of the  
4 confidence intervals obtained using the true exposure. Uncorrelated nonambient exposure  
5 concentration will not bias the effect estimate but may also widen the confidence  
6 intervals ([Sheppard et al., 2005](#); [Wilson and Suh, 1997](#)).

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#### 3.4.4.2 Long-Term Cohort Studies

7 For cohort epidemiologic studies of long-term human exposure to SO<sub>2</sub>, where the spatial  
8 difference in the magnitude of the ambient SO<sub>2</sub> exposure is often of most interest and if  
9  $C_{a,csm}$  is used as a surrogate for  $E_a$ , then  $\alpha$  can be considered to encompass the exposure  
10 measurement error related to uncertainties in the time-activity data and air exchange rate.  
11 Spatial variability in ambient SO<sub>2</sub> exposure concentrations across the study area could  
12 lead to bias in the health effect estimate if  $C_{a,csm}$  is not representative of  $E_a$ . This could  
13 occur, for example, if the study participants were clustered in a location where their SO<sub>2</sub>  
14 exposure concentration is higher or lower than the exposure concentration estimated at a  
15 modeled or measurement site.  $C_{a,csm}$  may be an acceptable surrogate for  $E_a$  if the central  
16 site monitor is located close to the study participants and the ambient SO<sub>2</sub> source  
17 (e.g., near the plume touch-down of a power plant) and spatial variability of the ambient  
18 SO<sub>2</sub> concentration across the study area where the study participants are located is  
19 minimal in the vicinity of each sample group.

20 For long-term epidemiologic studies, the lack of personal exposure data means that  
21 investigators must rely on central site monitoring data or model estimates. Concentration  
22 data may be used directly, averaged across counties or other geographic areas, or used to  
23 construct geospatial or regression models to assign exposure concentrations to  
24 unmonitored locations. The number of long-term studies of SO<sub>2</sub> exposure that permit  
25 evaluation of the relationship between long-term average SO<sub>2</sub> concentrations and  
26 personal or population exposures is limited, and the value of short-term exposure  
27 concentration data for evaluating long-term exposure concentration relationships is  
28 uncertain. If the longer averaging time (annual vs. daily or hourly) smoothes out  
29 short-term fluctuations, long-term concentrations may be well correlated with long-term  
30 exposure concentrations that can be employed in long-term epidemiologic studies. For  
31 example, [Guay et al. \(2011\)](#) observed high correlation between  
32 single-year/single-location SO<sub>2</sub> concentrations used for an exposure surrogate with  
33 concentrations averaged over a 22-year period when the annual SO<sub>2</sub> concentrations were  
34 assigned based on the study participants' census subdivision. However, lower correlation  
35 between long-term exposure and ambient concentration could occur if important

1 exposure determinants change over a period of several years, including activity pattern  
2 and residential air exchange rate.

3 Minimization of error in the exposure concentration estimate does not always minimize  
4 error in the health effect estimate. [Szpiro et al. \(2011\)](#) used simulation studies to evaluate  
5 the bias and uncertainty of the health effect estimate obtained when using correctly  
6 specified and misspecified long-term exposure concentration models. The correct  
7 exposure concentration model was considered to be an LUR with three covariates while  
8 the misspecified model included only two of these three covariates. The study authors  
9 estimated the exposure concentration model parameters using monitor data and predicted  
10 exposure concentrations at subject locations. They studied two conditions: where the  
11 variation in the third covariate was identical in the monitor and subject data versus where  
12 it was much smaller in the monitor data than in the subject data. [Szpiro et al. \(2011\)](#)  
13 showed that prediction accuracy of the exposure concentration estimate was always  
14 higher for the correctly specified model compared with the misspecified model.  
15 The health effect estimate had lower RMSE for the correct model when the third  
16 covariate had identical variability in the monitor and subject data. However, when the  
17 third covariate was much less variable in the monitor data, then the health effect estimate  
18 had lower RMSE for the misspecified model. The results of the [Szpiro et al. \(2011\)](#)  
19 simulations demonstrate one situation where use of a more accurately defined exposure  
20 concentration metric does not improve the health effect estimate.

21 Error correction is a relatively new approach to estimate the correct standard error and to  
22 potentially correct for bias in air pollution cohort studies. [Szpiro and Paciorek \(2013\)](#)  
23 established that two conditions must hold for the health effect estimate to be predicted  
24 correctly: (1) the exposure concentration estimates from monitors must come from the  
25 same underlying distribution as the true exposure concentrations and (2) the health effect  
26 model includes all covariates relevant to the population. [Szpiro and Paciorek \(2013\)](#) and  
27 [Bergen and Szpiro \(2015\)](#) developed methods to correct for bias from classical-like  
28 measurement error by exploiting asymptotic properties of the variability in exposure  
29 concentration model parameter estimates and propagating these variances through the  
30 health model by means of the delta method. Valid standard error estimates are obtained  
31 by means of the nonparametric bootstrap. Methods have also been proposed to correct for  
32 bias from Berkson-like error, but these require stronger conditions, including  
33 compatibility between subject and monitor locations and inclusion of spatially structured  
34 health model covariates in the exposure concentration model.

35 In the [Szpiro and Paciorek \(2013\)](#) study, when the assigned exposure concentration  
36 measurements were set to be uniform across space, the health effect estimate was biased  
37 away from the null with different standard error compared with the case when the

1 exposure subjects were collocated with the study participants. When an additional spatial  
2 covariate was omitted, the health effect estimate was biased towards the null with  
3 different standard errors compared with the correctly specified model. Bias correction  
4 and bootstrap calculation of the standard errors reduced bias in the model prediction,  
5 even when the true model contained several degrees of freedom (df). Furthermore, bias  
6 correction in conjunction with bootstrapped simulation of standard error improved the  
7 confidence interval coverage of the simulation. With no correction, nominal coverage of  
8 the 95% confidence interval was 80% with 5 df and decreased to 50% for 25 df. With  
9 bias correction and bootstrapping, nominal coverage of the confidence interval was  
10 maintained around 95% with an increase in the expected value of the standard error,  
11 regardless of the number of df constraining the model. These findings imply that without  
12 bias correction, effect estimates would be biased with standard errors that underestimate  
13 the true standard error. None of the epidemiologic studies cited in [Chapter 5](#) applied bias  
14 correction. [Spiegelman \(2013\)](#) noted that the new measurement error correction methods  
15 developed by [Szpiro and Paciorek \(2013\)](#) are a version of regression calibration. This  
16 study illustrated the influence of classical-like and Berkson-like errors on long-term  
17 exposure cohort study health effect estimates through these simulations.

18 Instrumentation bias could be expected to influence health effect estimates from  
19 epidemiologic studies of long-term SO<sub>2</sub> exposures in some situations. [Section 2.4.1](#)  
20 describes how the presence of copollutants can cause ambient SO<sub>2</sub> concentrations  
21 measured using central site monitors to be overestimated and how high relative humidity  
22 can cause ambient SO<sub>2</sub> concentration measurements to be underestimated. Relative  
23 humidity would not be expected to vary greatly within a city. However, local ambient  
24 copollutant concentrations may be spatially variable such that failure to account for  
25 differences in measurement errors could lead to some differential bias in health effect  
26 estimates across a city related to instrument error. Because climate and ambient sources  
27 are more likely to differ among cities, instrumentation error could have a larger influence  
28 on the comparison of health effect estimates among cities when central site monitors are  
29 used to estimate exposure concentrations.

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### 3.4.4.3 Panel Studies

30 Panel or small-scale cohort studies involving dozens of individuals (including some  
31 studies cited in [Section 5.2.2.2](#) and [Section 5.2.2.3](#)) may use more individualized  
32 exposure concentration measurements, including personal exposures, residential indoor  
33 or outdoor concentration measurements, or concentration data from local study-specific  
34 monitors. Modeled concentrations are typically not used as exposure surrogates in panel  
35 epidemiologic studies. A main disadvantage of the modeling approach is that the results

1 of modeling exposure concentration must be compared to an independent set of measured  
2 exposure concentration levels ([Klepeis, 1999](#)). In addition, a modeling approach requires  
3 resource-intensive development of validated and representative model inputs, such as  
4 human activity patterns, distributions of AER, and deposition rate. Therefore, modeled  
5 exposure concentrations are used much less frequently in panel epidemiologic studies.

6 [Section 3.4.2.4](#) describes the influence of high MDL on the relationship between  
7 measured ambient SO<sub>2</sub> concentrations and personal exposures for ambient SO<sub>2</sub>. Personal  
8 exposure measurements below MDL will likely cause the correlation between personal  
9 exposure measurements and ambient SO<sub>2</sub> concentrations to be low due to random noise  
10 in the signal. Noise in the exposure signal would add noise to the health effect estimate in  
11 a panel epidemiologic study as well. Below MDL measurements would be unlikely to  
12 bias the effect estimate, however, because the magnitude of exposure would be low  
13 whether measured with a high-precision or low-precision device.

14 It is also possible that the ratio of personal SO<sub>2</sub> exposure to ambient SO<sub>2</sub> concentration in  
15 panel studies is low due to the compound's low penetration and high reactivity. This  
16 results in attenuation of the magnitude of the exposure concentration-based effect  
17 estimate relative to the ambient concentration-based effect estimate (see [Equation 3-6](#)).  
18 However, if the ratio is approximately constant over time, the strength of the statistical  
19 association would be similar for ambient concentration- and exposure  
20 concentration-based effect estimates ([Sheppard, 2005](#); [Sheppard et al., 2005](#)).

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## 3.5 Summary and Conclusions

21 The 2008 SO<sub>x</sub> ISA ([U.S. EPA, 2008d](#)) evaluated studies of ambient SO<sub>2</sub> concentrations  
22 and exposures in multiple microenvironments, discussed methods for estimating personal  
23 and population exposure concentrations via monitoring and modeling, analyzed  
24 relationships between personal exposure and ambient concentrations, and discussed the  
25 implications of using ambient SO<sub>2</sub> concentrations as estimates of exposure concentration  
26 in epidemiologic studies. Key findings were that indoor SO<sub>2</sub> concentrations and personal  
27 SO<sub>2</sub> exposure concentrations tended to be below the detection limit of personal SO<sub>2</sub>  
28 samplers for averaging times of 24 hours or less, making it difficult to evaluate the  
29 relationship between ambient SO<sub>2</sub> concentrations and indoor or personal SO<sub>2</sub> exposure  
30 concentrations. However, in studies with the bulk of personal samples above the  
31 detection limit, personal measurements of SO<sub>2</sub> exposure were moderately correlated with  
32 ambient SO<sub>2</sub> concentrations. Regarding the influence of exposure concentration estimates  
33 on epidemiologic study results, high spatial variability of ambient SO<sub>2</sub> concentrations  
34 across an urban area results in highly variable correlations among urban SO<sub>2</sub> monitors.

1 Low correlations between individual monitored ambient SO<sub>2</sub> concentrations and the  
2 community average ambient SO<sub>2</sub> concentration tend to bias effect estimates toward the  
3 null, while variations in individual personal-ambient relationships across a community  
4 will tend to widen confidence intervals around the effect estimates compared with the  
5 nominal coverage that would be obtained if the true exposure were used in the  
6 epidemiologic model. All of these findings are supported by the recent evidence available  
7 since the previous ISA.

8 In the current ISA, increased focus has been placed on the use of exposure surrogates in  
9 epidemiologic studies. Multiple techniques can be used to assign SO<sub>2</sub> exposure  
10 concentrations for epidemiologic studies, including the use of central site monitor  
11 ambient SO<sub>2</sub> concentrations, personal SO<sub>2</sub> monitors, and various types of models. Each  
12 has strengths and limitations, as summarized in [Table 3-1](#). Central site monitors provide a  
13 continuous record of ambient SO<sub>2</sub> concentrations over many years, but they do not fully  
14 capture the relatively high spatial variability in ambient SO<sub>2</sub> concentration across an  
15 urban area, which tends to attenuate health effect estimates in time-series epidemiologic  
16 studies. For long-term studies, bias may occur in either direction depending on whether  
17 the monitor is over- or underestimating ambient SO<sub>2</sub> exposure concentration for the  
18 population of interest. In all study types, use of central site monitor ambient SO<sub>2</sub>  
19 concentrations in lieu of the true SO<sub>2</sub> exposures is expected to widen confidence intervals  
20 beyond the nominal coverage of the confidence intervals that would be obtained if the  
21 true exposure were used. Personal SO<sub>2</sub> monitors directly measure exposure, but low  
22 ambient SO<sub>2</sub> concentrations often result in a substantial fraction of the samples falling  
23 below the MDL for averaging times of 24 hours or less. Personal monitors also provide a  
24 relatively limited data set, making them more suitable for panel epidemiologic studies.

25 Computational models can be used to develop exposure concentration surrogates for  
26 individuals and large populations when personal exposure measurements are unavailable.  
27 Modeling approaches may include SPMs, LUR models, IDW, dispersion models, and  
28 CTMs. Strengths and limitations of each method are discussed in [Table 3-1](#). Briefly,  
29 SPMs, LUR, and IDW do not take into account atmospheric chemistry and physics.  
30 SPMs require only distances between SO<sub>2</sub> sources and receptors for input. EWPM also  
31 require emission rates. IDW is a weighted average of ambient SO<sub>2</sub> concentrations  
32 measured at several monitors. Other spatial interpolation techniques, such as kriging, also  
33 require ambient SO<sub>2</sub> concentrations from several monitors and apply more complex  
34 mathematical functions to interpolate among monitors. LUR regresses measured ambient  
35 SO<sub>2</sub> concentrations on local variables and then uses the resulting model to predict  
36 ambient SO<sub>2</sub> concentrations across a study area or at the locations of specific receptors.  
37 As such, LUR enables higher spatial resolution of predicted ambient SO<sub>2</sub> concentrations  
38 and requires more detailed input data compared with IDW and LUR. Mechanistic

1 models, such as dispersion models and CTMs, simulate the transport and dispersion of  
2 ambient SO<sub>2</sub>, and in the case of CTMs, the atmospheric chemistry. The strength of  
3 mechanistic models is increased accuracy of the ambient SO<sub>2</sub> concentration field over  
4 time and space. However, they are much more computationally intensive.

5 Microenvironmental models require personal sensor data for input and are resource  
6 intensive. The strength of these models is that they account for time the exposed  
7 population spend in different microenvironments. With the exception of  
8 microenvironmental models, these methods tend to be used in epidemiologic studies of  
9 long-term ambient SO<sub>2</sub> exposure. Depending on the modeling approach, there is the  
10 potential for bias and reduced precision due to model misspecification, missing sources,  
11 smoothing of concentration gradients, and complex topography. Evaluation of model  
12 results helps demonstrate the suitability of that approach for particular applications.

13 The current ISA also reviews the newly available literature regarding indoor and personal  
14 exposures to SO<sub>2</sub>. New studies of the relationship between indoor and outdoor SO<sub>2</sub>  
15 concentrations have focused on public buildings and are consistent with previous studies  
16 showing that indoor:outdoor ratios and slopes cover an extremely wide range, from near  
17 zero to near one. Differences in results among studies are due to the lack of indoor  
18 sources of SO<sub>2</sub>, indoor deposition of ambient SO<sub>2</sub>, building characteristics (e.g., forced  
19 ventilation, building age, and building type such as residences or public buildings),  
20 personal activities, and analytical approaches. When reported, correlations between  
21 indoor and outdoor SO<sub>2</sub> concentrations were relatively high (>0.75), suggesting that  
22 variations in outdoor SO<sub>2</sub> concentrations are driving indoor SO<sub>2</sub> concentrations. Several  
23 studies of personal-ambient SO<sub>2</sub> relationships available at the time of the previous ISA  
24 showed a large fraction of samples below the MDL, making them unsuitable for  
25 determining personal-ambient correlations. In a study with all personal samples above the  
26 MDL, personal exposure was moderately correlated with ambient concentration.

27 Additional factors that could contribute to error in estimating exposure to ambient SO<sub>2</sub>  
28 include time-location-activity patterns, spatial and temporal variability in SO<sub>2</sub>  
29 concentrations, and proximity of populations to central site monitors and sources.  
30 Activity patterns vary both among and within individuals, resulting in corresponding  
31 variations in exposure across a population and over time. Ambient SO<sub>2</sub> concentrations  
32 among different microenvironments and the amount of time spent in each location will  
33 jointly influence an individual's exposure to ambient SO<sub>2</sub> (see [Equation 3-3](#)). Time spent  
34 in different locations has also been found to vary by age, with younger and older age  
35 groups spending a greater percentage of time outdoors than adults of typical working age  
36 (18–64 years). These variations in activity pattern contribute to differences in exposure  
37 and introduce error into population-averaged SO<sub>2</sub> exposure estimates.

1 Spatial and temporal variability in ambient SO<sub>2</sub> concentrations can contribute to exposure  
2 error in epidemiologic studies, whether the study relies on central site monitor data or  
3 concentration modeling for exposure assessment. Ambient SO<sub>2</sub> concentrations have low  
4 to moderate spatial correlations between ambient monitors across urban geographic  
5 scales; thus, using ambient SO<sub>2</sub> concentration data measured at central site monitors as  
6 exposure surrogates in epidemiologic studies introduces exposure error into the resulting  
7 health effect estimate. Spatial variability in the magnitude of ambient SO<sub>2</sub> concentrations  
8 can affect cross-sectional and large-scale cohort studies by undermining the assumption  
9 that intra-urban ambient SO<sub>2</sub> exposure differences across space are less important than  
10 inter-urban differences. This issue may be less important for time-series studies, which  
11 rely on day-to-day temporal variability in ambient SO<sub>2</sub> exposure concentrations to  
12 evaluate health effects.

13 Proximity of populations to ambient SO<sub>2</sub> monitors may influence how well human  
14 exposure to ambient SO<sub>2</sub> is represented by measurements at the monitors, although  
15 factors other than distance also play an important role. While many ambient SO<sub>2</sub>  
16 monitors are located near dense population centers, other monitors are located near  
17 sources and may not fully represent ambient SO<sub>2</sub> concentrations experienced by  
18 populations in epidemiologic studies. Use of these near-source monitors introduces  
19 exposure error into health effect estimates, and this error may be mitigated by using  
20 average ambient SO<sub>2</sub> concentrations across multiple monitors in an urban area.

21 Exposure to copollutants may result in confounding of health effect estimates. For  
22 ambient SO<sub>2</sub>, daily concentrations generally exhibit low to moderate correlations with  
23 daily NAAQS copollutant concentrations at collocated monitors ([Figure 3-4](#)). However, a  
24 wide range of copollutant correlations is observed at different monitoring sites, from  
25 moderately negative to moderately positive. In studies where daily correlations of  
26 ambient SO<sub>2</sub> concentrations with ambient NO<sub>2</sub> and CO concentrations were observed to  
27 be high, it is possible the data were collected before rulemaking to reduce sulfur content  
28 in diesel fuel went into effect in 2006 (66 FR 5002). Sites with stronger correlations may  
29 introduce a greater degree of confounding into epidemiologic results, depending on the  
30 relationship between the copollutants and the health effect of interest. A similar impact is  
31 expected for epidemiologic studies of long-term ambient SO<sub>2</sub> exposure, because a wide  
32 range of copollutant correlations have also been reported over time periods of months to  
33 years.

34 Exposure error can contribute to variability in epidemiologic study results by biasing  
35 effect estimates toward or away from the null and widening confidence intervals beyond  
36 the nominal coverage of the confidence intervals that would be produced if the true  
37 exposure had been used. The importance of exposure error varies according to the study

1 design, especially regarding the study's spatial and temporal aspects. For example, in  
2 time-series and panel studies, low personal-ambient correlations tend to bias the effect  
3 estimate toward the null, while spatial variation in personal-ambient correlations across  
4 an urban area contributes to widening of the confidence interval around the effect  
5 estimate compared with the nominal confidence interval. For long-term studies, bias of  
6 the health effect estimate may occur in either direction depending on whether the monitor  
7 is over- or underestimating true ambient SO<sub>2</sub> exposure for the population of interest. In  
8 all study types, use of central site monitors in lieu of the true ambient SO<sub>2</sub> exposure is  
9 expected to decrease precision of the health effect estimate because spatial variation in  
10 personal-ambient correlations across an urban area contributes to widening of the  
11 confidence interval around the effect estimate compared with the nominal coverage of the  
12 confidence intervals obtained if the true ambient SO<sub>2</sub> exposure were used. Choice of  
13 exposure estimation method also influences the impact of exposure error on  
14 epidemiologic study results. Central site monitors offer a convenient source of time-series  
15 data. However, because they are in a fixed location, ambient SO<sub>2</sub> concentration  
16 measurements obtained from a central site monitor do not account for the effects of  
17 spatial variation in ambient SO<sub>2</sub> concentration, ambient and nonambient concentration  
18 differences, and varying activity patterns on personal exposure to ambient SO<sub>2</sub>. Personal  
19 exposure measurements, such as those made in panel epidemiologic studies, provide  
20 specific exposure estimates that may more accurately reflect spatial and temporal  
21 variability, but sample size is often small and only a limited set of health outcomes can be  
22 studied. Modeled ambient SO<sub>2</sub> concentration or exposure concentration estimates offer  
23 alternatives or supplementation to measurements, with the advantage of estimating  
24 ambient SO<sub>2</sub> exposure concentrations over a wide range of scales, populations, and  
25 scenarios, particularly for locations lacking monitoring data. Model estimates are most  
26 useful when compared to an independent set of measured ambient SO<sub>2</sub> concentrations or  
27 exposure concentrations. The various sources of exposure error and their potential impact  
28 are considered in the evaluation of epidemiologic study results in this ISA.

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## Chapter 4 Dosimetry and Mode of Action

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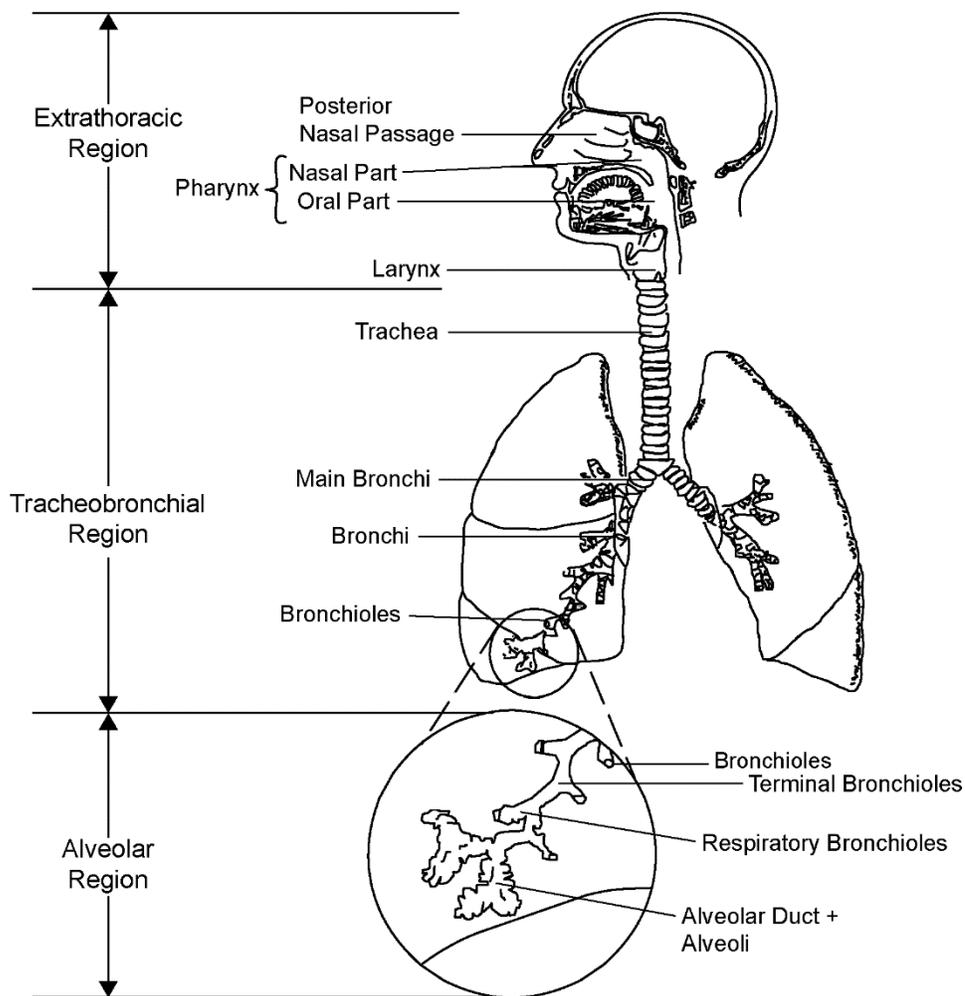
### 4.1 Introduction

1 [Chapter 4](#) begins by providing background information on the structure and function of  
2 the respiratory tract ([Section 4.1.1](#)) and breathing rates and habits ([Section 4.1.2](#)).  
3 The subsequent discussion of dosimetry of inhaled SO<sub>2</sub> ([Section 4.2](#)) considers the  
4 chemical properties of SO<sub>2</sub> and the processes of absorption, distribution, metabolism, and  
5 elimination, as well as sources and levels of exogenous and endogenous sulfite.  
6 The biological pathways that potentially underlie health effects are described in “Modes  
7 of Action of Inhaled Sulfur Dioxide” ([Section 4.3](#)). This section includes a description of  
8 processes by which inhaled SO<sub>2</sub> initiates a cascade of molecular and cellular responses  
9 and the organ-level responses that follow. Together, these sections provide the foundation  
10 for understanding how exposure to inhaled SO<sub>2</sub> may lead to health effects. This  
11 understanding may provide biological plausibility for effects observed in the  
12 epidemiologic studies.

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#### 4.1.1 Structure and Function of the Respiratory Tract

13 The basic structure of the human respiratory tract is illustrated in [Figure 4–1](#). In the  
14 literature, the terms extrathoracic (ET) region and upper airways or upper respiratory  
15 tract are used synonymously. The terms lower airways and lower respiratory tract are  
16 used to refer to the intrathoracic airways [i.e., the combination of the tracheobronchial  
17 (TB) region, which includes the conducting airways and the alveolar region, the  
18 functional part (parenchyma) of the lung where gas exchange occurs].



Source: Based on [ICRP \(1994\)](#).

**Figure 4-1** Diagrammatic representation of respiratory tract regions in humans.

## 4.1.2 Breathing Rates and Breathing Habit

### 4.1.2.1 Breathing Rates

1 Breathing rates vary across the day and are generally a function of an individual's age,  
 2 sex, and activity level. [Table 4-1](#) provides median ventilation rates extracted from  
 3 Tables 6-17 and 6-19 of the *Exposure Factors Handbook* ([U.S. EPA, 2011](#)). Additional  
 4 information for other ages and percentiles of the ventilation rate distribution are available

1 from those tables. Except for the oldest age range, ventilation rates (volume/time)  
 2 increase with activity level and age and are greater in men than women.

**Table 4-1 Ventilation rates in humans as a function of activity.**

		Median Ventilation Rate (L/min)			
Sex	Age (Years)	Sleep	Light Activity	Moderate Activity	Strenuous Activity
Male	3 to <6	4.29	11.1	20.6	37.8
	6 to <11	4.46	11.3	21.6	41.9
	21 to <61	5.71	13.6	29.7	52.9
	≥81	5.90	13.8	28.2	50.9
Female	3 to <6	4.1	10.7	19.8	33.3
	6 to <11	4.24	10.8	20.4	38.0
	21 to <61	4.06	11.1	23.0	44.2
	≥81	4.39	10.7 <sup>a</sup>	20.6	41.4

<sup>a</sup>No value for ≥81 provided, substituted 71 to <81 value.

3 Ventilation rates are also increased in overweight individuals compared to those of  
 4 normal weight ([Brochu et al., 2014](#)). For example, median daily ventilation rates (m<sup>3</sup>/day)  
 5 are about 1.2 times greater in overweight [>85th percentile body mass index (BMI)] than  
 6 normal-weight children (5–10 years of age). In 35–45-year-old adult males and females,  
 7 ventilation rates are 1.4 times greater in overweight (BMI ≥ 25 kg/m<sup>2</sup>) than  
 8 normal-weight (18.5 to <25 kg/m<sup>2</sup> BMI) individuals. Across all ages, overweight/obese  
 9 individuals respire greater amounts of air and associated pollutants than age-matched  
 10 normal-weight individuals.

11 Another way to consider differences in ventilation rates between adults and children is to  
 12 normalize to body weight. This metric is relevant especially for SO<sub>2</sub> absorbed in the nasal  
 13 airways and the fraction of absorbed SO<sub>2</sub> that distributes systemically (see [Section 4.2.3](#)).  
 14 Normalized to body mass, median daily ventilation rates (m<sup>3</sup>/kg-day) decrease over the  
 15 course of life ([Brochu et al., 2011](#)). This decrease in ventilation relative to body mass is  
 16 rapid and nearly linear from infancy through early adulthood. Relative to normal-weight  
 17 male and female adults (25–45 years of age; 0.271 m<sup>3</sup>/kg-day), ventilation rates

1 normalized to body mass are increased 1.5 times in normal-weight children (7–10 years  
2 of age; 0.402 m<sup>3</sup>/kg-day) and doubled in normal-weight infants (0.22–0.5 years of age;  
3 0.538 m<sup>3</sup>/kg-day). Although adults have greater absolute ventilation rates than children in  
4 terms of inhaled volume per unit time, normalized to body size children intake greater  
5 volumes of air and associated pollutants than adults.

6 The metric for effects on the bronchi and differences between children and adults in  
7 bronchial effects of SO<sub>2</sub> is likely to be SO<sub>2</sub> absorbed dose per bronchial surface area (see  
8 [Section 4.2.2](#)). Ventilation per tracheobronchial surface area is also used to approximate  
9 absorbed dose per bronchial surface area for interspecies extrapolation [see Appendix  
10 A of [U.S. EPA \(2009c\)](#)].

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#### 4.1.2.2 Breathing Habit

11 As humans, we breathe oronasally (i.e., through both our nose and mouth). In general, we  
12 breathe through our nose when at rest and increasingly through the mouth with increasing  
13 activity level. Few people breathe purely through their mouth. In contrast to the oronasal  
14 breathing of humans, rodents are obligate nasal breathers. Described in [Section 4.2.2](#), the  
15 nasal passages more efficiently remove SO<sub>2</sub> from inhaled air than the oral passage. As the  
16 fraction of inhaled air passing through the mouth increases so too does the amount of  
17 inhaled SO<sub>2</sub> reaching the tracheobronchial airways where SO<sub>2</sub> may cause  
18 bronchoconstriction. Thus, route of breathing (namely, the fraction of inhaled air passing  
19 through the mouth) is a critical determinate of dose to the lower airways and the potential  
20 respiratory effects of SO<sub>2</sub>. This section describes how route of breathing, also referred to  
21 as “respiratory mode” or “breathing habit” in the literature, is affected by age, sex,  
22 obesity, activity level, and upper respiratory tract anomalies.

23 One of the more commonly referenced studies in dosimetric papers is [Niinimaa et al.](#)  
24 [\(1981\)](#). These investigators found that most people, 87% (26 of 30) in the study, breathed  
25 through their nose until an activity level was reached where they switched to oronasal  
26 breathing. Thirteen percent (4 of 30) of the subjects, however, were oronasal breathers  
27 even at rest. These two subject groups are commonly referred to in the literature (e.g.,  
28 [ICRP, 1994](#)) as “normal augmenters” and “mouth breathers,” respectively. [Bennett et al.](#)  
29 [\(2003\)](#) reported a more gradual increase in oronasal breathing with males (n = 11;  
30 22 ± 4 years) tending to have a greater oral contribution than females (n = 11; 22 ± 2  
31 years) at rest (87 vs. 100% nasal, respectively) and during exercise (45 vs. 63% nasal at  
32 60% max workload, respectively).

33 Consistent with this trend for women to have a greater nasal contribution ([Bennett et al.,](#)  
34 [2003](#)), in a large study of children (63 M, 57 F; 4–19 years), [Leiberman et al. \(1990\)](#)

1 reported a statistically greater nasal fraction during inspiration in girls relative to boys (77  
2 and 62%, respectively;  $p = 0.03$ ) and a marginally significant difference during expiration  
3 (78 and 66%, respectively;  $p = 0.052$ ). Another large study (88 M, 109 F; 5–73 years),  
4 also reported a significant sex effect of route of breathing with females as having a  
5 greater nasal fraction than males ([Vig and Zajac, 1993](#)). This effect was largest in  
6 children (5–12 years) with an inspiratory nasal fraction of 66% in males and 86% in  
7 females. This study also reported that the partitioning between the nose and mouth was  
8 almost identical between inspiration and expiration. In children and adults, sex explains  
9 some inter-individual variability in route of breathing with females breathing more  
10 through the nose than males.

11 A few studies have attempted to measure oronasal breathing in children as compared to  
12 adults ([Bennett et al., 2008](#); [Becquemin et al., 1999](#); [James et al., 1997](#); [Vig and Zajac,](#)  
13 [1993](#)). [James et al. \(1997\)](#) found that children ( $n = 10$ ; 7–16 years) displayed more  
14 variability than older age groups ( $n = 27$ ; 17–72 years) with respect to their oronasal  
15 pattern of breathing with exercise. [Becquemin et al. \(1999\)](#) found that children ( $n = 10$ ;  
16 8–16 years) tended to display more oral breathing both at rest and during exercise than  
17 adults. The highest oral fractions were also found in the youngest children. Similarly,  
18 [Bennett et al. \(2008\)](#) reported children ( $n = 12$ ; 6–10 years) tended to have a greater oral  
19 contribution than adults ( $n = 11$ ; 18–27 years) at rest (68 vs. 88% nasal, respectively) and  
20 during exercise (47 vs. 59% nasal at 40% max workload, respectively). [Vig and Zajac](#)  
21 [\(1993\)](#) reported a statistically significant effect of age on route of breathing which was  
22 most apparent in males with the fraction of nasal breathing increasing from 67% in  
23 children (5–12 year olds) to 82% in teens (13–19 year olds), and 86% in adults  
24 ( $\geq 20$  years). Females had a nasal fraction of 86% in children and teens and 93% in adults.  
25 Based on these studies, the nasal fraction increases with age until adulthood.

26 Several large studies have reported an inverse correlation ( $r$  of 0.3 to 0.6) between nasal  
27 resistance and nasal breathing fraction ([Vig and Zajac, 1993](#); [Leiberman et al., 1990](#);  
28 [Leiter and Baker, 1989](#)). However, neither pharmaceutical constriction nor dilation of the  
29 nasal passages affected the nasal fraction ([Leiberman et al., 1990](#); [Leiter and Baker,](#)  
30 [1989](#)). Nasal resistance decreases with age and is lower in females and may account for  
31 larger nasal fractions in adults and females ([Vig and Zajac, 1993](#)). Smaller studies  
32 ( $n = 37$ ) have not found a significant correlation between nasal resistance and nasal  
33 fraction, but have noted that those having high resistance breathe less through the nose  
34 ([James et al., 1997](#)). [Bennett et al. \(2003\)](#) reported a tendency of lower nasal resistance in  
35 African-American blacks (5 M, 6 F;  $22 \pm 4$  years) relative to Caucasians (6 M, 5 F;  
36  $22 \pm 3$  years). The nasal fraction in blacks tended to be greater at rest and 40% max  
37 workload and achieved statistical significance relative to Caucasians at 20 and 60% max  
38 workload. ([Leiter and Baker, 1989](#)) reported that of the 15 mouth-breathing children as

1 identified by a dentist, pediatrician, or otolaryngologist in their study, the 3 having  
2 greatest nasal resistance breathed 100% through the mouth. These investigators also  
3 reported that the nasal fraction was negatively correlated ( $p \leq 0.004$ ) with nasal resistance  
4 during both inspiration and expiration; however, the correlation appears driven by the  
5 three individuals with 100% mouth breathing. Overall, breathing habit is related to nasal  
6 resistance and may explain some of the age and sex effect on breathing habit.

7 Diseases affecting nasal resistance may also affect breathing route. [Chadha et al. \(1987\)](#)  
8 found that the majority (11 of 12) of patients with asthma or allergic rhinitis breathe  
9 oronasally (i.e., they breathe partially through the mouth) even at rest. [James et al. \(1997\)](#)  
10 also reported the subjects ( $n = 37$ ; 7–72 years) having hay fever, sinus disease, or recent  
11 upper respiratory tract symptoms tended to have a greater oral contribution relative to  
12 those absent upper respiratory tract symptoms. [James et al. \(1997\)](#) additionally observed  
13 that two subjects (5.4%) breathed purely through the mouth, but provided no other  
14 characteristics of these individuals. Greater oral breathing may occur due to upper  
15 respiratory tract infection and inflammation.

16 Some studies of children suggest obesity also affects breathing habit. Using MRI,  
17 [Schwab et al. \(2015\)](#) examined anatomic risk factors of obstructive sleep apnea in  
18 children ( $n = 49$  obese with sleep apnea, 38 obese control, 50 lean controls; 11–16 years  
19 of age). In obese children with sleep apnea, adenoid size was increased relative to both  
20 obese and lean controls not having sleep apnea. The size the adenoid was also increased  
21 in male obese controls ( $n = 24$ ) relative to male lean controls ( $n = 35$ ), whereas adenoid  
22 size was similar between female obese controls ( $n = 14$ ) and female lean controls  
23 ( $n = 15$ ). Both nasopharyngeal cross-sectional area and minimum area were similar  
24 between lean and obese controls, but decreased in obese children with obstructive sleep  
25 apnea. In a longitudinal study of children ( $n = 47$  F, 35 M) assessed annually from 9 to  
26 13 years of age, [Crouse and Laine-Alava \(1999\)](#) found nasal cross-section was minimal at  
27 10 years of age. The authors speculated this may be due to prepubertal enlargement of the  
28 adenoids. In a 5-year longitudinal study of children ( $n = 17$  M, 9 F) following  
29 adenoidectomy, [Kerr et al. \(1989\)](#) reported a change in mode of breathing from oral to  
30 nasal. These studies suggest the obese children, especially boys, also have increased oral  
31 breathing relative to normal weight children.

32 In summary, breathing habit is affected by age, sex, nasal resistance, and perhaps by  
33 obesity. Numerous studies show children to inhale a larger fraction of air through their  
34 mouth than adults. Across all ages, males also inhale a larger fraction of air through their  
35 mouth than females. Other factors that increase nasal resistance such as allergies or acute  
36 upper respiratory infections can also increase the fraction of oral breathing. Obesity,

1 especially in boys, may also contribute to increased nasal resistance and an increased oral  
2 fraction of breathing relative to normal weight children.

---

## 4.2 Dosimetry of Inhaled Sulfur Dioxide

3 This section provides a brief overview of SO<sub>2</sub> dosimetry and updates information  
4 provided in the 2008 ISA for Sulfur Oxides ([U.S. EPA, 2008d](#)). Dosimetry of SO<sub>2</sub> refers  
5 to the measurement or estimation of the amount of SO<sub>2</sub> and its reaction products reaching  
6 and/or persisting at specific sites within the respiratory tract or systemically after  
7 exposure. One principal effect of inhaled SO<sub>2</sub> is to stimulate bronchial epithelial irritant  
8 receptors and initiate a reflexive contraction of smooth muscles in the bronchial airways.  
9 Health effects may be due to the inhaled SO<sub>2</sub> or its chemical reaction products. Complete  
10 identification of the causative agents and their integration into SO<sub>2</sub> dosimetry is a  
11 complex issue that has not been thoroughly evaluated. The major factors affecting the  
12 transport and fate of gases and aerosols in the respiratory tract are the morphology of the  
13 respiratory tract; the physicochemical properties of the epithelial lining fluid (ELF);  
14 respiratory functional parameters, such as tidal volume, flow rate, and route of breathing;  
15 physicochemical properties of the gas; and the physical processes that govern gas  
16 transport. Few studies have investigated SO<sub>2</sub> dosimetry since the 1982 AQCD for  
17 Particulate Matter and Sulfur Oxides ([U.S. EPA, 1982a](#)) and the 1986 Second Addendum  
18 ([U.S. EPA, 1986b](#)).

19 The following sections will address the chemistry, and the processes of absorption,  
20 distribution, metabolism, and elimination that pertain to the dosimetry of inhaled SO<sub>2</sub>.  
21 Studies investigating the dosimetry of SO<sub>2</sub> generally are for concentrations of SO<sub>2</sub> that  
22 are higher than those present in ambient air. However, these studies are included here  
23 because they provide the foundation for understanding SO<sub>2</sub> toxicokinetics and  
24 toxicodynamics. The discussion of dosimetry will conclude with a consideration of other  
25 sources of SO<sub>2</sub>-derived products in the body.

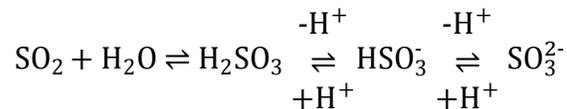
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### 4.2.1 Chemistry

26 Physicochemical properties of SO<sub>2</sub> most relevant to respiratory tract uptake include its  
27 solubility in the ELF and its chemical transformations and reactions that occur there.  
28 Henry's law relates the gas-phase and liquid-phase interfacial concentrations at  
29 equilibrium and is a function of temperature and pressure. The Henry's law constant,  
30 defined as the ratio of partial pressure or concentration of SO<sub>2</sub> in the gas phase to SO<sub>2</sub>  
31 dissolved in the liquid phase, is an inverse measure of solubility. Although the solubility

1 of most gases in the ELF is not known, the Henry's law constant is known for many  
 2 gases in water, and for SO<sub>2</sub>, it is 0.047 (mol/L)<sub>air</sub> per (mol/L)<sub>water</sub> at 37°C and  
 3 1 atmosphere ([Hales and Sutter, 1973](#)). For comparison, Henry's law constant for O<sub>3</sub> is  
 4 6.4 (mol/L)<sub>air</sub> per (mol/L)<sub>water</sub> under the same conditions ([Kimbell and Miller, 1999](#)).  
 5 Thus, SO<sub>2</sub> is nearly 140-times more soluble than O<sub>3</sub> in water. In general, the more soluble  
 6 a gas is in biological fluids, the more rapid, and proximal its absorption will be in the  
 7 respiratory tract. In addition to the Henry's law constant, it is also necessary to consider  
 8 the transport of SO<sub>2</sub> from the lumen to the ELF of the tracheobronchial airways (see  
 9 [Section 4.2.2](#)). When the partial pressure of SO<sub>2</sub> on mucosal surfaces exceeds that of the  
 10 gas phase, such as during expiration, some desorption of SO<sub>2</sub> from the ELF may be  
 11 expected (see [Section 4.2.5](#)).

12 Once SO<sub>2</sub> contacts the fluids lining the airways, it dissolves into the aqueous  
 13 compartment and rapidly hydrates to form H<sub>2</sub>SO<sub>3</sub>, which forms hydrogen (H<sup>+</sup>) ions,  
 14 bisulfite HSO<sub>3</sub><sup>-</sup> anions, and sulfite (SO<sub>3</sub><sup>2-</sup>) anions ([Gunnison et al., 1987a](#); [Gunnison,](#)  
 15 [1981](#)).



**Equation 4-1**

16 The prevalence of these sulfur species in solution is determined primarily by pH and, to a  
 17 lesser extent, by temperature and ionic strength. In the human respiratory tract (pH of 7.4  
 18 and 37°C), dissolved SO<sub>2</sub> exists as a mixture exclusively of bisulfite and sulfite with the  
 19 latter predominating ([Gunnison, 1981](#)). Subsequent reactions of bisulfite and sulfite such  
 20 as sulfitolysis, enzymatic detoxification, and auto-oxidation are described below.

---

## 4.2.2 Absorption

21 Because SO<sub>2</sub> is highly soluble in water, it is expected to be almost completely absorbed  
 22 in the nasal passages of both humans and laboratory animals under resting conditions.  
 23 The dosimetry of SO<sub>2</sub> can be contrasted with the lower solubility gas, O<sub>3</sub>, for which the  
 24 predicted tissue doses (O<sub>3</sub> flux to liquid-tissue interface) are very low in the trachea and  
 25 increase to a maximum in the terminal bronchioles or first airway generation in the  
 26 pulmonary region [see Chapter 5 of [U.S. EPA \(2013c\)](#)]. The mass transfer (cm/s) of SO<sub>2</sub>  
 27 from the air-phase to the ELF is proportion to the Sherwood number (dimensionless) and  
 28 diffusion coefficient of SO<sub>2</sub> in air (0.23 cm<sup>2</sup>/s) and inversely proportion to the diameter  
 29 (cm) of an airway [see Equation 10 of [Asgarian et al. \(2011\)](#)]. The Sherwood number  
 30 for various breathing patters from infants to young adults may be calculated using

1 Equation 13 of [Asgharian et al. \(2011\)](#) in combination with age specific airway  
2 morphology from [Phalen et al. \(1985\)](#). For 50th-percentile ventilation rates from [Brochu  
3 et al. \(2011\)](#), the mass transfer rates of SO<sub>2</sub> in the trachea and bronchi of infants  
4 (4-months) are about 1.8-times greater than in young adults (18 years). By 8.5 years of  
5 age, the mass transfer rate is only about 1.2-times greater than in young adults.

6 [Melville \(1970\)](#) measured the absorption of SO<sub>2</sub> [1.5 to 3.4 parts per million (ppm)]  
7 during nasal and oral breathing in 12 healthy volunteers. Total respiratory tract  
8 absorption of SO<sub>2</sub> (expressed as a percentage of the amount inhaled) was significantly  
9 greater ( $p < 0.01$ ) during nasal than oral breathing (85 vs. 70%, respectively) and was  
10 independent of the inspired concentration. Respired flows were not reported. [Andersen et  
11 al. \(1974\)](#) measured the nasal absorption of SO<sub>2</sub> (25.5 ppm) in seven volunteers at an  
12 average inspired flow of 23 L/minute [i.e., eucapnic hyperpnea (presumably to simulate  
13 light exertion)]. These investigators reported that the oropharyngeal SO<sub>2</sub> concentration  
14 was below their limit of detection (0.25 ppm), implying that at least 99% of SO<sub>2</sub> was  
15 absorbed in the nose of subjects during inspiration. [Speizer and Frank \(1966\)](#) also  
16 measured the absorption of SO<sub>2</sub> (16.1 ppm) in seven healthy subjects at an average  
17 ventilation of 8.5 L/minute (i.e., at rest). They reported that 14% of the inhaled SO<sub>2</sub> was  
18 absorbed within the first 2 cm into the nose. The concentration of SO<sub>2</sub> reaching the  
19 pharynx was below the limit of detection, suggesting that at least 99% was absorbed  
20 during inspiration.

21 [Frank et al. \(1969\)](#) and [Brain \(1970\)](#) investigated the oral and nasal absorption of SO<sub>2</sub> in  
22 the surgically isolated upper respiratory tract of anesthetized dogs. Radiolabeled SO<sub>2</sub>  
23 (<sup>35</sup>SO<sub>2</sub>) at concentrations of 1, 10, 25, or 50 ppm was passed separately through the nose  
24 and mouth at steady flows of 3.5 and 35 L/minute for 5 minutes by [Brain \(1970\)](#).  
25 The nasal absorption of SO<sub>2</sub> (1 ppm) was effectively 100% at 3.5 L/minute and 96.8% at  
26 35 L/minute. A negligible effect of SO<sub>2</sub> concentration was observed with nasal  
27 absorption increasing from 99.9% at 1 ppm to 99.99% at 10 ppm and 99.999% at 50 ppm.  
28 The oral absorption of SO<sub>2</sub> (1 ppm) was 99.56% at 3.5 L/minute, but only 34% at  
29 35 L/minute. There was a slight decrease in oral SO<sub>2</sub> absorption from 99.56 to 96.3%  
30 when the concentration was increased from 1 to 10 ppm at 3.5 L/minute, whereas nasal  
31 absorption was unaffected by changes in concentration (1–50 ppm). In an earlier  
32 experiment, [Frank et al. \(1967\)](#) showed that nasal absorption of 2.2 ppm <sup>35</sup>SO<sub>2</sub> at  
33 3.5 L/minute was 100% throughout the first 20 minutes of exposure. On average, there  
34 was a small reduction in <sup>35</sup>SO<sub>2</sub> absorption to 94% approaching 30 minutes of exposure.  
35 [Frank et al. \(1969\)](#) noted that the aperture of the mouth may vary considerably, and that  
36 this variation may affect SO<sub>2</sub> uptake in the mouth. Although there was a minor effect of  
37 inhaled concentration on SO<sub>2</sub> absorption, the route of breathing and rate of flow were the  
38 main factors affecting the magnitude of SO<sub>2</sub> absorption in the upper airways of dogs.

1 Modeling shows that virtually all SO<sub>2</sub> reaching the lower airways in young adults, as well  
2 as in dogs and rats, is absorbed in the bronchi and does not penetrate into the bronchioles  
3 or alveolar region ([Tsujino et al., 2005](#)). Considering the effect of age on SO<sub>2</sub> dose to the  
4 airways of humans, dose as ventilation per bronchial surface area can be estimated using  
5 bronchial morphology from [Phalen et al. \(1985\)](#) and 50th-percentile ventilation rates  
6 from [Brochu et al. \(2011\)](#). This approximation shows a gradual reduction in bronchial  
7 surface dose with decreasing age from young adults to infants. Using this approximation,  
8 an infant (4-months) would have approximately 80% of the bronchial surface dose of a  
9 young adult (18-years). However, as described in [Section 4.1.2.2](#), children breathe more  
10 through the mouth than adults, which is associated with greater SO<sub>2</sub> penetration to the  
11 lower respiratory tract. In addition, as described above, mass transfer rates of SO<sub>2</sub> from  
12 the lumen to the ELF in the trachea and bronchi increase with decreasing age. Based on  
13 these observations, it is expected that SO<sub>2</sub> penetrating through the upper airways is  
14 rapidly removed in the trachea and first several generations of bronchi and this may result  
15 in somewhat greater airway surface doses of SO<sub>2</sub> of children than adults in proximal  
16 bronchi.

17 In summary, inhaled SO<sub>2</sub> is readily absorbed in the upper airways of both humans and  
18 laboratory animals. During nasal breathing, the majority of available data suggests 95%  
19 or greater SO<sub>2</sub> absorption occurs in the nasal passages, even under ventilation levels  
20 comparable to exercise. Somewhat less SO<sub>2</sub> is absorbed in the oral passage than in the  
21 nasal passages. The difference in SO<sub>2</sub> absorption between the mouth and the nose is  
22 highly dependent on respired flow rates. With an increase in flow from 3.5 to  
23 35 L/minute, nasal absorption is relatively unaffected, whereas oral absorption is reduced  
24 from 100 to 34%. Inhaled SO<sub>2</sub> concentration has a negligible effect of nasal absorption,  
25 where oral absorption may decrease slightly with increasing concentration from 1 ppm to  
26 10 ppm SO<sub>2</sub>. Thus, the rate and route of breathing have a great effect on the magnitude of  
27 SO<sub>2</sub> absorption in the upper airways and on the penetration of SO<sub>2</sub> to the lower airways.  
28 Overall, the available data clearly show a pattern of SO<sub>2</sub> absorption that shifts from the  
29 upper airways to the tracheobronchial airways in conjunction with a shift from nasal to  
30 oronasal breathing and associated increased ventilatory rates in exercising humans. Due  
31 to their increased amount of oral breathing, children (particularly boys and the obese) and  
32 individuals with allergies or upper airway infections may be expected to have greater SO<sub>2</sub>  
33 penetration into the lower respiratory tract than healthy adults (see [Section 4.1.2](#)).  
34 Children may also be expected to have a greater intake dose of SO<sub>2</sub> per body mass than  
35 adults due to their ventilation rates (see [Section 4.1.2](#)).

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### 4.2.3 Distribution

1           Once inhaled, SO<sub>2</sub> is absorbed in the respiratory tract and SO<sub>2</sub>-derived products are  
2           widely distributed throughout the body, as was demonstrated in early studies using  
3           radiolabeled <sup>35</sup>SO<sub>2</sub>. Although rapid extrapulmonary distribution of SO<sub>2</sub>-derived products  
4           occurs, the highest tissue concentrations of the <sup>35</sup>S retained in the body at any given time  
5           are found primarily in the respiratory tract (upper and lower) and may be detected there  
6           for up to a week following inhalation ([Balchum et al., 1960](#), [1959](#)). [Frank et al. \(1967\)](#)  
7           observed <sup>35</sup>S in the blood and urine of dogs within 5 minutes, the first time point, after  
8           starting 22 ppm <sup>35</sup>SO<sub>2</sub> exposures of the surgically isolated nasal airways. At the end of  
9           30–60-minute exposures, the authors estimated that 5–18% of the administered <sup>35</sup>S was  
10          in the blood. [Balchum et al. \(1959\)](#) investigated the tissue distribution of <sup>35</sup>S in dogs  
11          exposed for 20–40 minutes to <sup>35</sup>SO<sub>2</sub> ranging in concentration from 1.1 to 141 ppm via  
12          tracheostomy or by nose/mouth breathing. At approximately 1-hour post-exposure,  
13          regardless of the exposure route or the <sup>35</sup>SO<sub>2</sub> exposure concentration, about 6% of the  
14          retained <sup>35</sup>S was found in the liver, with lesser amounts found in the heart, spleen, kidney,  
15          brain, and other tissues. However, the percent of retained <sup>35</sup>S was, on average, 13-times  
16          greater in the trachea and lungs of the tracheostomized group than in the nose/mouth  
17          breathing group, demonstrating the protection of the lower respiratory tract provided by  
18          SO<sub>2</sub> removal in the upper airways. Comparison of dogs retaining similar total amounts of  
19          <sup>35</sup>S (i.e., controlling for retained dose), showed that the blood concentrations of <sup>35</sup>S were  
20          higher in the tracheostomized dogs than in the nose/mouth breathing dogs. Given very  
21          high <sup>35</sup>S concentrations in the tongues of the nose/mouth breathing dogs and that blood  
22          concentrations had not decreased in two-thirds of these dogs by 1-hour post-exposure, the  
23          authors postulated that a substantial portion of the <sup>35</sup>SO<sub>2</sub> products may have been retained  
24          within the upper airways with only slow absorption into the blood. Studies in rabbits and  
25          rats also show that there can be an accumulation and retention of SO<sub>2</sub>-derived products  
26          within proximal regions of the respiratory tract (discussed below).

27          The distribution and clearance of inhaled SO<sub>2</sub> from the respiratory tract may involve  
28          several intermediate chemical reactions and transformations. In particular, hydrated SO<sub>2</sub>  
29          transforms to sulfite/bisulfite at physiologic pH. Sulfite can diffuse across cell  
30          membranes, and bisulfite can react with disulfide bonds (R<sub>1</sub>-S-S-R<sub>2</sub>) to form thiols  
31          (R<sub>1</sub>-SH) and S-sulfonates (R<sub>2</sub>-S-SO<sub>3</sub><sup>-</sup>) by a process termed sulfitolysis ([Gunnison and](#)  
32          [Benton, 1971](#)). Because disulfide bonds are important determinants of protein structure  
33          and function in biological systems, breaking such bonds may have important biologic  
34          effects. Secreted airway mucins contain many disulfide bonds, and breaking these bonds  
35          might alter their function and thereby alter mucociliary clearance.

1 Studies in rabbits and rats found measurable levels of sulfite and S-sulfonates in the  
2 upper respiratory tract following inhalation of 10–30 ppm SO<sub>2</sub>. Levels of sulfite and  
3 S-sulfonates were increased in tracheal washings of rabbits exposed to 10 ppm SO<sub>2</sub> for up  
4 to 72 hours ([Gunnison et al., 1981](#)). This implies reaction of sulfite with disulfide groups  
5 in mucus proteins in the ELF. In addition, tracheal tissue contained elevated levels of  
6 S-sulfonates, implicating reaction of sulfite with disulfide groups in tissue proteins.  
7 Bronchial tissue from rats had increased levels of sulfites and S-sulfonates when higher  
8 concentrations (30 ppm) of SO<sub>2</sub> were employed ([Gunnison et al., 1987b](#)). Under these  
9 conditions, no S-sulfonates were found in lung parenchyma, and neither sulfites nor  
10 S-sulfonates were found in the plasma. The lack of sulfites and S-sulfonates in the plasma  
11 of rats may have been due to their high levels of sulfite oxidase and rapid metabolism of  
12 sulfite (see [Section 4.2.4](#)). Consistent with <sup>35</sup>S rapidly appearing in the blood of  
13 <sup>35</sup>SO<sub>2</sub>-exposed dogs, S-sulfonates were found in plasma of rabbits following 10 ppm SO<sub>2</sub>  
14 exposure, providing evidence for absorption of sulfite into the blood of rabbits ([Gunnison](#)  
15 [et al., 1981](#); [Gunnison and Palmes, 1973](#)). Studies with ex vivo plasma suggested that  
16 disulfide bonds in albumin and fibronectin are reactive with sulfite ([Gregory and](#)  
17 [Gunnison, 1984](#)).

18 Exposure of humans to SO<sub>2</sub> also resulted in measurable S-sulfonates in plasma ([Gunnison](#)  
19 [and Palmes, 1974](#)). In this study, humans were exposed continuously to 0.3–6 ppm SO<sub>2</sub>  
20 for up to 120 hours and plasma levels of S-sulfonates were positively correlated with  
21 concentrations of SO<sub>2</sub> inhaled. The regression line for this relationship had a correlation  
22 coefficient of 0.61 and the slope was 1.1 nmol/mL of plasma S-sulfonate for each 1-ppm  
23 increment in SO<sub>2</sub> concentration. Recently, a subacute study measured sulfite plus  
24 S-sulfonate content of the lung, liver, and brain of mice exposed to 5, 10, or 20 ppm SO<sub>2</sub>,  
25 4 hours/day for 7 days ([Meng et al., 2005a](#)). A concentration-dependent increase in sulfite  
26 and S-sulfonate levels was observed. Thus, in humans and mice, the amount of  
27 SO<sub>2</sub>-derived species in blood and other tissues increases with the concentration in inhaled  
28 air. It should also be noted that measurable amounts of sulfite/S-sulfonate were found in  
29 tissues of humans and mice inhaling filtered air instead of SO<sub>2</sub> ([Meng et al., 2005a](#);  
30 [Gunnison and Palmes, 1974](#)). Besides inhaled SO<sub>2</sub>, sulfite is derived from other  
31 exogenous, as well as endogenous sources (see [Section 4.2.6](#)).

32 Inhaled SO<sub>2</sub> need not reach the lower airways for SO<sub>2</sub>-derived species to be found in the  
33 blood. During the 5 full day of SO<sub>2</sub> exposure in the [Gunnison and Palmes \(1974\)](#) study,  
34 volunteers were likely at rest or sleeping for much of their exposures. Given that  
35 ventilation rates would be relatively low and breathing would be largely nasal (see  
36 [Section 4.1.2](#)), most inhaled SO<sub>2</sub> would likely be absorbed in the extrathoracic airways  
37 (see [Section 4.2.2](#)). A number of studies also exposed the surgically isolated upper  
38 airways of dogs to <sup>35</sup>SO<sub>2</sub> and observed <sup>35</sup>S to rapidly appear in the blood and for the

1 concentration in blood to continually increase during exposure (e.g., [Yokoyama et al.,](#)  
2 [1971](#); [Frank et al., 1967](#)). [Frank et al. \(1969\)](#) proposed the majority of SO<sub>2</sub>-derived  
3 products found in the blood originated from SO<sub>2</sub> absorbed in the upper airways.

4 In summary, inhaled SO<sub>2</sub> is readily dissolved in the ELF where it exists as a mixture of  
5 bisulfite and sulfite with the latter predominating. Bisulfite reacts with disulfide groups  
6 forming S-sulfonates; sulfite can diffuse across cell membranes and reach the circulation.  
7 Following absorption in the respiratory tract, SO<sub>2</sub>-derived products (e.g., sulfite and/or  
8 S-sulfonates) are widely distributed throughout the body and have been observed in the  
9 blood and urine within 5 minutes of starting an SO<sub>2</sub> exposure of surgically isolated nasal  
10 airways. Measurable levels of S-sulfonates have been observed in plasma following  
11 inhalation of SO<sub>2</sub> in humans, dogs, mice, and rabbits. Perhaps due to higher levels of  
12 hepatic sulfite oxidase relative to other species, sulfites, and S-sulfonates are not found in  
13 the plasma of rats. Although the majority of SO<sub>2</sub>-derived products remain in the  
14 respiratory tract following exposure, extrapulmonary SO<sub>2</sub>-derived products are found in  
15 the liver, with lesser amounts found in the heart, spleen, kidney, brain, and other tissues.  
16 The amount of SO<sub>2</sub>-derived species in blood and other tissues increases with the  
17 concentration of SO<sub>2</sub> in inhaled air, while the distribution within the body is generally  
18 unaffected. A substantial portion of SO<sub>2</sub>-derived products appear to be retained within the  
19 upper airways, particularly during nasal breathing, with only slow absorption into the  
20 blood.

---

#### 4.2.4 Metabolism

21 The primary route of sulfite metabolism is by sulfite oxidase-catalyzed enzymatic  
22 oxidation to sulfate ([Gunnison, 1981](#)). Because of this pathway, intra-cellular steady-state  
23 concentrations of sulfite are low in normal individuals ([Gunnison et al., 1987a](#)). Sulfite  
24 oxidase is a molybdenum-containing enzyme that is found in mitochondria. Its  
25 distribution varies widely across tissues. While lung tissue has very low sulfite oxidase  
26 activity, liver has high sulfite oxidase activity and plays a major role in detoxification of  
27 circulating sulfite. [Maier et al. \(1999\)](#) examined the distribution of sulfite oxidase activity  
28 in the respiratory tract and liver of four beagle dogs. Sulfite oxidase activity was highest  
29 in the liver. The median sulfite oxidase activity in the nose was about 30% of the liver.  
30 Median activity levels in the trachea and bronchi were about 20% of the liver and the  
31 median activity levels in the lung parenchyma were only 10% of those in the liver.  
32 The 1982 AQCD ([U.S. EPA, 1982a](#)) noted that depleting the activity of sulfite oxidase in  
33 an animal model through a low-molybdenum diet supplemented with the competitive  
34 inhibitor tungsten resulted in a substantial lowering of the lethal dose for intraperitoneally  
35 injected bisulfite. A deficiency in sulfite oxidase activity may lead to toxicity even in the

1 absence of exogenous sulfite or bisulfite exposures. For example, humans and mice with  
2 homozygous genetic defects in the sulfite oxidase protein or in the enzymes required for  
3 synthesis of the essential molybdenum cofactor develop ultimately lethal neurologic  
4 disease attributable to accumulation of endogenous sulfite post-natally (i.e., following  
5 loss of maternal protection in utero) ([Johnson-Winters et al., 2010](#); [Reiss et al., 2005](#)).

6 Sulfite oxidase activity is highly variable among species. Liver sulfite oxidase activity in  
7 the rat is 10–20 times that in humans. Rapid metabolism of circulating sulfite to sulfate  
8 may explain the lack of sulfite/S-sulfonates found in blood of rats exposed by inhalation  
9 to 30 ppm SO<sub>2</sub>, whereas these products were found in other species ([Gunnison et al.,  
10 1987a](#)). In sulfite oxidase-deficient rats, plasma sulfite levels increase with the severity of  
11 the deficiency ([Gunnison et al., 1987b](#)).

12 [Gunnison and Benton \(1971\)](#) also identified S-sulfonate in blood as a reaction product of  
13 inhaled SO<sub>2</sub>. S-sulfonates, which are produced by the reaction of bisulfite with disulfide  
14 bonds, may be metabolized back to disulfides. Although the enzymatic pathways and  
15 cofactors are not clearly established for this repair process, it requires reducing  
16 equivalents, and thus, has a metabolic cost.

17 In summary, the primary route of sulfite metabolism is by sulfite oxidase-catalyzed  
18 oxidation into sulfate. The sulfite oxidase levels vary widely among tissues with very low  
19 levels found in the lung and high levels found in the liver, which plays a major role in the  
20 detoxification of circulating sulfite. Sulfite oxidase activity is also highly variable among  
21 species with liver sulfite oxidase activity in rats being 10–20 times greater than in  
22 humans.

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#### 4.2.5 Elimination

23 Mechanisms involved in elimination include both desorption of SO<sub>2</sub> from the respiratory  
24 tract and the clearance of reaction products from the body.

25 When the partial pressure of SO<sub>2</sub> on mucosal surfaces exceeds that of the gas phase, such  
26 as during expiration, some desorption of SO<sub>2</sub> from respiratory tract lining fluids may be  
27 expected. [Speizer and Frank \(1966\)](#) found that on expiration, 12% of the SO<sub>2</sub> absorbed  
28 during inspiration was desorbed into the expired air. During the first 15 minutes after the  
29 25- to 30-minute SO<sub>2</sub> exposure, another 3% was desorbed. In total, 15% of the amount of  
30 originally inspired and absorbed SO<sub>2</sub> was desorbed from the nasal mucosa. [Frank et al.  
31 \(1969\)](#) reported that up to 18% of the SO<sub>2</sub> was desorbed within ~10 minutes after  
32 exposure.

1 SO<sub>2</sub> that does not desorb is transformed to bisulfite/sulfite ([Section 4.2.1](#)). Because the  
2 lung tissue has a low activity of sulfite oxidase, diffusion into the circulation may be a  
3 more important route of sulfite clearance from the lung than enzyme-catalyzed  
4 transformation to sulfates. Within a period of minutes after starting <sup>35</sup>SO<sub>2</sub> inhalation  
5 exposures, <sup>35</sup>S was observed in the blood and urine of dogs and distributed about the  
6 body ([Frank et al., 1967](#); [Balchum et al., 1959](#)). At the end of 30–60-minute exposures,  
7 5–18% of the administered <sup>35</sup>S was in the blood, and 1–6% had been excreted in the  
8 urine by 3 hours post-exposure ([Yokoyama et al., 1971](#); [Frank et al., 1967](#)). The rate of  
9 urinary excretion was proportional to the blood concentration, and 92% of the urinary <sup>35</sup>S  
10 was in the form of sulfate ([Yokoyama et al., 1971](#)). In contrast, S-sulfonates formed in  
11 the circulation were reported to have a clearance half-time of 3.2 days ([Gunnison and](#)  
12 [Palmer, 1973](#)).

13 In summary, when the partial pressure of SO<sub>2</sub> on mucosal surfaces exceeds that of the gas  
14 phase, such as during expiration or following exposure, some desorption of SO<sub>2</sub> from the  
15 respiratory tract lining fluids may be expected. SO<sub>2</sub> that does not desorb is transformed to  
16 bisulfite/sulfite. Given the low activity of sulfite oxidase in the respiratory tract, sulfite is  
17 more likely to diffuse into the circulation or react with tissue constituents than be  
18 metabolized to sulfate. Circulating sulfite may subsequently react with constituents of the  
19 blood to form S-sulfonates or other species. It may appear in other organs, particularly  
20 the liver ([Section 4.2.3](#)), where it is efficiently metabolized to sulfate ([Section 4.2.4](#)).  
21 Urinary excretion of sulfate is rapid and proportional to the concentration of SO<sub>2</sub>  
22 products in the blood. S-sulfonates are cleared more slowly from the circulation with a  
23 clearance half-time of days. The portion of SO<sub>2</sub>-derived products that are retained within  
24 the respiratory tract are only slowly absorbed into the blood ([Section 4.2.3](#)).

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#### 4.2.6 Sources and Levels of Exogenous and Endogenous Sulfite

25 The primary endogenous contribution of sulfite is from the catabolism of  
26 sulfur-containing amino acids (namely, cysteine and methionine). Sulfite may  
27 subsequently be metabolized to sulfate in a reaction catalyzed by sulfite oxidase in most  
28 tissues, but especially in the liver ([Section 4.2.4](#)). Mean daily sulfate produced following  
29 ingestion of cysteine and methionine in the U.S. increases from 70 mg/kg-day in infants  
30 (2–6 months) to 100 mg/kg-day in young children (1–3 years) and then decreases to  
31 30 and 40 mg/kg-day in adult (19–50 years) females and males, respectively ([IOM,](#)  
32 [2005](#)). To facilitate comparison with exogenous sources, a mole of SO<sub>2</sub> can produce a  
33 mole of sulfate, but the SO<sub>2</sub> mass is only two-thirds of the sulfate mass.

1 Sulfite is also added to foods because it has antioxidant and antimicrobial properties  
2 ([Vandevijvere et al., 2010](#); [Gunnison, 1981](#)). In a study considering actual food  
3 consumption of Belgian adults and measured sulfite levels in food, [Vandevijvere et al.](#)  
4 [\(2010\)](#) observed a wide distribution in exogenous sulfite from ingestion. Expressed in  
5 terms of SO<sub>2</sub> equivalents, rates of exogenous sulfite ingestion may be described by a  
6 log-normal distribution with a median intake of 0.14 SO<sub>2</sub> mg/kg-day and a geometric  
7 standard deviation of 2.15. Individuals at the 5th and 95th percentiles of this distribution  
8 are estimated to consume 0.04 and 0.49 SO<sub>2</sub> mg/kg-day. In a comparison of theoretical  
9 food-consumption data with maximum permissible SO<sub>2</sub>/sulfites to foods, the Belgian  
10 adults in the [Vandevijvere et al. \(2010\)](#) study had a similar potential sulfite intake to U.S.  
11 adults. The estimated intake for children could be in the range of that for adults or less  
12 due to the likely minimal consumption of sulfite sources such as wine. Endogenous  
13 sulfite from catabolism of ingested sulfur-containing amino acids far exceeds exogenous  
14 sulfite from ingestion of food additives [by 140 and 180 times in adult (19–50 years)  
15 females and males, respectively, and by 500 times or more in young children  
16 (1–3 years)].

17 Exogenous sulfite may also be derived from SO<sub>2</sub> inhalation. For the purposes of  
18 comparisons herein, all inhaled SO<sub>2</sub> is assumed to contribute to systemic sulfite levels. In  
19 reality, as discussed in [Section 4.2.3](#), the majority of SO<sub>2</sub>-derived products from SO<sub>2</sub>  
20 inhalation are retained in the respiratory tract and may be detected there for up to a week  
21 following inhalation. The potential contribution of inhaled SO<sub>2</sub> to systemic sulfite levels  
22 varies with age, activity level, and SO<sub>2</sub> concentration. Using median and 97.5th percentile  
23 daily ventilation rates from [Brochu et al. \(2011\)](#), adults (25–45 years of age) are  
24 estimated to receive 0.004 and 0.006 mg SO<sub>2</sub> per kg body mass, respectively, from a full  
25 day exposure to 5 parts per billion (ppb) SO<sub>2</sub>. As an upper-bound estimate for ambient  
26 exposure in most locations, a full-day exposure to 75 ppb SO<sub>2</sub> (the level of the current  
27 National Ambient Air Quality Standard for SO<sub>2</sub>) would result in 0.053 SO<sub>2</sub> mg/kg-day  
28 and 0.085 SO<sub>2</sub> mg/kg-day for adults having median and 97.5th percentile ventilation  
29 rates, respectively. The estimated daily SO<sub>2</sub> intake (mg/kg-day) would be roughly  
30 1.5 times greater in children (7–10 years of age) and doubled in infants (0.22–0.5 years  
31 of age) due to the greater ventilation rate per body mass of children compared to adults  
32 (25–45 years of age). Even upper-bound sulfite levels from inhalation (75 ppb SO<sub>2</sub>,  
33 24 hours, 97.5th percentile ventilation) are far less than those derived from catabolism of  
34 sulfur-containing amino acids, by 230 to 300 times in adults (25–45 years) and nearly  
35 500 times in young children (1–3 years).

36 Comparison of sulfite derived from SO<sub>2</sub> inhalation with that from ingestion of food  
37 additives is more complicated. In adults (25–45 years), sulfite intake (mg/kg-day) from  
38 inhalation (75 ppb SO<sub>2</sub>, 24 hours, 97.5th percentile ventilation) is 1.6 times lower than

1 median sulfite intake from ingestion of food additives. In children (<10 years), assuming  
2 similar levels of sulfite intake as adults, sulfite intake from inhalation (75 ppb SO<sub>2</sub>,  
3 24 hours, 97.5th percentile ventilation) is approximately the same as median sulfite intake  
4 from ingestion of food additives. However, ingested sulfite absorbed into the blood goes  
5 directly to the liver where much of it will be metabolized into sulfate. The majority of  
6 sulfite derived from inhalation that enters the blood is rapidly distributed [as either sulfite  
7 or S-sulfonate ([Yokoyama et al., 1971](#); [Balchum et al., 1959](#))] about the body with  
8 around a quarter of total blood flow going to the liver ([ICRP, 2002](#)) where there is a high  
9 activity of sulfite oxidase compared to other tissues. For lower exposure concentrations  
10 and durations than considered above, sulfite (and/or S-sulfonate) levels in the blood  
11 following SO<sub>2</sub> inhalation could exceed those from ingestion of food additives,  
12 particularly in children.

13 In summary, exogenous sources contribute hundreds of times lower amounts of sulfite  
14 than the catabolism of sulfur-containing amino acids, when averaged across the entire  
15 body. Sulfite and sulfate derived from the catabolism of sulfur-containing amino acids  
16 are distributed broadly and do not accumulate in respiratory tract tissues. Following  
17 ingestion of sulfite-containing food additives, sulfite enters the circulation and is subject  
18 to first pass clearance in the liver where it is metabolized to sulfate. Following inhalation,  
19 a substantial portion of SO<sub>2</sub>-derived products accumulate and are retained within the  
20 respiratory tract; SO<sub>2</sub>-derived products that enter the circulation are rapidly distributed  
21 throughout the body, appear primarily in the liver, and are excreted via the urine  
22 ([Section 4.2.5](#)).

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### 4.3 Mode of Action of Inhaled Sulfur Dioxide

23 This section describes the biological pathways that potentially underlie health effects  
24 resulting from short-term and long-term exposure to SO<sub>2</sub>. Extensive research carried out  
25 over several decades in humans and in laboratory animals has yielded much information  
26 about these pathways. This section is not intended to be a comprehensive overview, but  
27 rather, it updates the basic concepts derived from the SO<sub>2</sub> literature presented in the  
28 AQCD ([U.S. EPA, 1982a](#)) and the 2008 ISA for Sulfur Oxides ([U.S. EPA, 2008d](#)) and  
29 introduces the recent relevant literature. While this section highlights findings of studies  
30 published since the 2008 SO<sub>x</sub> ISA ([U.S. EPA, 2008d](#)), earlier studies that represent the  
31 current state of the science are also discussed. Studies conducted at more environmentally  
32 relevant concentrations of SO<sub>2</sub> (i.e., ≤2 ppm, see [Section 1.2](#)) are of greater interest  
33 because biological pathways responsible for effects at higher concentrations may not be  
34 identical to those occurring at lower concentrations. Some studies at higher  
35 concentrations are included if they were early demonstrations of key biological pathways

1 or if they are recent demonstrations of potentially important new pathways. This  
2 information will be used to develop a mode of action framework for inhaled SO<sub>2</sub> that  
3 serves as a guide to interpreting health effects evidence presented in [Chapter 5](#).

4 Mode of action refers to a sequence of key events, endpoints, and outcomes that result in  
5 a given toxic effect ([U.S. EPA, 2005a](#)). Elucidation of mechanism of action provides a  
6 more detailed understanding of key events, usually at the molecular level ([U.S. EPA,  
7 2005a](#)). The framework developed in this chapter will include some mechanistic  
8 information on initiating events at the molecular level, but will mainly focus on the  
9 effects of SO<sub>2</sub> at the cellular, tissue, and organism level.

10 SO<sub>2</sub> is a highly reactive antioxidant gas. At physiologic pH, its hydrated forms include  
11 sulfurous acid, bisulfite, and sulfite, with the latter species predominating. Sulfite is a  
12 strong nucleophilic anion that readily reacts with nucleic acids, proteins, lipids, and other  
13 classes of biomolecules. It participates in many important types of reactions including  
14 sulfonation (sulfitolysis) and autoxidation with the generation of free radicals. This latter  
15 reaction may be responsible for the induction of oxidative stress that occurs as a result of  
16 exposure to SO<sub>2</sub>.

17 As described in [Section 4.2](#), SO<sub>2</sub> is a water-soluble gas that is absorbed almost entirely in  
18 the upper respiratory tract. However, under conditions of mouth breathing and exercise,  
19 some SO<sub>2</sub> may penetrate to the tracheobronchial region. The main effects of SO<sub>2</sub>  
20 inhalation are seen at the sites of absorption (i.e., the respiratory tract) and include  
21 (1) activation of sensory nerves in the respiratory tract resulting in neural reflex  
22 responses, (2) injury to airway mucosa, and (3) increased airway hyperreactivity and  
23 allergic inflammation. Effects outside the respiratory tract may occur at very high  
24 concentrations of inhaled SO<sub>2</sub>. Biologic pathways involved in mediating these responses  
25 to inhaled SO<sub>2</sub> will be discussed below. In addition, a brief synopsis of pathways involved  
26 in mediating the effects of endogenous SO<sub>2</sub>/sulfite will be presented. This section will  
27 conclude with the development of a mode of action framework.

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### 4.3.1 Activation of Sensory Nerves in the Respiratory Tract

28 SO<sub>2</sub> is classified as a sensory (or nasal) irritant in mice, guinea pigs, rats, and humans  
29 ([Alarie, 1973](#)). As such, it may stimulate trigeminal nerve endings when inhaled by the  
30 nose, which results in an inhibition of respiration. It may also stimulate trigeminal nerves  
31 in the larynx, which results in coughing, and in the cornea, which induces tearing. Other  
32 reflexes stimulated by trigeminal nerve endings include decreased heart rate, peripheral  
33 vasoconstriction, closure of the glottis, closure of the nares, and increased nasal flow  
34 resistance. These responses are variable among species. Increased nasal flow resistance

1 has been demonstrated in humans breathing SO<sub>2</sub> gas through the nose. Furthermore,  
2 desensitization of the respiratory rate response occurs with repeated exposure. Most  
3 sensory (or nasal) irritants, including SO<sub>2</sub>, also cause bronchoconstriction, but at  
4 concentrations higher than those stimulating nerve endings in the nose.

5 SO<sub>2</sub> is also classified as a pulmonary (or bronchial) irritant that evokes reflex reactions  
6 through effects on pulmonary nerve endings ([Alarie, 1973](#)). These reactions usually  
7 include an increase in respiratory rate accompanied by a decrease in tidal volume,  
8 sometimes preceded by coughing and brief apnea, and sometimes accompanied by  
9 bronchoconstriction. These responses have been observed in guinea pigs and cats  
10 breathing via a tracheal cannula, which bypasses the nose. In the cat, SO<sub>2</sub> exposure  
11 increased the activity of vagal afferent fibers by either stimulating or sensitizing  
12 tracheobronchial receptors on the nerve endings. SO<sub>2</sub> also increased airway resistance in  
13 guinea pigs and humans breathing through the nose, mouth, and/or tracheal cannula.  
14 Increased airway resistance may occur via a variety of mechanisms including  
15 accumulation of secretions, inflammatory changes of the airway walls, collapsing  
16 airways, and constrictions of the central and peripheral airways. Constriction may be due  
17 to direct action on the smooth muscle, axonal reflexes, vagal nerve stimulation, and  
18 release of mediators such as histamine.

19 Continuous or repeated exposure to inhaled SO<sub>2</sub> has a different pattern of responses in  
20 different species ([Alarie, 1973](#)). In guinea pigs, the increase in airway resistance rose to a  
21 plateau upon exposure and decreased to baseline with cessation of exposure. In humans  
22 and dogs, resistance increased with exposure but decreased after 10 minutes (humans) or  
23 3 minutes (dogs) despite the continuous presence of the gas. Studies in adults with  
24 asthma demonstrated a different pattern. When exposure to SO<sub>2</sub> occurred during a  
25 30-minute period with continuous exercise, the response to SO<sub>2</sub> developed rapidly and  
26 was maintained throughout the 30-minute exposure ([Kehrl et al., 1987](#); [Linn et al., 1987](#);  
27 [Linn et al., 1984c](#)). Sequential exposures in nonasthmatic human subjects and in cats  
28 resulted in a decreased response to SO<sub>2</sub> in the second exposure compared with the first,  
29 indicative of desensitization.

30 Early experiments demonstrated that SO<sub>2</sub>-induced reflexes were mediated by cholinergic  
31 parasympathetic pathways involving the vagus nerve and inhibited by atropine ([Grunstein  
32 et al., 1977](#); [Nadel et al., 1965a, b](#)). Bronchoconstriction was found to involve smooth  
33 muscle contraction because  $\beta$ -adrenergic agonists such as isoproterenol reversed the  
34 effects. Rapid shallow breathing was observed in SO<sub>2</sub>-exposed tracheotomized cats  
35 (bypassing the nose). Histamine was proposed to play a role in SO<sub>2</sub>-induced  
36 bronchoconstriction ([U.S. EPA, 1982a](#)), but this hypothesis remains unconfirmed.  
37 Hydrogen ions, sulfurous acid, sulfite, and bisulfite are all putative mediators of the

1 reflex responses ([Gunnison et al., 1987a](#)). In particular, sulfite-mediated sulfitolysis of  
2 disulfides present in receptor proteins on sensory nerve fibers has been postulated  
3 because S-sulfonate formation may potentially disrupt protein structure or function  
4 ([Alarie, 1973](#)).

5 More recent experiments in animal models conducted since 1982 have demonstrated that  
6 both cholinergic and noncholinergic mechanisms may be involved in SO<sub>2</sub>-induced  
7 effects. In two studies using bilateral vagotomy, vagal afferents were found to mediate  
8 the immediate ventilatory responses to SO<sub>2</sub> ([Wang et al., 1996](#)), but not the prolonged  
9 bronchoconstrictor response ([Barthelemy et al., 1988](#)). Other studies showed that atropine  
10 failed to block SO<sub>2</sub>-induced bronchoconstriction, and that a local axon reflex resulting in  
11 C-fiber secretion of neuropeptides (i.e., neurogenic inflammation) was responsible for the  
12 effect ([Hajj et al., 1996](#); [Atzori et al., 1992](#)). Neurogenic inflammation has been shown to  
13 play a key role in animal models of airway inflammatory disease ([Groneberg et al.,](#)  
14 [2004](#)). Furthermore, in isolated perfused and ventilated guinea pig lungs,  
15 bronchoconstriction to SO<sub>2</sub> was biphasic. The initial phase was mediated by a local axon  
16 reflex involving the release of the neuropeptide calcitonin gene-related peptide from  
17 sensory nerves, while the later phase involved other mechanisms ([Bannenberg et al.,](#)  
18 [1994](#)).

19 In humans, the mechanisms responsible for SO<sub>2</sub>-induced bronchoconstriction are not  
20 entirely understood. In nonasthmatic subjects, near complete attenuation of  
21 bronchoconstriction has been demonstrated using the anticholinergic agents atropine and  
22 ipratropium bromide ([Yildirim et al., 2005](#); [Snashall and Baldwin, 1982](#); [Tan et al.,](#)  
23 [1982](#)). However, in asthmatic subjects, these same anticholinergic agents ([Field et al.,](#)  
24 [1996](#); [Myers et al., 1986a](#)), as well as short- and long-acting β<sub>2</sub>-adrenergic agonists  
25 ([Gong et al., 1996](#); [Linn et al., 1988](#)), theophylline ([Koenig et al., 1992](#)), cromolyn  
26 sodium ([Myers et al., 1986a](#)), nedocromil sodium ([Bigby and Boushey, 1993](#)), and  
27 leukotriene receptor antagonists ([Gong et al., 2001](#); [Lazarus et al., 1997](#)) only partially  
28 blocked SO<sub>2</sub>-induced bronchoconstriction. That none of these therapies have been shown  
29 to completely attenuate the effects of SO<sub>2</sub> implies the involvement of both  
30 parasympathetic pathways and inflammatory mediators in asthmatic individuals. Strong  
31 evidence of this was borne out in a study by [Myers et al. \(1986a\)](#) in which asthmatic  
32 adults were exposed to SO<sub>2</sub> following pretreatment with cromolyn sodium (a mast cell  
33 stabilizer), atropine (a muscarinic receptor antagonist), and the two medications together.  
34 While both treatments individually provided some protection against the  
35 bronchoconstrictive effects of SO<sub>2</sub>, there was a much stronger and statistically significant  
36 effect following concurrent administration of the two medications. Besides mast cell  
37 stabilization, cromolyn sodium may also reduce the activity of lung irritant receptors

1 [\(Harries et al., 1981\)](#), providing an alternative mechanism for the reduction in  
2 SO<sub>2</sub>-induced bronchoconstriction observed.

3 It has been proposed that inflammation contributes to the enhanced sensitivity to SO<sub>2</sub>  
4 seen in asthmatic human subjects by altering autonomic responses ([Tunnicliffe et al.,](#)  
5 [2001](#)), enhancing mediator release ([Tan et al., 1982](#)), and/or sensitizing C-fibers and  
6 rapidly adapting receptors ([Lee and Widdicombe, 2001](#)). Whether local axon reflexes  
7 also play a role in SO<sub>2</sub>-induced bronchoconstriction in asthmatic individuals is not known  
8 ([Groneberg et al., 2004](#); [Widdicombe, 2003](#); [Lee and Widdicombe, 2001](#)). However,  
9 differences in respiratory tract innervation between rodents and humans suggest that  
10 C-fiber-mediated neurogenic inflammation may be unimportant in humans ([Groneberg et](#)  
11 [al., 2004](#); [Widdicombe, 2003](#); [Widdicombe and Lee, 2001](#)). Furthermore, enhanced  
12 sensitivity to SO<sub>2</sub> in asthmatic individuals may be related to genetic polymorphisms of  
13 inflammatory mediators, such as TNF- $\alpha$  ([Winterton et al., 2001](#)).

14 Studies in vitro provide support for SO<sub>2</sub> exposure-mediated effects that involve  
15 inflammatory cells. It is known that sulfite exposure of cultured rat basophil leukemia  
16 cells, a mast cell analog, causes immunoglobulin E (IgE)-independent degranulation,  
17 release of histamine, serotonin and other mediators, and intracellular production of  
18 reactive oxygen species ([Collaco et al., 2006](#)). In addition, peroxidases, such as  
19 neutrophil myeloperoxidase, oxidize bisulfite anion to several radical species that in turn  
20 attack proteins ([Ranguelova et al., 2013](#); [Ranguelova et al., 2012](#)). This represents a  
21 potentially important new toxicological pathway for sulfite, especially in the presence of  
22 neutrophilic and/or eosinophilic inflammation.

23 Irritant responses are indicative of a chemical's ability to damage the respiratory tract  
24 ([Alarie and Luo, 1986](#); [Alarie, 1981](#)). In the case of sensory irritation, there is a  
25 characteristic decrease in respiratory rate, which is often used to set health-protective  
26 standards for occupational exposures. Chemicals that are pulmonary irritants often lead to  
27 rapid shallow breathing. They typically induce pulmonary edema or congestion if inhaled  
28 for a long enough period of time. Some chemicals are both sensory and pulmonary  
29 irritants and pulmonary irritation may occur at concentrations below which sensory  
30 irritation occurs. In the case of SO<sub>2</sub>, a concentration-dependent hierarchy of effects has  
31 been noted in humans ([Kane et al., 1979](#)). Lethal or extremely severe injury to the  
32 respiratory tract has been reported at and above 190 ppm. Intolerable sensory irritation  
33 and respiratory tract injury that may occur with extended exposure has been associated  
34 with 10–15-minute exposures to 30–100 ppm SO<sub>2</sub>, and tolerable sensory irritation has  
35 been associated with 10-minute exposures to 5–11.5 ppm SO<sub>2</sub>. Minimal sensory irritation  
36 has been associated with exposures at and below 1 ppm. Increased airway resistance,  
37 likely due to pulmonary irritation and reflex bronchoconstriction, has been observed at

1 5 ppm in adults without asthma at rest and at 1 ppm SO<sub>2</sub> in adults without asthma while  
2 exercising ([Arts et al., 2006](#)). However, lung function changes have been observed at  
3 concentrations of SO<sub>2</sub> lower than 1 ppm in exercising adults with asthma. Thus,  
4 pulmonary irritation may occur at levels of SO<sub>2</sub> below those that cause sensory irritation,  
5 especially in exercising adults with asthma.

6 In summary, SO<sub>2</sub> acts as both a sensory and a pulmonary irritant through activation of  
7 sensory nerves in the respiratory tract resulting in neural reflex responses. This occurs in  
8 a variety of species, including humans. Pulmonary irritant responses due to SO<sub>2</sub> exposure  
9 result in reflex bronchoconstriction, especially in adults with asthma. Both cholinergic  
10 parasympathetic pathways involving the vagus nerve and inflammation contribute to  
11 reflex bronchoconstriction in asthmatic individuals.

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#### 4.3.2 Injury to Airway Mucosa

12 A common feature of irritant gases, including SO<sub>2</sub>, is the capacity to injure airway  
13 mucosa, resulting in decreased epithelial barrier function, inflammation, and  
14 compromised ciliary function ([Carson et al., 2013](#)). Despite being the initial site of SO<sub>2</sub>  
15 absorption and having low activity of sulfite oxidase, the respiratory tract of healthy  
16 humans is thought to be capable of detoxifying 5 ppm inhaled SO<sub>2</sub> ([Gunnison et al.,  
17 1987a](#)). In fact, exposure to 0.5–2 ppm SO<sub>2</sub> for 4 hours did not result in any measurable  
18 changes in biomarkers of oxidative stress or inflammation in exhaled breath condensate  
19 (EBC) or nasal lavage fluid (NALF) from healthy adults subjected to two periods of  
20 moderate exercise ([Raulf-Heimsoth et al., 2010](#)). In addition, no changes in nasal lining  
21 fluid ascorbic acid or uric acid levels were observed following 1-hour exposure of adults  
22 with asthma to 0.2 ppm SO<sub>2</sub> ([Tunnicliffe et al., 2003](#)).

23 However, respiratory tract injury has been observed in humans exposed for extended  
24 periods to SO<sub>2</sub> concentrations of 30 ppm and greater. In animal models, airway injury and  
25 histopathological changes, such as mucous cell metaplasia and intramural fibrosis, have  
26 generally been observed following chronic exposure to SO<sub>2</sub> concentrations of 10 ppm and  
27 higher ([U.S. EPA, 2008d](#)). Rats exposed to 20 ppm SO<sub>2</sub> for several weeks exhibit fibrotic  
28 remodeling of airway epithelium and mucus hypersecretion, key features of COPD and  
29 chronic asthma in humans ([Wagner et al., 2006](#)). Inflammatory changes have been noted  
30 in some animal models following subacute exposure to 5–100 ppm SO<sub>2</sub> ([U.S. EPA,  
31 2008d](#)). However, adults with asthma and animal models of allergic airway disease  
32 exhibit greater sensitivity to SO<sub>2</sub> (see below). Impaired mucociliary clearance has also  
33 been demonstrated at high concentrations of SO<sub>2</sub>. In humans, nasal mucus flow was  
34 decreased during a 5-hour exposure to 5 and 25 ppm SO<sub>2</sub> ([Gunnison et al., 1981](#)).

1 Impaired mucus flow in the trachea has been observed in rats exposed subacutely to  
2 11.4 ppm SO<sub>2</sub> and in dogs exposed chronically to 1 ppm SO<sub>2</sub> ([Gunnison et al., 1981](#);  
3 [Hirsch et al., 1975](#)). Whether these effects were due to compromised ciliary function or  
4 altered properties of the mucus due to sulfite-mediated sulfitolysis of disulfide bonds in  
5 mucus was not investigated.

6 Recent studies provide additional insight. An ultrastructural examination of nasal biopsy  
7 tissue by freeze fracture microscopy was conducted in humans exposed to 0.75 ppm SO<sub>2</sub>  
8 for 2 h ([Carson et al., 2013](#)). Evidence of fragmentation of the tight junctional complex  
9 and polymorphonuclear infiltrate was reported although no effects on ciliary membranes  
10 were observed. These subtle responses suggest a slight decrease in barrier function due to  
11 acute SO<sub>2</sub> exposure at this level. Furthermore, a subacute exposure of rats to 2.67 ppm  
12 SO<sub>2</sub> (6 hours/day, 7 days) resulted in altered lung mRNA levels for inducible nitric oxide  
13 synthase (involved in inflammation) and for bax (or B-cell lymphoma 2-like protein 4;  
14 involved in regulating apoptosis) ([Sang et al., 2010](#)). In this study, gene expression  
15 changes were also found in the heart and they were more pronounced than in the lung.  
16 These results suggest that, despite low sulfite oxidase activity, the respiratory tract may  
17 be more resistant than the heart to the effects of inhaled SO<sub>2</sub>.

18 In summary, exposure to SO<sub>2</sub> results in injury to airway mucosa, especially at higher  
19 concentrations and following extended periods of exposure. There is little evidence of  
20 injury or inflammation in response to acute exposures to concentrations of 2 ppm SO<sub>2</sub> or  
21 less in human subjects. However, one new study found subtle histopathological changes  
22 at the ultrastructural level following a 2-hour exposure to 0.75 ppm SO<sub>2</sub>. New evidence  
23 also suggests subtle changes in the lung related to inflammation and apoptosis in rats  
24 exposed over several days to 2.67 ppm SO<sub>2</sub>.

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### 4.3.3 Modulation of Airway Responsiveness and Allergic Inflammation

25 Asthma is a chronic inflammatory disease of the airways that is characterized by  
26 increased airway responsiveness [i.e., airway hyperresponsiveness (AHR)] and variable  
27 airflow obstruction. Respiratory irritants, including SO<sub>2</sub>, are thought to be a major cause  
28 of occupational asthma ([Baur et al., 2012](#); [Andersson et al., 2006](#)). Both peak high-level  
29 exposures and low-level persistent exposures have been associated with the development  
30 of irritant-induced asthma.

31 Studies in several different animal species have shown that a single exposure to SO<sub>2</sub> at a  
32 concentration of 10 ppm or less failed to induce AHR following a challenge agent ([U.S.  
33 EPA, 2008d](#)). However, in an animal model of allergic airway disease, SO<sub>2</sub> exposure  
34 enhanced airway responsiveness. In this study, sheep previously sensitized and

1 challenged with *Ascaris suum* extract were exposed to 5 ppm SO<sub>2</sub> for 4 hours ([Abraham](#)  
2 [et al., 1981](#)). Airway responsiveness to carbachol was increased at 24 hours, but not  
3 immediately, after SO<sub>2</sub> exposure. This response was not observed in sheep that had not  
4 been sensitized and challenged with *Ascaris suum* extract. The mechanism underlying the  
5 SO<sub>2</sub>-induced AHR was not investigated in this study. However, the AHR response could  
6 have resulted from sensitization of vagal irritant receptors, greater sensitivity of smooth  
7 muscle to bronchoconstriction agents, or enhanced concentrations of bronchoconstriction  
8 agents reaching the receptors or bronchial smooth muscle. The delayed nature of the  
9 response points to a possible role of inflammation in mediating AHR.

10 Two controlled human exposure studies in adults with asthma provide further evidence of  
11 AHR to an allergen when exposure to SO<sub>2</sub> was in combination with NO<sub>2</sub>. In one of these  
12 studies, exposure to 0.2 ppm SO<sub>2</sub> or 0.4 ppm NO<sub>2</sub> alone did not affect airway  
13 responsiveness to house dust mite allergen immediately after a 6-hour exposure at rest  
14 ([Devalia et al., 1994](#)). However, following exposure to the two pollutants in combination,  
15 subjects demonstrated an increase response to the inhaled allergen. [Rusznak et al. \(1996\)](#)  
16 confirmed these results in a similar study and found that AHR to dust mites persisted up  
17 to 48 post-exposure. These results provide further evidence that SO<sub>2</sub> may elicit effects  
18 beyond the short time period typically associated with this pollutant.

19 Several other studies have examined the effects of SO<sub>2</sub> exposure on allergic  
20 inflammation. One of these was a controlled human exposure study of adults with  
21 asthma. Subjects were exposed for 10 minutes to 0.75 ppm SO<sub>2</sub> while exercising at a  
22 moderate level ([Gong et al., 2001](#)). In addition to changes in lung function and  
23 symptoms, there was a statistically significant increase in eosinophil count in induced  
24 sputum 2 hours post-exposure. Pretreatment with a leukotriene receptor antagonist  
25 dampened these responses, implicating a role for leukotrienes in mediating SO<sub>2</sub>  
26 exposure-induced effects.

27 The other studies investigated the effects of repeated exposure to SO<sub>2</sub> on inflammatory  
28 and immune responses in an animal model of allergic airways disease. [Li et al. \(2007\)](#)  
29 demonstrated that in ovalbumin-sensitized rats, exposure to 2 ppm SO<sub>2</sub> for 1 hour  
30 followed by challenge with ovalbumin each day for 7 days resulted in an increased  
31 number of inflammatory cells in bronchoalveolar lavage fluid (BALF) and an enhanced  
32 histopathological response compared with rats treated with SO<sub>2</sub> or ovalbumin alone.  
33 Similarly, intercellular adhesion molecule 1 (ICAM-1), a protein involved in regulating  
34 inflammation, and mucin 5AC glycoprotein (MUC5AC), a mucin protein, were  
35 upregulated in lungs and trachea to a greater extent in rats treated both with SO<sub>2</sub> and  
36 ovalbumin. A follow up study involving the same exposure regimen (2 ppm SO<sub>2</sub> for  
37 1 hour) in the same allergic animal model (rats sensitized and challenged with

1 ovalbumin) also found that repeated SO<sub>2</sub> exposure enhanced inflammatory and allergic  
2 responses to ovalbumin ([Li et al., 2014](#)). Numbers of eosinophils, lymphocytes, and  
3 macrophages were greater in the BALF of SO<sub>2</sub>-exposed and ovalbumin-treated animals  
4 than in animals treated only with ovalbumin. In addition, SO<sub>2</sub> exposure enhanced  
5 upregulation and activation of nuclear factor kappa-light-chain-enhancer of activated B  
6 cells (NFκB), a transcription factor involved in inflammation, and upregulation of the  
7 cytokines interleukin-6 (IL-6) and interleukin-4 (IL-4) in lung tissue. Furthermore, BALF  
8 levels of IL-6 and IL-4 were increased to a greater extent in SO<sub>2</sub>-exposed and  
9 ovalbumin-treated animals compared with ovalbumin treatment alone. These results  
10 indicate that repeated SO<sub>2</sub> exposure enhanced activation of the NFκB inflammatory  
11 pathway and upregulation of inflammatory cytokines in ovalbumin-treated animals.  
12 Furthermore, SO<sub>2</sub> exposure enhanced the effects of ovalbumin on levels of interferon  
13 gamma (IFN-γ) (decreased) and IL-4 (increased) in BALF and on IgE levels in serum  
14 (increased). Because levels of IL-4 are often indicative of T helper 2 (Th2) status and  
15 levels of IFN-γ are indicative of a T helper 1 (Th1) status, these results suggest a shift in  
16 Th1/Th2 balance away from Th2 in rats made allergic to ovalbumin, an effect that was  
17 exacerbated by SO<sub>2</sub> exposure. These Th2-related changes are consistent with the  
18 observed increases in serum IgE and BALF eosinophils in ovalbumin-treated animals,  
19 effects that were also enhanced by SO<sub>2</sub> exposure. Taken together, these results indicate  
20 that repeated exposure to SO<sub>2</sub> exacerbated inflammatory and allergic responses in this  
21 animal model. It should be noted, however, that group 2 innate lymphoid cells can  
22 mediate Type 2 immunity, as has been described for O<sub>3</sub>-mediated responses in mice ([Ong  
23 et al., 2016](#)). Whether group 2 innate lymphoid cells mediate effects of inhalation of SO<sub>2</sub>,  
24 which like O<sub>3</sub> is an irritant gas, is unexplored.

25 Two other follow-up studies by the same laboratory examined the effects of inhaled SO<sub>2</sub>  
26 on the asthma-related genes encoding epidermal growth factor (EGF), epidermal growth  
27 factor receptor (EGFR), and cyclooxygenase-2 (COX-2), and on apoptosis-related genes  
28 and proteins in this same model based on sensitization with ovalbumin ([Xie et al., 2009](#);  
29 [Li et al., 2008](#)). While EGF and EGFR are related to mucus production and airway  
30 remodeling, COX-2 is related to apoptosis and may play a role in regulating airway  
31 inflammation. SO<sub>2</sub> exposure enhanced the effects of ovalbumin in this model, resulting in  
32 greater increases in mRNA and protein levels of EGF, EGFR and COX-2 in the trachea  
33 compared with ovalbumin treatment alone. SO<sub>2</sub> exposure enhanced other effects of  
34 ovalbumin in this model, resulting in a greater decline in mRNA and protein levels of  
35 tumor protein p53 (p53) and bax and a greater increase in mRNA and protein levels of  
36 B-cell lymphoma 2 (bcl-2) in the lungs compared with ovalbumin challenge alone.  
37 The increased ratio of bcl-2:bax, an indicator of susceptibility to apoptosis, observed  
38 following ovalbumin challenge, was similarly enhanced by SO<sub>2</sub>. Thus, repeated exposure

1 to SO<sub>2</sub> may impact numerous processes involved in inflammation and/or airway  
2 remodeling in allergic airways disease.

3 The effects of repeated SO<sub>2</sub> exposure on the development of an allergic phenotype and  
4 altered physiologic responses in naive animals was examined in two studies in which SO<sub>2</sub>  
5 exposure preceded allergen sensitization. Repeated exposure of guinea pigs to SO<sub>2</sub>  
6 promoted allergic sensitization and subsequently enhanced allergen-induced bronchial  
7 obstruction, as reported by [U.S. EPA \(2008d\)](#). [Riedel et al. \(1988\)](#) examined the effect of  
8 SO<sub>2</sub> exposure on local bronchial sensitization to inhaled antigen. Guinea pigs were  
9 exposed by inhalation to 0.1, 4.3, and 16.6 ppm SO<sub>2</sub> for 8 hours/day for 5 days. During  
10 the last 3 days, SO<sub>2</sub> exposure was followed by exposure to nebulized ovalbumin for  
11 45 minutes. Following bronchial provocation with inhaled ovalbumin (0.1%) 1 week  
12 later, bronchial obstruction was measured by examining the respiratory loop obtained by  
13 whole-body plethysmography. In addition, specific antibodies against ovalbumin were  
14 measured in serum and BALF. Results showed significantly higher bronchial obstruction  
15 in animals exposed to SO<sub>2</sub> (at all concentration levels) and ovalbumin, compared with  
16 animals exposed only to ovalbumin. In addition, significant increases in anti-ovalbumin  
17 immunoglobulin G (IgG) antibodies were detected in BALF lavage fluid of animals  
18 exposed to 0.1, 4.3, and 16.6 ppm SO<sub>2</sub> and in serum from animals exposed to 4.3 and  
19 16.6 ppm SO<sub>2</sub> compared with controls exposed only to ovalbumin. These results  
20 demonstrate that repeated exposure to SO<sub>2</sub> enhanced allergic sensitization in the guinea  
21 pig at a concentration as low as 0.1 ppm. In a second study, guinea pigs were exposed to  
22 0.1 ppm SO<sub>2</sub> for 5 hours/day for 5 days and sensitized with 0.1% ovalbumin aerosols for  
23 45 minutes on Days 4 to 5 ([Park et al., 2001](#)). One week later, animals were subjected to  
24 bronchial challenge with 0.1% ovalbumin and lung function was evaluated 24 hours later  
25 by whole-body plethysmography. Results demonstrated a significant increase in  
26 enhanced pause, a measure of airway obstruction, in animals exposed to SO<sub>2</sub> and  
27 ovalbumin but not in animals treated with ovalbumin or SO<sub>2</sub> alone. Results also  
28 demonstrated increased numbers of eosinophils in lavage fluid and an infiltration of  
29 inflammatory cells, bronchiolar epithelial cell damage, and plugging of the airway lumen  
30 with mucus and cells in the bronchial tissues of animals treated with both SO<sub>2</sub> and  
31 ovalbumin, but not in animals treated with ovalbumin or SO<sub>2</sub> alone. These experiments  
32 indicate that repeated exposure to near ambient levels of SO<sub>2</sub> plays a role in allergic  
33 sensitization and also exacerbates allergic inflammatory responses in the guinea pig.  
34 Furthermore, increases in bronchial obstruction observed in both studies suggest that  
35 repeated SO<sub>2</sub> exposure increased airway responsiveness.

36 Longer term exposure of naive newborn rats to SO<sub>2</sub> (2 ppm, 4 hours/day for 28 days)  
37 resulted in altered cytokine levels that suggest a shift in Th1/Th2 balance away from Th2  
38 ([Song et al., 2012](#)). Th2 polarization is one of the steps involved in allergic sensitization.

1 It should be noted, however, that group 2 innate lymphoid cells can mediate Type 2  
2 immunity, as has been described for O<sub>3</sub>-mediated responses in mice ([Ong et al., 2016](#)).  
3 Whether group 2 innate lymphoid cells mediate effects of inhalation of SO<sub>2</sub>, which like  
4 O<sub>3</sub> is an irritant gas, is unexplored. In naive animals exposed to SO<sub>2</sub>, levels of IL-4,  
5 which is indicative of a Th2 response, were increased and levels of IFN- $\gamma$ , indicative of a  
6 Th1 response, were decreased in BALF. In ovalbumin-sensitized newborn rats, SO<sub>2</sub>  
7 exposure resulted in a greater enhancement of lavage fluid IL-4 and an increase in serum  
8 IL-4 levels compared with ovalbumin-sensitization alone. In addition, SO<sub>2</sub> exposure led  
9 to AHR and airway remodeling, as indicated by increased content of airway smooth  
10 muscle, in the ovalbumin-sensitized animals. Stiffness and contractility of airway smooth  
11 muscle was assessed in vitro using cells from experimentally treated animals. In allergic  
12 rats, both stiffness and contractility were increased as a result of SO<sub>2</sub> exposure,  
13 suggesting an effect on the biomechanics of airway smooth muscle. This study provides  
14 evidence for allergic sensitization by SO<sub>2</sub> in naive newborn rats and for enhanced allergic  
15 inflammation, AHR, and airway remodeling in SO<sub>2</sub>-exposed allergic newborn rats.

16 Supportive evidence that SO<sub>2</sub> may promote allergic sensitization is provided by a study in  
17 mice that were first treated with sodium sulfite and then sensitized and challenged with  
18 house dust mite allergen ([Lin et al., 2011a](#)). Sulfite is formed in ELF following inhalation  
19 of SO<sub>2</sub> ([Section 4.2.1](#)). Repeated intranasal treatment with 10  $\mu$ L of a 5-mM solution of  
20 sodium sulfite aggravated inflammation (measured by histopathology) and allergic  
21 sensitization in this model. Specific IgE levels were higher in sulfite-treated and  
22 allergen-challenged animals compared with either sulfite treatment or allergen challenge  
23 alone. Specific IgG2 $\alpha$  levels, indicative of a Th1 response, were decreased as a result of  
24 sulfite treatment in house dust mite-challenged mice. In addition, interleukin-5 (IL-5)  
25 levels, indicative of a Th2 response, and the ratio of Il-5:IFN- $\gamma$ , a marker of Th2  
26 polarization, were higher in lung tissue from sulfite-treated and allergen-challenged mice  
27 compared with either sulfite treatment or allergen challenge alone.

28 Mixtures of SO<sub>2</sub> and other criteria pollutants have also been shown to modulate airway  
29 responsiveness and/or allergic inflammation. As discussed above, AHR to house dust  
30 mite allergen occurred in human subjects with mild allergy and asthma immediately  
31 following 6 hours of concurrent exposure to 0.2 ppm SO<sub>2</sub> and 0.4 ppm NO<sub>2</sub>, but not to  
32 either pollutant alone ([Rusznak et al., 1996](#); [Devalia et al., 1994](#)). This effect persisted for  
33 48 hours. Recently, the effects of simulated downwind coal combustion emissions  
34 (SDCCE) on allergic airway responses was investigated in mice ([Barrett et al., 2011](#)).  
35 Mice were sensitized and challenged with ovalbumin and exposed for 6 hours/day for  
36 3 days to several concentrations of SDCCE with and without a particle filter. SDCCE  
37 exposure was followed by another challenge with ovalbumin in some animals. Results  
38 demonstrated that both the particulate and the gaseous phases of SDCCE exacerbated

1 allergic airways responses. Airway responsiveness (measured by the forced oscillation  
2 technique) was enhanced by the gaseous phase of SDCCE in mice that were challenged  
3 with ovalbumin after SDCCE exposure. Concentration of SO<sub>2</sub> in the highest exposure  
4 was 0.2 ppm. Other gases present in this exposure were NO<sub>2</sub> (0.29 ppm), NO (0.59 ppm),  
5 and carbon monoxide (0.02 ppm). Results of this study are consistent with SO<sub>2</sub> playing a  
6 role in exacerbating AHR and allergic responses, although the other mixture components  
7 may have contributed to the observed effects.

8 In summary, a growing body of evidence supports a role for SO<sub>2</sub> in exacerbating AHR  
9 and/or allergic inflammation in animal models of allergic airway disease, as well as in  
10 asthmatic individuals. In addition, repeated or prolonged exposure to SO<sub>2</sub> promotes  
11 allergic sensitization in naive newborn animals. Furthermore, one study in newborn  
12 allergic rats suggests that airway remodeling may contribute to AHR following prolonged  
13 exposure to SO<sub>2</sub>.

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#### 4.3.4 Induction of Systemic Effects

14 As described in the 2008 SO<sub>x</sub> ISA ([U.S. EPA, 2008d](#)), two controlled human exposure  
15 studies reported that acute exposure to 0.2 ppm SO<sub>2</sub> resulted in changes in heart rate  
16 variability in healthy adults and in asthmatic adults ([Routledge et al., 2006](#); [Tunnicliffe et  
17 al., 2001](#)). More recently, altered parasympathetic regulation of heart rate was reported in  
18 rats exposed to 5 ppm SO<sub>2</sub> during the peri-natal and post-natal period ([Woerman and  
19 Mendelowitz, 2013a, b](#)). Whether these responses were due to activation of sensory  
20 nerves in the respiratory tract resulting in a neural reflex response and altered autonomic  
21 function or some other mechanism is not known.

22 Numerous studies over several decades have reported other extrapulmonary effects of  
23 inhaled SO<sub>2</sub> ([U.S. EPA, 2008d](#)). Most of these occur at concentrations far higher than  
24 those measured in ambient air. As discussed in [Section 4.2.3](#), studies in mice and humans  
25 demonstrating the presence of sulfite and S-sulfonates in blood and tissues outside of the  
26 respiratory tract point to the likely role of circulating sulfite in mediating these responses.  
27 A subacute study measured sulfite plus S-sulfonate content of the lung, liver, and brain of  
28 mice exposed to 5, 10, or 20 ppm SO<sub>2</sub> for 4 hours/day for 7 days ([Meng et al., 2005a](#)) and  
29 found a concentration-dependent increase. Similarly, exposure of human subjects to  
30 0.3–6 ppm SO<sub>2</sub> for up to 120 hours resulted in the appearance in the plasma of sulfite  
31 plus S-sulfonates ([Gunnison and Palmes, 1974](#)). The relationship between  
32 sulfite/sulfonate concentration and chamber SO<sub>2</sub> concentration was linear (regression  
33 coefficient of 0.61) with a slope of 1.1 nmol/mL of plasma S-sulfonate for each 1-ppm  
34 increment in SO<sub>2</sub> concentration. These results indicate that prolonged (i.e., hours to days)

1 exposure to as low as 0.3 ppm SO<sub>2</sub> results in measurable amounts of circulating sulfite in  
2 humans. The relationship between circulating sulfite/S-sulfonate and extrapulmonary  
3 effects of inhaled SO<sub>2</sub> has not yet been explored in human subjects.

4 Because the activity of sulfite oxidase is variable among species, the degree of sensitivity  
5 to SO<sub>2</sub>-mediated effects is likely to be variable among species. For example, sulfite  
6 oxidase in rats is 10–20 times greater than in humans and 3–5 times greater than in  
7 rabbits or rhesus monkeys ([Gunnison et al., 1987a](#); [Gunnison, 1981](#)). Thus, the toxicity of  
8 SO<sub>2</sub> may be less in rats due to more rapid metabolism of sulfite to sulfate.

9 Systemic effects are likely due to oxidative stress, possibly from sulfite autoxidation.  
10 Alternatively, sulfite-mediated S-sulfonate formation may disrupt protein function, and  
11 metabolic reduction of S-sulfonates may alter reduction-oxidation (redox) status.  
12 Moreover, sulfite may serve as a substrate for peroxidases, such as myeloperoxidase and  
13 eosinophil peroxidase, to produce free radicals, as has been demonstrated in neutrophils  
14 and eosinophils ([Ranguelova et al., 2013](#); [Ranguelova et al., 2012](#); [Ranguelova et al.,  
15 2010](#)). These sulfur-based free radical species may then initiate protein or lipid oxidation.

16 [Baskurt \(1988\)](#) found that exposure of rats to 0.87 ppm SO<sub>2</sub> for 24 hours resulted in  
17 increased hematocrit, sulfhemoglobin, and osmotic fragility, as well as decreased whole  
18 blood and packed cell viscosities. These results indicate a systemic effect of inhaled SO<sub>2</sub>  
19 and are consistent with an oxidative injury to red blood cells. Other studies have reported  
20 lipid peroxidation in erythrocytes and tissues of animals exposed to SO<sub>2</sub> ([Qin et al., 2012](#);  
21 [Ziemann et al., 2010](#); [Haider et al., 1982](#)). Supplementation with ascorbate and  
22 α-tocopherol decreased SO<sub>2</sub>-induced lipid peroxidation in erythrocytes ([Etlik et al.,  
23 1995](#)). Additionally, recent studies report mitochondrial changes in the hearts and brains  
24 of rats exposed to 1.34 ppm (4 hours/day) SO<sub>2</sub> for several weeks ([Qin et al., 2016](#); [Qin et  
25 al., 2012](#)). Demonstration of mitochondrial biogenesis in rat brain suggests that SO<sub>2</sub>  
26 exposure induces an adaptive response to oxidative stress ([Qin et al., 2012](#)). Changes in  
27 cardiac function were observed at higher concentrations (2.7 ppm SO<sub>2</sub>); however  
28 pretreatment with antioxidants blocked this effect ([Qin et al., 2016](#)). Other recent studies  
29 report altered markers of brain inflammation and synaptic plasticity following several  
30 weeks to months of exposure to 1.34 ppm (4 hours/day) SO<sub>2</sub> ([Yao et al., 2015](#); [Yao et al.,  
31 2014](#)). Further studies are required to confirm that inhalation exposures of SO<sub>2</sub> at or near  
32 ambient levels increase blood sulfite levels sufficiently for oxidative injury to occur in  
33 blood cells or other tissues.

34 In summary, exposure to SO<sub>2</sub> may result in effects outside the respiratory tract via  
35 activation of sensory nerves in the respiratory tract resulting in a neural reflex response or  
36 mediated by circulating sulfite. A few studies employing concentrations of 2 ppm SO<sub>2</sub> or  
37 less have demonstrated effects that are consistent with sulfite-mediated redox stress, such

1 as increased sulfhemoglobin in red blood cells and lipid peroxidation in the brain. Recent  
2 studies also suggest possible inflammation and other effects in tissues distal to the  
3 absorption site following several weeks to months of exposure to 1.34 ppm SO<sub>2</sub>.

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#### 4.3.5 Role of Endogenous Sulfur Dioxide/Sulfite

4 Endogenous SO<sub>2</sub>/sulfite is a product of normal metabolism of sulfur-containing amino  
5 acids (e.g., cysteine and methionine) ([Liu et al., 2010](#)). While SO<sub>2</sub> gas is measured in the  
6 head space gas of preparations of various tissues or bodily fluids ([Balazy et al., 2003](#)),  
7 sulfite/bisulfite is measured in soluble fractions. The distribution of SO<sub>2</sub> and enzymes  
8 responsible for SO<sub>2</sub> generation has been reported in tissues of the rat ([Luo et al., 2011](#)).  
9 Chemical transformations between bisulfite/sulfite/SO<sub>2</sub> and the gasotransmitter H<sub>2</sub>S also  
10 occur. H<sub>2</sub>S is similarly derived from sulfur-containing amino acids. Evidence has  
11 accumulated that endogenous H<sub>2</sub>S acts as a biological signaling molecule ([Filipovic et al.,  
12 2012](#)) and plays important roles in the cardiovascular ([Coletta et al., 2012](#)) and other  
13 systems. Recent studies suggest that endogenous SO<sub>2</sub> may also be a gasotransmitter ([Liu  
14 et al., 2010](#)). Like the other gasotransmitters NO and CO, SO<sub>2</sub> at physiologic levels may  
15 activate guanylyl cyclase to generate cyclic guanosine monophosphate (cGMP), which  
16 mediates effects through cGMP-dependent kinases ([Li et al., 2009](#)). However, SO<sub>2</sub> may  
17 also act through non-cGMP-dependent pathways. Experimental studies in animal models  
18 and in vitro systems demonstrate a myriad of effects of exogenous SO<sub>2</sub> on the  
19 cardiovascular system, including vasorelaxation, negative inotropic effects on cardiac  
20 function, anti-inflammatory and antioxidant effects in pulmonary hypertension, and  
21 decreased blood pressure (BP) and vascular remodeling in hypertensive animals, and  
22 cytoprotective([Liu et al., 2010](#)). Effects were in many cases concentration dependent.  
23 In vivo studies generally were conducted using 5 ppm and higher concentrations of SO<sub>2</sub>  
24 (or sulfite/bisulfite) ([Liu et al., 2010](#)). In summary, endogenous SO<sub>2</sub> is a newly  
25 recognized gasotransmitter that may play important roles in cardiovascular and other  
26 systems.

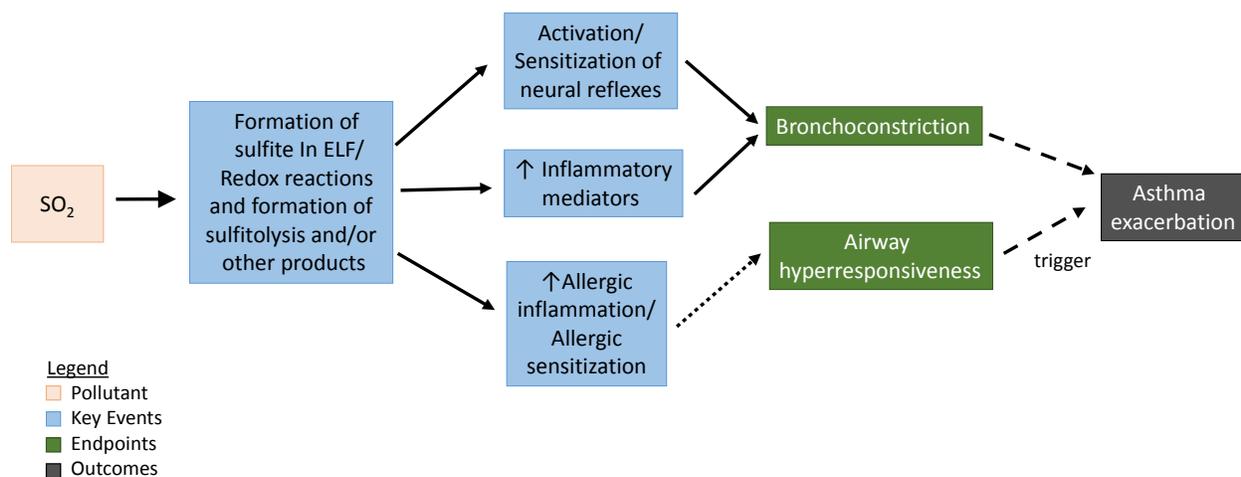
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#### 4.3.6 Mode of Action Framework

27 This section describes the key events, endpoints, and outcomes that comprise the modes  
28 of action of inhaled SO<sub>2</sub>. Here, key events are subclinical effects, endpoints are effects  
29 that are generally measured in the clinic, and outcomes are health effects at the organism  
30 level. Biological pathways discussed above that may contribute to health effects resulting  
31 from short-term and long-term exposures to SO<sub>2</sub> ([Chapter 5](#)) are summarized as a part of

1 this analysis. These proposed modes of action are based on the available evidence and  
2 may not reflect all of the pathophysiology underlying health effects.

3 [Figure 4-2](#) depicts the mode of action for respiratory effects due to short-term exposure  
4 to SO<sub>2</sub>.



ELF = epithelial lining fluid; redox = reduction-oxidation; SO<sub>2</sub> = sulfur dioxide.

Note: Pathways indicated by a dotted line are those for which evidence is limited to findings from experimental animal studies, while evidence from controlled human exposure studies is available for pathways indicated by a solid line. Dashed lines indicate proposed links to the outcomes of asthma exacerbation. Key events are subclinical effects, endpoints are effects that are generally measured in the clinic, and outcomes are health effects at the organism level.

Source: National Center for Environmental Assessment.

**Figure 4-2 Summary of evidence for the mode of action linking short-term exposure to sulfur dioxide and respiratory effects.**

5 A characteristic feature of individuals with asthma is an increased propensity of their  
6 airways to narrow in response to bronchoconstrictive stimuli relative to nonatopic  
7 individuals without asthma. This characteristic is termed airway hyperresponsiveness  
8 (AHR). Different kinds of stimuli can elicit bronchoconstriction, but in general they act  
9 on airway smooth muscle receptors (direct stimuli, e.g., methacholine) or act via the  
10 release of inflammatory mediators (indirect stimuli, e.g., allergens) ([O'Byrne et al.,  
11 2009](#)). SO<sub>2</sub> is a nonspecific bronchoconstrictive stimuli that is not easily classified as a  
12 direct or indirect stimuli, as was discussed in [Section 4.3.1](#).

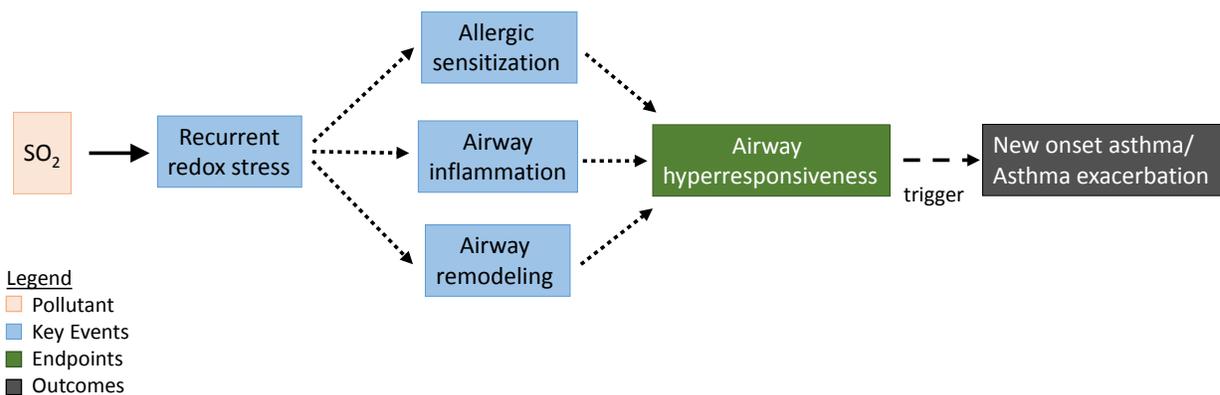
1 Because inhalation of SO<sub>2</sub> results in chemical reactions in the ELF, the initiating event in  
2 the development of respiratory effects is the formation of sulfite, sulfitolysis products,  
3 and/or other products. Both sulfite and S-sulfonates have been measured in tracheal and  
4 bronchial tissue as well as in tracheal washings of experimental animals exposed to SO<sub>2</sub>.  
5 Reactive products formed as a result of SO<sub>2</sub> inhalation are responsible for a variety of  
6 downstream key events, which may include activation or sensitization of sensory nerves  
7 in the respiratory tract resulting in neural reflex responses, release of inflammatory  
8 mediators, and modulation of allergic inflammation or sensitization. These key events  
9 may collectively lead to several endpoints, including bronchoconstriction and AHR.  
10 Bronchoconstriction is characteristic of an asthma attack. However, individuals who are  
11 not asthmatic may also experience bronchoconstriction in response to SO<sub>2</sub> inhalation;  
12 generally, this occurs at higher concentrations than in an individual who is asthmatic  
13 (>1 ppm). Additionally, SO<sub>2</sub> exposure may increase airway responsiveness to subsequent  
14 exposures of other stimuli such as allergens or methacholine. These pathways may be  
15 linked to the epidemiologic outcome of asthma exacerbation.

16 The strongest evidence for this mode of action comes from controlled human exposure  
17 studies. SO<sub>2</sub> exposure resulted in increased airway resistance due to bronchoconstriction  
18 in healthy adults and in adults with asthma. In adults without asthma, this response  
19 occurred primarily as a result of activation of sensory nerves in the respiratory tract  
20 resulting in neural reflex responses mediated by cholinergic parasympathetic pathways  
21 involving the vagus nerve. However, in adults with asthma, evidence indicates that the  
22 response is only partially due to vagal pathways and that inflammatory mediators such as  
23 histamine and leukotrienes also play an important role. Activation of sensory nerves in  
24 the respiratory tract, which result in neural reflex responses, has been studied in humans  
25 exposed to occupationally relevant concentrations of SO<sub>2</sub> (up to 2 ppm). Responses  
26 measured in these studies include increased respiratory rate and decreased tidal volume,  
27 which involve the vagus nerve, and increased nasal air-flow resistance, which involves  
28 the trigeminal nerve. These responses are not a part of the mode of action described here,  
29 but are mentioned because they are known irritant effects of SO<sub>2</sub>. Studies in experimental  
30 animals demonstrate that SO<sub>2</sub> exposure activates reflexes that are mediated by cholinergic  
31 parasympathetic pathways involving the vagus nerve. However, noncholinergic  
32 mechanisms may also play a role because some studies demonstrate that a local axon  
33 reflex resulting in C-fiber secretion of neuropeptides (i.e., neurogenic inflammation) is  
34 responsible for the effects of SO<sub>2</sub>.

35 Evidence demonstrates that SO<sub>2</sub> exposure modulates allergic inflammatory responses.  
36 Enhancement of allergic inflammation was observed in adults with asthma who were  
37 exposed for 10 minutes to 0.75 ppm SO<sub>2</sub> (i.e., leukotriene-mediated increases in numbers  
38 of sputum eosinophils). In an animal model of allergic airway disease, repeated exposure

to 2 ppm SO<sub>2</sub> led to an enhanced inflammatory response, as measured by numbers of BALF inflammatory cells, levels of BALF cytokines, histopathology, activation of the NFκB pathway, and upregulation of intracellular adhesion molecules, mucin, and cytokines, in lung tissue. Furthermore, repeated exposure to SO<sub>2</sub> enhanced Th2 polarization (or group 2 innate lymphoid cell-mediated Type 2 immunity), numbers of BALF eosinophils, and serum IgE levels in this same model. Other studies demonstrated that repeated exposure of naive animals to SO<sub>2</sub> (as low as 0.1 ppm) over several days promoted allergic sensitization (allergen-specific IgG levels) and enhanced allergen-induced bronchial obstruction (an indicator of AHR) and inflammation (airway fluid eosinophils and histopathology) when animals were subsequently sensitized and challenged with an allergen. Similarly, intranasal treatment with sulfite both aggravated allergic sensitization (Th2 cytokines and allergen specific IgE levels) and exacerbated allergic inflammatory responses (histopathology) in animals subsequently sensitized and challenged with allergen. These changes in allergic inflammation may enhance AHR and promote bronchoconstriction in response to a trigger. Thus, allergic inflammation and AHR may also link short-term SO<sub>2</sub> exposure to asthma exacerbation.

[Figure 4-3](#) depicts the mode of action for respiratory effects due to long-term exposure to SO<sub>2</sub>.



redox = reduction-oxidation; SO<sub>2</sub> = sulfur dioxide.

Note: Pathways indicated by a dotted line are those for which evidence is limited to findings from experimental animal studies, while evidence from controlled human exposure studies is available for pathways indicated by a solid line. Dashed lines indicate proposed links to the outcomes of new onset asthma/asthma exacerbation. Key events are subclinical effects, endpoints are effects that are generally measured in the clinic, and outcomes are health effects at the organism level.

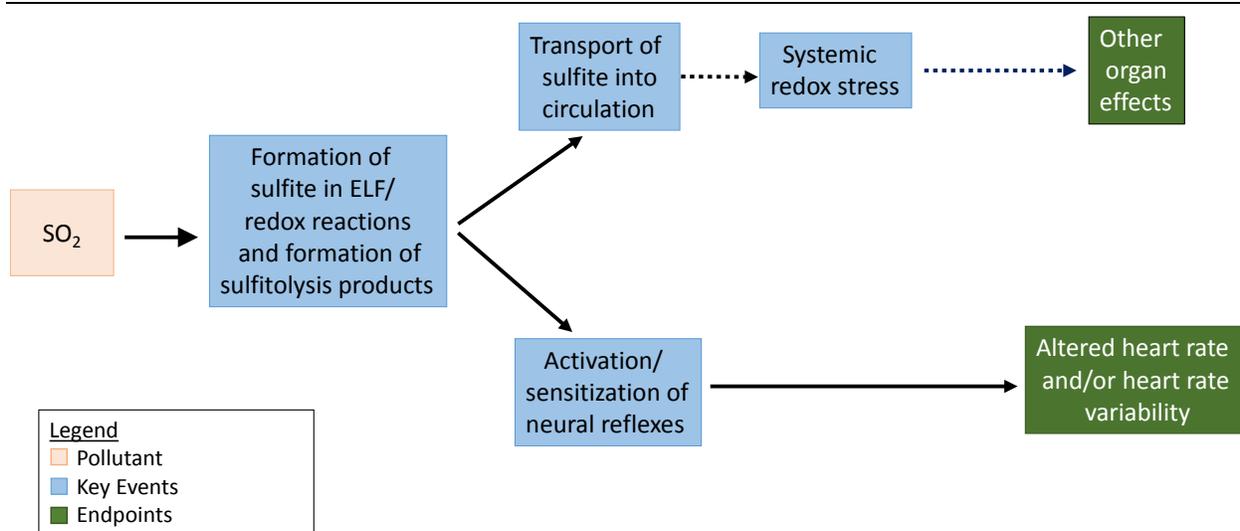
Source: National Center for Environmental Assessment.

**Figure 4-3 Summary of evidence for the mode of action linking long-term exposure to sulfur dioxide and respiratory effects.**

1 The initiating event in the development of respiratory effects due to long-term SO<sub>2</sub>  
2 exposure is the recurrent or prolonged redox stress due to the formation of reactive  
3 products in the ELF. This is the driving factor for the potential downstream key events,  
4 airway inflammation, allergic sensitization, and airway remodeling that may lead to the  
5 endpoint AHR. Airway inflammation, airway remodeling, and AHR are characteristic of  
6 asthma. The resulting outcome may be new asthma onset, which presents as an asthma  
7 exacerbation that leads to physician-diagnosed asthma.

8 Evidence for this mode of action comes from studies in both naive and allergic  
9 experimental animals. Exposure of naive newborn animals to SO<sub>2</sub> (2 ppm) for several  
10 weeks resulted in hyperemia in lung parenchyma, inflammation in the airways, and Th2  
11 polarization (or group 2 innate lymphoid cell-mediated Type 2 immunity), the latter of  
12 which is a key step involved in allergic sensitization. Support is also provided by  
13 short-term studies in naive animals in which repeated exposure to SO<sub>2</sub> (2 ppm) over  
14 several days led to pathologic changes, including inflammatory cell influx. Th2  
15 polarization (or other Type 2 immune responses) and airway inflammation may set the  
16 stage for AHR. In addition, short-term SO<sub>2</sub> exposure (0.1 ppm) promoted allergic  
17 sensitization and enhanced other allergic inflammatory responses and AHR when animals  
18 were subsequently sensitized with an allergen. Further, repeated exposure of allergic  
19 newborn animals to SO<sub>2</sub> (2 ppm) over several weeks enhanced allergic responses and  
20 resulted in morphologic responses indicative of airway remodeling and in AHR. Thus,  
21 repeated exposure to SO<sub>2</sub> in naive animals may lead to the development of allergic  
22 airway disease, which shares many features with asthma. Furthermore, repeated exposure  
23 of allergic animals to SO<sub>2</sub> may promote airway remodeling and AHR. The development  
24 of AHR may link long-term exposure to SO<sub>2</sub> to the epidemiologic outcome of new onset  
25 asthma.

26 [Figure 4-4](#) depicts the mode of action for extrapulmonary effects due to short-term or  
27 long-term exposure to SO<sub>2</sub>.



ELF = epithelial lining fluid; redox = reduction-oxidation; SO<sub>2</sub> = sulfur dioxide.

Note: Pathways indicated by a dotted line are those for which evidence is limited to findings from experimental animal studies, while evidence from controlled human exposure studies is available for pathways indicated by a solid line. No links to outcomes are proposed. Key events are subclinical effects and endpoints are effects that are generally measured in the clinic.

Source: National Center for Environmental Assessment.

**Figure 4-4 Summary of evidence for the mode of action linking exposure to sulfur dioxide and extrapulmonary effects.**

1 Although SO<sub>2</sub> inhalation results in extrapulmonary effects, there is uncertainty regarding  
 2 the mode of action underlying these responses. Evidence from controlled human  
 3 exposure studies (0.2 ppm, 1 hour) points to SO<sub>2</sub> exposure-induced  
 4 activation/sensitization of neural reflex responses as a key event leading to the endpoint  
 5 of altered heart rate or heart rate variability. Evidence also points to transport of sulfite  
 6 into the circulation. Controlled human exposure and experimental animal studies have  
 7 demonstrated the presence of sulfite and S-sulfonates in plasma, liver, or brain following  
 8 SO<sub>2</sub> exposure. This occurred at a concentration as low as 0.3 ppm SO<sub>2</sub> in humans  
 9 exposed for up to 120 hours. Sulfite is highly reactive and may be responsible for redox  
 10 stress (possibly through auto-oxidation or peroxidase-mediated reactions to produce free  
 11 radicals) in the circulation and extrapulmonary tissues. However, this is likely to occur  
 12 only at very high concentrations or during prolonged exposures because circulating  
 13 sulfite is efficiently metabolized to sulfate in a reaction catalyzed by hepatic sulfite  
 14 oxidase.

15 Besides inhalation of SO<sub>2</sub>, the ingestion of food additives and the catabolism of  
 16 sulfur-containing amino acids also contribute to levels of sulfite in the body  
 17 ([Section 4.3.5](#)). In humans, the amount of sulfite derived from inhaled SO<sub>2</sub> (assuming

1 100% absorption, 75 ppb and 24-hour exposure) is comparable to that derived from the  
2 expected daily consumption of food additives. The amount of sulfite derived from the  
3 breakdown of endogenous sulfur-containing amino acids is far greater. Sulfite derived  
4 from inhaled SO<sub>2</sub>, unlike that derived from food additives, enters the circulation without  
5 first passing through the liver, which efficiently metabolizes sulfite to sulfate. Thus, the  
6 potential exists for inhaled SO<sub>2</sub> to have a greater impact on circulating sulfite levels than  
7 sulfite derived from food additives. While the amount of sulfite derived from the  
8 breakdown of endogenous sulfur-containing amino acids is far greater, its metabolic  
9 pathways and impact on circulating sulfite levels are not clear. Thus, the potential exists  
10 for prolonged exposure to high concentrations of inhaled ambient SO<sub>2</sub> to result in  
11 extrapulmonary effects due to circulating sulfite.

12 In summary, this section provides a foundation for understanding how exposure to the  
13 gaseous air pollutant SO<sub>2</sub> may lead to health effects. This encompasses the many steps  
14 between uptake into the respiratory tract and biological responses that ensue.

15 The reaction of inhaled SO<sub>2</sub> with components of the ELF initiates a cascade of events  
16 occurring at the cellular, organ, and organism level. Biological responses discussed in  
17 this section were organized in a mode of action framework that serves as a guide to  
18 interpreting health effects evidence presented in [Chapter 5](#).

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# Chapter 5 Integrated Health Effects of Exposure to Sulfur Oxides

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## 5.1 Introduction

### 5.1.1 Scope of the Chapter

1 While the term “sulfur oxides” refers to multiple gaseous oxidized sulfur compounds  
2 (e.g., SO<sub>2</sub>, SO<sub>3</sub>), this chapter focuses on evaluating the health effects associated with  
3 exposure to SO<sub>2</sub>. As discussed in [Section 2.1](#), the presence of sulfur oxide species other  
4 than SO<sub>2</sub> in the atmosphere has not been demonstrated, and the available health evidence  
5 examines SO<sub>2</sub>. The health effects of particulate sulfur-containing compounds  
6 (e.g., sulfate) are considered in the current review of the NAAQS for PM and were  
7 evaluated in the 2009 ISA for PM ([U.S. EPA, 2009a](#)) (see [Section 1.1](#)).

8 This chapter evaluates the epidemiologic, controlled human exposure, and animal  
9 toxicological evidence of SO<sub>2</sub>-related respiratory ([Section 5.2](#)), cardiovascular  
10 ([Section 5.3](#)), reproductive and developmental ([Section 5.4](#)), total mortality ([Section 5.5](#)),  
11 and cancer ([Section 5.6](#)) effects. Evidence from epidemiologic and animal toxicological  
12 studies of other SO<sub>2</sub>-related effects are included in Supplemental Tables 5S-1 ([U.S. EPA,](#)  
13 [2016l](#)) and 5S-2 ([U.S. EPA, 2015e](#)). Sections for respiratory, cardiovascular, and  
14 mortality effects are divided into subsections describing the evidence for short-  
15 (i.e., 1 month or less) and long-term (i.e., more than 1 month) exposures. The evidence  
16 for reproductive and developmental and cancer effects is considered within one long-term  
17 exposure section, with time-windows of exposure addressed as appropriate. Causal  
18 conclusions are determined for both short- and long-term exposures by evaluating the  
19 evidence for each health effect and exposure category independently, using the causal  
20 framework [described in the [Preamble](#) to the ISAs ([U.S. EPA, 2015b](#))].

21 Each chapter section begins with a summary of the conclusions from the 2008 ISA for  
22 Sulfur Oxides, followed by an evaluation of recent studies (i.e., those published since the  
23 completion of the 2008 ISA for Sulfur Oxides) that build upon evidence from previous  
24 reviews. Within each of the sections focusing on morbidity outcomes (e.g., respiratory  
25 morbidity, cardiovascular morbidity), the evidence is organized into more refined  
26 outcome groupings (e.g., asthma exacerbation, myocardial infarction) that comprise a  
27 continuum of subclinical to clinical effects. The discussion of specific health outcomes is  
28 then organized by scientific discipline (i.e., epidemiology, controlled human exposure,  
29 toxicology). This structure helps in evaluating coherence and biological plausibility of the

1 effects observed in association with exposure to SO<sub>2</sub> and promotes the transparent  
2 characterization of the weight of evidence in drawing the causal conclusions found at the  
3 end of each section (e.g., see [Section 5.2.1.9](#)). Causal determinations for total mortality  
4 are based on the evidence for nonaccidental causes of mortality and informed by the  
5 extent to which evidence for the spectrum of cardiovascular and respiratory effects  
6 provides biological plausibility for SO<sub>2</sub>-related total mortality. Findings for  
7 cause-specific mortality inform multiple causal determinations. For example, studies of  
8 respiratory and cardiovascular mortality are used to assess the continuum of effects and  
9 inform the causal determinations for respiratory and cardiovascular morbidity. As  
10 described in [Section 1.2](#), judgments regarding causality are made by evaluating the  
11 evidence over the full range of exposures in animal toxicological, controlled human  
12 exposure, and epidemiologic studies defined in this ISA to be relevant to ambient  
13 exposure (i.e., ≤2,000 ppb).

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## 5.1.2 Evidence Evaluation and Integration to Form Causal Determinations

### 5.1.2.1 Evaluation of Individual Studies

14 As described in the [Preamble](#) to the ISAs ([U.S. EPA, 2015b](#)) (Section 5.a), causal  
15 determinations were informed by integrating evidence across scientific disciplines  
16 (e.g., exposure, animal toxicology, epidemiology) and related outcomes, as well as by  
17 judgments on the strength of inference from individual studies. These judgments were  
18 based on evaluating strengths, as well as various sources of bias and uncertainty related  
19 to study design, study population characterization, exposure assessment, outcome  
20 assessment, consideration of confounding, statistical methodology, and other factors.  
21 This evaluation was applied to controlled human exposure, animal toxicological, and  
22 epidemiologic studies included in this ISA, comprising studies from previous  
23 assessments as well as those studies published since the 2008 ISA for Sulfur Oxides.  
24 Aspects comprising the major considerations in the individual study evaluation are  
25 described in the [Annex for Chapter 5](#) of this ISA and are consistent with current best  
26 practices employed in other approaches for reporting or evaluating health science data.<sup>1</sup>  
27 Additionally, these aspects are compatible with published U.S. EPA guidelines related to

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<sup>1</sup> For example, National Toxicology Program Office of Health Assessment and Translation approach ([Rooney et al., 2014](#)), Integrated Risk Information System Preamble ([U.S. EPA, 2013e](#)), ToxRTTool ([Klimisch et al., 1997](#)), STROBE guidelines ([von Elm et al., 2007](#)), Animals in Research: Reporting In Vivo Experiments guidelines ([Kilkenny et al., 2010](#)).

1 cancer, neurotoxicity, reproductive toxicity, and developmental toxicity ([U.S. EPA,](#)  
2 [2005a,](#) [1998,](#) [1996a,](#) [1991](#)).

3 The aspects described in the [Annex for Chapter 5](#) were used as a guideline rather than a  
4 checklist or criteria to define the quality of a study. The presence or absence of a  
5 particular feature did not necessarily define a less informative study or preclude a study  
6 from consideration in the ISA. Further, these aspects were not criteria for a particular  
7 determination of causality in the five-level hierarchy. As described in the [Preamble](#) to the  
8 ISAs ([U.S. EPA, 2015b](#)), causal determinations were based on judgments of the overall  
9 strengths and limitations of the collective body of available studies and the coherence of  
10 evidence across scientific disciplines and related outcomes. Where possible,  
11 considerations such as exposure assessment and confounding (i.e., bias due to a  
12 relationship with the outcome and correlation with exposures to SO<sub>2</sub>), were framed to be  
13 specific to sulfur oxides. Thus, judgments of the strength of inference from a study can  
14 vary depending on the specific pollutant being assessed.

15 Evaluation of the extent to which the science informs the understanding of uncertainties  
16 related to the independent effect of sulfur oxides is of particular relevance in the review  
17 process. Because examination of copollutant confounding is based largely on copollutant  
18 models, the inherent limitations of such models are considered in drawing inferences  
19 about independent associations for SO<sub>2</sub>. For example, collinearity potentially affects  
20 model performance when highly correlated pollutants are modeled simultaneously, and  
21 inference can also be limited if differences in the spatial distributions of SO<sub>2</sub> and the  
22 copollutant do not satisfy the assumptions of equal measurement error or constant  
23 correlations for SO<sub>2</sub> and the copollutant ([Section 3.4.3](#)). Correlations of short-term SO<sub>2</sub>  
24 concentrations with other NAAQS pollutants are generally low to moderate, but may  
25 vary by location ([Section 3.5](#)). Thus, the interpretation of copollutant model results  
26 reported in epidemiologic studies depends on a variety of factors, which are discussed  
27 throughout the chapter, generally in the context of a specific study and/or health  
28 endpoint.

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### 5.1.2.2 Integration of Scientific Evidence

29 Causal determinations are made by considering the strength of inference from individual  
30 studies and on integrating multiple lines of evidence. As detailed in the [Preamble](#) to the  
31 ISAs ([U.S. EPA, 2015b](#)), evidence integration involved evaluating the consistency and  
32 coherence of findings within and across disciplines, as well as within and across related  
33 outcomes. Cross-disciplinary integration often addresses uncertainties within a particular  
34 discipline. Controlled human exposure and animal toxicological studies can provide

1 direct evidence for health effects related to SO<sub>2</sub> exposures. Coherence of experimental  
2 evidence with epidemiologic findings can advance our understanding about whether  
3 epidemiologic associations with health outcomes plausibly reflect an independent effect  
4 of ambient SO<sub>2</sub> exposure. For example, the coherence of effects observed in  
5 epidemiologic studies with human clinical studies demonstrating direct effects of SO<sub>2</sub> on  
6 lung function ([Section 5.2.1.2](#)), is drawn upon to reduce uncertainties in epidemiologic  
7 studies. Thus, the integration of evidence across a spectrum of related outcomes and  
8 across disciplines was used to clarify the understanding of uncertainties for a particular  
9 outcome or discipline due to chance, publication bias, selection bias, and confounding by  
10 copollutant exposures or other factors.

11 The integration of the scientific evidence is facilitated through the presentation of data  
12 from multiple studies within and across disciplines. To increase comparability of results  
13 across epidemiologic studies, the ISA presents effect estimates for associations with  
14 health outcomes scaled to the same increment of SO<sub>2</sub> concentration.<sup>1</sup> The increments for  
15 standardization vary by averaging time. For 24-h avg, effect estimates were scaled to a  
16 10-ppb increase for SO<sub>2</sub>. For 1-h daily max, effect estimates were scaled to a 40-ppb  
17 increase for SO<sub>2</sub>. Effect estimates for long-term exposures to SO<sub>2</sub> (i.e., annual or  
18 multiyear averages) were scaled to a 5-ppb increase. Units of dose in toxicological  
19 studies are typically presented in ppm; however, when toxicological data are summarized  
20 in the context of epidemiologic findings, units are converted to ppb for comparability.

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### 5.1.3 Summary

21 The subsequent sections review and synthesize the evidence of SO<sub>2</sub>-related health effects  
22 from multiple disciplines (e.g., exposure, animal toxicology, and epidemiology).  
23 Information on dosimetry and modes of action ([Chapter 4](#)) provides the foundation for  
24 understanding how exposure to inhaled SO<sub>2</sub> may lead to health effects, providing  
25 biological plausibility for effects observed in the health studies. The science related to  
26 sources, emissions, and atmospheric concentrations ([Chapter 2](#)), as well as the potential  
27 for human exposure to ambient sulfur oxides ([Chapter 3](#)), also informs the interpretation  
28 of the health effects evidence. Integrative “Summary and Causal Determination” sections  
29 for short- and long-term exposures follow the discussion of the evidence for each health  
30 outcome category. These integrative summary sections include assessments of the  
31 strength of inference from studies comprising the evidence base and integrate multiple

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<sup>1</sup> Versus reported effect estimates that are scaled to variable changes in concentration such as IQR for the study period or an arbitrary unit.

1 lines of evidence to characterize relationships between sulfur oxides and various health  
2 effects.

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## 5.2 Respiratory Effects

### 5.2.1 Short-Term Exposure

#### 5.2.1.1 Introduction

3 The 2008 ISA for Sulfur Oxides ([U.S. EPA, 2008d](#)) concluded that there is a causal  
4 relationship between respiratory effects and short-term exposure to SO<sub>2</sub>. The rationale for  
5 this causal determination was heavily based on evidence from multiple, high-quality  
6 controlled human exposure studies demonstrating decreased lung function and increased  
7 respiratory symptoms following SO<sub>2</sub> exposures of 5–10 minutes in exercising adults with  
8 asthma.

9 There was also epidemiologic evidence indicating associations between short-term  
10 increases in ambient SO<sub>2</sub> concentration and respiratory effects in populations living in  
11 locations with ambient concentrations below the previous 24-h avg NAAQS level of  
12 140 ppb. Evidence was strongest for increased respiratory symptoms and  
13 respiratory-related hospital admissions and ED visits, especially in children. Due to  
14 inadequate examination, a key uncertainty was potential confounding by copollutants,  
15 particularly PM. However, controlled human exposure studies of individuals with asthma  
16 clearly show that respiratory effects are caused by 5–10 minute SO<sub>2</sub> exposures.

17 In contrast with asthma exacerbation, there was little information to assess whether  
18 short-term SO<sub>2</sub> exposure exacerbated allergy or chronic obstructive pulmonary disease  
19 (COPD) or increased risk of respiratory infection. However, there was some experimental  
20 evidence for respiratory effects in healthy humans (>1,000 ppb) and animal models  
21 (100 ppb) exposed to SO<sub>2</sub>. Epidemiologic evidence in healthy populations was limited  
22 and inconsistent.

23 As described in the following sections, evidence from recent studies is generally  
24 consistent with that in the 2008 ISA and 1982 AQCD for Sulfur Oxides ([U.S. EPA,](#)  
25 [2008d, 1982a](#)). To clearly characterize differences in the weight of evidence and the  
26 extent of coherence among disciplines and related outcomes, the sections are organized  
27 by respiratory outcome group [asthma exacerbation ([Section 5.2.1.2](#)), allergy  
28 exacerbation ([Section 5.2.1.3](#)), COPD exacerbation ([Section 5.2.1.4](#)), respiratory

1 infection ([Section 5.2.1.5](#)), aggregated respiratory conditions ([Section 5.2.1.6](#)),  
2 respiratory effects in the general population and healthy individuals ([Section 5.2.1.7](#)), and  
3 respiratory mortality ([Section 5.2.1.8](#))]. Epidemiologic studies comprise most of the  
4 recent evidence base, and previous controlled human exposure and animal toxicological  
5 studies form the basis for characterizing and integrating evidence across disciplines.  
6 Recent epidemiologic evidence supports associations between ambient SO<sub>2</sub>  
7 concentrations and asthma-related symptoms, hospital admissions, and ED visits, but  
8 exposure measurement error and copollutant confounding remain uncertain. Recent  
9 epidemiologic studies add information on allergy and COPD exacerbation, respiratory  
10 infection, and respiratory effects in healthy populations, but relationships of these  
11 outcomes with short-term SO<sub>2</sub> exposure still are unclear because of inconsistent evidence  
12 or limited coherence among disciplines.

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### 5.2.1.2 Asthma Exacerbation

13 Asthma is a chronic lung disease with a broad range of characteristics and disease  
14 severity. Its main features are airway obstruction that is generally reversible, airway  
15 inflammation, and increased airway responsiveness. SO<sub>2</sub> exposure has been demonstrated  
16 to induce clinical features of asthma exacerbation, including decreased lung function  
17 (e.g., decreased forced expiratory volume in 1 sec [FEV<sub>1</sub>] or increased specific airway  
18 resistance [sRaw]), and increased symptoms (e.g., wheezing, cough, shortness of breath),  
19 as well as some subclinical effects such as inflammation. This section describes evidence  
20 for SO<sub>2</sub>-associated lung function changes and respiratory symptoms in people with  
21 asthma, hospital admissions and emergency department visits for asthma and related  
22 respiratory conditions, and subclinical effects underlying asthma such as pulmonary  
23 inflammation and oxidative stress.

24 As detailed in the previous 2008 ISA for Sulfur Oxides ([U.S. EPA, 2008d](#)), controlled  
25 human exposure studies reported increased respiratory symptoms and decreased lung  
26 function after short-term exposures of 5–10 minutes to 0.2–0.6 ppm SO<sub>2</sub> during exercise  
27 or eucapnic hyperpnea (a rapid and deep breathing technique through a mouthpiece that  
28 prevents an imbalance of CO<sub>2</sub> due to hyperventilation) in adults and adolescents  
29 (12–18 years) with asthma. In contrast, the majority of the controlled human exposure  
30 studies evaluating the respiratory effects of SO<sub>2</sub> in healthy adults demonstrated increased  
31 airway resistance and decreased FEV<sub>1</sub> following exposures to concentrations  
32 >1.0–5.0 ppm ([Section 5.2.1.7](#)). While children may be especially susceptible to the  
33 respiratory effects of SO<sub>2</sub> for dosimetric reasons ([Section 4.2.2](#)), there are no available  
34 controlled human exposure studies in children under 12, partly due to ethical concerns.

1 Coherent with controlled human exposure findings, epidemiologic evidence indicated  
2 that short-term increases in ambient SO<sub>2</sub> concentration were associated with  
3 asthma-related hospital admissions, ED visits, and symptoms. The strongest evidence  
4 was for children, which is consistent with their greater oral breathing and higher  
5 ventilation rates relative to their size than adults and the consequent potential for them  
6 receiving a higher SO<sub>2</sub> dose to the tracheobronchial airways of the lower respiratory tract  
7 ([Section 4.1.2](#), [Section 4.2.2](#)). Epidemiologic evidence for SO<sub>2</sub>-related lung function  
8 decrements was inconsistent among both children and adults with asthma. A key  
9 uncertainty in the epidemiologic evidence was whether findings reflected an independent  
10 association for SO<sub>2</sub> because the studies assigned exposure from central site monitors  
11 (i.e., those used to determine attainment with the NAAQS, [Section 3.3.1.1](#)). Also, few of  
12 the studies examined potential confounding by PM<sub>2.5</sub> or other copollutants.

13 The 2008 SO<sub>x</sub> ISA ([U.S. EPA, 2008d](#)) also provided limited evidence for a relationship  
14 between SO<sub>2</sub> concentrations and allergic responses and inflammation in individuals with  
15 asthma. Children and adults with atopy plus asthma were found to be at greater risk of  
16 SO<sub>2</sub>-associated respiratory effects such as respiratory symptoms and lung function  
17 decrements. In addition, animal toxicological studies demonstrated that repeated  
18 exposure to SO<sub>2</sub> enhanced inflammation and allergic responses in animal models of  
19 allergic airway disease.

20 Together recent studies and the evidence presented in the 2008 ISA for Sulfur Oxides  
21 link short-term SO<sub>2</sub> exposure to asthma exacerbation. Most recent studies are  
22 epidemiologic, which continue to show ambient SO<sub>2</sub>-associated increases in asthma  
23 symptoms, hospital admissions, and ED visits among children. However, exposure  
24 measurement error and copollutant confounding remain uncertainties in the  
25 epidemiologic evidence. A few recent animal toxicological studies add support for  
26 SO<sub>2</sub>-induced allergic inflammation. While there are no recent controlled human exposure  
27 studies in individuals with asthma (see [Section 5.2.1.7](#) for recent studies in healthy  
28 individuals), previous evidence from controlled human exposure studies provides support  
29 for an independent effect of SO<sub>2</sub> exposure on asthma exacerbation.

### **Lung Function Changes in Populations with Asthma**

30 The 2008 SO<sub>x</sub> ISA ([U.S. EPA, 2008d](#)) reported strong evidence for the effects of SO<sub>2</sub>  
31 exposure on decrements in lung function in controlled human exposure studies in adults  
32 with asthma under increased ventilation conditions. Controlled human exposure studies,  
33 none of which are new since the 2008 SO<sub>x</sub> ISA ([U.S. EPA, 2008d](#)), also demonstrated a  
34 subset of individuals (i.e., responders) within this population who are particularly  
35 sensitive to the effects of SO<sub>2</sub> exposure. This finding is most evident in the recent

1 analysis of several published studies by [Johns et al. \(2010\)](#). Some additional data from  
2 the previous studies has also become available since the 2008 SO<sub>x</sub> ISA and is  
3 summarized in [Table 5-2](#), [Table 5-3](#), and [Table 5-4](#). Recent epidemiologic findings are  
4 inconsistent overall. A few recent epidemiologic studies add evidence for SO<sub>2</sub> measured  
5 at children's school or in copollutant models with PM, NO<sub>2</sub>, or O<sub>3</sub>, albeit with pollutants  
6 measured at central site monitors. There is a paucity of evidence from animal  
7 toxicological studies. While some animal toxicological studies of short-term exposure to  
8 SO<sub>2</sub> have examined changes in lung function, these experiments were conducted in naive  
9 animals rather than in models of allergic airway disease, which share many phenotypic  
10 features with asthma in humans.

### ***Controlled Human Exposure Studies***

11 Bronchoconstriction in individuals with asthma is the most sensitive indicator of  
12 SO<sub>2</sub>-induced lung function effects. A characteristic feature of individuals with asthma is  
13 an increased propensity of their airways to narrow in response to bronchoconstrictive  
14 stimuli relative to nonatopic individuals without asthma. This characteristic is termed  
15 airway hyperresponsiveness (AHR). Different kinds of stimuli can elicit  
16 bronchoconstriction, but in general, they act on airway smooth muscle receptors (direct  
17 stimuli, e.g., methacholine) or act via the release of inflammatory mediators (indirect  
18 stimuli, e.g., allergens) ([O'Byrne et al., 2009](#)). SO<sub>2</sub> is a nonspecific bronchoconstrictive  
19 stimulus that is not easily classified as a direct or indirect, as discussed in [Section 4.3.1](#).

20 Bronchoconstriction, evidenced by decrements in lung function, is observed in controlled  
21 human exposure studies after approximately 5–10-minute exposures and can occur at  
22 SO<sub>2</sub> concentrations as low as 0.2 ppm in exercising individuals with asthma; more  
23 consistent decrements are seen at concentrations of 0.4 ppm and greater ([U.S. EPA,  
24 2008d](#)). In contrast, healthy adults are relatively insensitive to the respiratory effects of  
25 SO<sub>2</sub> below 1 ppm ([Section 5.2.1.7](#)). In all individuals, bronchoconstriction is mainly seen  
26 during conditions of increased ventilation rates, such as exercise or eucapnic hyperpnea.  
27 This effect is likely due to a shift from nasal breathing to oral/nasal breathing, which  
28 increases the concentration of SO<sub>2</sub> reaching the airways ([Section 4.2.2](#)). The majority of  
29 controlled human exposures to SO<sub>2</sub> were conducted with adult volunteers, although a  
30 limited number were also conducted with adolescents (12–18 years). Characteristics of  
31 controlled exposure studies in individuals with asthma are summarized in [Table 5-1](#).  
32 Controlled exposure studies individuals without asthma are discussed in [Section 5.2.1.7](#).

**Table 5-1 Study-specific details from controlled human exposure studies of individuals with asthma.**

<b>Study</b>	<b>Disease Status; n; Sex; (Age<sup>a</sup>)</b>	<b>Exposure Details (Concentration; Duration)</b>	<b>Outcomes Examined</b>
<a href="#">Balmes et al. (1987)</a>	Asthma; n = 8; 6 M, 2 F (23–39 yr)	0, 0.5, or 1 ppm SO <sub>2</sub> for 1, 3, and 5 min during eucapnic hyperpnea (60 L/min)	sRaw
<a href="#">Bethel et al. (1983)</a>	Asthma; n = 10; 8 M, 2 F (22–36 yr)	0 or 0.5 ppm SO <sub>2</sub> for 5 min with exercise 750 kg m/min (125 watts)	sRaw
<a href="#">Bethel et al. (1984)</a>	Asthma; n = 7; 5 M, 2 F (24–36 yr)	0.5 ppm SO <sub>2</sub> for 3 min with room temperature and cold air	sRaw
<a href="#">Bethel et al. (1985)</a>	Asthma; n = 19; 16 M, 3 F (22–46 yr)	0 or 0.25 ppm SO <sub>2</sub> for 5 min during heavy exercise [bicycle, 750 (n = 19) or 1,000 (n = 9) kg m/min; 125 or 167 watts, respectively]	sRaw
<a href="#">Gong et al. (1995)</a>	Asthma; n = 14; 12 M, 2 F (18–50 yr)	0 or 0.5, 1.0 ppm SO <sub>2</sub> with light, medium, and heavy exercise (average ventilation 30, 36, and 43 L/min) for 10 min	sRaw, FEV <sub>1</sub> , symptoms, psychophysical (stamina) changes
<a href="#">Gong et al. (1996)</a>	Asthma; n = 10; 2 M, 8 F (19–49 yr)	0 or 0.75 ppm SO <sub>2</sub> for 10 min with exercise (29 L/min) at 1, 12, 18, and 24 h after pretreatment with placebo or salmeterol (long-acting B <sub>2</sub> -agonist)	FEV <sub>1</sub> , symptoms
<a href="#">Gong et al. (2001)</a>	Asthma; n = 12; 2 M, 10 F (20–48 yr)	0 or 0.75 ppm SO <sub>2</sub> for 10 min with exercise (35 L/min) with or w/o pretreatment to montelukast sodium (10 mg/d for 3 d)	sRaw, FEV <sub>1</sub> , symptoms, eosinophil counts in induced sputum
<a href="#">Horstman et al. (1986)</a>	(1) Asthma; n = 27; 27 M w/asthma and sensitive to inhaled methacholine (19–33 yr) (2) n = 4 from study population above	(1) 0, 0.25, 0.5, or 1.00 ppm SO <sub>2</sub> for 10 min with exercise (treadmill, 21 L/min per m <sup>2</sup> body surface area) (2) 2 ppm SO <sub>2</sub> for 10 min with exercise (treadmill, 21 L/min per m <sup>2</sup> body surface area)	sRaw
<a href="#">Horstman et al. (1988)</a>	Asthma; n = 12; 12 M (22–37 yr)	0 or 1.0 ppm SO <sub>2</sub> for 0, 0.5, 1.0, 2.0, and 5.0 min with exercise (treadmill 40 L/min)	sRaw, symptoms

**Table 5-1 (Continued): Study specific details from controlled human exposure studies of individuals with asthma.**

Study	Disease Status; n; Sex; (Age <sup>a</sup> )	Exposure Details (Concentration; Duration)	Outcomes Examined
<a href="#">Jörres and Magnussen (1990)</a>	Asthma; n = 14; 10 M, 4 F (21–55 yr, 34 ± 14 yr)	0 or 0.25 ppm NO <sub>2</sub> , or 0.5 ppm SO <sub>2</sub> at rest followed by challenge with 0.75 ppm SO <sub>2</sub> during voluntary eucapnic hyperpnea. Ventilation increased in 15 L/min steps, each lasting 3 min	sRaw
<a href="#">Kehrl et al. (1987)</a>	Asthma; n = 10; 10 M (20–30 yr)	0 or 1 ppm SO <sub>2</sub> for 1 h with exercise (3 × 10 min at 41 L/min on a treadmill)	sRaw
<a href="#">Koenig et al. (1980)</a>	Asthma; n = 9; 7 M, 2 F (14–18 yr)	0 or 1 ppm SO <sub>2</sub> with 1 mg/m <sup>3</sup> of NaCl droplet aerosol, 1 mg/m <sup>3</sup> NaCl droplet aerosol for 60 min exposure with mouthpiece at rest	FEV <sub>1</sub> , RT, FRC, V <sub>max50</sub> , V <sub>max75</sub> , symptoms
<a href="#">Koenig et al. (1981)</a>	Asthma; n = 8; 6 M, 2 F (14–18 yr)	0 or 1 ppm SO <sub>2</sub> with 1 mg/m <sup>3</sup> of NaCl droplet aerosol, 1 mg/m <sup>3</sup> NaCl droplet aerosol for 30 min exposure via mouthpiece at rest followed by 10 min exercise on a treadmill (six-fold increase in min vent)	FEV <sub>1</sub> , RT, FRC, V <sub>max50</sub> , V <sub>max75</sub> , symptoms
<a href="#">Koenig et al. (1983)</a>	(1) Asthma w/EIB; n = 9; 6 M, 3 F (12–16 yr) (2) Asthma w/EIB; n = 7 from study population above	(1) 1 g/m <sup>3</sup> of NaCl droplet aerosol, 1 ppm SO <sub>2</sub> + 1 mg/m <sup>3</sup> NaCl, 0.5 ppm SO <sub>2</sub> + 1 mg/m <sup>3</sup> NaCl for 30 min exposure via mouthpiece at rest followed by 10 min exercise on treadmill (five- to six-fold increase in V <sub>E</sub> ) (2) 0.5 ppm SO <sub>2</sub> + 1 mg/m <sup>3</sup> NaCl via a face mask with no nose clip with exercise conditions the same as above	FEV <sub>1</sub> , RT, FRC, V <sub>max50</sub> , V <sub>max75</sub> , symptoms
<a href="#">Koenig et al. (1987)</a>	Allergic w/EIB; n = 10; 3 M 7 F (13–17 yr)	0 or 0.75 ppm SO <sub>2</sub> (mouthpiece) with exercise (33.7 L/min) for 10 and 20 min prior pretreatment (placebo or 180 µg albuterol)	FEV <sub>1</sub> , RT, FRC, symptoms
<a href="#">Koenig et al. (1988)</a>	Asthma w/EIB; n = 8; 2 M, 6 F (13–17 yr)	1.0 ppm SO <sub>2</sub> 10 min (mouthpiece, treadmill, 35 L/min) with pretreatment (placebo 20, 40, 60 mg cromolyn) 20 min prior, no control, air exposure	FEV <sub>1</sub> , RT
<a href="#">Koenig et al. (1990)</a>	Asthma w/EIB; n = 13; 8 M, 5 F (12–18 yr)	0.1 ppm SO <sub>2</sub> for 15 min preceded by air or 0.12 ppm O <sub>3</sub> for 45 min during intermittent exercise (2 × 15 min at 30 L/min on a treadmill), no control, air exposure	FEV <sub>1</sub> , RT, FRC, V <sub>max50</sub> , symptoms
<a href="#">Koenig et al. (1992)</a>	Asthma; n = 8; 2 M, 6 F (18–46 yr; 27.5 ± 9.6 yr)	1 ppm SO <sub>2</sub> for 10 min with exercise (V <sub>E</sub> = 13.4–31.3 L/min) with or w/o pretreatment to theophylline	FEV <sub>1</sub> , RT

**Table 5-1 (Continued): Study specific details from controlled human exposure studies of individuals with asthma.**

Study	Disease Status; n; Sex; (Age <sup>a</sup> )	Exposure Details (Concentration; Duration)	Outcomes Examined
<a href="#">Lazarus et al. (1997)</a>	Asthma; n = 12; 7 M, 5 F (24–43 yr)	0, 0.25, 0.5, 1.0, 2.0, 4.0, or 8.0 ppm SO <sub>2</sub> w/eucapnic hyperpnea (20 L/min) for 4 min sequential exposures with pretreatment with zafirlukast (placebo or 20 mg) 2 or 10 h earlier	sRaw
<a href="#">Linn et al. (1983b)</a>	Asthma; n = 23; 13 M, 10 F (19–31 yr)	(1) 0, 0.2, 0.4, or 0.6 ppm SO <sub>2</sub> w/low humidity or high humidity for 10 min w/exercise (bicycle, 5 min 50 L/min) (2) 0 or 0.6 ppm SO <sub>2</sub> w/warm air or cold air w/exercise (bicycle, 50 L/min, ~5 min)	sRaw, sGaw, FVC, FEV <sub>1</sub> , symptoms
<a href="#">Linn et al. (1983a)</a>	Asthma; n = 23; 15 M, 8 F (18–30 yr, 23 ± 4 yr)	0 or 0.75 ppm SO <sub>2</sub> with unencumbered breathing and mouth only breathing (with exercise 40 L/m, 10 min bicycle)	sRaw, thoracic gas volume, symptoms, FVC, FEV <sub>1</sub> , PEF <sub>R</sub> , V <sub>max50</sub> , V <sub>max25</sub>
<a href="#">Linn et al. (1984c)</a>	Asthma; n = 24; 13 M, 11 F (19–31 yr)	0, 0.3, or 0.6 ppm SO <sub>2</sub> at 21°, 7°, and –6°C, rH 80% (bicycle 50 L/min, ~5 min)	sRaw, sGaw, symptoms
<a href="#">Linn et al. (1984a)</a>	Asthma: n = 14; 12 M, 2 F (18–33 yr)	0 or 0.6 ppm SO <sub>2</sub> for 6 h with exercise on day 1 and 2 (2 × 5-min exercise, bicycle, 50 L/min per exposure)	sRaw, sGaw, symptoms
<a href="#">Linn et al. (1984b)</a>	(1) Asthma; n = 8; 4 M, 4 F (19–29 yr) (2) Asthma; n = 24; 17 M 7 F (18–30 yr)	(1) 0, 0.2, 0.4, or 0.6 ppm SO <sub>2</sub> at 5°C, 50 and 85% rH with exercise (5 min, 50 L/min) (2) 0 or 0.6 ppm SO <sub>2</sub> at 5 and 22°C, 85% rH with exercise (5 min, 50 L/min)	sRaw, sGaw, FEV <sub>1</sub> , symptoms
<a href="#">Linn et al. (1985b)</a>	Asthma; n = 22; 13 M, 9 F (18–33 yr)	0 or 0.6 ppm SO <sub>2</sub> at 21 and 38°C and 20 and 80% rH with exercise (~5 min, 50 L/min)	sRaw, sGaw, symptoms
<a href="#">Linn et al. (1985a)</a>	COPD; n = 24; 15 M, 9 F (49–68 yr)	0, 0.4, or 0.8 ppm SO <sub>2</sub> for 1 h with exercise (2 × 15 min, bicycle, 18 L/min)	sRaw, FVC, FEV <sub>1</sub> , MMFR, symptoms

**Table 5-1 (Continued): Study specific details from controlled human exposure studies of individuals with asthma.**

Study	Disease Status; n; Sex; (Age <sup>a</sup> )	Exposure Details (Concentration; Duration)	Outcomes Examined
<a href="#">Linn et al. (1987)</a>	Healthy; n = 24; 15 M, 9 F (18–37 yr) Atopic; n = 21; 12 M, 9 F (18–32 yr) Minimal or mild asthma; n = 16; 10 M, 6 F (20–33 yr) Moderate or severe asthma; n = 24; 10 M, 14 F (18–35 yr) Moderate or severe asthma; n = 24	0, 0.2, 0.4, or 0.6 ppm SO <sub>2</sub> 1 h exposures 3 x 10-min exercise (bicycle) periods ~40 L/min Two rounds of exposures were conducted	Lung function measure pre-exposure, ~15 min and ~55 min into exposure sRaw, FVC, FEV <sub>1</sub> , peak expiratory flow rate, maximal midexpiratory flow rate Continuously—EKG Midway—HR Before, during, 1-d after, and 1-wk after-symptom score, self-rated activity Immediately after exposure—bronchial reactivity percentage change in FEV <sub>1</sub> induced by 3 min normocapnic hyperpnea with cold, dry air
<a href="#">Linn et al. (1988)</a>	Asthma; n = 20; 13 M, 7 F (19–36 yr)	Three pretreatment groups (1) metaproterenol sulfate (2) placebo (3) no treatment 0, 0.3, or 0.6 ppm SO <sub>2</sub> 10 min with exercise (bike 50 L/min)	Lung function—pre, post 60 min, 90 min, 120 min, Symptoms—pre, post, 20 min post, 60 min post, 120 min post, 24 h post, 1 wk post
<a href="#">Linn et al. (1990)</a>	Asthma; n = 21; 6 M, 15 F (19–48 yr)	0, 0.3, or 0.6 ppm SO <sub>2</sub> 10 min with exercise 50 L/min (1) low medication use; (2) normal; (3) high (usual medication supplemented by inhaled metaproterenol before exposure)	Lung function and symptoms measured before and after exposure
<a href="#">Magnussen et al. (1990)</a>	Asthma; n = 46; 24 M, 22 F (28 ± 14 yr) Healthy; n = 12 (24 ± 5 yr)	0 or 0.5 ppm SO <sub>2</sub> 10 min tidal breathing followed by 10 min of isocapnic hyperventilation (30 L/min) Histamine challenge—(8 mg/mL)	sRaw
<a href="#">Myers et al. (1986a)</a>	Asthma; n = 10; 7 M, 3 F (19–40 yr)	0, 0.25, 0.5, 1, 2, 4, or 8 ppm SO <sub>2</sub> 3 min sequential exposures (mouthpiece, 40 L/min) with pretreatment 30 min prior with cromolyn (placebo, 20, or 200 mg)	sRaw
<a href="#">Myers et al. (1986b)</a>	(1) Asthma; n = 9; 7 M, 2 F (19–40 yr) (2) Asthma; n = 7; 7 M (19–40 yr)	0, 0.25, 0.5, 1, 2, 4, or 8 ppm SO <sub>2</sub> 3 min sequential exposures (mouthpiece, eucapnic hyperpnea 40 L/min) with pretreatment 30 min prior (1) atropine (2 mg) and cromolyn (200 mg); (2) placebo and cromolyn (200 mg); (3) atropine (2 mg) and placebo; (4) placebo	sRaw

**Table 5-1 (Continued): Study specific details from controlled human exposure studies of individuals with asthma.**

Study	Disease Status; n; Sex; (Age <sup>a</sup> )	Exposure Details (Concentration; Duration)	Outcomes Examined
<a href="#">Roger et al. (1985)</a>	Asthma; n = 28; 28 M (19–33 yr)	75 min 0, 0.25, 0.5, or 1.0 ppm SO <sub>2</sub> Three 10 min periods of exercise 42.4 L/min	Raw; sRaw; FVC, FEV <sub>1</sub> , FEF <sub>25–75</sub> , FEF <sub>max</sub> , FEF <sub>50</sub> , FEF <sub>75</sub> ,
<a href="#">Rubinstein et al. (1990)</a>	Asthma; n = 9; 5 M, 4 F (23–34 yr)	0 or 0.3 ppm NO <sub>2</sub> during exercise followed by challenge with 0.25 to 4.0 ppm SO <sub>2</sub> , in doubling dose increments, for 4 min each until sRaw increased by 8 sRaw units above baseline	sRaw, FVC, FEV <sub>1</sub> , single-breath nitrogen test
<a href="#">Sheppard et al. (1983)</a>	Asthma; n = 8; 4 M, 4 F (22–36 yr)	0.5 ppm SO <sub>2</sub> for 3 min eucapnic hyperpnea	sRaw, symptoms
<a href="#">Trenka et al. (1999)</a>	Asthma; n = 47; 14 M, 33 F (18–39 yr)	0.5 ppm SO <sub>2</sub> for 10 min during moderate exercise	FEV <sub>1</sub> , FVC, FEV <sub>1</sub> /FVC, PEF, FEF <sub>25–75</sub> , symptoms ratings
<a href="#">Trenka et al. (2001)</a>	Asthma; n = 17; 5 M, 12 F (19–38 yr)	0.1 or 0.25 ppm SO <sub>2</sub> for 10 min w/moderate exercise (treadmill)	FVC, FEV <sub>1</sub> , FEF <sub>25–75</sub> , PEF, symptoms
<a href="#">Tunnicliffe et al. (2003)</a>	Asthma; n = 12 (adults, 35.7 yr) Healthy; n = 12 (adults, 34.5 yr)	0 or 0.2 ppm SO <sub>2</sub> at rest	Symptoms, FEV <sub>1</sub> , FVC, MMEF, exhaled NO, ascorbic and uric acid in nasal lavage fluid

COPD = chronic obstructive pulmonary disease; EIB = exercise-induced bronchospasm; EKG = electrocardiogram; F = female; FEV = forced expiratory volume; FEV<sub>1</sub> = forced expiratory volume in 1 sec; FVC = forced vital capacity; FEF<sub>25–75%</sub> = forced expiratory flow at 25–75% of forced vital capacity; FEF<sub>50%</sub> = forced expiratory flow at 50% of forced vital capacity; FEF<sub>75%</sub> = forced expiratory flow at 75% of forced vital capacity; FEF<sub>max</sub> = maximum forced expiratory flow; FRC = functional residual capacity; HR = heart rate; M = male; MMEF = maximum midexpiratory flow; MMFR = maximal midexpiratory flow rate; n = sample size; NaCl = sodium chloride; NO = nitric oxide; NO<sub>2</sub> = nitrogen dioxide; O<sub>3</sub> = ozone; PEF = peak expiratory flow; PEF<sub>R</sub> = peak expiratory flow rates; ppm = parts per million; Raw = airway resistance; rH = relative humidity; RT = total respiratory resistance; SD = standard deviation; sGAW = specific airway conductance; sRaw = specific airway resistance; SO<sub>2</sub> = sulfur dioxide; V<sub>E</sub> = minute volume; V<sub>max</sub> = maximal flow of expired vital capacity; V<sub>max75</sub> = flow rate with 75% of FVC remaining to be expired; V<sub>max50</sub> = flow rate with 50% of FVC remaining to be expired; V<sub>max25</sub> = flow rate with 25% of FC remaining to be expired.

<sup>a</sup>Range or Mean ± SD.

1 Several investigators ([Linn et al., 1990](#); [Linn et al., 1988](#); [Linn et al., 1987](#); [Bethel et al.,](#)  
2 [1985](#); [Linn et al., 1984a](#); [Linn et al., 1983b](#)) demonstrated ≥100% increase in sRaw or  
3 ≥15% decrease in FEV<sub>1</sub> after 5–10-minute exposures to low concentrations  
4 (0.2–0.3 ppm) of SO<sub>2</sub> in exercising adults with asthma, with effects being more  
5 pronounced following 5–10-minute exposures to 0.4–0.6 ppm SO<sub>2</sub> ([Linn et al., 1990](#);  
6 [Magnussen et al., 1990](#); [Linn et al., 1988](#); [Linn et al., 1987](#); [Roger et al., 1985](#); [Linn et al.,](#)  
7 [1983b](#)).

1 SO<sub>2</sub>-induced bronchoconstriction occurs rapidly and is transient with recovery following  
2 cessation of exposure. Bronchoconstriction occurs in as little as 2 minutes from the start  
3 of exposure in adults with asthma who have increased ventilation rates due to exercise or  
4 eucapnic hyperpnea ([Horstman et al., 1988](#); [Balmes et al., 1987](#); [Sheppard et al., 1983](#)).  
5 During exposure to SO<sub>2</sub> over a 30-minute period with continuous exercise, the response  
6 to SO<sub>2</sub> develops rapidly and is maintained throughout the 30-minute exposure ([Kehrl et  
7 al., 1987](#); [Linn et al., 1987](#); [Linn et al., 1984c](#)). [Linn et al. \(1984a\)](#) reported decrements in  
8 lung function in adults with asthma immediately after each exercise period (one early and  
9 one late into the exposure) in two 6-hour exposures to 0.6 ppm SO<sub>2</sub> on successive days.  
10 The decrements in lung function observed in the early and late exercise periods were not  
11 statistically significantly different from each other, and the response observed after the  
12 second day of SO<sub>2</sub> exposure was slightly less than the response observed after the first  
13 day of SO<sub>2</sub> exposure. These results demonstrate transient rather than cumulative  
14 bronchoconstriction effects. These effects are generally observed to diminish to baseline  
15 levels within 1 hour post exposure ([Linn et al., 1987](#)).

16 Other factors that affect responses to SO<sub>2</sub> include temperature and humidity.  
17 The majority of controlled human exposure studies were conducted at 20–25°C and at  
18 relative humidities ranging from ~25–90%. Some evidence indicates that the respiratory  
19 effects of SO<sub>2</sub> are exacerbated by colder and dryer conditions ([Linn et al., 1985b](#); [Bethel  
20 et al., 1984](#); [Linn et al., 1984b](#)).

21 **Responders versus nonresponders to SO<sub>2</sub>.** At the time of the 2008 SO<sub>x</sub> ISA ([U.S. EPA,  
22 2008d](#)), it was well documented that some individuals have a greater response to SO<sub>2</sub>  
23 than others with similar disease status ([Table 5-2](#)) ([Linn et al., 1990](#); [Magnussen et al.,  
24 1990](#); [Linn et al., 1988](#); [Linn et al., 1987](#); [Horstman et al., 1986](#); [Bethel et al., 1985](#);  
25 [Roger et al., 1985](#); [Linn et al., 1984b](#); [Linn et al., 1983b](#)).

**Table 5-2 Percentage of adults with asthma in controlled human exposure studies experiencing sulfur dioxide-induced decrements in lung function and respiratory symptoms.**

SO <sub>2</sub> Conc (ppm)	Exposure Duration (min)	N	Ventilation (L/min)	Cumulative Percentage of Responders (Number of Subjects) <sup>a</sup>				Study	Respiratory Symptoms: Supporting Studies	
				sRaw	≥100% ↑	≥200% ↑	≥300% ↑			
				FEV <sub>1</sub>	≥15% ↓	≥20% ↓	≥30% ↓			
0.2	5	23	~48	sRaw	9% (2) <sup>b</sup>	0	0	<a href="#">Linn et al. (1983b)</a>	Limited evidence of SO <sub>2</sub> -induced increases in respiratory symptoms in some people with asthma: ( <a href="#">Linn et al. (1990)</a> ; <a href="#">Linn et al. (1988)</a> ; <a href="#">Linn et al. (1987)</a> ; <a href="#">Schachter et al. (1984)</a> ; <a href="#">Linn et al. (1983b)</a> )	
	10	40	~40	sRaw	7.5% (3) <sup>c</sup>	2.5% (1) <sup>c</sup>	0 <sup>c</sup>			<a href="#">Linn et al. (1987)<sup>c</sup></a>
	10	40	~40	FEV <sub>1</sub>	9% (3.5) <sup>c</sup>	2.5% (1) <sup>c</sup>	1% (0.5) <sup>c</sup>			<a href="#">Linn et al. (1987)<sup>c</sup></a>
0.25	5	19	~50-60	sRaw	32% (6)	16% (3)	0	<a href="#">Bethel et al. (1985)</a> <a href="#">Bethel et al. (1985)</a>		
	5	9	~80-90	sRaw	22% (2)	0	0			
	10	28	~40	sRaw	4% (1)	0	0	<a href="#">Roger et al. (1985)</a>		
0.3	10	20	~50	sRaw	10% (2)	5% (1)	5% (1)	<a href="#">Linn et al. (1988)<sup>d</sup></a>		
	10	21	~50	sRaw	33% (7)	10% (2)	0	<a href="#">Linn et al. (1990)<sup>d</sup></a>		
	10	20	~50	FEV <sub>1</sub>	15% (3)	0	0	<a href="#">Linn et al. (1988)</a>		
	10	21	~50	FEV <sub>1</sub>	24% (5)	14% (3)	10% (2)	<a href="#">Linn et al. (1990)</a>		
0.4	5	23	~48	sRaw	13% (3)	4% (1)	0	<a href="#">Linn et al. (1983b)</a>	Stronger evidence with some statistically significant increases in respiratory symptoms: <a href="#">Balmes et al. (1987)<sup>f</sup></a> , <a href="#">Gong et al. (1995)</a> ( <a href="#">Linn et al. (1987)</a> ; <a href="#">Linn et al. (1983b)</a> ) <a href="#">Roger et al. (1985)</a>	
	10	40	~40	sRaw	24% (9.5) <sup>c</sup>	9% (3.5) <sup>c</sup>	4% (1.5) <sup>c</sup>	<a href="#">Linn et al. (1987)<sup>c</sup></a>		
	10	40	~40	FEV <sub>1</sub>	27.5% (11) <sup>c</sup>	17.5% (7) <sup>c</sup>	10% (4) <sup>c</sup>	<a href="#">Linn et al. (1987)<sup>c</sup></a>		
0.5	5	10	~50-60	sRaw	60% (6)	40% (4)	20% (2)	<a href="#">Bethel et al. (1983)</a>		
	10	28	~40	sRaw	18% (5)	4% (1)	4% (1)	<a href="#">Roger et al. (1985)</a>		
	10	45	~30	sRaw	36% (16)	16% (7)	13% (6)	<a href="#">Magnussen et al. (1990)<sup>f</sup></a>		

**Table 5-2 (Continued): Percentage of adults with asthma in controlled human exposure studies experiencing sulfur dioxide induced decrements in lung function and respiratory symptoms.**

SO <sub>2</sub> Conc (ppm)	Exposure Duration (min)	N	Ventilation (L/min)	Cumulative Percentage of Responders (Number of Subjects) <sup>a</sup>				Study	Respiratory Symptoms: Supporting Studies
				sRaw	≥100% ↑	≥200% ↑	≥300% ↑		
				FEV <sub>1</sub>	≥15% ↓	≥20% ↓	≥30% ↓		
0.6	5	23	~48	sRaw	39% (9)	26% (6)	17% (4)	<a href="#">Linn et al. (1983b)</a>	Clear and consistent increases in SO <sub>2</sub> -induced respiratory symptoms: ( <a href="#">Linn et al. (1990)</a> ; <a href="#">Linn et al. (1988)</a> ; <a href="#">Linn et al. (1987)</a> ; <a href="#">Linn et al. (1983b)</a> ), <a href="#">Gong et al. (1995)</a> , <a href="#">Horstman et al. (1988)</a> )
	10	40	~40	sRaw	34% (13.5) <sup>c</sup>	24% (9.5) <sup>c</sup>	19% (7.5) <sup>c</sup>	<a href="#">Linn et al. (1987)<sup>c</sup></a>	
	10	20	~50	sRaw	60% (12)	35% (7)	10% (2)	<a href="#">Linn et al. (1988)</a>	
	10	21	~50	sRaw	62% (13)	29% (6)	14% (3)	<a href="#">Linn et al. (1990)</a>	
	10	40	~40	FEV <sub>1</sub>	47.5% (19) <sup>c</sup>	39% (15.5) <sup>c</sup>	17.5% (7) <sup>c</sup>	<a href="#">Linn et al. (1987)<sup>c</sup></a>	
	10	20	~50	FEV <sub>1</sub>	55% (11)	55% (11)	5% (1)	<a href="#">Linn et al. (1988)</a>	
	10	21	~50	FEV <sub>1</sub>	43% (9)	38% (8)	14% (3)	<a href="#">Linn et al. (1990)</a>	
1.0	10	28	~40	sRaw	50% (14)	25% (7)	14% (4)	<a href="#">Roger et al. (1985)<sup>e</sup></a>	
	10	10	~40	sRaw	60% (6)	20% (2)	0	<a href="#">Kehrl et al. (1987)</a>	

Conc = concentration; FEV<sub>1</sub> = forced expiratory volume in 1 sec; sRaw = specific airway resistance; SO<sub>2</sub> = sulfur dioxide.

<sup>a</sup>Data presented from all references from which individual data were available. Percentage of individuals who experienced greater than or equal to a 100, 200, or 300% increase in specific airway resistance, or a 15, 20, or 30% decrease in FEV<sub>1</sub>. Lung function decrements are adjusted for the effects of exercise in clean air (calculated as the difference between the percent change relative to baseline with exercise/SO<sub>2</sub> and the percent change relative to baseline with exercise/clean air).

<sup>b</sup>Numbers in parenthesis represent the number of subjects experiencing the indicated effect.

<sup>c</sup>Responses of people with mild and moderate asthma reported in [Linn et al. \(1987\)](#) have been combined. Data are the average of the first and second round exposure responses following the first 10 min period of exercise.

<sup>d</sup>Analysis includes data from only people with mild [Linn et al. \(1988\)](#) and moderate [Linn et al. \(1990\)](#) asthma who were not receiving supplemental medication.

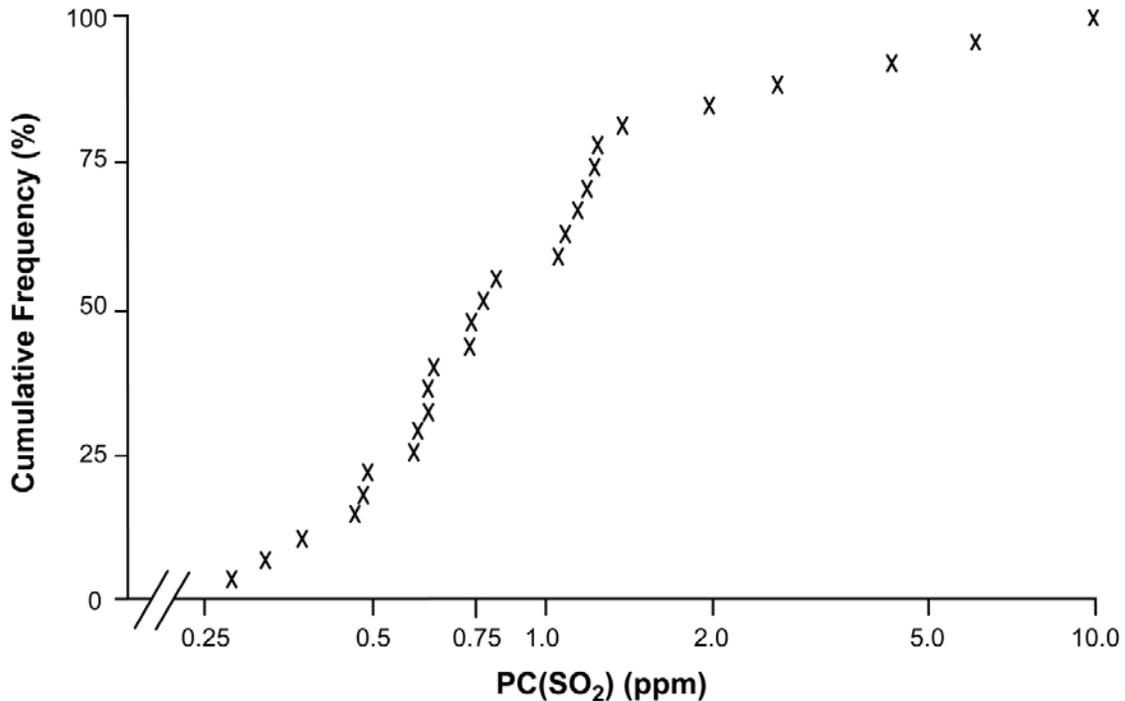
<sup>e</sup>One subject was not exposed to 1 ppm due to excessive wheezing and chest tightness experienced at 0.5 ppm. For this subject, the values used for 0.5 ppm were also used for 1.0 ppm under the assumption that the response at 1.0 ppm would be equal to or greater than the response at 0.5 ppm.

<sup>f</sup>Indicates studies in which exposures were conducted using a mouthpiece rather than a chamber.

1 [Horstman et al. \(1986\)](#) reported that individuals required different concentrations of SO<sub>2</sub>  
2 to produce a doubling of sRaw ( $\geq 100\%$ ) compared to clean air exposure [provocative  
3 concentration of SO<sub>2</sub>, PC(SO<sub>2</sub>)] ([Figure 5-1](#)). This study described the distribution of  
4 individual bronchial sensitivity to SO<sub>2</sub>, measured by sRaw, in 27 subjects with asthma  
5 that were sensitive to methacholine; nonsensitive volunteers were excluded from further  
6 participation in the study. Individuals were exposed to concentrations of SO<sub>2</sub> between 0  
7 and 2 ppm for 10 minutes under exercising conditions ( $V_E = 42$  L/minute). While six of  
8 the subjects (22%) reached a PC(SO<sub>2</sub>) below 0.5 ppm SO<sub>2</sub>, two subjects (7.4%)  
9 experienced a moderate decrease  $\leq 0.3$  ppm ([Figure 5-1](#)). On the other end of the  
10 spectrum, four subjects (14.8%) did not demonstrate  $\geq 100\%$  increase in sRaw even when  
11 exposed to 2.0 ppm SO<sub>2</sub> and eight (29.6%) subjects required an SO<sub>2</sub> concentration  
12 between 1.0 and 2.0 ppm to elicit a response. The authors noted that the effects of SO<sub>2</sub> on  
13 sRaw are similar to a variety of nonspecific bronchoconstrictive stimuli. However, they  
14 observed only a weak correlation between airway responsiveness to SO<sub>2</sub> and  
15 methacholine ( $r = 0.31$ ,  $p = 0.12$ ). This study demonstrates substantial interindividual  
16 variability in sensitivity to the bronchoconstrictive effects of SO<sub>2</sub> in exercising adults  
17 with asthma.

18 Completed after the 2008 SO<sub>x</sub> ISA ([U.S. EPA, 2008d](#)), an analysis by [Johns et al. \(2010\)](#)  
19 of publicly available primary data from published studies clearly demonstrates disparate  
20 responses among 177 adults with asthma. Data from five studies of individuals with  
21 asthma exposed to multiple concentration of SO<sub>2</sub> for 5–10 minutes with elevated  
22 ventilation rates ([Linn et al., 1990](#); [Linn et al., 1988](#); [Linn et al., 1987](#); [Roger et al., 1985](#);  
23 [Linn et al., 1983b](#)) were analyzed after classifying individuals by responder status.  
24 Classification of responders versus nonresponders was based on the magnitude of sRaw  
25 and FEV<sub>1</sub> changes in response to the highest SO<sub>2</sub> concentration to which subjects were  
26 exposed (0.6 or 1.0 ppm). Responders were defined as subjects experiencing  $\geq 100\%$   
27 increase in sRaw or  $\geq 15\%$  decrease in FEV<sub>1</sub> after exposure. Response status was assigned  
28 separately for sRaw and FEV<sub>1</sub>. Among responders, significant decreases in FEV<sub>1</sub> were  
29 observed for concentrations as low as 0.3 ppm SO<sub>2</sub> ( $p = 0.005$ ) ([Table 5-3](#)). In addition,  
30 marginally significant increases in sRaw were demonstrated at 0.3 ppm SO<sub>2</sub> ( $p = 0.009$ ),  
31 with statistically significant increases observed at 0.4 and 0.5 ppm ( $p < 0.001$ )  
32 ([Table 5-4](#)). [Due to multiple comparisons, [Johns et al. \(2010\)](#) designated a critical  
33  $p$ -value of 0.005 as significant, using the Bonferroni multiple comparison correction.]  
34 Overall, these data demonstrate a bimodal distribution of airway responsiveness to SO<sub>2</sub> in  
35 individuals with asthma, with one subpopulation that is insensitive to the  
36 bronchoconstrictive effects of SO<sub>2</sub> even at concentrations as high as 1.0 ppm, and another  
37 subpopulation that has an increased risk for bronchoconstriction at low concentrations of  
38 SO<sub>2</sub>. The [Winterton et al. \(2001\)](#) study suggests that a TNF- $\alpha$  promoter polymorphism in

1 some individuals with asthma may be associated with increased airway responsiveness to  
2 SO<sub>2</sub>.



PC = provocative concentration; SO<sub>2</sub> = sulfur dioxide.  
Note: Each data point represents the PC(SO<sub>2</sub>) for an individual subject.  
Source: [Horstman et al. \(1986\)](#).

**Figure 5-1 Distribution of individual airway sensitivity to sulfur dioxide. The cumulative percentage of subjects is plotted as a function of provocative concentration, which is the concentration of sulfur dioxide that provoked a 100% increase in specific airway resistance compared to clean air.**

3 A recent analysis of four previously published studies ([Horstman et al., 1988](#); [Horstman](#)  
4 [et al., 1986](#); [Schachter et al., 1984](#); [Sheppard et al., 1984](#)) in which individuals with  
5 asthma were exposed to multiple SO<sub>2</sub> concentrations or had their response recorded over  
6 multiple durations of SO<sub>2</sub> exposure was provided by [Goodman et al. \(2015\)](#). However,  
7 the analysis conducted by [Goodman et al. \(2015\)](#) did not consider the log-normal  
8 distribution of airway responsiveness data and instead used an arithmetic mean and  
9 standard deviation in their analysis. Eight of 56 individuals were identified as sensitive to  
10 the effects of SO<sub>2</sub> by [Goodman et al. \(2015\)](#).

**Table 5-3 Percent change in post- versus pre-exposure measures of forced expiratory volume in 1 second relative to clean air control after 5–10-minute exposures to sulfur dioxide during exercise.**

	SO <sub>2</sub> Concentration ppm	Number of Exposures	FEV <sub>1</sub>			p-Value
			% Decrease	95% Confidence Limits		
				Lower	Upper	
Responders	0.2	37	-5.0	-8.9	-1.1	0.012
	0.3	20	-7.6	-13.0	-2.3	0.005 <sup>a,b</sup>
	0.4	37	-17.4	-21.3	-13.6	<0.001 <sup>a,b</sup>
Nonresponders	0.2	43	0.4	-4.3	5.2	0.854
	0.3	21	-3.6	-9.6	2.5	0.252
	0.4	43	-4.3	-9.2	0.6	0.086

FEV<sub>1</sub> = forced expiratory volume in 1 sec; ppm = parts per million; SO<sub>2</sub> = sulfur dioxide.

A generalized linear latent and mixed models (GLLMM) procedure was used that included study as a fixed effect, concentration dummy variables as a covariate, and subject and the times a subject was exposed to a sequence of exposures as random variables. Data were included from [Linn et al. \(1987\)](#), [Linn et al. \(1988\)](#), and [Linn et al. \(1990\)](#).

<sup>a</sup>Indicates significance at 0.05 level using the Bonferroni multiple comparison correction.

<sup>b</sup>Indicates significance at 0.05 level using Dunnett's test.

**Table 5-4 Percent change in post- versus pre-exposure measures of specific airway resistance relative to clean air control after 5–10-minute exposures to sulfur dioxide during exercise.**

	SO <sub>2</sub> Concentration ppm	Number of Exposures	% Increase	sRaw		p-Value
				95% Confidence Limits		
				Lower	Upper	
Responders	0.2	36	10.2	-3.6	24.0	0.147
	0.25	14	19.5	-4.0	43.1	0.104
	0.3	25	25.4	6.5	44.3	0.009
	0.4	36	75.7	53.4	98.0	<0.001 <sup>a,b</sup>
	0.5	14	68.0	33.2	102.8	<0.001 <sup>a,b</sup>
Nonresponders	0.2	67	7.9	-4.9	20.7	0.227
	0.25	14	12.6	-10.5	35.7	0.286
	0.3	16	16.4	-5.2	38.1	0.137
	0.4	67	16.2	1.8	30.6	0.028
	0.5	14	14.7	-12.3	41.7	0.285

ppm = parts per million; sRaw = specific airway resistance; SO<sub>2</sub> = sulfur dioxide.

A generalized linear latent and mixed models (GLLAMM) procedure was used that included study as a fixed effect, concentration dummy variables as a covariate, and subject and the times a subject was exposed to a sequence of exposures as random variables. Data were included from [Linn et al. \(1983b\)](#), [Linn et al. \(1987\)](#), [Linn et al. \(1988\)](#), [Linn et al. \(1990\)](#), and [Roger et al. \(1985\)](#).

<sup>a</sup>Indicates significance at 0.05 *p* level, using the Bonferroni multiple comparison correction.

<sup>b</sup>Indicates significance at 0.05 level using Dunnett's test.

1           **Effects of asthma severity on SO<sub>2</sub>-induced response.** The influence of asthma severity  
2           on the degree of responsiveness to SO<sub>2</sub> exposure has been examined ([Trenga et al., 1999](#);  
3           [Linn et al., 1987](#)). One study involved exposure to SO<sub>2</sub> under conditions of increased  
4           ventilation (i.e., exercise) ([Linn et al., 1987](#)). Adults with asthma were divided into two  
5           groups, minimal/mild and moderate/severe, mainly based on the individual's use of  
6           medication to control asthma. Individuals that did not regularly use asthma medication  
7           were classified as minimal/mild; however, even the moderate/severe group consisted of  
8           adults who had well-controlled asthma, were generally able to withhold medication, were  
9           not dependent on corticosteroids, and were able to engage in moderate to heavy levels of  
10          exercise. Thus, this moderate/severe group would likely be classified as moderate by

1 today's classification standards ([Johns et al., 2010](#); [Reddel, 2009](#)). [Linn et al. \(1987\)](#)  
2 found similar relative decrements in lung function in response to SO<sub>2</sub> exposure between  
3 the groups. However, the moderate/severe group demonstrated larger absolute changes in  
4 lung function compared to the mild group ([Linn et al., 1987](#)). This greater decrement in  
5 lung function was attributable to a larger response to the exercise component of the  
6 exposure protocol in the moderate/severe group compared with the mild group. [Trenga et](#)  
7 [al. \(1999\)](#) found a correlation between asthma severity and response to SO<sub>2</sub>. Adults with  
8 asthma were divided into four groups based on medication usage as an indicator of  
9 asthma severity. The role of exercise was not determined in this study, so it unclear  
10 whether individuals with more severe asthma had a greater response to exercise  
11 compared to individuals with less severe asthma. However, both studies suggest that  
12 adults with moderate/severe asthma may have more limited reserve to deal with an insult  
13 compared with individuals with mild asthma.

14 **Asthma with medication.** Asthma medications have been shown to mitigate  
15 SO<sub>2</sub>-induced bronchoconstriction ([U.S. EPA, 2008d](#)). Medications evaluated include  
16 short-acting and long-acting beta-adrenergic bronchodilators ([Gong et al., 1996](#); [Linn et](#)  
17 [al., 1990](#); [Linn et al., 1988](#); [Koenig et al., 1987](#)), cromolyn sodium ([Koenig et al., 1988](#);  
18 [Myers et al., 1986b](#)), theophylline ([Koenig et al., 1992](#)), and leukotriene receptor  
19 antagonists ([Gong et al., 2001](#); [Lazarus et al., 1997](#)). While these therapies have been  
20 shown to mitigate the respiratory effects of SO<sub>2</sub>, they did not completely eliminate these  
21 effects in all studies.

22 **Children and adolescents.** Several studies have examined the responsiveness to SO<sub>2</sub> of  
23 adolescents (ages 12–18 years) with asthma or allergic with EIB ([Koenig et al., 1990](#);  
24 [Koenig et al., 1988](#); [Koenig et al., 1987](#)). Of these studies, only [Koenig et al. \(1987\)](#)  
25 included a control air exposure, so that the bronchoconstrictive effects of SO<sub>2</sub> itself  
26 (rather than, e.g., due to EIB), can be assessed. On average, based on the data provided in  
27 Table 1 of this paper, adolescents experienced a pre-to-post reduction in FEV<sub>1</sub> of 15.4%  
28 following exposure to 0.75 ppm SO<sub>2</sub> and a reduction in FEV<sub>1</sub> of 3.46% following air  
29 exposure. Although the adolescents in this study were allergic with EIB, they did not  
30 have extrinsic asthma. Nevertheless, they are discussed here because allergies affect  
31 airway responsiveness ([Burrows et al., 1995](#)) and because their response to SO<sub>2</sub> is similar  
32 to that observed in other studies of individuals with asthma. The pre-to-post reduction in  
33 FEV<sub>1</sub> of 15.4% following 0.75 ppm SO<sub>2</sub> observed by [Koenig et al. \(1987\)](#) is similar to the  
34 pre-to-post reduction in FEV<sub>1</sub> of 13.9% found in adolescents with asthma following  
35 exposure to 1.0 ppm SO<sub>2</sub> observed by [Koenig et al. \(1988\)](#). For potential comparison to  
36 the results of adolescents, three studies of adults with asthma were conducted at 0.75 ppm  
37 ([Gong et al., 2001](#); [Gong et al., 1996](#); [Linn et al., 1983a](#)). Of these, only [Gong et al.](#)  
38 [\(2001\)](#) provided pre-to-post data for both exposures to air and SO<sub>2</sub>. Similar to the [Koenig](#)

1 [et al. \(1987\)](#) results, [Gong et al. \(2001\)](#) observed a pre-to-post reduction of 15.8% in  
2 FEV<sub>1</sub> following SO<sub>2</sub> exposure in adults based on Table 2 of their paper. Adjusted for the  
3 responses occurring with air exposure, [Koenig et al. \(1987\)](#) observed an 11.8% reduction  
4 in FEV<sub>1</sub> in adolescents, similar to the 12.7% reduction observed in adults by [Gong et al.](#)  
5 [\(2001\)](#). These two studies differ in that the adolescents were exposed via a mouthpiece,  
6 whereas the adults were exposed in a chamber without a mouthpiece. Breathing on a  
7 mouthpiece is expected to produce a somewhat larger FEV<sub>1</sub> decrement than  
8 unencumbered breathing ([Linn et al., 1983a](#)). Although generally similar effects of SO<sub>2</sub>  
9 on adolescents and adults have been observed, exact comparisons of SO<sub>2</sub> effects between  
10 adolescents and adults are not possible given the available data.

11 There is also evidence that adolescents (ages 12–18 years) with asthma or atopy are  
12 responsive to coexposures of SO<sub>2</sub> and sodium chloride (NaCl) droplet aerosol ([Koenig et](#)  
13 [al., 1983, 1981; Koenig et al., 1980](#)). Exposure concentrations in these studies ranged  
14 from 0.1 to 1.0 ppm SO<sub>2</sub>. [Koenig et al. \(1983\)](#) observed average FEV<sub>1</sub> decrements of 15  
15 and 23% in exercising adolescents (12 to 16 year old) with asthma after a 10-minute  
16 exposure to 0.5 ppm SO<sub>2</sub> or 1.0 ppm SO<sub>2</sub> plus 1 mg/m<sup>3</sup> NaCl droplet aerosols,  
17 respectively. No significant changes were observed following exposure to the NaCl  
18 droplet aerosol alone. However, the observed effect may be the result of the presence of  
19 hygroscopic particles that carry SO<sub>2</sub> deeper into the lung.

20 There are no controlled human exposure studies for children less than 12 years of age that  
21 were exposed to SO<sub>2</sub>. However, the responsiveness of children to SO<sub>2</sub> relative to  
22 adolescents and adults may be inferred by the responses to other nonspecific  
23 bronchoconstrictive stimuli. [Horstman et al. \(1986\)](#) noted that the effects of SO<sub>2</sub> on sRaw  
24 are similar to that of a variety of nonspecific bronchoconstrictive stimuli. Indeed, SO<sub>2</sub> is a  
25 nonspecific bronchial challenge agent that has been used to assess changes in airway  
26 responsiveness of individuals with asthma following NO<sub>2</sub> and O<sub>3</sub> exposures ([Trenga et](#)  
27 [al., 2001; Jörres and Magnussen, 1990; Rubinstein et al., 1990](#)). Airway responsiveness  
28 to methacholine, a history of respiratory symptoms, and atopy were significant predictors  
29 of airway responsiveness to SO<sub>2</sub> in healthy adults [Nowak et al. \(1997\)](#). Thus, potential  
30 differences in airway responsiveness of children to SO<sub>2</sub> relative to adolescents and adults  
31 may be gleaned from the literature on airway responsiveness to other nonspecific stimuli  
32 such as methacholine.

33 A number of cross-sectional studies have assessed airway responsiveness of children with  
34 and without asthma to methacholine [e.g., ([Mochizuki et al., 1995; Morikawa et al., 1994;](#)  
35 [Avital et al., 1991; Hopp et al., 1986; Hopp et al., 1985](#))]. Studies show a clear decrease  
36 in airway responsiveness of healthy children with increasing age beyond 5–7 years of age  
37 through adolescence ([Mochizuki et al., 1995; Hopp et al., 1986; Hopp et al., 1985](#)). In

1 studies of children with asthma, some have reported airway responsiveness increased  
2 with asthma severity but was not affected by age ([Avital et al., 1991](#); [Hopp et al., 1986](#)),  
3 whereas others have found airway responsiveness to increase with asthma severity and  
4 decrease with age beyond 6–7 years of age ([Mochizuki et al., 1995](#); [Morikawa et al.,](#)  
5 [1994](#)). The study by [Mochizuki et al. \(1995\)](#) suggested that airway responsiveness in both  
6 healthy children and those affected by asthma increases from ages 2–3 years up to  
7 6–7 years, after which airway responsiveness begins decreasing.

8 More confidence in the effect of age on airway responsiveness may be placed on data  
9 from longitudinal studies than from the cross-sectional studies discussed above. In a  
10 longitudinal study of methacholine responsiveness conducted at 9, 11, 13, and 15 years of  
11 age, [Le Souëf et al. \(1995\)](#) found that responsiveness (1) decreases with age; (2) is  
12 greater in boys (n = 389) than girls (n = 429); and (3) is greater in those reporting  
13 wheeze, although responsiveness decreased with age in these individuals as well. Asthma  
14 prevalence and symptoms such as wheeze are greater in boys than girls during childhood  
15 and become similar or reversed around the time of puberty ([Almqvist et al., 2008](#)). In a  
16 subset of the cohort as used by [Le Souëf et al. \(1995\)](#), [Burrows et al. \(1995\)](#) investigated  
17 the effects of age (n = 573, 49% female), atopy (n = 558), and serum IgE (n = 473) on  
18 airway responsiveness. At 9 years of age, a larger fraction of boys experienced bronchial  
19 responsiveness than did girls. By the age of 15 years, there was little to no difference in  
20 responsiveness between the sexes. Relative to atopic children, those without atopy or  
21 with only minimal atopy had lower airway responsiveness and showed a more evident  
22 decrease in airway responsiveness with increasing age. In the most atopic children (41 of  
23 558), about 40% experienced severe bronchial responsiveness, which did not decrease  
24 with age. Across all ranges of serum IgE, there was a decrease in responsiveness from  
25 age 9 to age 15 years. By 15 years of age, there was minimal bronchial reactivity in the  
26 children having the lowest IgE levels, and bronchial reactivity increased with increasing  
27 serum IgE levels ( $p < 0.0001$ ). In biennial assessments of childhood responsiveness,  
28 [Burrows et al. \(1995\)](#) observed considerable intra-individual variability in bronchial  
29 reactivity, but they observed a statistically significant trend for the more allergic children  
30 to experience persistent bronchial hyperresponsiveness among their biennial assessments.

31 Under the assumption that bronchial responsiveness to methacholine is an appropriate  
32 surrogate for bronchial responsiveness to SO<sub>2</sub>, these studies suggest that greater airway  
33 responsiveness to SO<sub>2</sub> occurs in school-aged children, particularly boys, than in  
34 adolescents. Additionally, the methacholine data also suggest that greater airway  
35 responsiveness to SO<sub>2</sub> in school-aged children and adolescents who are allergic or  
36 experience wheeze is expected to occur than in those without these conditions. Children,  
37 particularly boys, breathe more through the mouth than adults, and ventilation rates  
38 relative to body mass are greater in children than adults (see [Section 4.1.2](#)). Allergic

1 rhinitis can lead to increased nasal resistance, which also results in less nasal and more  
2 oral breathing. Obese children also tend to have increased nasal resistance, increased oral  
3 breathing, and increased ventilation rates relative to normal-weight children (see  
4 [Section 4.1.2](#)). Oral breathing allows greater SO<sub>2</sub> penetration into the lower airways,  
5 where it may cause bronchoconstriction, than does nasal breathing (see [Section 4.2.2](#)).  
6 Overall, school-aged children having asthma-like symptoms might be expected to  
7 experience greater responsiveness (i.e., larger decrements in pulmonary function)  
8 following exposure to SO<sub>2</sub> than normal-weight adolescents and adults.

9 **Mixtures effects.** The health effects of SO<sub>2</sub> can be potentially modified by the interaction  
10 with other pollutants during or prior to exposure. A few controlled human exposure  
11 studies have examined the interactive effects of O<sub>3</sub> and SO<sub>2</sub> both sequentially and in  
12 combination. Exercising adolescents with asthma exposed to 0.1 ppm SO<sub>2</sub> for 15 minutes  
13 after a 45-minute exposure to 0.12 ppm O<sub>3</sub> had a significant decrease (8%) in FEV<sub>1</sub> (8%)  
14 ( $p < 0.05$ ), a significant increase in total respiratory resistance (R<sub>T</sub>) (19%) ( $p < 0.05$ ), and  
15 a significant decrease in maximal flow at 50% of expired vital capacity (V<sub>max50</sub>) (15%)  
16 ( $p < 0.05$ ), while air followed by SO<sub>2</sub>, and O<sub>3</sub> followed by O<sub>3</sub> exposures did not cause  
17 significant changes in lung function ([Koenig et al., 1990](#)). In a more recent study in  
18 exercising adults with asthma, [Trenga et al. \(2001\)](#) observed greater decrements in lung  
19 function after 45 minutes of exposure to 0.12 ppm O<sub>3</sub> followed by 15 minutes of  
20 0.25 ppm SO<sub>2</sub> compared to air followed by SO<sub>2</sub>.

21 [Jörres and Magnussen \(1990\)](#) and [Rubinstein et al. \(1990\)](#) investigated the effects of prior  
22 NO<sub>2</sub> exposure on SO<sub>2</sub>-induced bronchoconstriction in adults with asthma. While [Jörres](#)  
23 [and Magnussen \(1990\)](#) observed that tidal breathing of NO<sub>2</sub> increased airway  
24 responsiveness to subsequent hyperventilation of SO<sub>2</sub>, [Rubinstein et al. \(1990\)](#) noted NO<sub>2</sub>  
25 induced greater airway responsiveness to inhaled SO<sub>2</sub> in only one subject.

26 While SO<sub>2</sub> acts as a nonspecific bronchial challenge agent that causes reductions in lung  
27 function in individuals with asthma after brief exposure, it can also increase airway  
28 responsiveness to subsequent exposures involving other stimuli such as allergens or  
29 methacholine. Two studies of adults with asthma provide evidence for AHR to allergens  
30 when exposure to SO<sub>2</sub> was in combination with NO<sub>2</sub> ([Rusznak et al., 1996](#); [Devalia et al.,](#)  
31 [1994](#)). In the first of these studies, exposure to 0.2 ppm SO<sub>2</sub> or 0.4 ppm NO<sub>2</sub> did not  
32 affect airway responsiveness to house dust mite allergen immediately after a 6-hour  
33 exposure at rest. In considering the effect of SO<sub>2</sub> alone, because volunteers were exposed  
34 at rest, it is unlikely that enough SO<sub>2</sub> reached the bronchial airways to cause an effect.  
35 Following exposure to the two pollutants in combination, volunteers demonstrated an  
36 increased response to inhaled allergen ([Devalia et al., 1994](#)). [Rusznak et al. \(1996\)](#)  
37 confirmed these results in a similar study and found that AHR to dust mites persisted up

1 to 48-hours post-exposure. These results provide further evidence that SO<sub>2</sub> may elicit  
2 effects beyond the short time period typically associated with this pollutant.

### ***Epidemiologic Studies***

3 Unlike controlled human exposure studies, epidemiologic studies inconsistently indicate  
4 SO<sub>2</sub>-related lung function decrements in populations with asthma. This applies to  
5 previous ([U.S. EPA, 2008d](#)) and recent ([Table 5-5](#) and [Table 5-6](#)) studies as well as  
6 adults and children with asthma. Epidemiologic studies examined longer SO<sub>2</sub> averaging  
7 times and lags and had uncertainty in exposures estimated from central site monitors. For  
8 the few findings of SO<sub>2</sub>-associated lung function decrements, confounding by moderately  
9 to highly correlated PM and NO<sub>2</sub> ( $r = 0.54\text{--}0.9$ ) was not examined. A few recent studies  
10 address some of these uncertainties, but they persist in the evidence overall.

11 **Adults.** Previous studies were limited to Europe and Asia. A recent study shows an  
12 SO<sub>2</sub>-associated decrease in lung function in adults with asthma in the U.S. ([Qian et al.,](#)  
13 [2009b](#)). Recent studies in Europe and Asia do not ([Maestrelli et al., 2011](#); [Wiwatanadate](#)  
14 [and Liwsrisakun, 2011](#); [Canova et al., 2010](#)) ([Table 5-5](#)). Mean and upper percentile SO<sub>2</sub>  
15 concentrations tended to be lower in recent studies than in previous studies (e.g., means  
16 for 24-h avg 0.87–4.8 ppb vs. 1.6–90 ppb). However, lower concentrations do not appear  
17 to account for the weak recent evidence in adults with asthma as previous studies with  
18 mean SO<sub>2</sub> concentrations of 5.2 to 90 ppb did not observe SO<sub>2</sub>-associated lung function  
19 decrements ([Park et al., 2005](#); [Peters et al., 1996a](#)). Recent studies did not differ in  
20 temporal variability (e.g., ratio of the mean concentration to standard deviation) in SO<sub>2</sub>  
21 concentrations, which is the basis of analysis in these repeated measure studies.

22 The U.S. multicity study provides supporting evidence but has the same uncertainty in  
23 the exposure estimate as do other studies in adults with asthma. All studies estimated SO<sub>2</sub>  
24 exposure from central site monitors, either a single monitor or average of many monitors.  
25 Ambient SO<sub>2</sub> concentrations tend to show high spatiotemporal variability within a city,  
26 and correlations with personal exposure are poorly characterized ([Section 3.4.1.3](#)).  
27 Studies did not discuss whether measurements at the monitors adequately represented the  
28 spatiotemporal variability in ambient SO<sub>2</sub> concentrations in the study area. Uncertainty is  
29 high in the U.S. study, which averaged SO<sub>2</sub> concentrations across monitors within 32 km  
30 of subjects' ZIP code centroid ([Qian et al., 2009b](#)). Ambient SO<sub>2</sub> concentrations show  
31 large, transient peaks ([Section 2.5.3](#)), which may be important based on results from  
32 controlled human exposure studies showing that 5- to 10-minute exposures to  
33 200–600 ppb SO<sub>2</sub> induce rapid and short-lived lung function decrements. Epidemiologic  
34 studies examined same-day (lag 0) SO<sub>2</sub> concentrations, but the daily average. Daily  
35 average SO<sub>2</sub> concentrations may not represent peak exposures or capture the transient  
36 effects of peak exposures implicated in controlled human exposure studies.

1 Some recent studies that did not observe SO<sub>2</sub>-related lung function decrements had small  
2 sample sizes (N = 19 or 32) ([Maestrelli et al., 2011](#); [Canova et al., 2010](#)). However, it is  
3 unclear whether sample size explains the inconsistency among adults with asthma  
4 overall. Similarly sized studies ([Boezen et al., 2005](#); [Neukirch et al., 1998](#)) observed  
5 associations, and larger studies do not show evidence for association ([Wiwatanadate and](#)  
6 [Liwsrisakun, 2011](#); [Park et al., 2005](#); [Peters et al., 1996a](#)). In panel studies, the number of  
7 repeated measurements is also important, and [Canova et al. \(2010\)](#) measured lung  
8 function for five 30-day periods. Many studies that had a large number of repeated  
9 measurements examined lung function measured by subjects at home not supervised by a  
10 trained technician. Results were inconsistent for both methodologies.

11 A few recent epidemiologic studies add information on response modification by asthma  
12 phenotype but produce no clear finding. Previous results support an SO<sub>2</sub> association with  
13 decreased lung function or increased airway responsiveness in adults with asthma plus  
14 atopy ([Boezen et al., 2005](#); [Taggart et al., 1996](#)), but recent results do not ([Maestrelli et](#)  
15 [al., 2011](#)). A 10-ppb increase in 24-h avg SO<sub>2</sub> was associated with a -2.1 point change  
16 (95% CI: -6.6, 2.3) in percent predicted FEV<sub>1</sub>. Of note, the previous studies specified  
17 examining adults with AHR. Similar to controlled human exposure studies,  
18 epidemiologic studies do not clearly show that SO<sub>2</sub>-associated lung function decrements  
19 depend on asthma severity. An association was observed in adults with mild to moderate  
20 asthma ([Neukirch et al., 1998](#)), and the results varied among populations with more  
21 severe asthma ([Maestrelli et al., 2011](#); [Canova et al., 2010](#); [Qian et al., 2009b](#)). In contrast  
22 with the controlled human exposure studies, the U.S. asthma medication trial observed an  
23 SO<sub>2</sub>-related decrease in lung function in adults randomized to daily inhaled corticosteroid  
24 use [-8.4 L/minute change in PEF (95% CI: -13, -3.4) per 10-ppb increase in 24-h avg  
25 SO<sub>2</sub>] ([Qian et al., 2009b](#)). Decrements were not observed in the beta-agonist or placebo  
26 groups ([Table 5-5](#)). These two groups had more frequent asthma exacerbation during the  
27 study than the corticosteroid group but similar PEF and mean age ([Lazarus et al., 2001](#)).  
28 All three groups had persistent asthma. Thus, a clear explanation for the pattern of SO<sub>2</sub>  
29 associations is not apparent. There is no clear rationale for attributing null findings to the  
30 lack of analysis stratified by corticosteroid use, particularly for results that were adjusted  
31 for such use ([Maestrelli et al., 2011](#); [Canova et al., 2010](#)).

32 Across studies, the potential influence of copollutants is largely unaddressed. No study in  
33 adults with asthma examined PM<sub>2.5</sub> total mass, and previous studies observed lung  
34 function decrements in association with larger sized PM metrics that were highly  
35 correlated with SO<sub>2</sub> concentrations ( $r = 0.8-0.9$ ) and sulfate ([Neukirch et al., 1998](#); [Peters](#)  
36 [et al., 1996a](#)). That some cities had a coal-fired power plant or used coal for heating may  
37 explain some of the high correlations with PM and moderate correlations with NO<sub>2</sub>  
38 ( $r = 0.54$ ) ([Neukirch et al., 1998](#); [Taggart et al., 1996](#)). Copollutant interactions were not

1 assessed. Only the recent U.S. study analyzed confounding, but the potential for  
2 confounding is unclear. SO<sub>2</sub> was moderately correlated with NO<sub>2</sub> ( $r = 0.58$ , no report on  
3 PM<sub>10</sub>) but was associated with PEF in different medication use groups than NO<sub>2</sub> or PM<sub>10</sub>  
4 ([Qian et al., 2009b](#)). SO<sub>2</sub> was associated with PEF in the corticosteroid group, and effect  
5 estimates decreased slightly with adjustment for PM<sub>10</sub>, NO<sub>2</sub>, or O<sub>3</sub> ([Table 5-5](#)).  
6 Associations for PM<sub>10</sub> and NO<sub>2</sub> were observed in the beta-agonist and placebo groups,  
7 respectively, and were attenuated with SO<sub>2</sub> adjustment. However, inference from the  
8 results is weak due to numerous comparisons across pollutants, lags, and medication  
9 groups and questionable reliability in the exposures estimated from monitors up to 32 km  
10 away.

11 **Children.** As with adults, evidence from neither the 2008 ISA for Sulfur Oxides ([U.S.](#)  
12 [EPA, 2008d](#)) nor recent studies ([Table 5-6](#)) consistently links increases in ambient SO<sub>2</sub>  
13 concentration with lung function decrements in children with asthma, including recent  
14 U.S. multicity studies ([Ierodiakonou et al., 2015](#); [O'Connor et al., 2008](#)).

15 The inconsistency does not appear to be explained by lung function measured under  
16 supervised conditions or by subjects at home, asthma severity, or prevalence of asthma  
17 medication use. In contrast to adults with asthma, SO<sub>2</sub>-associated lung function  
18 decrements were not observed in children with asthma who took inhaled corticosteroids  
19 ([Ierodiakonou et al., 2015](#); [Liu et al., 2009b](#)). Among children with asthma in Windsor,  
20 ON, the association was limited to nonusers ([Liu et al., 2009b](#)). For some recent studies,  
21 including a U.S. multicity study, inference about an SO<sub>2</sub> effect is weak because the  
22 association was isolated to one lung function parameter or exposure lag among numerous  
23 lung function parameters, lags, pollutants, and/or asthma medication groups examined  
24 ([Ierodiakonou et al., 2015](#); [Wiwatanadate and Trakultivakorn, 2010](#)). A few recent  
25 studies aimed to address uncertainty in the exposure estimates or copollutant confounding  
26 ([Greenwald et al., 2013](#); [Dales et al., 2009](#); [Liu et al., 2009b](#)) and provide limited  
27 indication of SO<sub>2</sub>-associated lung function decrements.

**Table 5-5 Recent epidemiologic studies of lung function in adults with asthma.**

Study Population and Methodological Details	SO <sub>2</sub> Exposure Estimates (ppb)	SO <sub>2</sub> Averaging Time and Lag Day	Effect Estimate (95% CI) Single-Pollutant Model <sup>a</sup>	Copolutant Examination <sup>a</sup>
<p>†<a href="#">Qian et al. (2009b)</a>            Boston, MA; New York, NY; Philadelphia, PA; Madison, WI; Denver, CO; San Francisco, CA; 1997–1999            N = 154, ages 12–65 yr. 100% persistent asthma. 1/3 ICS use, 1/3 beta-agonist use, 1/3 placebo use.            Daily measures for 16 wk. Home PEF. Recruited from clinics as part of an asthma medication trial. Multiple comparisons—many pollutants, lags, medication use analyzed.</p>	<p>Monitors averaged within 32 km of subject ZIP code centroid.            Mean (SD): 4.8 (3.9)            75th percentile: 6.2            Max: 32</p>	<p>24-h avg            0  <hr/>           0–2 avg</p>	<p>Change in PEF (L/min)            All subjects: –0.12 (–3.0, 2.7)            ICS: –8.4 (–13, –3.4)            Beta-agonist: 4.4 (–0.49, 9.3)            Placebo: 3.3 (–1.4, 8.0)  <hr/>           All subjects: –1.9 (–5.6, 1.7)            ICS: –13 (–18, –6.4)            Beta-agonist: 6.4 (0.14, 13)            Placebo: 0.85 (–5.2, 6.9)</p>	<p>Copolutant model, ICS users, lag 0 with PM<sub>10</sub>: –7.3 (–15, 0) with NO<sub>2</sub>: –7.6 (–13, –1.8) with O<sub>3</sub>: –6.5 (–12, –1.4)            PM<sub>10</sub> association in placebo group, NO<sub>2</sub> in beta-agonist group. No association with O<sub>3</sub>. PM<sub>2.5</sub> not examined.            NO<sub>2</sub> and PM<sub>10</sub> associations attenuated with SO<sub>2</sub> adjustment.            SO<sub>2</sub> moderately correlated with NO<sub>2</sub>, <math>r = 0.58</math>. Correlation NR for PM<sub>10</sub>.</p>
<p>†<a href="#">Maestrelli et al. (2011)</a>            Padua, Italy, 2004–2005            N = 32, mean (SD) age 40 (7.5) yr. 81% persistent asthma. 69% ICS use. 90% atopy.            6 measures over 2 yr. Supervised spirometry. Recruited from database of beta-agonist users (&gt;6 times per yr for 3 yr).</p>	<p>Two monitors in city            Medians across seasons: 0.87–2.7            75th percentiles across seasons: 1.3–4.1</p>	<p>24-h avg            0</p>	<p>Change in % predicted FEV<sub>1</sub>            All subjects: –2.1 (–6.6, 2.3)            Nonsmokers: –11 (–40, 18)</p>	<p>No copollutant model            CO associated with FEV<sub>1</sub>. No association with personal or central site PM<sub>2.5</sub>. No association for central site PM<sub>10</sub>, NO<sub>2</sub>, O<sub>3</sub>.            Copollutant correlations NR.</p>
<p>†<a href="#">Canova et al. (2010)</a>            Padua, Italy, 2004–2005            N = 19, ages 15–44 yr. 79% moderate/severe asthma. 58% ICS use.            Daily measures for five 30-d periods over 2 yr. Home PEF/FEV<sub>1</sub>. Part of same cohort as <a href="#">Maestrelli et al. (2011)</a> above.</p>	<p>Two monitors in city            Mean (SD): 1.4 (1.1)            Max: 4.9</p>	<p>24-h avg            0, 1, 2, 3, 0–1 avg, 0–3 avg</p>	<p>Quantitative effect estimates NR. Figure shows negative but imprecise associations for PEF and FEV<sub>1</sub> with wide 95% CIs.</p>	<p>Copolutant model with CO            CO association with PEF not FEV<sub>1</sub> robust to SO<sub>2</sub> adjustment. No association for PM<sub>10</sub> or NO<sub>2</sub>. PM<sub>2.5</sub> not examined.            SO<sub>2</sub> moderately correlated with CO, PM<sub>10</sub>, and NO<sub>2</sub>. Spearman <math>r = 0.50, 0.51, 0.54</math>.</p>

**Table 5-5 (Continued): Recent epidemiologic studies of lung function in adults with asthma.**

Study Population and Methodological Details	SO <sub>2</sub> Exposure Estimates (ppb)	SO <sub>2</sub> Averaging Time and Lag Day	Effect Estimate (95% CI) Single-Pollutant Model <sup>a</sup>	Copolutant Examination <sup>a</sup>
<p>†<a href="#">Wiwatanadate and Liwsrisakun (2011)</a>                      Chiang Mai, Thailand, 2005–2006                      N = 121, ages 13–78 yr. 48% moderate/severe persistent asthma.                      Daily measures for 10 mo. Home PEF.                      Recruited from allergy clinics.</p>	<p>Monitor within 10 km of home                      Mean (SD): 1.7 (0.62)                      90th percentile: 2.4                      Max: 3.9</p>	<p>24-h avg                      4</p>	<p>NR</p>	<p>Only multipollutant models analyzed                      SO<sub>2</sub> increment and units of PEF NR.                      with PM<sub>2.5</sub> and NO<sub>2</sub>                      Evening PEF: 0.90 (0.34, 1.5)                      Average PEF: 0.48 (0, 0.96)                      No associations with PM<sub>2.5</sub>, PM<sub>10</sub>, CO, O<sub>3</sub>.                      SO<sub>2</sub> weakly correlated with NO<sub>2</sub>, PM<sub>2.5</sub>. <math>r = 0.23, -0.07</math>.</p>

CI = confidence interval; CO = carbon monoxide; FEV<sub>1</sub> = forced expiratory volume in 1 sec; ICS = inhaled corticosteroid; N = sample size; NO<sub>2</sub> = nitrogen dioxide; NR = not reported; O<sub>3</sub> = ozone; PEF = peak expiratory flow; PM<sub>2.5</sub> = particulate matter with a nominal aerodynamic diameter less than or equal to 2.5 μm; PM<sub>10</sub> = particulate matter with a nominal aerodynamic diameter less than or equal to 10 μm;  $r$  = correlation coefficient; SD = standard deviation; SO<sub>2</sub> = sulfur dioxide.

<sup>a</sup>Effect estimates are standardized to a 10-ppb increase in 24-h avg SO<sub>2</sub>.

†Studies published since the 2008 Integrated Science Assessment for Sulfur Oxides.

1 For children in El Paso, TX, [Greenwald et al. \(2013\)](#) measured SO<sub>2</sub> at schools, which  
2 may better represent some component of exposure than a monitor not sited in a subject's  
3 microenvironment. For children attending the school near a major road, a 10-ppb increase  
4 in lag 0–3 avg SO<sub>2</sub> was associated with a –31% change (95% CI: –52, –2.0) in FEV<sub>1</sub>.  
5 This is the largest effect estimate among children or adults with asthma, but a 10-ppb  
6 increase in 4-day avg SO<sub>2</sub> is unlikely in the area [school mean 0.84 (SD: 0.54) ppb].  
7 Results are inconsistent for 24-h avg SO<sub>2</sub> assigned from monitors up to 2.3–50 km from  
8 children's homes or schools ([Amadeo et al., 2015](#); [Ierodiakonou et al., 2015](#); [Dales et al.,  
9 2009](#); [Liu et al., 2009b](#); [O'Connor et al., 2008](#)). Lung function decreased with increases in  
10 SO<sub>2</sub> concentrations at a monitor located a median distance of 2.3 km from children's  
11 homes ([O'Connor et al., 2008](#)) but not a monitor within 50 km of children's ZIP code  
12 centroid ([Ierodiakonou et al., 2015](#)) ([Table 5-6](#)). Studies did not describe the adequacy of  
13 monitors at these distances to represent temporal variation in SO<sub>2</sub> exposure. No  
14 association was observed with the change in PEF after a 6-minute exercise ([Amadeo et  
15 al., 2015](#)), but this protocol does not mimic controlled human exposure studies because  
16 PEF was examined in relation to 13-day avg SO<sub>2</sub>.

17 In children with asthma, associations with lung function were mixed for temporally  
18 resolved SO<sub>2</sub> metrics. However, the extent to which concentrations at monitors up to  
19 4.8–10 km from homes represent children's 1- to 12-hour exposures is not known.  
20 Previous studies observed an association with 1-h max SO<sub>2</sub> ([Delfino et al., 2003b](#)) but not  
21 8-h max or 3-h avg (8–11 a.m.) SO<sub>2</sub> ([Delfino et al., 2003a](#); [Mortimer et al., 2002](#)). Recent  
22 results also are mixed. Morning and bedtime FEV<sub>1</sub> were not associated with 8-hour or  
23 12-hour overnight (12 a.m. or 8 p.m.–8 a.m.) or 12-hour daytime (8 a.m.–8 p.m.) avg  
24 SO<sub>2</sub> concentrations, but the diurnal change in FEV<sub>1</sub> decreased with an increase in 12-hour  
25 daytime avg SO<sub>2</sub> ([Dales et al., 2009](#)) ([Table 5-6](#)). Previous studies associated lung  
26 function decrements with lag 0 day SO<sub>2</sub> concentrations ([Delfino et al., 2003b](#); [Peters et  
27 al., 1996a](#)). Recent studies point to associations with 3- to 5-day avg concentrations  
28 ([Greenwald et al., 2013](#); [Liu et al., 2009b](#); [O'Connor et al., 2008](#)), and effect estimates are  
29 larger than those for lag 0 or 1 ([Table 5-6](#)). There is limited support from a controlled  
30 human exposure study for lung function decreasing after exposure on 2 days. Repeated  
31 SO<sub>2</sub> exposures enhance allergic inflammation in rodents, and allergic  
32 inflammation-mediated lung function decrements could explain associations with  
33 multiday SO<sub>2</sub> concentrations. Most studies did not report the prevalence of atopy, but a  
34 U.S. multicity study observed an association in a population with 100% atopy and asthma  
35 ([O'Connor et al., 2008](#)). The results agree with previous findings in children with asthma  
36 plus atopy ([Segala et al., 1998](#)).

**Table 5-6 Recent epidemiologic studies of lung function in children with asthma.**

Study Population and Methodological Details	SO <sub>2</sub> Exposure Estimates (ppb)	SO <sub>2</sub> Averaging Time and Lag Day	Effect Estimate (95% CI) Single-Pollutant Model <sup>a</sup>	Copollutant Examination <sup>a</sup>
<p>†<a href="#">Greenwald et al. (2013)</a> El Paso, TX, Mar–Jun 2010 N = 38, mean age 10 yr. 47% daily asthma medication use. Weekly measures for 13 wk. Supervised spirometry. Recruited from schools.</p>	<p>Monitor at school A: residential area B: 91 m from major road Mean (SD): 1.2 (0.44) and 0.84 (0.54) Upper percentiles NR.</p>	<p>24-h avg 0–3 avg</p>	<p>Percent change in FEV<sub>1</sub> A: 15 (–60, 210) B: –31 (–52, –2.0)</p>	<p>No copollutant model Association with BC, NO<sub>2</sub>, BTEX, cleaning product VOCs (a-pinene, dichlorobenzene, d-limonene) at school B. No association with PM<sub>2.5</sub>. SO<sub>2</sub> weakly correlated with BC, NO<sub>2</sub>, BTEX, cleaning product VOCs. Pearson <math>r = -0.14, -0.22, -0.07, 0.14</math></p>
<p>†<a href="#">Dales et al. (2009)</a> Windsor, ON, Oct–Dec 2005 N = 182, ages 9–14 yr. 37% ICS use, 35% beta-agonist use. Daily measures for 4 wk. Home FEV<sub>1</sub>. Recruited from schools. Mean 1.6 and 2.2 h/d spent outdoors for two study groups.</p>	<p>Two monitors averaged 99% homes within 10 km of sites. Median: 4.5 95th percentile: 16</p>	<p>12-h avg 8 a.m.–8 p.m. 8 p.m.–8 a.m. 8-h avg 12 a.m.–8 a.m. 24-h avg</p>	<p>Percent change in FEV<sub>1</sub> Bedtime: 0 (–0.92, 0.93) Diurnal: –1.41 (–2.73, –0.08) Bedtime: –0.17 (–0.98, 0.65) Morning: 0.63 (–0.28, 1.55) Bedtime: –0.14 (–1.03, 0.76)</p>	<p>Copollutant model results in figure. SO<sub>2</sub> association with diurnal change in FEV<sub>1</sub> persists with adjustment for PM<sub>2.5</sub>, NO<sub>2</sub>, or O<sub>3</sub>. NO<sub>2</sub> and PM<sub>2.5</sub> associations persist with adjustment for SO<sub>2</sub>. No association with O<sub>3</sub>. SO<sub>2</sub> moderately correlated with PM<sub>2.5</sub>, weakly correlated with NO<sub>2</sub>. Pearson <math>r = 0.43, 0.31</math>.</p>
<p>†<a href="#">Liu et al. (2009b)</a>, <a href="#">Liu (2013)</a> Windsor, ON, Oct–Dec 2005 N = 182, ages 9–14 yr. 37% ICS use, 35% beta-agonist use. Weekly measures for 4 wk. Supervised spirometry. Same cohort as <a href="#">Dales et al. (2009)</a> above.</p>	<p>Two monitors averaged 99% homes within 10 km of sites. Median: 4.5 95th percentile: 16</p>	<p>24-h avg 0 0–2 avg</p>	<p>Percent change FEV<sub>1</sub>: –0.46 (–2.0, 1.1) FEF<sub>25–75%</sub>: –1.5 (–4.7, 2.0) Change in percent predicted FEV<sub>1</sub>: –2.0 (–4.6, 0.74) FEF<sub>25–75%</sub>: –5.7 (–11, –2.2)</p>	<p>Copollutant model, lag 0–2 avg, FEF<sub>25–75%</sub> with PM<sub>2.5</sub>: 7.2 (–2.8, 18) with NO<sub>2</sub>: –2.4 (–8.7, 4.3) with O<sub>3</sub>: –5.4 (–11, –0.19) NO<sub>2</sub> and PM<sub>2.5</sub> associations persist with adjustment for SO<sub>2</sub>. No association with O<sub>3</sub>. SO<sub>2</sub> moderately correlated with PM<sub>2.5</sub>, weakly correlated with NO<sub>2</sub> and O<sub>3</sub>. Spearman <math>r = 0.56, 0.18, -0.02</math>.</p>

**Table 5-6 (Continued): Recent epidemiologic studies of lung function in children with asthma.**

Study Population and Methodological Details	SO <sub>2</sub> Exposure Estimates (ppb)	SO <sub>2</sub> Averaging Time and Lag Day	Effect Estimate (95% CI) Single-Pollutant Model <sup>a</sup>	Copolutant Examination <sup>a</sup>
<p><a href="#">†O'Connor et al. (2008)</a> Inner-City Asthma Study cohort: Boston, MA; Bronx, NY; New York, NY; Chicago, IL; Dallas, TX; Tucson, AZ; Seattle, WA; 1998–2001 N = 861, ages 5–12 yr. 100% persistent asthma. 100% atopy. Daily measures for four 2-wk periods. Home FEV<sub>1</sub>/PEF. Recruited from intervention study.</p>	<p>Monitors averaged close to home and not near industry. Median 2.3 km to site. Quantitative SO<sub>2</sub> data NR.</p>	<p>24-h avg 1–5 avg</p>	<p>Change in percent predicted FEV<sub>1</sub>: –1.29 (–2.04, –0.54) PEF: –1.73 (–2.49, –0.96) No association for lag 1.</p>	<p>No copollutant model Associations observed with PM<sub>2.5</sub>, NO<sub>2</sub>. Associations with CO and O<sub>3</sub> imprecise with wide 95% CIs. SO<sub>2</sub> weakly correlated with PM<sub>2.5</sub>, moderately correlated with NO<sub>2</sub>. <i>r</i> = 0.37, 0.59.</p>
<p><a href="#">†Amadeo et al. (2015)</a> Pointe-à-Pitre, Guadeloupe, 2008–2009 N = 71, ages 8–13 yr. Cross-sectional. Supervised spirometry. Recruited from schools.</p>	<p>Monitors in city Number and distance NR Mean (SD): 1.8 (1.4) Max: 4.9</p>	<p>24-h avg 0–13 avg</p>	<p>Change in prerun PEF (L/min) 93 (–28, 214) Percent change post 6-min run –1.6 (–36, 33)</p>	<p>No copollutant model No association observed with PM<sub>10</sub>, NO<sub>2</sub>, or O<sub>3</sub>. PM<sub>2.5</sub> not examined. Copolutant correlations NR.</p>
<p><a href="#">†Ierodiakonou et al. (2015)</a> Childhood Asthma Management Program cohort: Boston, MA; Baltimore, MD; St. Louis, MO; Denver, CO; Albuquerque, NM; San Diego, CA; Toronto, ON, 1993–1999 N = 1,003, ages 5–12 yr. 100% mild/moderate asthma. 30% ICS use. 30% mast cell inhibitor use. 14 measures over 4 yr. Supervised spirometry. Recruited from clinics. Multiple comparisons—many pollutants, lags, exposure durations, medication use analyzed.</p>	<p>Nearest monitor within 50 km of ZIP code centroid. Medians across cities: 2–6 90th percentiles across cities: 5–24</p>	<p>24-h avg 0</p>	<p>Change in percent predicted Prebronchodilator FEV<sub>1</sub> All subjects 0.25 (–0.13, 0.63) ICS: 0.38 (–0.30, 1.1) Post-bronchodilator FEV<sub>1</sub> ICS: 0 (–0.73, 0.75)  Change in methacholine that induces a 20% drop in FEV<sub>1</sub> Mast cell inhibitor: –13% (–25, 1.3)</p>	<p>No copollutant model Association with CO, not O<sub>3</sub> or NO<sub>2</sub>. PM<sub>2.5</sub> not examined. SO<sub>2</sub> weakly to moderately correlated with CO, O<sub>3</sub>, and NO<sub>2</sub> across cities. Spearman <i>r</i> = 0.19–0.34, –0.41 to –0.05, 0.15–0.54.</p>

**Table 5-6 (Continued): Recent epidemiologic studies of lung function in children with asthma.**

Study Population and Methodological Details	SO <sub>2</sub> Exposure Estimates (ppb)	SO <sub>2</sub> Averaging Time and Lag Day	Effect Estimate (95% CI) Single-Pollutant Model <sup>a</sup>	Copollutant Examination <sup>a</sup>
<a href="#">†Wiwatanadate and Trakultivakorn (2010)</a> Chiang Mai, Thailand, 2005–2006 N = 31, ages 4–11 yr. 100% with symptoms in previous yr. 52% mild intermittent asthma Daily measures for 1 yr. Home PEF. Recruited from allergy clinic. Multiple comparisons—many pollutants, lags, lung function parameters analyzed.	Monitor within 25 km of home	24-h avg	Change in PEF (L/min)	Copollutant model, lag 4, daily average PEF.
	Mean (SD): 1.7 (0.62)	0	Evening PEF	with O <sub>3</sub> , lag 5: -16 (-31, -1.1)
	90th percentile: 2.4	4	-8.1 (-25, 9.2)	O <sub>3</sub> association persists with adjustment for SO <sub>2</sub> . No association with PM <sub>2.5</sub> , CO, NO <sub>2</sub> .
	Max: 3.9 ppb	0	-21 (-38, -4.1)	SO <sub>2</sub> weakly correlated with O <sub>3</sub> , PM <sub>2.5</sub> , CO, NO <sub>2</sub> . <i>r</i> = -0.04, -0.07, 0.38, 0.23
		4	Daily average PEF	
			-0.3 (-15, 15)	
			-18 (-32, -2.8)	

BC = black carbon; BTEX = benzene, toluene, ethylbenzene, xylene; CI = confidence interval; CO = carbon monoxide; FEF<sub>25–75%</sub> = forced expiratory flow at 25–75% of forced vital capacity; FEV<sub>1</sub> = forced expiratory volume in 1 sec; ICS = inhaled corticosteroid; L/min = liters per min; N = sample size; NO<sub>2</sub> = nitrogen dioxide; NR = not reported; O<sub>3</sub> = ozone; PEF = peak expiratory flow; PM<sub>2.5</sub> = particulate matter with a nominal aerodynamic diameter less than or equal to 2.5 µm; PM<sub>10</sub> = particulate matter with a nominal aerodynamic diameter less than or equal to 10 µm; *r* = correlation coefficient; SD = standard deviation; SO<sub>2</sub> = sulfur dioxide; VOC = volatile organic compound.

<sup>a</sup>Effect estimates are standardized to a 10-ppb increase in 8-h to 24-h avg SO<sub>2</sub>.

†Studies published since the 2008 Integrated Science Assessment for Sulfur Oxides.

1 Where SO<sub>2</sub> was associated with lung function decrements in children with asthma,  
2 associations also were observed with PM<sub>2.5</sub>, PM<sub>10</sub>, sulfate, BC, OC, TSP, NO<sub>2</sub>, or various  
3 VOCs ([Greenwald et al., 2013](#); [Dales et al., 2009](#); [Liu et al., 2009b](#); [O'Connor et al.,  
4 2008](#); [Delfino et al., 2003b](#); [Peters et al., 1996a](#)). These copollutants were often  
5 moderately to highly correlated with SO<sub>2</sub> ( $r = 0.56$ – $0.9$ ), particularly in previous studies.  
6 SO<sub>2</sub> averaging times varied across studies, making it difficult to assess whether higher  
7 correlations are due to higher air pollution levels in the past. Copollutant confounding  
8 and interactions are poorly studied, and unstudied for children living near a coal-fired  
9 power plant ([Peters et al., 1996a](#)). O<sub>3</sub> may not influence the associations observed with  
10 SO<sub>2</sub>. SO<sub>2</sub> and O<sub>3</sub> measurements at central site monitors were not correlated ( $r = -0.02$ ),  
11 and SO<sub>2</sub> associations persisted with adjustment for O<sub>3</sub> ([Dales et al., 2009](#); [Liu et al.,  
12 2009b](#)). A recent study adds information on SO<sub>2</sub> results adjusted for correlated  
13 copollutants. Among children with asthma in Windsor, ON, the SO<sub>2</sub> association persisted  
14 with adjustment for PM<sub>2.5</sub> or NO<sub>2</sub> for 12-h avg SO<sub>2</sub> ([Dales et al., 2009](#)) but not 24-h avg  
15 SO<sub>2</sub> ([Liu, 2013](#); [Liu et al., 2009b](#)) ([Table 5-6](#)). Associations for PM<sub>2.5</sub> were robust to SO<sub>2</sub>  
16 adjustment, but inference about confounding is weak due to the moderate SO<sub>2</sub>-PM<sub>2.5</sub>  
17 correlation ( $r = 0.56$ ) and the potential differential exposure error for SO<sub>2</sub> and PM<sub>2.5</sub>  
18 measurements, which were made up to 10 km from subjects' homes. Weak inference also  
19 applies to results in a Los Angeles, CA cohort showing an imprecise association for SO<sub>2</sub>  
20 after adjustment for benzene [ $-34$  L/minute change in PEF (95% CI:  $-120, 52$ ) per  
21 40-ppb increase in 1-h max SO<sub>2</sub>] ([Delfino et al., 2003b](#)). SO<sub>2</sub> was highly correlated with  
22 benzene ( $r = 0.70$ ), and pollutants were measured up to 4.8 km from home or school.

### ***Summary of Lung Function Changes in Populations with Asthma***

23 Controlled human exposure studies provide strong evidence for SO<sub>2</sub>-induced lung  
24 function decrements in adults with asthma under increased ventilation conditions.  
25 Short-term exposures for 5–10 minutes to 0.2–0.3 ppm SO<sub>2</sub> resulted in 5–30% of  
26 exercising individuals with asthma experiencing moderate or greater decrements (defined  
27 in terms of a  $\geq 15\%$  decrease in FEV<sub>1</sub> or  $\geq 100\%$  increase in sRaw; [Table 5-2](#)). Exposures  
28 for 5–10-minutes to SO<sub>2</sub> at concentrations  $\geq 0.4$  ppm results in moderate or greater  
29 decrements in lung function in 20–60% of exercising individuals with asthma. A group  
30 of responders (defined as having  $\geq 15\%$  decrease in FEV<sub>1</sub> after exposure to 0.6 or 1.0 ppm  
31 SO<sub>2</sub>) showed statistically significant decrements in FEV<sub>1</sub> following exposure for  
32 5–10 minutes to 0.3 ppm SO<sub>2</sub> ([Table 5-3](#)). Less evidence is available from controlled  
33 human exposure studies to assess SO<sub>2</sub>-induced lung function decrements in children with  
34 asthma. However, school-aged children, particularly boys and perhaps obese children,  
35 should be expected to experience greater responsiveness (i.e., larger decrements in lung  
36 function) following exposure to SO<sub>2</sub> than normal-weight adolescents and adults.

1 For both adults and children with asthma, epidemiologic evidence is inconsistent for lung  
2 function decrements associated with ambient SO<sub>2</sub> concentrations ([Table 5-5](#) and  
3 [Table 5-6](#)), but most results indicate associations in populations with asthma plus atopy.  
4 In the few controlled human exposure and epidemiologic studies, findings of increased  
5 airway responsiveness could not be attributed to exposure to SO<sub>2</sub> alone versus a  
6 copollutant or mixture. A limitation across epidemiologic studies is the uncertainty in the  
7 SO<sub>2</sub> exposure estimates. A recent study observed an association with SO<sub>2</sub> measured at  
8 children's schools, but others used monitors located 2.3–50 km from subjects' homes or  
9 schools. It is unclear whether the SO<sub>2</sub> concentrations at central site monitors adequately  
10 represent the variation in personal exposure, especially if peak exposures are important as  
11 indicated by controlled human exposure studies. The influence of copollutants on  
12 epidemiologic results remains largely uncharacterized, including associations in  
13 populations with asthma plus atopy and populations living near SO<sub>2</sub> sources. SO<sub>2</sub>-related  
14 lung function decrements in adults and children with asthma are inconsistently observed  
15 after adjustment for PM<sub>2.5</sub>, PM<sub>10</sub>, or NO<sub>2</sub>, but the implications of these results are unclear  
16 because of uncertainty in the exposure estimates and potential differential exposure error.

### **Respiratory Symptoms in Populations with Asthma**

17 The 2008 SO<sub>x</sub> ISA ([U.S. EPA, 2008d](#)) reported strong evidence for the effects of SO<sub>2</sub>  
18 exposure on respiratory symptoms in controlled human exposure studies in individuals  
19 with asthma under increased ventilation conditions. No new controlled human exposure  
20 studies have been reported since the previous ISA. In contrast, previous and recent  
21 epidemiologic evidence for SO<sub>2</sub>-associated increases in respiratory symptoms is weak in  
22 adults with asthma. However, epidemiologic evidence supports associations in children  
23 with asthma, and recent studies add evidence for estimates of SO<sub>2</sub> exposure at school  
24 and/or home. Overall, the influence of copollutants remains largely unexamined.

#### ***Controlled Human Exposure Studies***

25 As reviewed in the 2008 ISA for Sulfur Oxides and the 1986 Supplement to the Second  
26 Addendum ([U.S. EPA, 2008d, 1994](#)), controlled human exposure studies demonstrate  
27 increases in incidence or severity of respiratory symptoms (i.e., cough, chest tightness,  
28 throat irritation) in individuals with asthma exposed to SO<sub>2</sub> concentrations between 0.2  
29 and 0.6 ppm for 5–10 minutes during exercise ([Table 5-2](#) and [Table 5-7](#)). Statistically  
30 significant increases are observed at SO<sub>2</sub> concentrations  $\geq 0.4$  ppm.

**Table 5-7 Study-specific details from controlled human exposure studies of respiratory symptoms.**

<b>Study</b>	<b>Disease Status; n; Sex; (Age<sup>a</sup>)</b>	<b>Exposure Details (Concentration; Duration)</b>	<b>Time of Symptom Assessment</b>
<a href="#">Gong et al. (1995)</a>	Asthma; n = 14; 12 M, 2 F; (27 ± 11 yr)	0, 0.5, or 1.0 ppm SO <sub>2</sub> with light, medium, and heavy exercise (average ventilation 30, 36, and 43 L/min) for 10 min	Before, during, and immediately after exposure
<a href="#">Gong et al. (1996)</a>	Asthma; n = 10; 2 M, 8 F; (30.3 ± 9.2 yr)	0 or 0.75 ppm SO <sub>2</sub> with exercise (29 L/min) for up to 24 h with or w/o pretreatment with salmeterol (long-acting B <sub>2</sub> -agonist)	Before and immediately after exposure
<a href="#">Gong et al. (2001)</a>	Asthma; n = 11; 2 M, 9 F; (30.8 ± 11.3 yr)	0 or 0.75 ppm SO <sub>2</sub> for 10 min with exercise (35 L/min) with or w/o pretreatment to montelukast sodium (10 mg/d for 3 d)	Before, immediately after, and 1 and 2 h after exposure
<a href="#">Horstman et al. (1988)</a>	Asthma; n = 12 M; (28.6 ± 5.5 yr)	0 or 1.0 ppm SO <sub>2</sub> for 0, 0.5, 1.0, 2.0, and 5.0 min with exercise (treadmill, 40 L/min)	Before and immediately after exposure
<a href="#">Magnussen et al. (1990)</a>	Asthma; n = 46; 21 M, 25 F; (28 ± 14 yr)	0 or 0.5 ppm SO <sub>2</sub> for 20 min. 10 min rest followed by 10 min isocapnic hyperventilation (30 L/min)	Before exposure and immediately after hyperventilation
<a href="#">Kehrl et al. (1987)</a>	Asthma; n = 10 M; (26.8 ± 4.4 yr)	0 or 1 ppm SO <sub>2</sub> for 1 h with exercise (3 × 10 min, 41 L/min, treadmill)	Before and during exposure/exercise
<a href="#">Koenig et al. (1980)</a>	Asthma; n = 9; 7 M, 2 F; (15.7 ± 1.1 yr)	0 or 1 ppm SO <sub>2</sub> with 1 mg/m <sup>3</sup> of NaCl droplet aerosol, 1 mg/m <sup>3</sup> NaCl droplet aerosol for 60 min exposure with mouthpiece at rest	Before, during, and immediately after exposure
<a href="#">Koenig et al. (1981)</a>	Asthma; n = 8; 6 M, 2 F; (14–18 yr)	0 or 1 ppm SO <sub>2</sub> with 1 mg/m <sup>3</sup> of NaCl droplet aerosol, 1 mg/m <sup>3</sup> NaCl droplet aerosol for 30 min exposure via mouthpiece at rest followed by 10 min exercise on a treadmill (sixfold increase in V <sub>E</sub> )	Before, during, and immediately after exposure
<a href="#">Koenig et al. (1983)</a>	Phase 1: Asthma with EIB; n = 9; 6 M, 3 F; (12–16 yr) Phase 2: Asthma with EIB; n = 7 (sex NR); (12–16 yr)	Phase 1: 1 g/m <sup>3</sup> of NaCl droplet aerosol, 1 ppm SO <sub>2</sub> , 1 mg/m <sup>3</sup> NaCl, 0.5 ppm SO <sub>2</sub> + 1 mg/m <sup>3</sup> NaCl for 30 min exposure via mouthpiece at rest followed by 10 min exercise on treadmill (five- to sixfold increase in V <sub>E</sub> ) Phase 2: 0.5 ppm SO <sub>2</sub> + 1 mg/m <sup>3</sup> NaCl via a face mask with no nose clip with exercise conditions the same as <a href="#">Koenig et al. (1981)</a>	Before and immediately after exposure

**Table 5-7 (Continued): Study specific details from controlled human exposure studies of respiratory symptoms.**

Study	Disease Status; n; Sex; (Age <sup>a</sup> )	Exposure Details (Concentration; Duration)	Time of Symptom Assessment
<a href="#">Koenig et al. (1987)</a>	Allergy with EIB; n = 10; 3 M, 7 F; (13–17 yr)	0 or 0.75 ppm SO <sub>2</sub> (mouthpiece) with exercise (33.7 L/min) for 10 min and 20 min prior pretreatment (0 or 180 µg albuterol)	Before and immediately after pretreatment and exposure
<a href="#">Koenig et al. (1990)</a>	Asthma with EIB; n = 13; 8 M, 5 F (14.3 ± 1.8 yr)	0.1 ppm SO <sub>2</sub> for 15 min preceded by air or 0.12 ppm O <sub>3</sub> for 45 min during intermittent exercise (2 × 15 min, 30 L/min, treadmill), no control, air exposure	Before and immediately after exposure
<a href="#">Koenig et al. (1992)</a>	Asthma; n = 8; 2 M, 6 F; (27.5 ± 9.6 yr)	1 ppm SO <sub>2</sub> for 10 min with exercise ( $\dot{V}_E = 13.4\text{--}31.3$ L/min) with or w/o pretreatment to theophylline	Before and immediately after exposure
<a href="#">Linn et al. (1983b)</a>	Asthma; n = 23; 13 M, 10 F; (23.3 ± 4.4 yr)	0, 0.2, 0.4, or 0.6 ppm SO <sub>2</sub> with low humidity or high humidity for 10 min with exercise (bicycle, 5 min 50 L/min) 0 or 0.6 ppm SO <sub>2</sub> with warm air or cold air with exercise (bicycle, 50 L/min, ~5 min)	Before and immediately after exposure
<a href="#">Linn et al. (1983a)</a>	Asthma; n = 23; 15 M, 8 F (23 ± 4 yr)	0 or 0.75 ppm SO <sub>2</sub> with unencumbered breathing and mouth only breathing with exercise (40 L/m, 10 min, bicycle)	Before and immediately after exposure
<a href="#">Linn et al. (1984a)</a>	Asthma; n = 14; 12 M, 2 F (24.1 ± 4.7 yr)	0, 0.3, or 0.6 ppm SO <sub>2</sub> at 21°, 7°, and –6°C, rH 80% with exercise (bicycle, 50 L/min, ~5 min)	Before, during, immediately after, and a week after exposure
<a href="#">Linn et al. (1984c)</a>	Asthma; n = 24; 13 M, 11 F; (24.0 ± 4.3 yr)	0, 0.3, or 0.6 ppm SO <sub>2</sub> at 21°, 7 and –6°C and 80% rH with exercise (5 min, 50 L/min)	Before, immediately after, and 24 h after exposure
<a href="#">Linn et al. (1984b)</a>	Asthma; Phase 1 (Pilot) n = 8; 4 M, 4 F; (24.5 ± 3.9 yr) Phase 2 n = 24; 19 M, 5 F; (24.0 ± 4.3 yr)	Phase 1: 0, 0.2, 0.4, or 0.6 ppm SO <sub>2</sub> at 5°C, 50, and 85% rH with exercise (5 min, 50 L/min) Phase 2: 0 and 0.6 ppm SO <sub>2</sub> at 5° and 22°C, 85% rH with exercise (5 min, 50 L/min)	Phase 1: before and immediately after exposure Phase 2: before, immediately after, 1 d after, and 1 wk after exposure
<a href="#">Linn et al. (1985b)</a>	Asthma; n = 22; 13 M, 9 F; (23.5 ± 4.0 yr)	0 or 0.6 ppm SO <sub>2</sub> at 21 and 38°C, 20 and 80% rH with exercise (~5 min, 50 L/min)	Before, immediately after, and 24 h after exposure
<a href="#">Linn et al. (1985a)</a>	Asthma with COPD; n = 24; 15 M, 9 F; (60 yr; Range: 49–68 yr)	0, 0.4, or 0.8 ppm SO <sub>2</sub> for 1 h with exercise (2 × 15 min, bicycle, 18 L/min)	Before, during, immediately after, 24 h after, and 7 d after exposure

**Table 5-7 (Continued): Study specific details from controlled human exposure studies of respiratory symptoms.**

Study	Disease Status; n; Sex; (Age <sup>a</sup> )	Exposure Details (Concentration; Duration)	Time of Symptom Assessment
<a href="#">Linn et al. (1987)</a>	Healthy; n = 24; 15 M, 9 F; (18–37 yr)  Atopic (sensitive to common airborne allergens but no asthma); n = 21; 12 M, 9 F; (18–35 yr)  Minimal or mild asthma; n = 16; 10 M, 6 F; (20–33 yr)  Moderate or severe asthma; n = 24; 10 M, 14 F; (18–35 yr)	0, 0.2, 0.4, or 0.6 ppm SO <sub>2</sub> for 1 h with exercise (3 × 10-min, bicycle, ~40 L/min)	Before and during exposure (after first exercise and after last exercise)
<a href="#">Linn et al. (1988)</a>	Asthma; n = 20; 13 M, 7 F; (28 ± 5 yr)	Three pretreatment groups (1) metaproterenol sulfate, (2) placebo, (3) no treatment  0, 0.3, and 0.6 ppm SO <sub>2</sub> for 10 min with exercise (bike, 50 L/min)	Before, immediately after, 10 min, 30 min, 60 min, 120 min, 24 h, and 1 wk after exposure
<a href="#">Linn et al. (1990)</a>	Asthma; n = 21; 6 M, 15 F; (34.8 ± 8.9 yr)	0, 0.3, or 0.6 ppm SO <sub>2</sub> 10 min with exercise (50 L/min)  (1) low medication use, (2) normal, (3) high usual medication supplemented by inhaled metaproterenol before exposure	Before exposure, after pretreatment, immediately after, 30 min after, and 60 min after exposure
<a href="#">Myers et al. (1986a)</a>	Asthma; n = 10; 7 M, 3 F; (27.6 ± 5.5 yr)	Three pretreatment groups (1) 200 mg cromolyn, (2) 20 mg cromolyn, (3) placebo  Doubling concentrations of SO <sub>2</sub> during sequential 3 min exposures, from 0.25 to 8 ppm	Before and after each 3-min exposure to an increasing SO <sub>2</sub> concentration
<a href="#">Sheppard et al. (1983)</a>	Asthma; n = 8; 4 M, 4 F; (26.6 ± 4.3 yr)	0.5 ppm SO <sub>2</sub> for 3 min eucapnic hyperpnea	Before and immediately after exposure
<a href="#">Trenka et al. (1999)</a>	Asthma; n = 47; 14 M, 33 F; (21.1 yr; Range: 18–39 yr)	0.5 ppm SO <sub>2</sub> for 10 min with moderate exercise	Before and immediately after exposure
<a href="#">Trenka et al. (2001)</a>	Asthma; n = 17; 5 M, 12 F; (27.4 ± 6.3 yr)	0.5 ppm SO <sub>2</sub> for 10 min with moderate exercise (treadmill)	Before and immediately after exposure

COPD = chronic obstructive pulmonary disease; EIB = exercise-induced bronchospasm; F = female; M = male; n = sample size; NaCl = sodium chloride; NR = not reported; O<sub>3</sub> = ozone; ppm = parts per million; rH = relative humidity; SD = standard deviation; SO<sub>2</sub> = sulfur dioxide; V<sub>E</sub> = minute volume.

<sup>a</sup>Range or Mean ± SD.

1 [Linn et al. \(1983b\)](#) reported the severity of respiratory symptoms following 5-minute  
2 exposures to 0, 0.2, 0.4, and 0.6 ppm SO<sub>2</sub> in heavily exercising individuals with mild to  
3 moderate asthma. Total symptom score changes were significant ( $0.01 < p < 0.05$ ) after  
4 0.2 ppm SO<sub>2</sub> exposure, but when scores were separated by categories, significance was  
5 not reached until concentrations were  $\geq 0.4$  ppm SO<sub>2</sub>. Subsequently, a similar study with a  
6 slightly lower level of exercise demonstrated that 43% of subjects with asthma  
7 experienced increases in respiratory symptoms after a 15-minute exposure to 0.6 ppm  
8 SO<sub>2</sub> ([Linn et al., 1987](#)). [Smith \(1993\)](#) provided additional support for increasing  
9 respiratory symptoms at concentrations as low as 0.4 ppm SO<sub>2</sub>.

10 Additional studies examining concentrations of  $\geq 0.5$  ppm SO<sub>2</sub> demonstrated SO<sub>2</sub>-induced  
11 increases in respiratory symptoms. Total and lower respiratory symptom scores were  
12 significantly increased with increasing SO<sub>2</sub> concentrations (0, 0.5, and 1.0 ppm SO<sub>2</sub>)  
13 following 10-minute exposures with varying levels of exercise ([Gong et al., 1995](#)).  
14 [Trenga et al. \(1999\)](#) confirmed these results, observing a significant correlation between  
15 FEV<sub>1</sub> decrements and increases in respiratory symptoms following 10-minute exposures  
16 to 0.5 ppm SO<sub>2</sub> via mouthpiece. Respiratory symptoms have also been observed  
17 following exposure durations as low as 3 minutes to 0.5 ppm SO<sub>2</sub> via mouthpiece during  
18 eucapnic hyperpnea ( $V_E = 0$  L/minute), in which seven out of eight individuals with  
19 asthma developed respiratory symptoms ([Balmes et al., 1987](#)).

20 As with lung function, increased respiratory symptoms in response to short-term  
21 exposure to SO<sub>2</sub> in individuals with asthma is dependent on exercise. [Linn et al. \(1983b\)](#)  
22 reported significant changes in total symptom scores after 0.2 ppm SO<sub>2</sub> exposure in  
23 heavily exercising individuals with asthma. In contrast, [Tunnicliffe et al. \(2003\)](#) found no  
24 association between respiratory symptoms (i.e., throat irritation, cough, wheeze) and  
25 1-hour exposures to 0.2 ppm SO<sub>2</sub> in adults with asthma at rest.

### ***Epidemiologic Studies***

26 Compared with controlled human exposure studies, epidemiologic evidence for  
27 SO<sub>2</sub>-associated increases in symptoms is variable, being supportive in children with  
28 asthma but weak in adults with asthma. A recent study not restricted to a certain lifestage  
29 does not support an association with asthma medication use but is limited by analysis of  
30 beta-agonist levels in wastewater rather than use ascertained for individual subjects and  
31 only reporting the lack of statistically significant associations ([Fattore et al., 2016](#))  
32 ([Table 5-8](#)). The evidence base specifically in children with asthma is larger and more  
33 informative, providing results for home and/or school SO<sub>2</sub> exposure estimates and  
34 temporally resolved SO<sub>2</sub> metrics. Also, while they do not settle questions, studies in  
35 children with asthma aim to assess copollutant confounding and interactions. Although

1 the evidence overall is less consistent in recent than previous studies, the aforementioned  
2 strengths are features of many recent studies of children with asthma.

3 **Adults.** SO<sub>2</sub> concentrations were lower in recent than previous studies (0.87–2.7 ppb vs.  
4 1.6–90 ppb for means), but this does not appear to explain the weak evidence because  
5 previous results also are inconsistent [Supplemental Figure 5S-1 ([U.S. EPA, 2016g](#))]. All  
6 studies have uncertainty in the SO<sub>2</sub> exposure estimates assigned from a single central site  
7 monitor or averaged across multiple monitors. No study indicated whether measurements  
8 at the monitors adequately represented the spatiotemporal variability in ambient SO<sub>2</sub>  
9 concentrations in the study area or the temporal variation in people’s exposures.

10 All epidemiologic studies of adults examined 24-h avg SO<sub>2</sub> concentrations, longer than  
11 the 5–10-minute exposures implicated in controlled human exposure studies ([Table 5-2](#)).  
12 Similar to previous studies, recent epidemiologic evidence does not indicate associations  
13 for respiratory symptoms with same-day (lag 0) SO<sub>2</sub> concentrations ([Anyenda et al.,](#)  
14 [2016](#); [Maestrelli et al., 2011](#)). Atopy was prevalent in [Maestrelli et al. \(2011\)](#) (90%);  
15 previous findings supported an association in adults with atopy plus asthma ([Boezen et](#)  
16 [al., 2005](#)). A recent study linked an increase in SO<sub>2</sub> concentration to an increase in  
17 nighttime asthma symptoms with a 5-day lag ([Wiwatanadate and Liwsrisakun, 2011](#)), but  
18 inference is weak because results were inconsistent among the many lags, pollutants, and  
19 health effects examined. Also, SO<sub>2</sub> exposures were assessed from a monitor up to 10 km  
20 from subjects’ homes. There is some consistency for SO<sub>2</sub> concentrations lagged 2 or  
21 5 days or averaged over 3 or 5 days, including recent results ([Anyenda et al., 2016](#))  
22 [Supplemental Figure 5S-1 ([U.S. EPA, 2016g](#))]. In these studies, symptoms were also  
23 associated with moderately to highly correlated PM metrics ( $r = 0.60$ – $0.9$ ). Whether the  
24 magnitude of copollutant correlations influences the consistency of association for SO<sub>2</sub>  
25 with respiratory symptoms in adults with asthma cannot be determined in this small  
26 evidence base. As examined only in a recent study, SO<sub>2</sub> associations persisted with  
27 adjustment for PAH or NO<sub>2</sub> ([Anyenda et al., 2016](#)). However, uncertainty in the  
28 exposures estimated from a single central site monitor and a different site for PAH limits  
29 inferences that can be drawn about an independent association for SO<sub>2</sub>. Controlled human  
30 exposure studies show symptoms to resolve once exposure ends, but SO<sub>2</sub>-induced allergic  
31 inflammation could be a pathway by which SO<sub>2</sub> exposure induces symptoms after several  
32 days or over multiple days.

**Table 5-8 Recent epidemiologic studies of respiratory symptoms in populations with asthma.**

Study Population and Methodological Details	SO <sub>2</sub> Exposure Estimates (ppb)	SO <sub>2</sub> Averaging Time and Lag Day	Effect Estimate (95% CI) Single-Pollutant Model <sup>a</sup>	Copollutant Examination <sup>a</sup>
<b>Adults With Asthma</b>				
<p><a href="#">†Maestrelli et al. (2011)</a> Padua, Italy, 2004–2005 N = 32, mean (SD) age 40 (7.5 yr). 81% persistent asthma. 69% ICS use. 90% atopy. Six measures over 2 yr. Symptoms assessed in clinic. Recruited from database of beta-agonist users (&gt;6 times per yr for 3 yr).</p>	<p>Two monitors in city Medians across seasons: 0.87–2.7 75th percentiles across seasons: 1.3–4.1</p>	<p>24-h avg 0</p>	<p>Asthma control score Increase = better control All subjects: 0.77 (–1.1, 2.6) Nonsmokers: 0.10 (–2.2, 2.4) n = 22</p>	<p>No copollutant model Association observed with CO and personal PM<sub>10</sub>. No association with personal or central site PM<sub>2.5</sub>. No association with central site NO<sub>2</sub>, O<sub>3</sub>. Copollutant correlations NR.</p>
<p><a href="#">†Wiwatanadate and Liwsrisakun (2011)</a> Chiang Mai, Thailand, 2005–2006 N = 121, ages 13–78 yr. 48% moderate/severe persistent asthma. Daily diary for 10 mo. Recruited from allergy clinics. Multiple comparisons—many pollutants, lags, health endpoints analyzed.</p>	<p>Monitor within 10 km of home Mean (SD): 1.7 (0.62) 90th percentile: 2.4 Max: 3.9</p>	<p>24-h avg 2 5</p>	<p>SO<sub>2</sub> increment NR. Results reported only for statistically significant lags.  Daytime symptoms OR: 0.90 (0.81, 0.99)  Nighttime symptoms OR: 1.16 (1.04, 1.29)</p>	<p>Copollutant model with NO<sub>2</sub> SO<sub>2</sub> and NO<sub>2</sub> association reported not statistically significant. Quantitative results NR. Association observed with PM<sub>10</sub> but no copollutant model. PM<sub>2.5</sub> not examined.  SO<sub>2</sub> weakly correlated with NO<sub>2</sub>, PM<sub>10</sub>. <i>r</i> = 0.23 for both.</p>
<p><a href="#">†Anyenda et al. (2016)</a> Kanazawa, Japan, Jan–June 2011 N = 83, ages 23–84 yr. 54% atopy. Daily diary for mean 153 d. Recruited from hospital outpatients.</p>	<p>One monitor in city Mean (SD): 1.6 (1.3) Max: 7.3</p>	<p>24-h avg 0 2 0-2 avg</p>	<p>Cough  0.67 (0.34, 1.31)  2.19 (1.34, 3.54)  2.53 (1.05, 6.08)</p>	<p>Copollutant model, lag 2 with PAH: 1.98 (1.31, 3.05) with NO<sub>2</sub>: 1.94 (1.16, 3.58) Adjustment for SO<sub>2</sub> does not alter PAH association but attenuates NO<sub>2</sub> association.  SO<sub>2</sub> moderately correlated with PAH, NO<sub>2</sub>. Spearman <i>r</i> = 0.60, 0.56.</p>

**Table 5-8 (Continued): Recent epidemiologic studies of respiratory symptoms in populations with asthma.**

Study Population and Methodological Details	SO <sub>2</sub> Exposure Estimates (ppb)	SO <sub>2</sub> Averaging Time and Lag Day	Effect Estimate (95% CI) Single-Pollutant Model <sup>a</sup>	Copollutant Examination <sup>a</sup>
<b>Children With Asthma</b>				
<p>†<a href="#">Spira-Cohen et al. (2011)</a>, <a href="#">Spira-Cohen (2013)</a> Bronx, NY, 2002–2005 N = 40, ages 10–12 yr. 44% with asthma ED visit or hospital admission in previous 12 mo. Daily diaries for 1 mo. Recruited from schools by referrals from school nurses.</p>	<p>Monitor at school Concentrations NR Most children walk to school</p>	<p>1-h max (a.m.) 0</p>	<p>Cough RR: 1.60 (1.20, 2.12) Wheeze RR: 1.81 (1.15, 2.84) Shortness of breath RR: 1.45 (0.90, 2.84)</p>	<p>Copollutant model for cough with school EC: 1.32 (0.93, 1.87) No association with PM<sub>2.5</sub>. EC association robust to SO<sub>2</sub> adjustment. School SO<sub>2</sub> moderately correlated with EC. <i>r</i> = 0.45.</p>
<p>†<a href="#">Velická et al. (2015)</a> Ostrava, Czech Republic, Nov 2013–Feb 2014 N = 147, ages 6–18 yr. 67% mild persistent asthma. 33% moderate persistent asthma. 79% atopy. 97% regular asthma medication use. Daily diaries for 4 mo. Recruited from clinics.</p>	<p>Five monitors and dispersion model 0.5 x 0.5 km resolution Weighted avg by time at home and school Median: 4.0 75th percentile: 12</p>	<p>24-h avg 0</p>	<p>Cough OR: 0.92 (0.74, 1.17) Breathing difficulty-wheeze OR: 2.29 (1.55, 3.39) Reliever inhaler use OR: 1.84 (1.32, 2.56) Restricted activities OR: 1.25 (1.00, 1.62)</p>	<p>No copollutant model Associations observed with PM<sub>10</sub> and NO<sub>2</sub>. PM<sub>2.5</sub> not examined. Copollutant correlations NR.</p>
<p>†<a href="#">Dales et al. (2009)</a> Windsor, ON, Oct–Dec 2005 N = 182, ages 9–14 yr. 37% ICS use. 35% beta-agonist use. Daily diaries for 4 wk. Recruited from schools. Mean 1.6 and 2.2 h/d spent outdoors.</p>	<p>Two monitors averaged 99% homes within 10 km of sites Median: 4.5 95th percentile: 16</p>	<p>24-h avg</p>	<p>OR for SO<sub>2</sub> ≥8.8 vs. &lt;2.3 ppb Chest tightness 1.30 (1.06, 1.58) ORs for difficulty breathing, cough, and wheeze reported not statistically significant.</p>	<p>No copollutant model Associations with PM<sub>2.5</sub>, NO<sub>2</sub>, O<sub>3</sub> reported not statistically significant. Quantitative results NR.</p>
<p>†<a href="#">O'Connor et al. (2008)</a> Inner-City Asthma Study cohort: Boston, MA; Bronx, NY; New York, NY; Chicago, IL; Dallas, TX; Tucson, AZ; Seattle, WA; 1998–2001 N = 861, ages 5–12 yr. 100% persistent asthma. 100% atopy. Daily diaries for four 2-wk periods. Recruited from intervention study.</p>	<p>Monitors averaged close to home and not near industry Median 2.3 km to site Quantitative SO<sub>2</sub> data NR.</p>	<p>24-h avg 1–19 avg</p>	<p>Wheeze-cough RR: 1.05 (0.89, 1.23) Nighttime asthma RR: 1.11 (0.91, 1.36) Slow play RR: 1.06 (0.88, 1.27) Missed school RR: 1.10 (0.82, 1.49)</p>	<p>No copollutant model Associations observed with NO<sub>2</sub> and CO. PM<sub>2.5</sub> associated with missed school. SO<sub>2</sub> moderately correlated with NO<sub>2</sub>, weakly with CO and PM<sub>2.5</sub>. <i>r</i> = 0.59, 0.32, 0.37.</p>

**Table 5-8 (Continued): Recent epidemiologic studies of respiratory symptoms in populations with asthma.**

Study Population and Methodological Details	SO <sub>2</sub> Exposure Estimates (ppb)	SO <sub>2</sub> Averaging Time and Lag Day	Effect Estimate (95% CI) Single-Pollutant Model <sup>a</sup>	Copolutant Examination <sup>a</sup>
<p>†<a href="#">Gent et al. (2009)</a>                      New Haven county, CT, 2000–2004                      N = 149, ages 4–12 yr. 45% intermittent asthma.                      Daily diaries reported monthly for 1 yr.                      Recruited from larger cohort, clinic, and school.</p>	<p>Monitor 0.9–30 km of home                      Mean 10 km to site                      Concentrations NR</p>	<p>24-h avg                      0</p>	<p>NR</p>	<p>Only multipollutant model analyzed with six PM<sub>2.5</sub> component factors                      Wheeze: 1.04 (0.92, 1.19)                      SO<sub>2</sub> moderately correlated with motor vehicle factor. <i>r</i> = 0.45.</p>
<b>Children and Adults with Asthma</b>				
<p>†<a href="#">Fattore et al. (2016)</a>                      Milan, Italy, Sep–Dec 2013                      N = 84 days                      Daily wastewater samples for 84 days analyzed for levels of the beta-agonist salbutamol.</p>	<p>3 monitors averaged                      Mean (SD): 2.2 (1.3)                      Max: 5.9</p>	<p>24-h avg                      0 to 10                      (single-day)</p>	<p>Beta-agonist levels in wastewater                      No quantitative results. RRs reported not statistically significant.</p>	<p>No copollutant model                      Associations observed with PM<sub>2.5</sub> and PM<sub>10</sub>.                      SO<sub>2</sub> moderately correlated with PM<sub>2.5</sub> and PM<sub>10</sub>. Pearson <i>r</i> = 0.66, 0.65.</p>

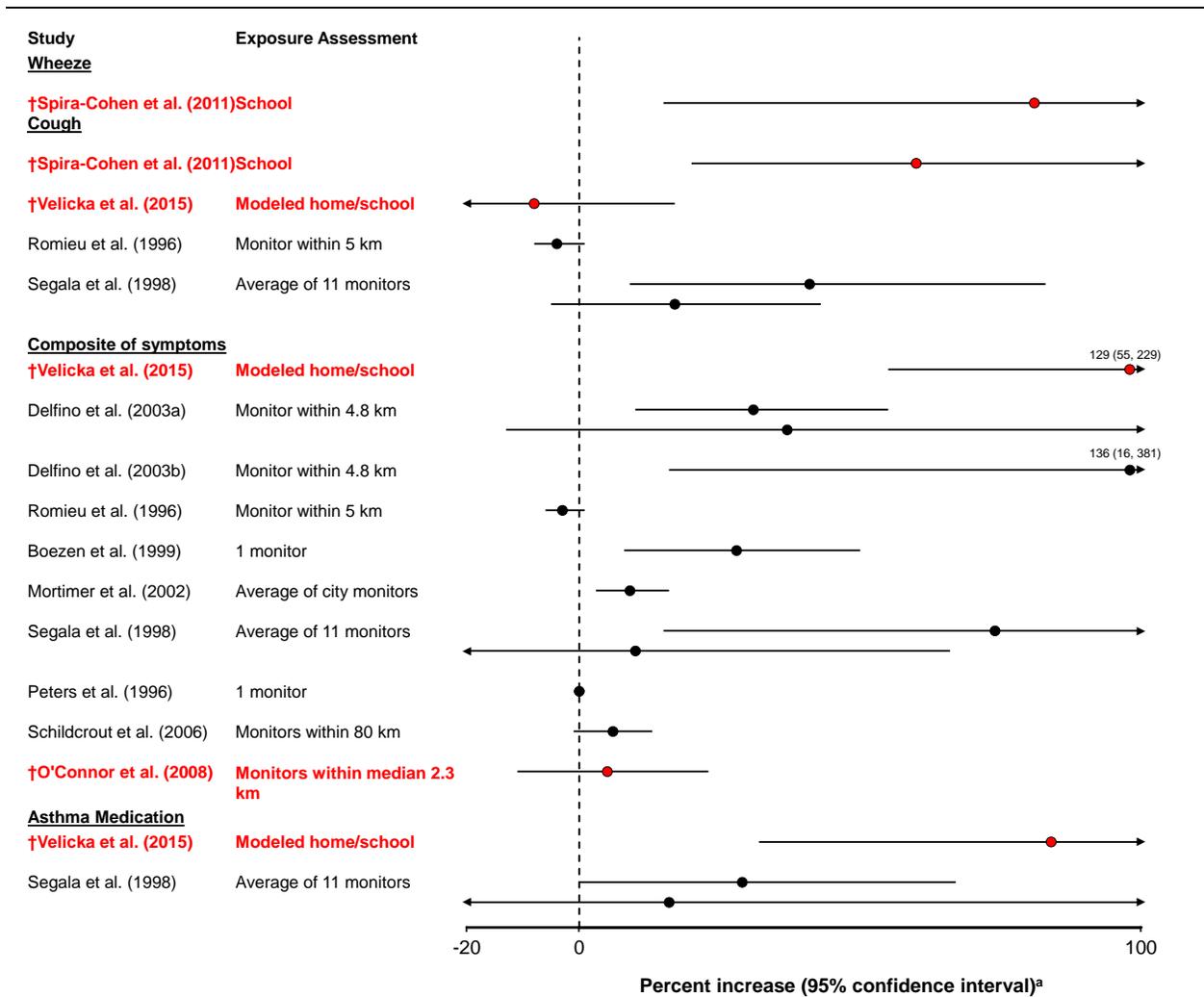
CI = confidence interval; CO = carbon monoxide; EC = elemental carbon; ED = emergency department; ICS = inhaled corticosteroids; N = sample size; NO<sub>2</sub> = nitrogen dioxide; NR = not reported; O<sub>3</sub> = ozone; OR = odds ratio; PAH = polycyclic aromatic hydrocarbon; PM<sub>2.5</sub> = particulate matter with a nominal aerodynamic diameter less than or equal to 2.5 μm; PM<sub>10</sub> = particulate matter with a nominal aerodynamic diameter less than or equal to 10 μm; RR = relative risk; SD = standard deviation; SO<sub>2</sub> = sulfur dioxide.

<sup>a</sup>Effect estimates are standardized to a 10-ppb increase in 24-h avg SO<sub>2</sub> and 40-ppb increase in 1-h max SO<sub>2</sub>.

†Studies published since the 2008 Integrated Science Assessment for Sulfur Oxides.

1 **Children.** As a whole, epidemiologic evidence indicates associations between higher SO<sub>2</sub>  
2 concentrations and increased respiratory symptoms in children with asthma, particularly  
3 when examined as a composite index of multiple symptoms ([Figure 5-2](#)). Associations  
4 also are observed for asthma medication use or activity restriction but not consistently for  
5 wheeze or cough. Results vary in magnitude and precision ([Figure 5-2](#)). In some study  
6 areas, the SO<sub>2</sub> concentrations were much lower ([Spira-Cohen et al., 2011](#); [Delfino et al.,](#)  
7 [2003a](#); [Delfino et al., 2003b](#)) or higher ([Mortimer et al., 2002](#)) than the 10-ppb increment  
8 used to standardize effect estimates. Although recent studies give inconsistent results  
9 ([Table 5-8](#)), associations are observed with SO<sub>2</sub> measured or modeled for school or  
10 home, which may represent exposure better than measurements at central site monitors.  
11 Recent studies reported lower SO<sub>2</sub> concentrations than many previous studies (for  
12 24-h avg, median ~ 4 ppb vs. means 8.3 and 90 ppb). It is unclear whether the  
13 inconsistency is due to lower concentrations; previous studies observed associations in  
14 locations with similar SO<sub>2</sub> concentrations [median 24-h avg 2.2–7.4 ppb in [Schildcrout et](#)  
15 [al. \(2006\)](#), mean 8-h max 4.6 ppb in [Delfino et al. \(2003a\)](#), [Delfino et al. \(2003b\)](#)].

16 [Spira-Cohen et al. \(2011\)](#) is notable not only for monitoring SO<sub>2</sub> at schools but also for  
17 examining 1-h max concentrations. In the population of children in Bronx, NY, increases  
18 in SO<sub>2</sub> were linked to increased odds of cough and wheeze but not shortness of breath  
19 ([Table 5-8](#)). Previous U.S. studies also associated symptoms with temporally resolved  
20 SO<sub>2</sub> metrics [i.e., 1-h max, 8-h max, 3-h avg (8–11 a.m.)] but had more uncertainty in  
21 exposures estimated from monitors up to 4.8 km from children’s homes/schools ([Delfino](#)  
22 [et al., 2003a](#); [Delfino et al., 2003b](#)) or monitors averaged across the city ([Mortimer et al.,](#)  
23 [2002](#)). [Spira-Cohen et al. \(2011\)](#) did not report SO<sub>2</sub> concentrations to compare to  
24 previous studies but reported that most children walked to school, improving the  
25 relevance of 1-h max SO<sub>2</sub> concentrations at school to children’s peak exposures. [Velická](#)  
26 [et al. \(2015\)](#) also aimed to improve exposure assessment for children in Ostrava, Czech  
27 Republic. A dispersion model and five monitors were used to estimate SO<sub>2</sub>  
28 concentrations at 0.5 km resolution and calculate a time-weighted 24-h avg for each child  
29 based on the school and home location. SO<sub>2</sub> was associated with breathing difficulty-  
30 wheeze, reliever inhaler use, and restricted activities, but not cough ([Table 5-8](#)).  
31 The study population had a high prevalence of atopy (79%); thus, results agree with  
32 [Boezen et al. \(1999\)](#) and [Segala et al. \(1998\)](#) but may have less uncertainty in exposure  
33 estimates ([Section 3.5](#)).



Note: † and Red = recent studies published since the 2008 Integrated Science Assessment for Sulfur Oxides, black = studies from the 2008 Integrated Science Assessment for Sulfur Oxides.  
<sup>a</sup>Effect estimates are standardized to a 10-ppb increase in 24-h avg sulfur dioxide concentration and a 40-ppb increase in 1-h max concentrations.  
 Study details are presented in [Table 5-8](#). Results from [Gent et al. \(2009\)](#) are not presented in the figure because they are based on a multipollutant model. Corresponding quantitative results are reported in Supplemental Table 5S-3 ([U.S. EPA, 2016i](#)).

**Figure 5-2 Associations between short-term average ambient sulfur dioxide concentrations and respiratory symptoms and asthma medication use in children with asthma.**

1 Other recent studies largely do not provide evidence for SO<sub>2</sub>-associated increases in  
 2 respiratory symptoms in children with asthma ([Dales et al., 2009](#); [Gent et al., 2009](#);  
 3 [O'Connor et al., 2008](#)). But, they have more questionable implications due to (1) the large  
 4 distance between the SO<sub>2</sub> monitor and children’s homes (e.g., up to 10 km, median  
 5 2.3 km, mean 10 km); (2) a lack of quantitative results ([Dales et al., 2009](#)); (3) analysis of  
 6 19-day avg SO<sub>2</sub> concentrations, which are more subject to residual temporal confounding

1 [\(O'Connor et al., 2008\)](#); or (4) analysis of SO<sub>2</sub> only as part of a multipollutant model with  
2 six PM<sub>2.5</sub> component source factors ([Gent et al., 2009](#)).

3 For the associations observed between SO<sub>2</sub> and respiratory symptoms in children with  
4 asthma, including those with atopy, the influence of copollutants is poorly addressed.  
5 Symptoms were not associated with personal or school PM<sub>2.5</sub> but with other PM metrics:  
6 PM<sub>10</sub>, EC, OC, BS, and TSP. Associations also were observed with NO<sub>2</sub>, VOCs such as  
7 benzene and xylene, and O<sub>3</sub> ([Table 5-8](#)). Except for O<sub>3</sub>, these copollutants were  
8 moderately to highly correlated with SO<sub>2</sub> ( $r = 0.45\text{--}0.9$ ). Correlations were highest in  
9 previous studies, but recent studies did not report SO<sub>2</sub> concentrations ([Spira-Cohen et al.,](#)  
10 [2011](#)) or copollutant correlations ([Velická et al., 2015](#)) to assess whether the magnitude  
11 of correlation varied by SO<sub>2</sub> levels. Copollutant models were analyzed in few studies and  
12 for few copollutants. For a Los Angeles, CA cohort, no SO<sub>2</sub>-VOC interaction was  
13 indicated, and SO<sub>2</sub> associations persisted with adjustment for benzene, xylene, or toluene  
14 for some but not all symptoms ([Delfino et al., 2003a](#); [Delfino et al., 2003b](#)). Associations  
15 for VOCs were attenuated as well, and copollutant model results are uncertain because of  
16 the moderate to high correlations with SO<sub>2</sub> ( $r = 0.58\text{--}0.78$ ) and because exposures were  
17 assessed from monitors 4.8 km from children's homes or schools. Potential exposure  
18 error also limits inference from results showing associations for joint increases in SO<sub>2</sub>  
19 with PM<sub>10</sub>, NO<sub>2</sub>, or CO that were similar to each single-pollutant association ([Schildcrout](#)  
20 [et al., 2006](#)). The recent Bronx, NY study analyzed copollutant models for school SO<sub>2</sub>  
21 and EC, which may have more comparable exposure error. SO<sub>2</sub> and EC were moderately  
22 correlated ( $r = 0.45$ ), consistent with the location in a high diesel truck traffic area ([Spira-](#)  
23 [Cohen et al., 2011](#)). In the copollutant model, the odds ratio for cough was robust for EC  
24 but decreased in magnitude and precision for SO<sub>2</sub> from 1.60 (95% CI: 1.20, 2.12) to 1.32  
25 (95% CI: 0.93, 1.87) per 40-ppb increase in 1-h max SO<sub>2</sub>.

### ***Summary of Respiratory Symptoms in Populations with Asthma***

26 Controlled human exposure studies provide strong evidence for the effects of SO<sub>2</sub>  
27 exposure on respiratory symptoms in adults with asthma under increased ventilation  
28 conditions. Exposures for 5–10 minutes to 0.2–0.6 ppm SO<sub>2</sub> induced respiratory  
29 symptoms in exercising individuals with asthma, with the most consistent evidence from  
30 exposures to 0.4–0.6 ppm SO<sub>2</sub> ([Table 5-2](#)). Epidemiologic evidence in adults with asthma  
31 is weak, but increases in ambient SO<sub>2</sub> concentration are generally associated with  
32 increased risk of asthma symptoms in children ([Figure 5-2](#); [Table 5-8](#)). Assessing  
33 coherence specifically with controlled human exposure studies of adolescents with  
34 asthma is difficult because those studies lacked an appropriate control exposure. Limited  
35 findings support associations in children and adults with asthma plus atopy.

1 Epidemiologic results in children are less consistent in recent than previous studies but  
2 support associations for 1-h max SO<sub>2</sub> measured at schools or 24-h avg SO<sub>2</sub> modeled for  
3 school and home. School or home SO<sub>2</sub> measures may better represent exposures than the  
4 concentrations at central site monitors examined in most studies, particularly for 1-h max.  
5 These SO<sub>2</sub> metrics are longer than the 5–10 minutes SO<sub>2</sub> exposures in controlled human  
6 exposure studies, which show transient responses. And, the role of confounding or an  
7 interaction with copollutants such as PM<sub>2.5</sub>, EC, NO<sub>2</sub>, and VOCs remains uncertain for  
8 epidemiologic associations, including those for populations with asthma plus atopy and  
9 for residents near a coal-fired power plant. However, evidence for allergic inflammation  
10 enhanced by repeated 1-hour exposures, albeit 2 ppm SO<sub>2</sub>, to some extent supports the  
11 biological plausibility of SO<sub>2</sub>-associated increases in respiratory symptoms, especially in  
12 populations with asthma plus atopy.

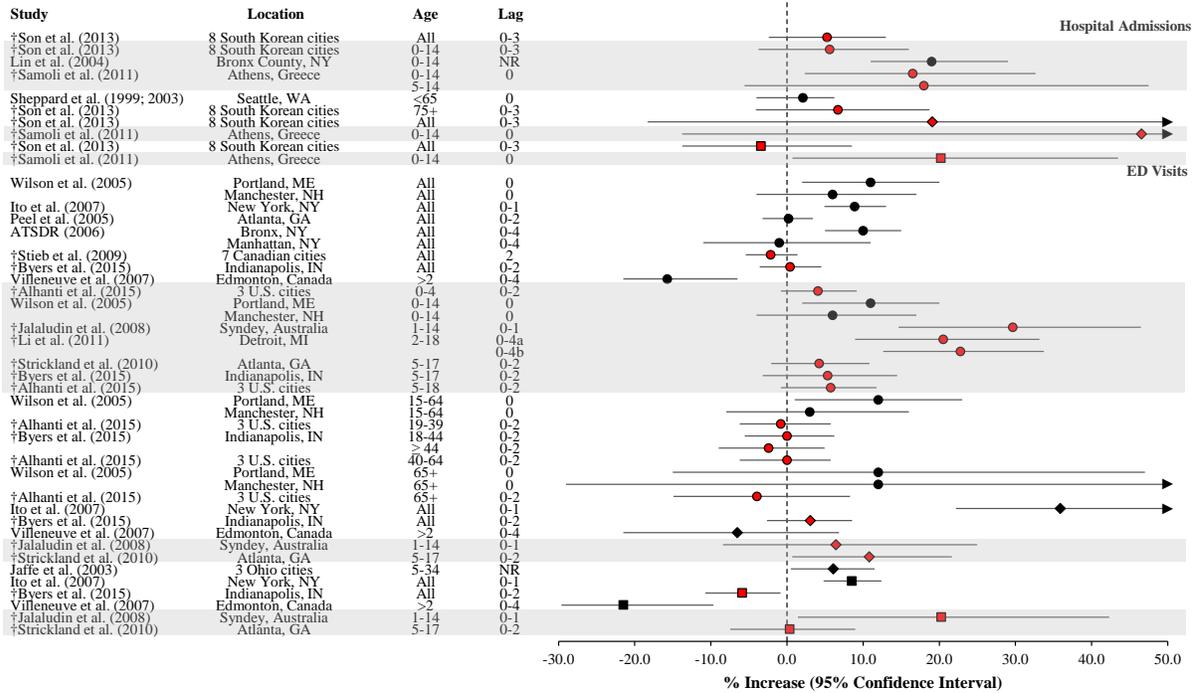
### **Hospital Admission and Emergency Department Visits for Asthma**

13 Since the completion of the 2008 SO<sub>x</sub> ISA, epidemiologic studies have continued to  
14 examine the association between short-term exposure to ambient SO<sub>2</sub> concentrations and  
15 respiratory-related hospital admissions and ED visits, but are primarily limited to  
16 single-city studies. The sections within this chapter detailing the respiratory-related  
17 hospital admissions and ED visits studies characterize recent studies in the context of the  
18 collective body of evidence evaluated in the 2008 SO<sub>x</sub> ISA. The 2008 SO<sub>x</sub> ISA ([U.S.  
19 EPA, 2008d](#)) included the first thorough evaluation of respiratory morbidity in the form  
20 of respiratory-related hospital admissions and ED visits, including asthma. These studies  
21 reported generally positive associations with short-term SO<sub>2</sub> exposures, with associations  
22 that are often larger in magnitude for children ([Figure 5-3](#)). Additionally, SO<sub>2</sub>  
23 associations with asthma hospital admissions and ED visits were often attenuated, but  
24 remained positive in copollutant models with PM, NO<sub>2</sub>, or O<sub>3</sub>.

25 Within this section focusing on asthma, as well as the rest of the chapter,  
26 respiratory-related hospital admissions and ED visit studies are evaluated separately  
27 because only a small percentage of respiratory-related ED visits result in hospital  
28 admission. Additionally, when evaluating asthma ED visit and hospital admission studies  
29 that focus on children (i.e., defined age ranges <18 years of age), it is important to note  
30 that it is often difficult to reliably diagnose asthma in children <5 years of age, which  
31 may add some uncertainty to the results including this age range ([NAEPP, 2007](#)).

32 For each of the studies evaluated in this section, [Table 5-9](#) presents the air quality  
33 characteristics of each city, or across all cities, the exposure assignment approach used,  
34 and information on copollutants examined in each asthma hospital admission and ED  
35 visit study. Other recent studies of asthma hospital admissions and ED visits are not the

1 focus of this evaluation because they were conducted in small single-cities, encompassed  
 2 a short study duration, had insufficient sample size, or did not examine potential  
 3 copollutant confounding. The full list of these studies, as well as study specific details,  
 4 can be found in Supplemental Table 5S-5 ([U.S. EPA, 2016m](#)).



ED = emergency department.

Note: † and red = recent studies published since the 2008 ISA for Sulfur Oxides. Black = U.S. and Canadian studies evaluated in the 2008 ISA for Sulfur Oxides; Circle = all-year; diamond = warm/summer months; square = cold/winter months. a = time-series results; b = case-crossover results. Gray shading depicts studies that present results for children (i.e., <18 yr of age). Corresponding quantitative results are reported in Supplemental Table 5S-4 ([U.S. EPA, 2016j](#)).

**Figure 5-3 Percent increase in asthma hospital admissions and emergency department visits from U.S. and Canadian studies evaluated in the 2008 SO<sub>x</sub> ISA and recent studies in all-year and seasonal analyses for a 10-ppb increase in 24-h avg or 40-ppb increase in 1-h max sulfur dioxide concentrations.**

**Table 5-9 Study-specific details and mean and upper percentile concentrations from asthma hospital admission and emergency department visit studies conducted in the U.S. and Canada and evaluated in the 2008 SO<sub>x</sub> ISA and studies published since the 2008 SO<sub>x</sub> ISA.**

Study	Location Years	Exposure Assignment	Metric	Mean Concentration ppb	Upper Percentile Concentrations ppb	Copollutants Examination
<b>Hospital admissions</b>						
<a href="#">Lin et al. (2004)</a>	Bronx County, NY (1991–1993)	Avg of SO <sub>2</sub> concentrations from two monitoring sites	24-h avg	Cases: 16.8 Controls: 15.6	NR	NR
<a href="#">(Sheppard (2003); Sheppard et al. (1999))</a>	Seattle, WA (1987–1994)	Avg of SO <sub>2</sub> concentrations from multiple monitors	24-h avg	8.0	75th: 10.0 90th: 13.0	Correlation ( <i>r</i> ): PM <sub>10</sub> : 0.31 PM <sub>2.5</sub> : 0.22 PM <sub>10-2.5</sub> : 0.34 O <sub>3</sub> : 0.07 CO: 0.24 Copollutant models: none
<a href="#">†Son et al. (2013)</a>	Eight South Korean cities (2003–2008)	Avg of hourly ambient SO <sub>2</sub> concentrations from monitors in each city	24-h avg	3.2–7.3	NR	Correlation ( <i>r</i> ): PM <sub>10</sub> : 0.5 O <sub>3</sub> : -0.1 NO <sub>2</sub> : 0.6 CO: 0.6 Copollutant models: none
<a href="#">†Zheng et al. (2015)</a>	Meta-analysis (1988–2014)	NR	24-h avg	3.1–45.5 <sup>a</sup>	NR	Correlations ( <i>r</i> ): NR Copollutant models: none
<a href="#">†Samoli et al. (2011)</a>	Athens, Greece (2001–2004)	Avg of SO <sub>2</sub> concentrations across multiple monitors	24-h avg	6.4	75th: 8.4	Correlation ( <i>r</i> ): O <sub>3</sub> : -0.19 NO <sub>2</sub> : 0.55 Copollutant models: PM <sub>10</sub> , SO <sub>2</sub> , NO <sub>2</sub> , O <sub>3</sub>

**Table 5-9 (Continued): Study specific details and mean and upper percentile concentrations from asthma hospital admission and emergency department visit studies conducted in the U.S. and Canada and evaluated in the 2008 SO<sub>x</sub> ISA and studies published since the 2008 SO<sub>x</sub> ISA.**

Study	Location Years	Exposure Assignment	Metric	Mean Concentration ppb	Upper Percentile Concentrations ppb	Copollutants Examination
<b>ED visits</b>						
<a href="#">Jaffe et al. (2003)</a>	Cincinnati, Cleveland, and Columbus, OH (1991–1996)	When more than one monitoring station operating in a day, monitor reporting highest 24-h avg SO <sub>2</sub> concentration used	24-h avg	Cincinnati: 13.7 Cleveland: 15.0 Columbus: 4.2	Max: Cincinnati: 50 Cleveland: 64 Columbus: 22	Correlations ( <i>r</i> ) (range across cities) NO <sub>2</sub> : 0.07–0.28 O <sub>3</sub> : 0.14–0.26 PM <sub>10</sub> : 0.29–0.42 Copollutant models: none
<a href="#">Ito et al. (2007)</a>	New York, NY (1999–2002)	Average SO <sub>2</sub> concentrations across 19 monitors	24-h avg	7.8	75th: 10 95th: 17	Correlations ( <i>r</i> ): NR Copollutant models: PM <sub>2.5</sub> , NO <sub>2</sub> , O <sub>3</sub> , CO
<a href="#">ATSDR (2006)</a>	Bronx and Manhattan, NY (1999–2000)	SO <sub>2</sub> concentrations from one monitor in Bronx and one in Manhattan	24-h avg	Manhattan: 12 Bronx: 11	NR	Correlations ( <i>r</i> ): Bronx: O <sub>3</sub> : –0.49 NO <sub>2</sub> : 0.50 PM <sub>2.5</sub> : 0.39 Max PM <sub>10</sub> : 0.034 Manhattan: O <sub>3</sub> : –0.40 NO <sub>2</sub> : 0.47 PM <sub>2.5</sub> : 0.26 PM <sub>10</sub> : 0.24 Copollutant models: O <sub>3</sub> , FRM and Max PM <sub>2.5</sub> , NO <sub>2</sub>

**Table 5-9 (Continued): Study specific details and mean and upper percentile concentrations from asthma hospital admission and emergency department visit studies conducted in the U.S. and Canada and evaluated in the 2008 SO<sub>x</sub> ISA and studies published since the 2008 SO<sub>x</sub> ISA.**

Study	Location Years	Exposure Assignment	Metric	Mean Concentration ppb	Upper Percentile Concentrations ppb	Copollutants Examination
<a href="#">Peel et al. (2005)</a>	Atlanta, GA (1993–2000)	Average of SO <sub>2</sub> concentrations from monitors for several monitoring networks	1-h max	16.5	90th: 39.0	Correlations ( <i>r</i> ): PM <sub>2.5</sub> : 0.17 PM <sub>10</sub> : 0.20 PM <sub>10-2.5</sub> : 0.21 UFP: 0.24 PM <sub>2.5</sub> water soluble metals: 0.00 PM <sub>2.5</sub> sulfate: 0.08 PM <sub>2.5</sub> acidity: -0.03 PM <sub>2.5</sub> OC: 0.18 PM <sub>2.5</sub> EC: 0.20 Oxygenated HCs: 0.14 O <sub>3</sub> : 0.19 CO: 0.26 NO <sub>2</sub> : 0.34 Copollutant models: none
<a href="#">Wilson et al. (2005)</a>	Portland, ME, and Manchester, NH (1996–2000)	SO <sub>2</sub> concentrations from one monitor in each city	24-h avg	Portland: 11.1 Manchester: 16.5	NR	Correlation ( <i>r</i> ) (Range across cities): O <sub>3</sub> : 0.05–0.24 Copollutant models: none
<a href="#">†Stieb et al. (2009)</a>	Seven Canadian cities (1992–2003)	Average SO <sub>2</sub> concentrations across all monitors in each city. Number of SO <sub>2</sub> monitors in each city ranged from 1–11.	24-h avg	2.6–10.0	75th: 3.3–13.4	Correlations ( <i>r</i> ) only reported by city and season Copollutant models: none
<a href="#">†Orazio et al. (2009)</a>	Six Italian cities (1996–2002)	Average of SO <sub>2</sub> concentrations across all monitors in each city	24-h avg	All-year: 2.1–8.1 Warm (Apr–Sep): 1.3–9.0 Cold (Oct–Mar): 2.6–7.3	NR	Correlations ( <i>r</i> ): NR Copollutant models: none

**Table 5-9 (Continued): Study specific details and mean and upper percentile concentrations from asthma hospital admission and emergency department visit studies conducted in the U.S. and Canada and evaluated in the 2008 SO<sub>x</sub> ISA and studies published since the 2008 SO<sub>x</sub> ISA.**

Study	Location Years	Exposure Assignment	Metric	Mean Concentration ppb	Upper Percentile Concentrations ppb	Copollutants Examination
<a href="#">†Alhanti et al. (2016)</a>	Three U.S. cities Atlanta, GA (1993–2009) Dallas, TX (2006–2009) St. Louis, MO (2001–2007)	Population-weighted average using data available from all monitors measuring SO <sub>2</sub>	1-h max	Atlanta: 10.7 Dallas: 2.7 St. Louis: 10.7	NR	Correlations ( <i>r</i> ): NR Copollutant models: none
<a href="#">†Zheng et al. (2015)</a>	Meta-analysis (1988–2014)	NR	24-h avg	4.6–39.1 <sup>a</sup>	NR	Correlations ( <i>r</i> ): NR Copollutant models: none
<a href="#">†Strickland et al. (2010)</a>	Atlanta, GA (1993–2004)	Population-weighted average using data available from all monitors measuring SO <sub>2</sub>	1-h max	All-year: 10.8 Warm (May–Oct): 9.6 Cold (Nov–Apr): 12.0	NR	Correlations ( <i>r</i> ): NR Copollutant models: none
<a href="#">†Li et al. (2011)</a>	Detroit, MI (2004–2006)	Average of SO <sub>2</sub> concentrations across two monitors in Detroit metropolitan area that measure SO <sub>2</sub>	24-h avg	3.8	75th: 5.1 Max: 27.3	Correlations ( <i>r</i> ), range across monitors: CO: 0.17–0.31 PM <sub>2.5</sub> : 0.40–0.53 NO <sub>2</sub> : 0.42–0.55 Copollutant models: none
<a href="#">†Byers et al. (2015)</a>	Indianapolis, IN (2007–2011)	Double-weighted average (distance from monitor to ZIP code centroid and age-specific census population) of two SO <sub>2</sub> monitors	1-h max	All-year: 10.1 Warm: 10.5 Cold: 9.8	NR	Correlations ( <i>r</i> ): All-year: PM <sub>2.5</sub> : 0.34 Warm: 1-h max O <sub>3</sub> : 0.45 8-h max O <sub>3</sub> : 0.42 PM <sub>2.5</sub> : 0.38 Cold: PM <sub>2.5</sub> : 0.29

**Table 5-9 (Continued): Study specific details and mean and upper percentile concentrations from asthma hospital admission and emergency department visit studies conducted in the U.S. and Canada and evaluated in the 2008 SO<sub>x</sub> ISA and studies published since the 2008 SO<sub>x</sub> ISA.**

Study	Location Years	Exposure Assignment	Metric	Mean Concentration ppb	Upper Percentile Concentrations ppb	Copollutants Examination
<a href="#">†Villeneuve et al. (2007)</a>	Edmonton, AB (1992–2002)	Average of SO <sub>2</sub> concentrations across three monitoring stations	24-h avg	Summer (Apr–Sep) 50th: 2.0 Winter (Oct–Mar) 50th: 3.0	Summer 75th: 3.0 Winter 75th: 4.0	Correlations ( <i>r</i> ): NR Copollutant models: NR
<a href="#">†Jalaludin et al. (2008)</a>	Sydney, Australia (1997–2001)	Average of SO <sub>2</sub> concentrations across 14 monitoring stations	24-h avg	All-year: 1.07 Warm: 1.03 Cold: 1.1	Max All-year: 4.1 Warm: 4.1 Cold: 3.9	Correlations ( <i>r</i> ): (warm, cold) PM <sub>10</sub> : 0.37, 0.46 PM <sub>2.5</sub> : 0.27, 0.46 O <sub>3</sub> : 0.45, –0.04 CO: 0.46, 0.51 NO <sub>2</sub> : 0.52, 0.56 Copollutant models: PM <sub>10</sub> , PM <sub>2.5</sub> , O <sub>3</sub> , CO, NO <sub>2</sub>
<a href="#">†Smargiassi et al. (2009)</a>	Montreal, QC (1996–2004)	SO <sub>2</sub> concentrations measured at two monitoring sites east and southwest of the refinery At-home estimates of daily exposure by estimating SO <sub>2</sub> concentrations at centroid of residential postal codes using AERMOD	24-h avg	Regional: 4.3 East: 6.9 Southwest: 4.4 AERMOD: East + Southwest: 3.0 East: 3.7 Southwest: 2.4	75th: Regional: 5.3 East: 9.2 Southwest: 5.9 AERMOD: East + Southwest: 4.3 East: 5.5 Southwest: 3.0	NR

**Table 5-9 (Continued): Study specific details and mean and upper percentile concentrations from asthma hospital admission and emergency department visit studies conducted in the U.S. and Canada and evaluated in the 2008 SO<sub>x</sub> ISA and studies published since the 2008 SO<sub>x</sub> ISA.**

Study	Location Years	Exposure Assignment	Metric	Mean Concentration ppb	Upper Percentile Concentrations ppb	Copollutants Examination
<a href="#">†Winguist et al. (2014)</a>	Atlanta, GA, U.S. (1998–2004)	Population-weighted average using data available from all monitors measuring SO <sub>2</sub>	1-h max	Warm (May–Oct): 8.3 Cold (Nov–April): 10.8	75th: Warm: 11.4 Cold: 14.6	Correlations ( <i>r</i> ): Warm: O <sub>3</sub> : 0.27 CO: 0.32 NO <sub>2</sub> : 0.44 PM <sub>2.5</sub> : 0.28 EC: 0.31 Sulfate: 0.24 Secondary PM <sub>2.5</sub> : 0.24  Cold: O <sub>3</sub> : 0.05 CO: 0.22 NO <sub>2</sub> : 0.41 PM <sub>2.5</sub> : 0.07 EC: 0.18 Sulfate: 0.02 Secondary PM <sub>2.5</sub> : 0.08 Copollutant models: none
<a href="#">†Pearce et al. (2015)</a>	Atlanta, GA	SO <sub>2</sub> concentrations from one monitor	1-h max	14.6	NR	Correlations ( <i>r</i> ): NR Copollutant models: none

**Table 5-9 (Continued): Study specific details and mean and upper percentile concentrations from asthma hospital admission and emergency department visit studies conducted in the U.S. and Canada and evaluated in the 2008 SO<sub>x</sub> ISA and studies published since the 2008 SO<sub>x</sub> ISA.**

Study	Location Years	Exposure Assignment	Metric	Mean Concentration ppb	Upper Percentile Concentrations ppb	Copollutants Examination
<b>Outpatient and physician visits</b>						
† <a href="#">Burra et al. (2009)</a>	Toronto, ON (1992–2001)	Average of SO <sub>2</sub> concentrations across six monitors	1-h max	9.7	75th: 12.0 95th: 35.0 Max: 62.0	Correlations ( <i>r</i> ): NR Copollutant models: none
† <a href="#">Sinclair et al. (2010)</a>	Atlanta, GA, U.S. (1998–2002)	SO <sub>2</sub> concentrations collected as part of AIRES at SEARCH Jefferson street site	1-h max	1998–2000: 19.3 2000–2002: 17.6 1998–2002: 18.3	NR	Correlations ( <i>r</i> ): NR Copollutant models: none

AERMOD = American Meteorological Society/U.S. EPA Regulatory Model; AIRES = Aerosol Research Inhalation Epidemiology Study; CO = carbon monoxide; EC = elemental carbon; FRM = federal reference method; HCs = hydrocarbons; NO<sub>2</sub> = nitrogen dioxide; NR = not reported; O<sub>3</sub> = ozone; OC = organic carbon; PM<sub>10</sub> = particulate matter with a nominal aerodynamic diameter less than or equal to 10 µm; PM<sub>2.5</sub> = particulate matter with a nominal aerodynamic diameter less than or equal to 2.5 µm; PM<sub>10-2.5</sub> = particulate matter with a nominal aerodynamic diameter less than or equal to 10 µm and greater than 2.5 µm; SEARCH = Southeast Aerosol Research Characterization; SO<sub>2</sub> = sulfur dioxide; UFP = ultrafine particle.

<sup>a</sup>Range of mean concentrations across all studies included in the meta-analysis.

† = studies published since the 2008 SO<sub>x</sub> ISA.

### **Hospital Admissions**

1 The 2008 SO<sub>x</sub> ISA identified only two U.S.-based studies and no Canadian studies that  
 2 examined the association between short-term SO<sub>2</sub> exposures and asthma hospital  
 3 admissions. These studies reported positive associations; however, they were limited to  
 4 studies of individual cities ([Figure 5-3](#)). The asthma hospital admission studies averaged  
 5 SO<sub>2</sub> concentrations over multiple monitors and only examined 24-h avg exposure  
 6 metrics, which may not adequately capture the spatial and temporal variability in SO<sub>2</sub>  
 7 concentrations ([Section 3.4.2.2](#) and [Section 3.4.2.3](#)). While correlations between 24-h avg  
 8 and 1-h max SO<sub>2</sub> concentrations are high ( $r > 0.75$ ) at most monitors, lower correlations  
 9 may occur at some monitors and in individual studies, adding uncertainty to the ability of  
 10 24-h avg metrics to capture peak SO<sub>2</sub> concentrations. Additionally, relatively few studies  
 11 have examined the potential confounding effects of other pollutants on the SO<sub>2</sub>-asthma  
 12 hospital admissions relationship.

13 To date a limited number of studies have been published since the 2008 SO<sub>x</sub> ISA that  
 14 focus on the relationship between short-term SO<sub>2</sub> exposures and asthma hospital

1 admissions. In a time-series study conducted in Athens, Greece, [Samoli et al. \(2011\)](#)  
2 evaluated the association between multiple ambient air pollutants and pediatric asthma  
3 hospital admissions for ages 0–14 years. In an all-year analysis, the authors reported a  
4 positive association with SO<sub>2</sub> [16.5 % (95% CI: 2.3, 32.6); lag 0 increase for a 10-ppb  
5 increase in 24-h avg SO<sub>2</sub> concentrations]. In copollutant analyses, the authors found SO<sub>2</sub>  
6 risk estimates to be robust in models with PM<sub>10</sub> [13.0% (95% CI: –1.5, 29.7)] and O<sub>3</sub>  
7 [16.5% (95% CI: 2.3, 32.6)]. However, in models with NO<sub>2</sub> there was an increase in the  
8 SO<sub>2</sub> risk estimate [21.3% (95% CI: 1.1, 45.5)]. SO<sub>2</sub> was low ( $r < 0.4$ ) to moderately  
9 ( $r$  ranging from 0.4–0.7) correlated with other pollutants examined in the study, with the  
10 highest correlation with NO<sub>2</sub> ( $r = 0.55$ ).

11 The association between short-term SO<sub>2</sub> exposures and asthma hospital admissions was  
12 also examined by [Son et al. \(2013\)](#) in a study of eight South Korean cities. In addition to  
13 focusing on asthma, the authors examined allergic disease hospital admissions, which  
14 encompass asthma. For all ages, the authors reported a 5.3% increase (95% CI: –2.4,  
15 13.0) in asthma hospital admissions for a 10-ppb increase in 24-h avg SO<sub>2</sub> concentrations  
16 and a 3.1% increase (95% CI: –3.7, 10.7) in allergic diseases hospital admissions. In  
17 analyses focusing on children (ages 0–14) and older adults ( $\geq 75$  years of age), the authors  
18 reported associations that were larger in magnitude, compared to all ages for both asthma  
19 and allergic diseases hospital admissions ([Figure 5-3](#)).

20 The evidence from studies evaluated in the 2008 SO<sub>x</sub> ISA, as well as recent studies  
21 indicating a positive association between short-term SO<sub>2</sub> exposure and asthma hospital  
22 admissions, is supported by a meta-analysis conducted by ([Zheng et al., 2015](#)) that  
23 focused on all studies examining air pollution and asthma hospital admissions and ED  
24 visits published between 1988 and 2014. For SO<sub>2</sub>, the authors reported a 2.1% increase  
25 (95% CI: 0.5, 3.70) in asthma hospital admissions for a 10-ppb increase in 24-h avg SO<sub>2</sub>  
26 concentrations based on estimates from 31 studies. The results from [Zheng et al. \(2015\)](#)  
27 are smaller in magnitude compared to the other asthma hospital admission studies  
28 summarized in [Figure 5-3](#), but this could be a reflection of the meta-analysis only  
29 including single-day lag estimates from each of the studies. The results of the  
30 meta-analysis were found to be robust in sensitivity analyses examining publication bias;  
31 however, the publication bias analysis was not conducted separately for asthma hospital  
32 admissions and ED visits results.

### ***Emergency Department Visits***

33 The majority of studies, examining respiratory-related hospital admissions and ED visits,  
34 have focused on asthma ED visits. Studies evaluated in the 2008 SO<sub>x</sub> ISA were primarily  
35 limited to single-city studies that provided generally positive associations between SO<sub>2</sub>  
36 and asthma ED visits, with positive associations being reported in some study locations

1 and evidence of no association in other locations ([Figure 5-3](#)). Additionally, there was  
2 limited evidence for potential seasonal differences in SO<sub>2</sub> associations with asthma ED  
3 visits. As with the hospital admission studies, there has been limited analyses examining  
4 the potential confounding effects of copollutants on the SO<sub>2</sub>-asthma ED visit relationship.

5 Recent studies that examined the association between short-term SO<sub>2</sub> exposures and  
6 asthma ED visits have primarily focused on either children or the entire population, with  
7 a few studies examining whether effects differ by lifestage. Additionally, unlike the  
8 hospital admission studies, the ED visit studies examined both 24-h avg and 1-h max  
9 exposure metrics, which can provide some additional insight, on a population level, into  
10 the short-term exposures that result in respiratory effects in controlled human exposure  
11 and animal toxicological studies (see previous subsections of [Section 5.2.1.2](#)).

12 [Strickland et al. \(2010\)](#) examined the association between SO<sub>2</sub> exposure and pediatric  
13 asthma ED visits (ages 5–17 years) in Atlanta, GA, using air quality data over the same  
14 years as [Tolbert et al. \(2007\)](#), who examined all respiratory ED visits. However, unlike  
15 [Tolbert et al. \(2007\)](#), who used a single-site monitor, [Strickland et al. \(2010\)](#) used  
16 population-weighting, a more refined exposure assignment approach, to combine daily  
17 pollutant concentrations across monitors. As discussed in [Section 3.4.2](#), a study by  
18 [Goldman et al. \(2012\)](#) shows that the bias in health effect estimates decreases when using  
19 population-weighted averages for assigning exposure instead the values from a central  
20 site monitor. In [Strickland et al. \(2010\)](#), the authors developed a statistical model using  
21 hospital-specific, time-series data that is essentially equivalent to a time-stratified,  
22 case-crossover analysis (i.e., using interaction terms between year, month, and  
23 day-of-week to mimic the approach of selecting referent days within the same month and  
24 year as the case day). [Strickland et al. \(2010\)](#) observed a 4.2% (95% CI: -2.1, 10.8)  
25 increase in ED visits for a 40-ppb increase in 1-h max SO<sub>2</sub> concentrations at lag 0–2 days  
26 in an all-year analysis. The potential confounding effects of other pollutants on the  
27 SO<sub>2</sub>-asthma ED visit relationship was not assessed in this study, and correlations between  
28 pollutants were not presented. However, when evaluating the correlation of pollutants  
29 examined over the same study years in [Tolbert et al. \(2007\)](#), SO<sub>2</sub> had a low correlation  
30 with all pollutants ( $r \leq 0.36$ ).

31 Positive associations between short-term SO<sub>2</sub> exposures and pediatric asthma ED visits  
32 were also observed in a study conducted by [Li et al. \(2011\)](#) in Detroit, MI that focused on  
33 whether there was evidence of a threshold in the air pollution-asthma ED visit  
34 relationship. In the main nonthreshold analysis, the authors conducted both time-series  
35 and time-stratified case-crossover analyses. [Li et al. \(2011\)](#) observed similar results in  
36 both analyses, which indicated an association between SO<sub>2</sub> and asthma ED visits, [time  
37 series: 20.5% (95% CI: 8.9, 33.2); lag 0–4 for a 10-ppb increase in 24-h avg SO<sub>2</sub>

1 concentrations; case-crossover: 22.8% (95% CI: 12.6, 33.7); lag 0–4]. The results of the  
2 U.S.-based studies focusing on children conducted by [Strickland et al. \(2010\)](#) and [Li et al.](#)  
3 [\(2011\)](#) are consistent with those of [Jalaludin et al. \(2008\)](#) in a study of children  
4 1–14 years of age conducted in Sydney, Australia. In addition to conducting the analysis  
5 focusing on ages 1–14, the authors also examined whether risks varied among age ranges  
6 within this study population ([Chapter 6](#)). [Jalaludin et al. \(2008\)](#) examined single day lags  
7 ranging from 0 to 3 days as well as the average of 0–1 days. In the 1–14 years of age  
8 analysis, the authors observed slightly larger associations at lag 0–1 days [29.7% (95%  
9 CI: 14.7, 46.5)] compared to lag 0 [22.0% (95% CI: 9.1, 34.5)] for a 10-ppb increase in  
10 24-h avg SO<sub>2</sub> concentrations. An examination of the potential confounding effects of  
11 other pollutants was assessed in copollutant models with PM<sub>10</sub>, PM<sub>2.5</sub>, O<sub>3</sub>, CO, or NO<sub>2</sub> at  
12 lag 0. SO<sub>2</sub> was found to be weakly to moderately correlated with these pollutants,  
13  $r = 0.27$ – $0.52$ . [Jalaludin et al. \(2008\)](#) reported that the SO<sub>2</sub>-asthma ED visit association  
14 was slightly attenuated, but remained positive in all copollutant models, with the  
15 magnitude of the association ranging from a 13.2–16.1% increase in asthma ED visits.

16 [Byers et al. \(2015\)](#) in a study conducted in Indianapolis, IN examined asthma ED visits  
17 across all ages as well as various lifestages (i.e., 5–17, 18–44, and  $\geq 45$  years of age).  
18 The authors used a double-weighted approach to assign exposure where they first  
19 weighted air pollution concentrations by distance from a monitor to the ZIP code centroid  
20 and then weighted concentrations by the age-specific census population. In an all-year  
21 analysis for all ages, the authors reported a 0.4% increase in asthma ED visits (95% CI:  
22 –3.6, 4.5) at lag 0–2 for a 40-ppb increase in 1-h max SO<sub>2</sub> concentrations, with evidence  
23 of a larger association when focusing on pediatric asthma ED visits [5.4% (95% CI: –3.2,  
24 14.5); lag 0–2], which is consistent with [Strickland et al. \(2010\)](#), [Li et al. \(2011\)](#), and  
25 [Jalaludin et al. \(2008\)](#). Although copollutant analyses were not conducted, SO<sub>2</sub> was found  
26 to have a low correlation with PM<sub>2.5</sub> ( $r < 0.4$ ) in all-year and seasonal analyses, and  
27 moderate correlation with 1-h max and 8-h max O<sub>3</sub> in warm season analyses  
28 ( $r = 0.42$ – $0.45$ ). Additionally, when examining SO<sub>2</sub> concentrations across the entire study  
29 period, the authors noted that only 36 days (i.e., 2.1% of days) had 1-h max SO<sub>2</sub>  
30 concentrations that exceeded the NAAQS.

31 [Alhanti et al. \(2016\)](#) also used the approach of assigning exposure using  
32 population-weighting similar to [Strickland et al. \(2010\)](#), but expanded the study area to  
33 include two additional cities, Dallas, TX and St. Louis, MO, as well as Atlanta, GA.  
34 The analysis focused on examining whether there was evidence of differential risk across  
35 lifestages (i.e., 0–4, 5–18, 19–39, 40–64, and 65+ years of age) for asthma ED visits  
36 across a number of air pollutants, including SO<sub>2</sub>. Analyses were conducted for each  
37 individual city, and an overall estimate across all three cities was calculated by taking the  
38 inverse-variance weighted average of the city-specific risk estimate. Across the

1 individual cities, there was evidence of positive and negative associations for all age  
2 categories examined except ages 5–18 where positive associations were observed across  
3 all cities, which is consistent with the single-city studies detailed above. In the combined  
4 analysis across the three cities, [Alhanti et al. \(2016\)](#) reported positive associations for  
5 ages 0–4 [4.1% (95% CI: –0.8, 9.2); lag 0–2 for 40-ppb increase in 1-h max SO<sub>2</sub>  
6 concentrations] and 5–18 [5.7% (95% CI: –0.8, 11.8); lag 0–2] ([Sarnat, 2016](#)). In  
7 sensitivity analyses, the results were found to be robust to alternative model  
8 specifications for both control for temporal trends and weather covariates.

9 As detailed in the asthma hospital admissions section, [Zheng et al. \(2015\)](#) conducted a  
10 meta-analysis of asthma hospital admission and ED visit studies. In the analysis focusing  
11 on ED visit studies, the authors reported a 3.5% increase (95% CI: 1.9, 5.1) in asthma ED  
12 visits for a 10-ppb increase in 24-h avg SO<sub>2</sub> concentrations based on single-day lag  
13 estimates from 34 studies. This result is in the range of risk estimates reported in studies  
14 that observed positive associations between short-term SO<sub>2</sub> exposure and asthma ED  
15 visits ([Figure 5-3](#)).

16 Although a number of recent studies add to the evidence from the 2008 SO<sub>x</sub> ISA  
17 indicating a positive association between asthma ED visits and short-term SO<sub>2</sub> exposures,  
18 not all studies have reported positive associations. Both [Stieb et al. \(2009\)](#) and [Villeneuve  
19 et al. \(2007\)](#), in studies conducted in seven Canadian cities and Edmonton, AB,  
20 respectively, did not observe evidence of a positive association between short-term SO<sub>2</sub>  
21 exposures and asthma ED visits ([Figure 5-3](#)). The evidence of no association was  
22 observed over multiple lag structures (i.e., both single and multiday lags) ([Stieb et al.,  
23 2009](#); [Villeneuve et al., 2007](#)) as well as subdaily exposure metrics (i.e., 3-h avg pollutant  
24 concentrations) ([Stieb et al., 2009](#)).

### ***Hospital Admissions and Emergency Department Visits for Respiratory Conditions Associated with Asthma***

25 As stated previously, asthma is difficult to diagnose in children less than 5 years of age  
26 ([NAEPP, 2007](#)); however, asthma-like symptoms in children within this age range are  
27 often presented in the form of transient wheeze. Although studies that examine ED visits  
28 for wheeze do not directly inform upon the relationship between short-term SO<sub>2</sub>  
29 exposures and asthma, they can add supporting evidence. [Orazzo et al. \(2009\)](#) examined  
30 the association between short-term SO<sub>2</sub> exposures and wheeze ED visits, in children  
31 (ages 0–2 years) in six Italian cities. In a time-stratified case-crossover analysis, [Orazzo  
32 et al. \(2009\)](#) examined associations for multiday lags ranging from 0–1 to 0–6 days.  
33 The authors reported the strongest evidence for an association between short-term SO<sub>2</sub>  
34 exposures and wheeze ED visits at lags of 0–3 to 0–6 days with estimates ranging from

1 2.1 to 4.3%, respectively, for a 10-ppb increase in 24-h avg SO<sub>2</sub> concentrations. Within  
2 this study, copollutant analyses or correlations with other pollutants were not presented.

3 [Smargiassi et al. \(2009\)](#) also provided additional information on whether there is an  
4 association between short-term SO<sub>2</sub> exposures and health effects that may be closely  
5 related to asthma. The distinction between asthma and asthma-related outcomes is made  
6 in this case because the study focused on asthma hospital admissions and ED visits in  
7 children 2–4 years of age. This age range may not necessarily represent an asthma  
8 exacerbation in the same context as those studies discussed earlier in this section that  
9 include older individuals in whom asthma is more easily diagnosed. Within this study,  
10 the authors examined the influence of a point source of SO<sub>2</sub> (i.e., stack emissions from a  
11 refinery) in Montreal on asthma hospital admissions and ED visits using data from two  
12 fixed-site monitors as well as estimates of SO<sub>2</sub> concentrations from a dispersion model,  
13 AERMOD. The authors examined both daily mean and daily peak SO<sub>2</sub> concentrations.  
14 When comparing SO<sub>2</sub> concentrations at one monitoring site east of the refinery with  
15 those obtained via AERMOD the authors observed a modest correlation (daily mean SO<sub>2</sub>,  
16  $r = 0.43$ ; daily peak SO<sub>2</sub>,  $r = 0.36$ ). An examination of hospital admissions and ED visits  
17 for both monitor locations, east and southwest of the refinery, found that associations  
18 were slightly larger in magnitude for the same-day daily peak [hospital admissions: 1.46  
19 (95% CI: 1.10, 1.93); ED visits: 1.18 (95% CI: 1.05, 1.33) for a 40-ppb increase in  
20 1-h max SO<sub>2</sub> concentrations] compared to daily mean concentrations [hospital  
21 admissions: 1.36 (95% CI: 1.05, 1.81); ED visits: 1.15 (95% CI: 1.02, 1.27) for a 10-ppb  
22 increase in 24-h avg SO<sub>2</sub> concentrations] in an unadjusted model at lag 0. When  
23 examining associations using SO<sub>2</sub> concentrations from the fixed monitoring sites,  
24 [Smargiassi et al. \(2009\)](#) did not find consistent evidence of an increase in asthma hospital  
25 admissions or ED visits, which is indicative of the fact that a monitor located far from a  
26 point source may not adequately capture population exposures for residences of interest  
27 located closer to that source (see [Section 3.4.2](#)). The authors also examined an adjusted  
28 model to control for daily weather variables and all other regional pollutants (i.e., PM<sub>2.5</sub>,  
29 SO<sub>2</sub>, NO<sub>2</sub>, and O<sub>3</sub>), but these results are not presented because, as discussed within this  
30 ISA, the evaluation of potential copollutant confounding is limited to two-pollutant  
31 models because the results from multipollutant models are difficult to interpret due to  
32 multicollinearity between pollutants. However, the results from the unadjusted  
33 (i.e., single-pollutant model) and adjusted models were generally similar.

### ***Outpatient and Physician Visits Studies of Asthma***

34 Several recent studies examined the association between ambient SO<sub>2</sub> concentrations and  
35 physician or outpatient (nonhospital, non-ED) visits for asthma. In Toronto, [Burra et al.](#)  
36 [\(2009\)](#) examined asthma physician visits among patients aged 1–17 and 18–64 years in a

1 study focusing on differences by sex and income within each age category. For children,  
2 the authors reported evidence of consistent positive associations between short-term  
3 increases in SO<sub>2</sub> concentrations and asthma physician visits for most of the single and  
4 multiday lags examined (i.e., 0, 0–1, 0–2, 0–3), with no evidence of an association for a  
5 0–4 day lag. In the analysis of adults, a similar pattern of associations was observed;  
6 however, there was no evidence of an association at the two longest lags examined, 0–3  
7 and 0–4 days.

8 In a study conducted in Atlanta, GA, [Sinclair et al. \(2010\)](#) examined the association  
9 between multiple respiratory outcomes, including asthma and outpatient visits from a  
10 managed care organization. The authors separated the analysis into two time periods (the  
11 first 25 months of the study period and the second 28 months of the study period) in order  
12 to compare the air pollutant concentrations and relationships between air pollutants and  
13 acute respiratory visits for the 25-month time period examined in [Sinclair and Tolsma](#)  
14 [\(2004\)](#) (i.e., August 1998–August 2000), and an additional 28-month time period of  
15 available data from the Atlanta Aerosol Research and Inhalation Epidemiology Study  
16 (ARIES) (i.e., September 2000–December 2002). As detailed in [Table 5-9](#), SO<sub>2</sub>  
17 concentrations were relatively similar between periods, differing by less than 2 ppb.  
18 A comparison of the two time periods indicated that risk estimates across outcomes  
19 tended to be larger in the earlier 25-month period compared to the later 28-month period,  
20 with evidence of consistent positive associations across the lags examined for asthma  
21 (both child and adult), but confidence intervals were relatively large.

### ***Examination of Seasonal Differences***

22 In addition to examining the association between short-term SO<sub>2</sub> exposures and asthma  
23 hospital admissions and ED visits in all-year analyses, some studies also conducted  
24 seasonal analyses. When evaluating these studies, it is important to note that the  
25 difference in the geographic locations examined across studies complicates the ability to  
26 draw overall conclusions regarding the seasonal patterns of associations.

27 In the study of eight South Korean cities, [Son et al. \(2013\)](#) examined potential seasonal  
28 differences across respiratory hospital admission outcomes. For asthma and allergic  
29 disease hospital admissions, the association with SO<sub>2</sub> was largest in magnitude during the  
30 summer, although confidence intervals were quite large [asthma: 19.1% (95% CI: –18.3,  
31 73.9), lag 0–3; allergic disease: 21.9% (95% CI: –6.7, 58.6), lag 0–3 for a 10-ppb  
32 increase in 24-h avg SO<sub>2</sub> concentrations]. Across the eight cities, mean 24-h avg SO<sub>2</sub>  
33 concentrations were lowest during the summer season (4.4 ppb compared to a range of  
34 4.8 to 7.0 in the other seasons), which was also observed for NO<sub>2</sub>, PM<sub>10</sub>, and CO.  
35 The seasonal asthma hospital admission results of [Son et al. \(2013\)](#) are similar to those  
36 reported in [Samoli et al. \(2011\)](#) in a study conducted in Athens, Greece. [Samoli et al.](#)

1 [\(2011\)](#) observed the largest magnitude of an association during the summer months  
2 [46.6% (95% CI: -13.8, 149.3); lag 0 for a 10-ppb increase in 24-h avg SO<sub>2</sub>  
3 concentrations], but also reported a similar association in the autumn months [42.6 %  
4 (95% CI: -0.5, 104.4); lag 0]. Although positive, associations for the winter and spring  
5 months were smaller in magnitude, 20.2 and 31.8%, respectively.

6 The initial indication of larger associations during the summer for asthma hospital  
7 admissions is further supported by the analysis of [Strickland et al. \(2010\)](#) examining  
8 short-term SO<sub>2</sub> exposures and pediatric asthma ED visits in Atlanta. The authors reported  
9 evidence of asthma ED visit associations larger in magnitude during the summer [10.8%  
10 (95% CI: 0.7, 21.7); lag 0–2 for a 40-ppb increase in 1-h max SO<sub>2</sub> concentrations], with  
11 no evidence of an association during the winter [0.4% (95% CI: -7.5, 9.0)]. These results  
12 are consistent with [Byers et al., 2015](#), who reported associations larger in magnitude in  
13 the summer for all ages [3.1% (95% CI: -2.6, 8.6); lag 0–2 for a 40-ppb increase in  
14 1-h max SO<sub>2</sub> concentrations], and particularly children 5–17 years of age [13.0% (95%  
15 CI: 0.8, 26.8); lag 0–2], and no evidence of an association in the cold season across all  
16 ages examined. However, in another study focusing on asthma physician visits in Atlanta,  
17 [Sinclair et al. \(2010\)](#) reported inconsistent evidence of seasonal differences in risk  
18 estimates, with the pattern of associations being different in each of the time periods  
19 examined in the study. It is important to note that the results of [Sinclair et al. \(2010\)](#) may  
20 be a reflection of the severity of asthma exacerbations requiring medical attention and  
21 people proceeding directly to a hospital for treatment instead of first visiting a physician.  
22 Therefore, the study may not be able to adequately capture associations, and specifically,  
23 any potential seasonal differences.

24 The meta-analysis conducted by [Zheng et al., 2015](#) provides some additional supporting  
25 evidence for potential seasonal differences in SO<sub>2</sub>-asthma hospital admission and ED  
26 visit associations. In a combined analysis including both asthma hospital admission and  
27 ED visit studies that reported seasonal results, [Zheng et al. \(2015\)](#) reported slightly larger  
28 associations in the warm [4.8% (95% CI: 2.7, 7.0) for a 10-ppb increase in 24-h avg SO<sub>2</sub>  
29 concentrations] compared to the cold season [3.2% (95% CI: 0.5, 5.9)], but confidence  
30 intervals did overlap.

31 Although there is some evidence for larger associations during the summer, studies  
32 conducted by [Villeneuve et al. \(2007\)](#) in Edmonton, AB and [Jalaludin et al. \(2008\)](#) in  
33 Sydney, Australia present conflicting results. As stated above, [Villeneuve et al. \(2007\)](#)  
34 did not find evidence of an association between short-term SO<sub>2</sub> exposures and asthma ED  
35 visits, including in seasonal analysis, while [Jalaludin et al. \(2008\)](#) reported evidence of  
36 larger associations during the cold months (May–October) compared to the warm months  
37 (November–April) ([Figure 5-3](#)).

1 Overall, the results of [Samoli et al. \(2011\)](#), [Son et al. \(2013\)](#), [Strickland et al. \(2010\)](#), and  
2 [Byers et al. \(2015\)](#) suggest that associations are larger in magnitude during the summer  
3 season, but this conclusion should be viewed with caution because the results of each  
4 study are highly imprecise, as reflected by the wide confidence intervals for each  
5 seasonal result. Additionally, the interpretation of results from these studies is  
6 complicated by the lack of copollutant analyses, and the results from [Villeneuve et al.  
7 \(2007\)](#) and [Jalaludin et al. \(2008\)](#) that do not find evidence of larger associations during  
8 the summer or warm season.

### ***Lag Structure of Associations***

9 When examining associations between air pollution and a specific health outcome, such  
10 as respiratory-related hospital admissions, it is informative to assess whether exposure to  
11 an air pollutant results in an immediate, delayed, or prolonged effect on health. Recent  
12 studies that examine both multiple single- and multiday lags can help provide information  
13 on whether there is a specific exposure window(s) that contribute to SO<sub>2</sub>-related asthma  
14 hospital admissions and ED visits.

15 [Son et al. \(2013\)](#) examined the lag structure of associations for multiple  
16 respiratory-related hospital admissions, including asthma and allergic disease, by  
17 analyzing both single- and multiday lags. Across single-day lags of 0 to 3 days, positive  
18 associations were observed across each lag, but the magnitude of the association varied  
19 across single-day lags for each outcome. For both asthma and allergic disease hospital  
20 admissions, the largest association, in terms of magnitude, for SO<sub>2</sub> was observed for each  
21 of the multiday lags examined, with the largest occurring at lag 0–3 days [asthma: 5.3%  
22 (95% CI: -2.4, 13.0); allergic disease: 3.1% (95% CI: -3.7, 10.7) for a 10-ppb increase in  
23 24-h avg SO<sub>2</sub> concentrations].

24 Studies conducted by [Samoli et al. \(2011\)](#) and [Jalaludin et al. \(2008\)](#) report evidence for  
25 the strongest SO<sub>2</sub>-asthma hospital admission and ED visit associations occurring rather  
26 immediately (lag 0) as well as over the first few days after exposure, average of lags from  
27 0 up to 2 days. [Samoli et al. \(2011\)](#) in the examination of single- and multiday lags for  
28 associations between SO<sub>2</sub> and asthma hospital admissions in Athens, Greece found  
29 associations of similar magnitude at lag 0 and a 0–2 day distributed lag, but the  
30 distributed lag association was imprecise (i.e., larger confidence intervals) (quantitative  
31 results not presented). The associations reported for single-day lags of 1 and 2 days were  
32 small and close to null. [Jalaludin et al. \(2008\)](#) in a study in Sydney, Australia found when  
33 examining single-day lags of 0 to 3 days that asthma ED visit associations were largest  
34 for lag 0 [22.0% (95% CI: 9.1, 34.5) for a 10-ppb increase in 24-h avg SO<sub>2</sub>  
35 concentrations] and 1 day [16.1% (95% CI: 5.1, 26.5)]. This is further reflected in the

1 largest SO<sub>2</sub> association being observed for the multiday lag of 0–1 days [29.7% (95% CI:  
2 14.7, 46.5)].

3 Only a limited number of studies have examined the lag structure of associations and the  
4 results across studies are not fully supported by the rest of the literature base. [Villeneuve  
5 et al. \(2007\)](#), when studying asthma ED visits in seven Canadian cities, examined  
6 single-day lags of 0 and 1 day, along with multiday lags of 0–2 and 0–4 days.  
7 The authors reported no evidence of an association between short-term SO<sub>2</sub> exposures  
8 and asthma ED visits at any lag. Additionally, [Orazzo et al. \(2009\)](#) in the study of wheeze  
9 ED visits in six Italian cities, examined multiday lags ranging from 0–1 to 0–6 days.  
10 Across the lags examined, the authors reported evidence of increasing magnitude of the  
11 association as the length of the multiday lag increased, with lag 0–6 days showing the  
12 largest association.

### ***Exposure Assignment***

13 Questions often arise in air pollution epidemiologic studies about the method used to  
14 assign exposure (see [Section 3.3.3](#)). [Strickland et al. \(2011\)](#), using ED visit data from  
15 Atlanta, GA, assessed the effect of various exposure assignment approaches on the  
16 relationship between short-term air pollution exposures and asthma ED visits.  
17 The authors used warm season data from [Strickland et al. \(2010\)](#) to examine the relative  
18 influence of different exposure assignment approaches (i.e., central monitor, unweighted  
19 average across available monitors, and population-weighted average) on the magnitude  
20 and direction of associations between SO<sub>2</sub> and pediatric asthma ED visits. SO<sub>2</sub> exhibited  
21 a relatively low chi-square goodness-of-fit statistic compared with other pollutants, which  
22 the authors attributed to spatial heterogeneity in SO<sub>2</sub> concentrations ([Section 3.4.2.2](#)).  
23 [Strickland et al. \(2011\)](#) reported that effect estimates per IQR increase in SO<sub>2</sub> were  
24 similar across the metrics; however, based on a standardized increment (i.e., 20 ppb in the  
25 study), the magnitude of the association between SO<sub>2</sub> and pediatric asthma ED visits  
26 varied [central monitor 3.0% (95% CI: –0.4, 8.4); unweighted average 12.8% (95% CI:  
27 2.8, 23.4); population-weighted average 10.9% (95% CI: 0.8, 21.9) for a 40-ppb increase  
28 in 1-h max SO<sub>2</sub> concentrations at lag 0–2 days]. The difference in associations observed  
29 across the various exposure assignment approaches when using the standardized  
30 increment can be attributed to the value (i.e., a 1-h max SO<sub>2</sub> concentration of 20 ppb) not  
31 reflecting an increase in SO<sub>2</sub> concentrations that is reflective of the SO<sub>2</sub> distribution in  
32 Atlanta (e.g., in the study the standardized increment for 1-h max SO<sub>2</sub> is 20 ppb, but the  
33 IQR, which is often used to calculate the relative risk, differs across the exposure  
34 assignment approaches, varying from 9.6 to 13.9 ppb). Although the [Strickland et al.  
35 \(2011\)](#) study was only conducted in one city, the study suggests that it is appropriate to  
36 consider the distribution of air pollutant concentrations when calculating a relative risk

1 (i.e., IQR), but also that the different approaches used to assign exposure across the  
2 studies evaluated may alter the magnitude, not direction, of the associations observed.

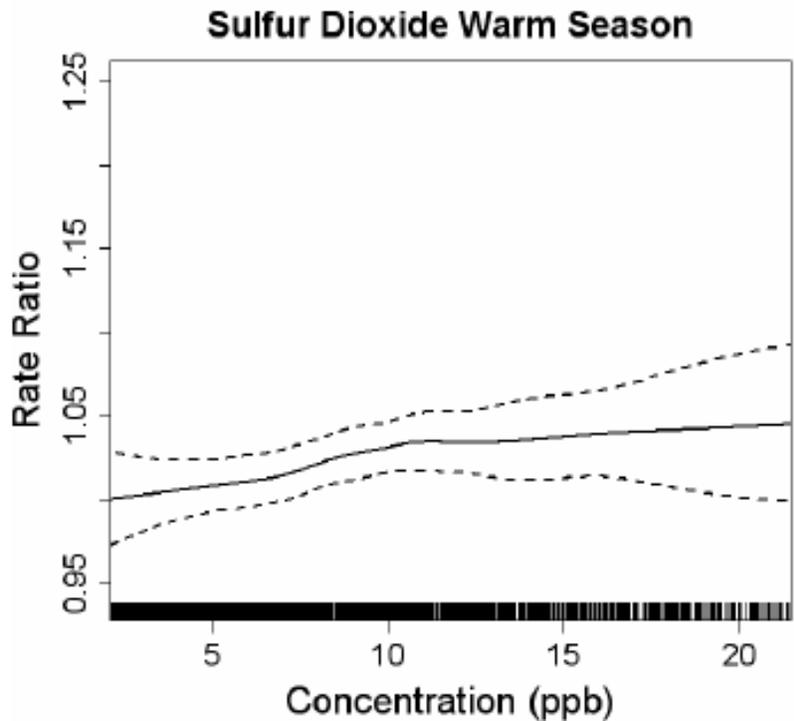
### **Concentration-Response Relationship**

3 To date, few studies have examined the C-R relationship between SO<sub>2</sub> exposures and  
4 respiratory morbidity. In recent studies, [Strickland et al. \(2010\)](#) and [Li et al. \(2011\)](#)  
5 examined the shape of the SO<sub>2</sub>-pediatric asthma ED visit relationship using different  
6 analytical approaches.

7 [Strickland et al. \(2010\)](#) examined the C-R relationship by conducting quintile and locally  
8 weighted scatterplot smoothing (LOESS) C-R analyses. In the quintile analysis, SO<sub>2</sub>  
9 associations were examined in both the warm and cold seasons; however, no associations  
10 were observed for the cold season for any quintile. Focusing on the warm season, the  
11 authors found evidence of an increase in the magnitude of the association for  
12 concentrations within the range of 7 to <24.2 ppb, relative to the first quintile (i.e., SO<sub>2</sub>  
13 concentrations <3.1 ppb). The smallest associations were observed for the 5th quintile,  
14 which represented concentrations ranging from 24.2 to ≤149 ppb; however, this quintile  
15 represented the extreme end of the distribution of SO<sub>2</sub> concentrations where data density  
16 was low. Additionally, the LOESS C-R relationship analysis provides evidence of a  
17 linear relationship between short-term SO<sub>2</sub> exposures and asthma ED visits along the  
18 distribution of concentrations from the 5th (2.1 ppb) to 95th (21.5 ppb) percentile ([Sacks,  
19 2015](#)) ([Figure 5-4](#)). Collectively, these analyses do not provide evidence of a threshold.

20 In a study conducted in Detroit, MI, [Li et al. \(2011\)](#) examined whether there is evidence  
21 of a nonlinear C-R relationship for air pollutants and pediatric asthma ED visits.  
22 Associations with SO<sub>2</sub> were examined in both a time-series and time-stratified,  
23 case-crossover study design assuming (1) a linear relationship and (2) a nonlinear  
24 relationship starting at 8 ppb [i.e., the maximum likelihood estimate within the 10th to  
25 95th percentile concentration where a change in linearity may occur (~91st percentile)]. It  
26 is important to note the analysis that assumed a nonlinear relationship did not assume  
27 zero risk below the inflection point. The focus of the analysis was on identifying whether  
28 risk increased above that observed in the linear models at SO<sub>2</sub> concentrations above  
29 8 ppb. In the analyses assuming linearity, the authors examined single-day lags of 3 and  
30 5 days and multiday lags of 0–2 and 0–4 days. Positive associations were observed for all  
31 lags examined and were relatively consistent across models, with the strongest  
32 association for a 0–4 day lag [time series: 20.5% (95% CI: 8.9, 33.2); case-crossover:  
33 22.8% (95% CI: 12.6, 33.7) for a 10-ppb increase in 24-h avg SO<sub>2</sub> concentrations]. In the  
34 models that assumed a nonlinear relationship, the authors did not observe evidence of  
35 increased risk above ~8 ppb. However, it is important to note that the data density is low

1 at concentrations greater than 8 ppb, as reflected by this value representing the ~91st  
2 percentile of SO<sub>2</sub> concentrations.



Note: solid line = smoothed concentration-response estimate. Dashed line = twice-standard error estimates.  
Source: Reprinted with permission of the American Thoracic Society. [Strickland et al. \(2010\)](#).

**Figure 5-4 Concentration-response for associations between 3-day average (lag 0–2) sulfur dioxide concentrations and emergency department visits for pediatric asthma at the 5th to 95th percentile of sulfur dioxide concentrations in the Atlanta, GA area.**

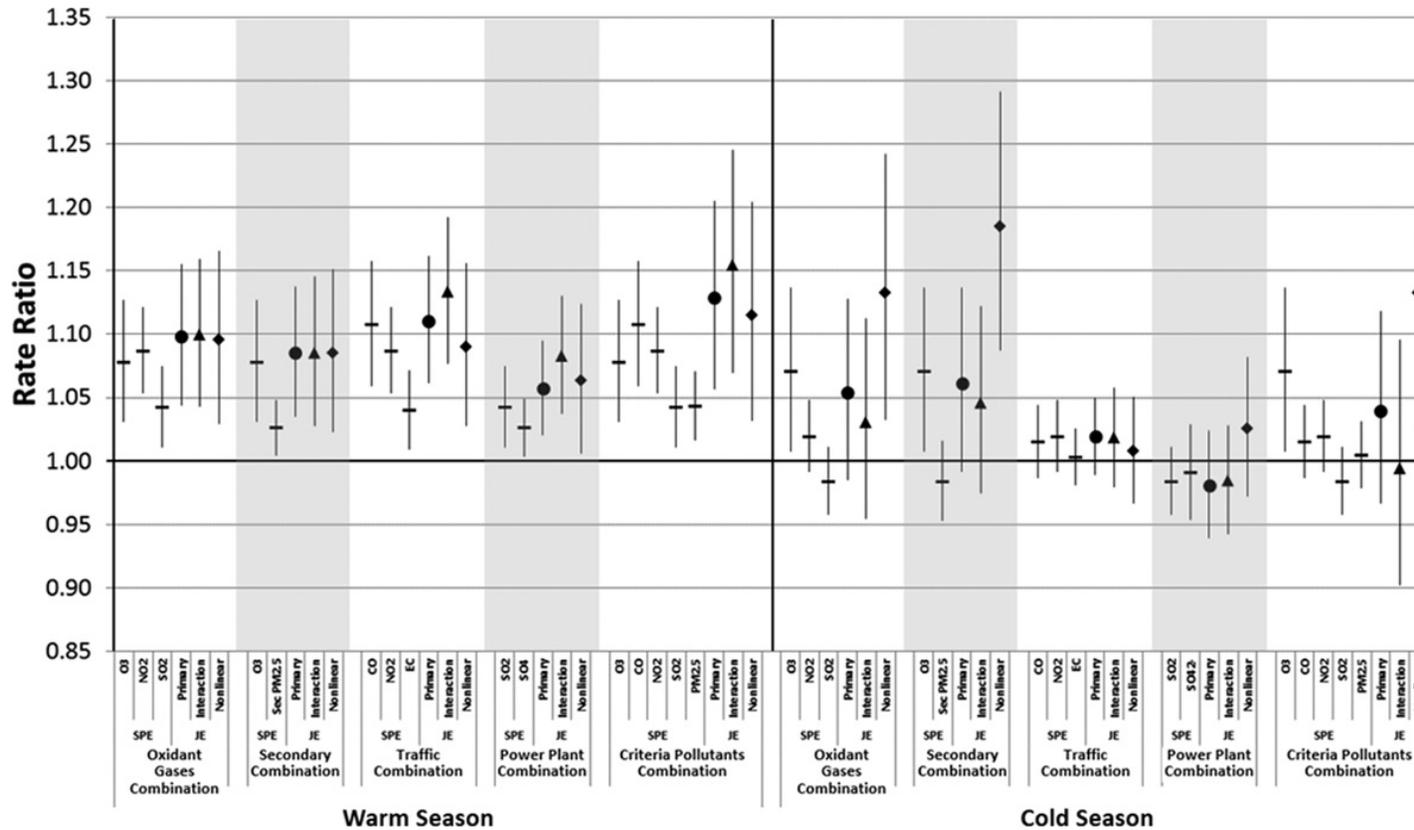
### ***Sulfur Dioxide within the Multipollutant Mixture***

3 An important question often encountered during the review of any criteria air pollutant, is  
4 whether the pollutant has an independent effect on human health. However, ambient  
5 exposures to criteria air pollutants are in the form of mixtures, which make answering  
6 this question difficult. Epidemiologic studies traditionally attempt to identify the  
7 independent effect of a criteria air pollutant through the use of copollutant models, but  
8 these methods do not consider the broader air pollution mixture. Recent studies  
9 conducted by [Winqvist et al. \(2014\)](#) and [Pearce et al. \(2015\)](#) using pediatric asthma ED  
10 visits data from Atlanta assessed whether specific mixtures are more strongly associated

1 with health effects compared to others. Although the primary objective of these types of  
2 studies is not to directly assess the independent effects of a pollutant, they can inform the  
3 understanding of the role of SO<sub>2</sub> in the air pollution mixture (e.g., contributing to an  
4 additive or synergistic effect).

5 [Winquist et al. \(2014\)](#) examined multipollutant mixtures by focusing on the joint effect  
6 (i.e., the combined effect of multiple pollutants) of pollutants often associated with  
7 specific air pollution sources. Associations between short-term SO<sub>2</sub> exposures and  
8 pediatric asthma ED visits (i.e., ages 5–17) were examined in single-pollutant models and  
9 also in a multipollutant context in joint models for pollutant combinations representative  
10 of irritant gases (i.e., O<sub>3</sub>, NO<sub>2</sub>, and SO<sub>2</sub>), power plants (i.e., SO<sub>2</sub> and SO<sub>4</sub><sup>2-</sup>), and NAAQS  
11 pollutants (i.e., O<sub>3</sub>, CO, NO<sub>2</sub>, SO<sub>2</sub>, and PM<sub>2.5</sub>). It is important to note that the pollutant  
12 combination analyses attempt to address a different question (i.e., what is the risk  
13 associated with exposure to a combination of pollutants?) than a traditional copollutant  
14 analysis, which focuses on identifying the independent effect of a pollutant. Using the  
15 model detailed in [Strickland et al. \(2010\)](#), the authors examined the relationship between  
16 each combination and pediatric asthma ED visits using a Poisson model in the context of  
17 a time-referent case-crossover analysis. The authors reported results for an IQR increase  
18 for lag 0–2 days in single-pollutant analyses as well as three types of joint effect models  
19 [i.e., no interaction terms (primary), first-order multiplicative interactions between  
20 pollutants (interactions), and nonlinear pollutant terms (nonlinear)] ([Figure 5-5](#)).

21 In single-pollutant analyses, SO<sub>2</sub> associations were smaller in magnitude compared to the  
22 other pollutants that comprised each pollutant combination, but the uncertainty  
23 surrounding each SO<sub>2</sub> estimate was relatively small. Across pollutant combinations that  
24 contained SO<sub>2</sub>, joint effect models reported consistent positive associations with pediatric  
25 asthma ED visits in the warm season. Additionally, for each pollutant combination the  
26 association observed was larger in magnitude than any single-pollutant association,  
27 including SO<sub>2</sub>, but not equivalent to the sum of each individual pollutant association for a  
28 specific combination. In the warm season analyses, associations across the different joint  
29 effect models were relatively similar. Overall, the results during the cold season were  
30 more variable.



JE = joint model estimate; NO<sub>2</sub> = nitrogen dioxide; O<sub>3</sub> = ozone; PM<sub>2.5</sub> = particulate matter with a nominal aerodynamic diameter less than or equal to 2.5 μm; SO<sub>2</sub> = sulfur dioxide; SPE = single-pollutant model estimate.

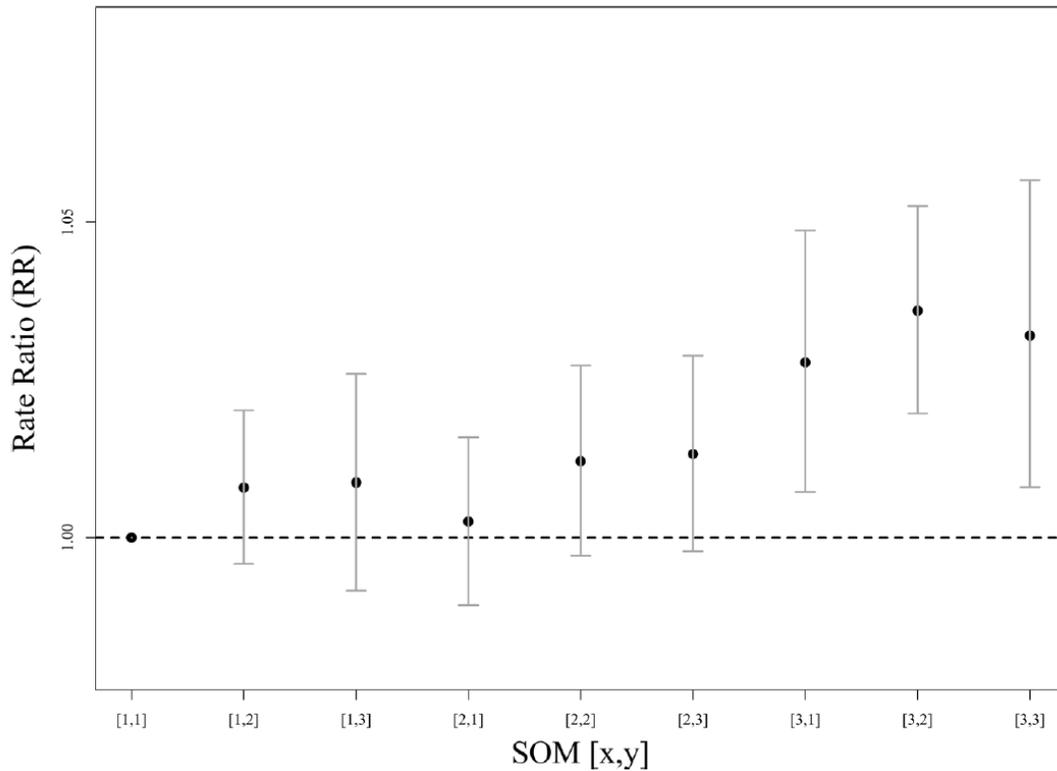
Note: Interquartile range for 1-h max SO<sub>2</sub> concentrations = 10.51 ppb.

Source: [Winquist et al., 2014](#).

**Figure 5-5** Rate ratio and 95% confidence intervals for single-pollutant and joint effect models for each pollutant combination in warm and cold season analyses for an interquartile range increase in each pollutant at lag 0–2 days.

1  
2 [Pearce et al. \(2015\)](#) took a different approach to examining multipollutant mixtures by  
3 using an unsupervised learning tool, the self-organizing map (SOM), which is similar to  
4 cluster analysis. Using air pollution concentrations for 10 pollutants from a single  
5 monitor, the authors identified nine distinct day types representative of air quality in  
6 Atlanta during the study period. These unique days were then used as indicator variables  
7 to examine associations with pediatric asthma ED visits using the same statistical  
8 approach as [Strickland et al. \(2010\)](#) and [Winquist et al. \(2014\)](#). Across the nine SOMs,  
9 some pollutant combinations represented days consisting of high single pollutant  
10 extremes, which included a day with high 1-h max SO<sub>2</sub> concentrations (i.e., mean  
11 concentration of 48.8 ppb and concentrations ranging from 8.5–23.7 ppb for all other  
12 SOMs). In analyses of all SOMs focusing on lag 1, the strongest associations were  
13 observed for days representing above average concentrations for all pollutants, and for  
14 days representing a collection of primary (i.e., CO, NO<sub>2</sub>, NO<sub>x</sub>, EC, and OC) or secondary  
15 pollutants (i.e., O<sub>3</sub>, NH<sub>4</sub><sup>+</sup>, and SO<sub>4</sub><sup>2+</sup>) ([Figure 5-6](#)). Additional evidence of associations  
16 with pediatric asthma ED visits was observed for days with single pollutant extremes,  
17 including days with high SO<sub>2</sub> concentrations and generally lower concentrations for all  
18 other pollutants ([Figure 5-6](#)). Interestingly, when comparing SOMs results with  
19 single-pollutant results in sensitivity analyses, the authors reported a null association with  
20 SO<sub>2</sub> at lag 1. This result differs from that observed in [Strickland et al. \(2010\)](#) and  
21 [Winquist et al. \(2014\)](#), but the difference could be due to the fact that [Pearce et al. \(2015\)](#)  
22 focused only on lag 1 because they were examining distinct pollution profiles that often  
23 do not occur on multiple days in a row. In contrast, [Strickland et al. \(2010\)](#) and [Winquist](#)  
24 [et al. \(2014\)](#) examined associations over a multiday average of 0–2 days. Additionally,  
25 the difference between the SOM and single-pollutant SO<sub>2</sub> result could be because the  
26 SOM with high SO<sub>2</sub> concentrations was better able to capture the immediate respiratory  
27 response due to higher peak concentrations, which would be consistent with the effects  
28 observed in controlled human exposure and animal toxicological studies.

29 Although the single-pollutant results of [Winquist et al. \(2014\)](#) and [Pearce et al. \(2015\)](#)  
30 differ due to the lags examined, the studies contribute to evidence that SO<sub>2</sub> alone and in  
31 combination with other pollutants is associated with asthma ED visits. The studies also  
32 highlight the difficulty in separating out the independent effect of a pollutant that is part  
33 of a mixture because multiple pollutants are often highly correlated.



SOM = self-organizing map.

Note: [2,2] = days with high sulfur dioxide concentrations. [3,3] and [3,1] = days with primary and secondary pollutants, respectively. [3,2] = days with above average concentrations for all pollutants.

Source: (Pearce et al., 2015).

**Figure 5-6** Rate ratio and 95% confidence interval for association between self-organizing map-based multipollutant day type and pediatric asthma emergency department visits at lag 1.

***Summary of Asthma Hospital Admission and Emergency Department Visits***

1 Recent studies that examined the association between short-term SO<sub>2</sub> exposure and  
 2 asthma hospital admissions and ED visits generally report positive associations in studies  
 3 examining all ages, children (i.e., <18 years of age), and older adults (i.e., 65 years of age  
 4 and older) (Figure 5-3). The pattern of associations observed across studies focusing on  
 5 all ages as well as age-stratified analyses is consistent with those studies evaluated in the  
 6 2008 SO<sub>x</sub> ISA. Across asthma hospital admission and ED visit studies that evaluated the  
 7 lag structure of associations, the most consistent evidence indicated that associations  
 8 were largest in magnitude for multiday lags that encompassed the first few days after  
 9 exposure (i.e., average of 0–2 and 0–3 day lags). This evidence generally supports the

1 timing of SO<sub>2</sub> effects observed in the controlled human exposure and animal  
2 toxicological studies ([Section 5.2.1.2](#)). The examination of potential copollutant  
3 confounding was rather limited in the body of studies that focused on asthma hospital  
4 admissions and ED visits. Across studies, SO<sub>2</sub> was found to be low ( $r < 0.4$ ) to  
5 moderately ( $r = 0.4\text{--}0.7$ ) correlated with other pollutants examined. Evidence from these  
6 studies is consistent with those studies evaluated in the 2008 SO<sub>x</sub> ISA and adds to the  
7 body of evidence indicating that SO<sub>2</sub>-asthma hospital admission and ED visit associations  
8 remain relatively unchanged in magnitude in copollutant models.

9 A number of recent studies also examined whether there was evidence that the  
10 association between short-term SO<sub>2</sub> exposures and asthma hospital admissions and ED  
11 visits was modified by season or some other individual- or population-level factor  
12 ([Chapter 6](#)). An examination of seasonal differences in SO<sub>2</sub>-asthma hospital admission  
13 and ED visit associations provide some evidence of SO<sub>2</sub> effects being larger in magnitude  
14 in the summer or warm season, but the lack of this pattern across all studies that  
15 conducted seasonal analyses suggests that seasonal associations may vary by geographic  
16 location. Studies of individual- and population-level factors provide evidence of  
17 differences in associations by lifestage, with larger SO<sub>2</sub> effects for children and older  
18 adults, and more limited evidence for differences by sex ([Chapter 6](#)).

19 Additionally, some recent studies examined various study design issues, including model  
20 specification and exposure assignment. An examination of model specification, as  
21 detailed in [Section 5.2.1.6](#), indicates that the relationship between short-term SO<sub>2</sub>  
22 exposures and respiratory-related hospital admissions, including those for asthma and  
23 allergic disease, are sensitive to using less than 7 degrees of freedom (df) per year to  
24 account for temporal trends, but robust to alternative lags and df ranging from 3 to 6 for  
25 weather covariates ([Son et al., 2013](#)). The results of [Son et al. \(2013\)](#) are supported by the  
26 sensitivity analyses examining model specification conducted by [Alhanti et al. \(2016\)](#) for  
27 asthma ED visits where the results were relatively consistent when the number of df for  
28 temporal trends was increased and alternative covariates for weather used. An  
29 examination of various exposure assignment approaches, including single central site,  
30 average of multiple monitors, and population-weighted average, suggests that each  
31 approach may influence the magnitude, but not direction, of the SO<sub>2</sub>-asthma ED visit risk  
32 estimate ([Strickland et al., 2011](#)).

33 Finally, a few recent studies examined whether the shape of the SO<sub>2</sub>-asthma ED visits  
34 relationship is linear or provides evidence of a threshold. These studies provide initial  
35 evidence of a linear, no-threshold relationship between short-term SO<sub>2</sub> exposures and  
36 asthma ED visits ([Li et al., 2011](#); [Strickland et al., 2010](#)).

## **Subclinical Effects Underlying Asthma Exacerbation: Pulmonary Inflammation and Oxidative Stress**

1 Pulmonary inflammation is a key subclinical effect in the pathogenesis of asthma. It  
2 consists of both acute and chronic responses and involves the orchestrated interplay of  
3 the respiratory epithelium and both the innate and adaptive immune system.

4 The immunohistopathologic features of chronic inflammation involve infiltration of  
5 inflammatory cells such as eosinophils, lymphocytes, mast cells, and macrophages and  
6 the release of inflammatory mediators such as cytokines and leukotrienes. Oxidative  
7 stress is also relevant to asthma exacerbation. For example, many transcription factors  
8 regulating the expression of pro-inflammatory cytokines are redox sensitive.

9 This section characterizes the evidence on SO<sub>2</sub> exposure effects on pulmonary  
10 inflammation and oxidative stress in humans with asthma and in animal models of  
11 allergic airway disease (see [Section 5.2.1.7](#) for healthy humans and animal models).  
12 The 2008 SO<sub>x</sub> ISA ([U.S. EPA, 2008d](#)) concluded that evidence from the limited number  
13 of controlled human exposure, epidemiologic, and animal toxicological studies was  
14 insufficient to determine that exposure to SO<sub>2</sub> at current ambient concentrations was  
15 associated with inflammation in the airway. However, several studies provided evidence  
16 for subclinical effects related to allergic inflammation. There are no recent controlled  
17 human exposure studies, but there is additional investigation in epidemiologic and animal  
18 toxicological studies. Epidemiologic results are inconsistent for pulmonary inflammation  
19 and oxidative stress, including those for SO<sub>2</sub> measured at or near children's schools.  
20 However, recent findings in rats link short-term SO<sub>2</sub> exposure to allergic inflammation.

### ***Controlled Human Exposure Studies***

21 Pulmonary inflammation following 5–10 minute exposure to SO<sub>2</sub> was discussed in the  
22 previous ISA; no new studies were available for review. Briefly, [Tunnicliffe et al. \(2003\)](#)  
23 measured levels of exhaled NO (eNO), an indirect marker for pulmonary inflammation,  
24 in individuals with asthma before and after a 1 hour exposure to 0.2 ppm SO<sub>2</sub> under  
25 resting conditions. NALF levels of the antioxidants, ascorbic and uric acid, were also  
26 measured pre- and post-exposure. No statistically significant differences were observed  
27 between pre- and post-exposure for any of these indicators. Because subjects were  
28 exposed at rest and exposed to low concentrations, it is unlikely that enough SO<sub>2</sub> reached  
29 the airways to cause an effect. [Gong et al. \(2001\)](#) evaluated the response of individuals  
30 with asthma to 0.75 ppm SO<sub>2</sub> during exercise. In addition to changes in lung function and  
31 symptoms, there was a statistically significant increase in eosinophil count in induced  
32 sputum 2 hours after a 10-minute exposure. This response was significantly dampened by  
33 pretreatment with a leukotriene receptor antagonist. These results provided some  
34 evidence that SO<sub>2</sub> elicits an inflammatory response in the airways of individuals with

1 asthma that extends beyond the immediate bronchoconstriction response typically  
2 associated with SO<sub>2</sub> exposure. Additionally, this study provides further evidence that the  
3 bronchoconstriction response is only partially due to neural reflexes and that  
4 inflammatory mediators play an important role ([Section 4.3.1](#)).

### ***Epidemiologic Studies***

5 Recent epidemiologic evidence is inconsistent for associations of short-term increases in  
6 ambient SO<sub>2</sub> concentration with pulmonary inflammation and oxidative stress in adults  
7 and children with asthma ([Table 5-10](#)). Outcomes were assessed at varying frequency:  
8 daily, weekly, or seasonally. All studies examined eNO. Higher eNO has been linked to  
9 higher eosinophil counts ([Brody et al., 2013](#)) as well as prevalence and exacerbation of  
10 asthma ([Soto-Ramos et al., 2013](#); [Carraro et al., 2007](#); [Jones et al., 2001](#); [Kharitonov and  
11 Barnes, 2000](#)). An SO<sub>2</sub>-associated increase in eNO was observed in a population of adults  
12 with asthma with high prevalence of atopy (90%) ([Maestrelli et al., 2011](#)) ([Table 5-10](#)).  
13 [Maestrelli et al. \(2011\)](#) did not observe associations with lung function or asthma control  
14 score, but their results for pulmonary inflammation agree with results for lung function  
15 and symptoms in other populations with asthma plus atopy. Their results are also  
16 supported by findings that allergic inflammation in rats persists 24 hours after SO<sub>2</sub>  
17 exposures repeated over many days. The multicity U.S. asthma medication trial observed  
18 imprecise associations for eNO with wide 95% CIs in the ICS, beta-agonist, and placebo  
19 groups ([Qian et al., 2009a](#)). Both studies of adults with asthma estimated SO<sub>2</sub> exposure  
20 from central site monitors. Neither indicated whether the measurements adequately  
21 represented the spatiotemporal variability in SO<sub>2</sub> concentrations in the study area, and the  
22 U.S. study averaged concentrations from monitors within 32 km of each subject's ZIP  
23 code centroid.

24 Two recent studies measured SO<sub>2</sub> at or 0.65 km from children's schools ([Greenwald et  
25 al., 2013](#); [Lin et al., 2011b](#)), which may better represent some component of subjects'  
26 exposure. Results are inconsistent. Percent changes in eNO were 31 (95% CI: -24, 119)  
27 per 10-ppb increase in SO<sub>2</sub> measured at a school in El Paso, TX ([Greenwald et al., 2013](#))  
28 and 5.5 (95% CI: 2.7, 8.3) per 10-ppb increase in SO<sub>2</sub> measured near a school in Beijing,  
29 China before and after the 2008 Olympics ([Lin et al., 2011b](#)). Among children with  
30 asthma not using ICS in Windsor, ON, SO<sub>2</sub> concentrations at a monitor within 10 km of  
31 homes were not associated with eNO but were associated with markers of oxidative stress  
32 in exhaled breath condensate (EBC) ([Liu et al., 2009b](#)). The school-based studies differed  
33 in lags examined, and an association was observed with lag 0 SO<sub>2</sub> ([Lin et al., 2011b](#)) but  
34 not lag 0–3 avg SO<sub>2</sub> ([Greenwald et al., 2013](#)). For SO<sub>2</sub> measured at central site monitors,  
35 associations were observed with both lag 0 and lag 0–2 avg concentrations ([Liu et al.,  
36 2009b](#)). Prevalence of atopy was not reported for the study populations of children.

1 Copollutant confounding is an uncertainty in addition to inconsistent findings for SO<sub>2</sub>  
2 associations with pulmonary inflammation and oxidative stress in children and adults  
3 with asthma. Associations were observed with PM<sub>2.5</sub>, BC, CO, O<sub>3</sub>, and NO<sub>2</sub> ([Lin et al.,  
4 2011b](#); [Maestrelli et al., 2011](#); [Liu et al., 2009b](#)). Only [Liu et al. \(2009b\)](#) reported  
5 SO<sub>2</sub>-copollutant correlations, indicating the potential for confounding with PM<sub>2.5</sub>  
6 ( $r = 0.56$ ), less so with NO<sub>2</sub> ( $r = 0.18$ ), and likely not with O<sub>3</sub> ( $r = -0.02$ ). [Maestrelli et al.  
7 \(2011\)](#) did not examine copollutant models, and results in children with asthma are  
8 conflicting. For pollutants measured 0.65 km from school, SO<sub>2</sub> associations with eNO  
9 persisted with adjustment for PM<sub>2.5</sub> or BC but nevertheless decreased ([Lin et al., 2011b](#)).  
10 The effect estimate decreased for PM<sub>2.5</sub> but was robust for BC. Based on pollutants  
11 measured up to 10 km from home, the SO<sub>2</sub> association with oxidative stress decreased  
12 with adjustment for NO<sub>2</sub> and became imprecise with adjustment for PM<sub>2.5</sub> ([Liu et al.,  
13 2009b](#)) ([Table 5-10](#)). However, inference about SO<sub>2</sub> associations is weak because of  
14 uncertainty in the SO<sub>2</sub> exposure estimates and because PM<sub>2.5</sub> and NO<sub>2</sub> associations  
15 decreased with SO<sub>2</sub> adjustment.

### ***Animal Toxicological Studies***

16 The 2008 SO<sub>x</sub> ISA ([U.S. EPA, 2008d](#)) discussed several studies that investigated the  
17 effects of exposure to SO<sub>2</sub> on inflammatory responses. While one study failed to  
18 demonstrate inflammation following a single subacute exposure to 1 ppm SO<sub>2</sub> ([U.S.  
19 EPA, 2008d](#)), other studies found that repeated SO<sub>2</sub> exposure enhanced the development  
20 of an allergic phenotype and altered physiologic responses in animal models of allergic  
21 airway disease. These studies demonstrating effects of repeated SO<sub>2</sub> exposures in models  
22 of allergic airway disease are listed in [Table 5-11](#) and described here. In addition, other  
23 studies involving repeated SO<sub>2</sub> exposures in naive rats, including studies that demonstrate  
24 increased sensitivity to allergens, have been conducted and are described below in  
25 [Section 5.2.1.7](#).

**Table 5-10 Recent epidemiologic studies of pulmonary inflammation and oxidative stress in populations with asthma.**

Study Population and Methodological Details	SO <sub>2</sub> Exposure Estimates (ppb)	SO <sub>2</sub> Averaging Time and Lag Day	Effect Estimate (95% CI) Single-Pollutant Model <sup>a</sup>	Copollutant Examination <sup>a</sup>
<b>Adults with Asthma</b>				
<p><a href="#">†Qian et al. (2009b)</a>            Boston, MA; New York, NY; Philadelphia, PA; Madison, WI; Denver, CO; San Francisco, CA; 1997–1999            N = 119, ages 12–65 yr. 100% persistent asthma. 1/3 ICS use, 1/3 beta-agonist use, 1/3 placebo use.            Examined every 2–4 wk for 16 wk. Recruited from clinics as part of an asthma medication trial. Multiple comparisons—many pollutants, lags, medication use analyzed.</p>	<p>Monitors averaged within 32 km of subject ZIP code centroid.            Mean (SD): 5.3 (4.4)            75th percentile: 7.6            Max: 27</p>	<p>24-h avg            0              0–3 avg</p>	<p>Change in eNO (ppb)            All subjects: 0.09 (–0.07, 0.25)            ICS: 0.17 (–0.11, 0.44)            Beta-agonist: 0.04 (–0.18, 0.27)              All subjects: 0.07 (–0.12, 0.26)            ICS: 0.15 (–0.13, 0.43)            Beta-agonist: 0.10 (–0.19, 0.38)</p>	<p>Copollutant model, all subjects, lag 0 with PM<sub>10</sub>: 0.16 (–0.08, 0.40) with NO<sub>2</sub>: 0 (–0.18, 0.18) with O<sub>3</sub>: 0.05 (–0.12, 0.22)            NO<sub>2</sub> and PM<sub>10</sub> associations persist with SO<sub>2</sub> adjustment. No association with O<sub>3</sub>. SO<sub>2</sub> moderately correlated with NO<sub>2</sub>, <i>r</i> = 0.58. Correlation NR for PM<sub>10</sub>.</p>
<p><a href="#">†Maestrelli et al. (2011)</a>            Padua, Italy, 2004–2005            N = 32, mean (SD) age 40 (7.5) yr. 81% persistent asthma. 69% ICS use. 90% atopy.            Six measures over 2 yr. Recruited from database of beta-agonist users (&gt;6 times per yr for 3 yr).</p>	<p>Two monitors in city            Medians across seasons: 0.87–2.7            75th percentiles across seasons: 1.3–4.1</p>	<p>24-h avg            0</p>	<p>Change in eNO (ppb)            All subjects: 55 (–2.3, 113)            Nonsmokers: 82 (3.1, 161)              Change in EBC pH            Decrease = more inflammation            All subjects: 0.46 (–0.20, 1.1)            Nonsmokers: 0.18 (–0.34, 0.69)            n = 22</p>	<p>No copollutant model            Association observed with CO and O<sub>3</sub>. No association with personal or central site PM<sub>2.5</sub> or PM<sub>10</sub>. No association with central site NO<sub>2</sub>.            Copollutant correlations NR.</p>

**Table 5-10 (Continued): Recent epidemiologic studies of pulmonary inflammation and oxidative stress in populations with asthma.**

Study Population and Methodological Details	SO <sub>2</sub> Exposure Estimates (ppb)	SO <sub>2</sub> Averaging Time and Lag Day	Effect Estimate (95% CI) Single-Pollutant Model <sup>a</sup>	Copollutant Examination <sup>a</sup>
<b>Children with Asthma</b>				
† <a href="#">Greenwald et al. (2013)</a> El Paso, TX, Mar–Jun 2010 N = 38, mean age 10 yr. 47% daily asthma medication use. Weekly measures for 13 wk. Recruited from schools.	Monitor at school A: residential area B: 91 m from major road Mean (SD): 1.2 (0.44) and 0.84 (0.54) Upper percentiles NR.	24-h avg 0–3 avg	Percent change in eNO A: –59 (–89, 36) B: 31 (–24, 119)	No copollutant model Association observed with BC, NO <sub>2</sub> , BTEX, cleaning product VOCs (α-pinene, dichlorobenzene, d-limonene) at school B. No association with PM <sub>2.5</sub> . SO <sub>2</sub> weakly correlated with BC, NO <sub>2</sub> , BTEX, cleaning product VOCs. Pearson $r = -0.14, -0.22, -0.07, 0.14$ .
† <a href="#">Lin et al. (2011b)</a> Beijing, China N = 8, ages 9–12 yr Daily measures for five 2-wk periods before and after Olympics. Recruitment from school.	Monitor 0.65 km from school Means across five periods before and after Olympics: 3.7–45	24-h avg 0 1	Percent change in eNO 5.5 (2.7, 8.3) 3.4 (1.4, 5.4)	Copollutant model with BC or PM <sub>2.5</sub> Results presented only in a figure. SO <sub>2</sub> associations persist but decrease in magnitude with adjustment for BC or PM <sub>2.5</sub> . BC association not altered by SO <sub>2</sub> adjustment; PM <sub>2.5</sub> association slightly attenuated. Associations observed for CO and NO <sub>2</sub> . Copollutant correlations NR.
† <a href="#">Liu et al. (2009b)</a> , <a href="#">Liu (2013)</a> Windsor, ON Oct–Dec 2005 N = 182, ages 9–14 yr. 37% ICS use. 35% beta-agonist use. Weekly measures for 4 wk. Recruited from schools. Mean 1.6 and 2.2 h/d spent outdoors for two study groups.	Two monitors averaged 99% homes within 10 km of sites Median: 4.5 95th percentile: 16	24-h avg 0 0–2 avg	Percent change eNO: 9.0 (–7.6, 29) TBARS: 28 (0.46, 63) 8-Isoprostane: 23 (3.9, 44) eNO: –5.6 (–28, 24) TBARS: 77 (31, 131) 8-Isoprostane: –0.55 (–28, 38)	Copollutant model, lag 0–2 avg, TBARS with PM <sub>2.5</sub> : 53 (–21, 158) with NO <sub>2</sub> : 51 (0.93, 112) with O <sub>3</sub> : 74 (26, 128) PM <sub>2.5</sub> and NO <sub>2</sub> association attenuated with SO <sub>2</sub> adjustment. SO <sub>2</sub> moderately correlated with PM <sub>2.5</sub> , weakly correlated with NO <sub>2</sub> and O <sub>3</sub> . Spearman $r = 0.56, 0.18, -0.02$ .

BC = black carbon; BTEX = benzene, toluene, ethylbenzene, xylene; CI = confidence interval; CO = carbon monoxide; EBC = exhaled breath condensate; eNO = exhaled nitric oxide; ICS = inhaled corticosteroid; N = sample size; NO<sub>2</sub> = nitrogen dioxide; O<sub>3</sub> = ozone; PM<sub>2.5</sub> = particulate matter with nominal aerodynamic diameter less than or equal to 2.5 μm; PM<sub>10</sub> = particulate matter with nominal aerodynamic diameter less than or equal to 10 μm; SO<sub>2</sub> = sulfur dioxide; TBARS = thiobarbituric acid reactive substances.

<sup>a</sup>Effect estimates are standardized to a 10-ppb increase in 24-h avg SO<sub>2</sub>.

†Studies published since the 2008 Integrated Science Assessment for Sulfur Oxides.

**Table 5-11 Study-specific details from animal toxicological studies of subclinical effects underlying asthma.**

Study	Species (Strain); n; Sex; Lifestage/Age or Weight	Exposure Details (Concentration; Duration)	Endpoints Examined
<a href="#">Li et al. (2007)</a>	Rats (Wistar); n = 6/group; M; age NR	Sensitization by i.p. injection of 100 mg ovalbumin followed by booster injection of 10 mg ovalbumin after 7 d followed by: (1) Challenge with 1% ovalbumin aerosol for 30 min for 7 d beginning at 15 d, (2) Exposure to 2 ppm SO <sub>2</sub> for 1 h/d for 7 d, or (3) SO <sub>2</sub> exposure followed by ovalbumin aerosol challenge for 7 d	Endpoints examined 24 h following the last challenge BALF—inflammatory cell counts Lung—histopathology, immunohistochemistry Lung and tracheal tissue—mRNA and protein levels of MUC5AC and ICAM-1
<a href="#">Li et al. (2008)</a>	Rats (Wistar); n = 6/group; M; age NR; 180–200 g	Sensitization by i.p. injection of 100 mg ovalbumin followed by booster injection of 10 mg ovalbumin after 7 d followed by: (1) Challenge with 1% ovalbumin aerosol for 30 min for 7 d beginning at 15 d, (2) Exposure to 2 ppm SO <sub>2</sub> for 1 h/d for 7 d, or (3) SO <sub>2</sub> exposure followed by ovalbumin aerosol challenge for 7 d	Endpoints examined 24 h following the last challenge BALF—total and differential cell counts, EGF Lung tissue—histopathology Lung and tracheal tissue—mRNA levels of EGF, EGFR, COX-2 Lung tissue—protein levels of EGFR, COX-2
<a href="#">Xie et al. (2009)</a>	Rats (Wistar); n = 6/group; M; age NR	Sensitization by i.p. injection of 100 mg ovalbumin followed by booster injection of 10 mg ovalbumin after 7 d followed by: (1) Challenge with 1% ovalbumin aerosol for 30 min for 7 d beginning at 15 d, (2) Exposure to 2 ppm SO <sub>2</sub> for 1 h/d for 7 d, or (3) SO <sub>2</sub> exposure followed by ovalbumin aerosol challenge for 7 d	Endpoints examined 24 h following the last challenge Lung tissue—mRNA levels of p53, bax, bcl-2 Lung—protein levels of p53, bax, bcl-2

**Table 5-11 (Continued): Study specific details from animal toxicological studies of subclinical effects underlying asthma.**

Study	Species (Strain); n; Sex; Lifestage/Age or Weight	Exposure Details (Concentration; Duration)	Endpoints Examined
<a href="#">Li et al. (2014)</a>	Rats (Wistar); n = 6/group; M; age NR; 180–200 g	Sensitization by i.p. injection of 100 mg ovalbumin followed by booster injection of 10 mg ovalbumin after 7 d followed by: (1) Challenge with 1% ovalbumin aerosol for 30 min for 7 d beginning at 15 d, (2) Exposure to 2 ppm SO <sub>2</sub> for 1 h/d for 7 d, or (3) SO <sub>2</sub> exposure followed by ovalbumin aerosol challenge for 7 d	Endpoints examined BALF—inflammatory cell counts and cytokines IL-4, IFN- $\gamma$ , TNF $\alpha$ , IL-6 Serum—IgE Lung—histopathology Lung and tracheal tissue—mRNA and protein levels of NF $\kappa$ B, I $\kappa$ B $\alpha$ , IKK $\beta$ , IL-6, IL-4, TNF $\alpha$ , FOXP3 EMSA NF $\kappa$ B binding activity

BALF = bronchoalveolar lavage fluid; bax = B-cell lymphoma 2-like protein 4; bcl-2 = B-cell lymphoma 2; COX-2 = cyclooxygenase-2; EGF = epidermal growth factor; EGFR = epidermal growth factor receptor; EMSA = electrophoretic mobility shift assay; FOXP3 = forkhead box p3 ICAM-1 = intercellular adhesion molecule 1; IFN- $\gamma$  = interferon gamma; IgE = immunoglobulin E; IKK $\beta$  = inhibitor of nuclear factor kappa-B kinase subunit beta; IL-4 = interleukin-4; IL-6 = interleukin-6; I $\kappa$ B $\alpha$  = nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha; i.p. = intraperitoneal; M = male; MUC5AC = mucin 5AC glycoprotein; n = sample size; NF $\kappa$ B = nuclear factor kappa-light-chain-enhancer of activated B cells; NR = not reported; p53 = tumor protein p53; SD = standard deviation; SO<sub>2</sub> = sulfur dioxide; TNF- $\alpha$  = tumor necrosis factor alpha.

1  
2 Repeated exposure to SO<sub>2</sub> promoted an allergic phenotype when ovalbumin sensitization  
3 and challenge preceded SO<sub>2</sub> exposure. As described in the 2008 SO<sub>x</sub> ISA ([U.S. EPA,](#)  
4 [2008d](#)), [Li et al. \(2007\)](#) demonstrated that rats, which were first sensitized and challenged  
5 with ovalbumin and subsequently exposed to 2 ppm SO<sub>2</sub> for 1 hour/day for 7 days, had  
6 an increased number of inflammatory cells in BALF and an enhanced histopathological  
7 response compared with those treated with ovalbumin or SO<sub>2</sub> alone. Similarly, ICAM-1,  
8 a protein involved in regulating inflammation, and MUC5AC, a mucin protein, were  
9 upregulated in lungs and trachea to a greater extent in rats treated with ovalbumin and  
10 SO<sub>2</sub> than in those treated with ovalbumin or SO<sub>2</sub> alone. A follow-up study involving the  
11 same exposure regimen (2 ppm SO<sub>2</sub> for 1 hour) in the same allergic animal model (rats  
12 sensitized and challenge with ovalbumin) also found that repeated SO<sub>2</sub> exposure  
13 enhanced inflammatory and allergic responses to ovalbumin ([Li et al., 2014](#)). Numbers of  
14 eosinophils, lymphocytes and macrophages were greater in BALF of SO<sub>2</sub>-exposed and  
15 ovalbumin-treated animals than in animals treated only with ovalbumin. In addition, SO<sub>2</sub>  
16 exposure enhanced upregulation and activation of NF $\kappa$ B, a transcription factor involved  
17 in inflammation and upregulation of the cytokines IL-6 and IL-4 in lung tissue in this  
18 model of allergic airway disease. Furthermore, BALF levels of IL-6 and IL-4 were  
19 increased to a greater extent in SO<sub>2</sub>-exposed and ovalbumin-treated animals compared  
20 with ovalbumin treatment alone. These results indicate that repeated SO<sub>2</sub> exposure  
21 enhanced activation of the NF $\kappa$ B inflammatory pathway and upregulation of  
22 inflammatory cytokines in ovalbumin-treated animals. Furthermore, SO<sub>2</sub> exposure

1 enhanced the effects of ovalbumin on levels of IFN- $\gamma$  (decreased) and IL-4 (increased) in  
2 BALF and on IgE levels in serum (increased). Because levels of IL-4 are indicative of  
3 Th2 status and levels of IFN- $\gamma$  are indicative of Th1 status, these results suggest a shift in  
4 Th1/Th2 balance away from Th2 in rats made allergic to ovalbumin, an effect  
5 exacerbated by SO<sub>2</sub> exposure. These Th2-related changes are consistent with the  
6 observed increases in serum IgE and BALF eosinophils in ovalbumin-treated animals,  
7 effects which were also enhanced by SO<sub>2</sub> exposure. Alternatively, Th2-related changes  
8 may reflect a Type 2 immune response mediated by group 2 innate lymphoid cells. Taken  
9 together, these results indicate that repeated exposure to SO<sub>2</sub> exacerbated inflammatory  
10 and allergic responses in this animal model.

11 Two other follow-up studies by the same laboratory examined the effects of inhaled SO<sub>2</sub>  
12 on the asthma-related genes encoding epidermal growth factor (EGF), epidermal growth  
13 factor receptor (EGFR), and cyclooxygenase-2 (COX-2) and on apoptosis-related genes  
14 and proteins in this same model based on sensitization with ovalbumin ([Xie et al., 2009](#);  
15 [Li et al., 2008](#)). While EGF and EGFR are related to mucus production and airway  
16 remodeling, COX-2 is related to inflammation and apoptosis and may play a role in  
17 regulating airway inflammation. SO<sub>2</sub> exposure enhanced the effects of ovalbumin  
18 challenge in this model, resulting in greater increases in mRNA and protein levels of  
19 EGF, EGFR, and COX-2 in the trachea compared with ovalbumin challenge alone. SO<sub>2</sub>  
20 exposure enhanced other effects of ovalbumin in this model, resulting in a greater decline  
21 in mRNA and protein levels of p53 and bax and a greater increase in mRNA and protein  
22 levels of bcl-2 in the lungs compared with ovalbumin challenge alone. The increased  
23 ratio of bcl-2:bax, an indicator of susceptibility to apoptosis, observed following  
24 ovalbumin challenge, was similarly enhanced by SO<sub>2</sub>. Thus, repeated exposure to SO<sub>2</sub>  
25 may impact numerous processes that may be involved in inflammation and/or airway  
26 remodeling in allergic airway disease.

### ***Summary of Subclinical Effects Underlying Asthma Exacerbation***

27 Whereas previous evidence was limited and inconsistent, recent evidence from  
28 experimental studies supports a relationship between short-term exposure to SO<sub>2</sub> and  
29 allergic responses related to asthma. This includes findings of eosinophilic inflammation  
30 in individuals with asthma exposed acutely to SO<sub>2</sub>. In addition, enhanced inflammation  
31 and allergic responses were demonstrated in animals made allergic to ovalbumin and  
32 exposed repeatedly to SO<sub>2</sub>. Epidemiologic findings are inconsistent overall, including  
33 recent results based on SO<sub>2</sub> measured at or near children's schools. However, coherent  
34 with experimental studies, an SO<sub>2</sub>-associated increase in pulmonary inflammation was  
35 observed in adults with asthma plus atopy. Copollutant confounding is not addressed in  
36 these results, but the evidence from animal toxicological studies provides some biological

1 plausibility for an effect of SO<sub>2</sub> exposure, particularly because effects in rats were shown  
2 to occur with repeated exposures and 24 hours after exposure ended. The evidence for  
3 SO<sub>2</sub>-related allergic inflammation also supports evidence across disciplines for SO<sub>2</sub>  
4 effects on asthma symptoms, hospital admissions, and ED visits, as well as lung function  
5 decrements in people with asthma.

### Summary of Asthma Exacerbation

6 The 2008 ISA for Sulfur Oxides did not explicitly draw a conclusion about a relationship  
7 between short-term SO<sub>2</sub> exposure and asthma exacerbation but described strong support  
8 from controlled human exposure studies for SO<sub>2</sub>-induced lung function decrements and  
9 increases in respiratory symptoms in adults with asthma when ventilation rates were  
10 increased. Such effects in adolescents with asthma are less clear due to a paucity of data,  
11 but effects appear similar to adults. There are no laboratory studies of children exposed to  
12 SO<sub>2</sub>; however, a number of studies have assessed airway responsiveness of children and  
13 adults exposed to the bronchoconstrictive stimuli methacholine. Based largely on those  
14 studies, school-aged children, particularly boys and perhaps obese children, might be  
15 expected to have greater responses (i.e., larger decrements in lung function) following  
16 exposure to SO<sub>2</sub> than adolescents and adults.

17 In adults with asthma, short-term exposures for 5–10 minutes to 0.2–0.3 ppm SO<sub>2</sub>  
18 resulted in 5–30% of exercising individuals experiencing moderate or greater decrements  
19 (i.e., ≥15% decrease in FEV<sub>1</sub> or ≥100% increase in sRaw; [Table 5-2](#)). Decrements in  
20 FEV<sub>1</sub> at 0.3 ppm SO<sub>2</sub> were statistically significant in responsive individuals (defined as  
21 those having an FEV<sub>1</sub> decrease of ≥15% after exposure to 0.6 or 1.0 ppm SO<sub>2</sub>;  
22 [Table 5-3](#)). At concentrations greater than or equal to 0.4 ppm, 20–60% of asthmatics  
23 experienced SO<sub>2</sub>-induced decrements in lung function, which were frequently  
24 accompanied by respiratory symptoms. There is a clear concentration-response  
25 relationship for exposures to SO<sub>2</sub> between 0.2 and 1.0 ppm, both in terms of increasing  
26 severity of effect and percentage of asthmatics affected. These concentrations are in the  
27 range of the highest 5-minute ambient SO<sub>2</sub> concentrations in some U.S. cities during  
28 2010–2012 ([Table 2-9](#)).

29 Epidemiologic evidence generally supports SO<sub>2</sub>-associated increases in asthma hospital  
30 admissions and ED visits, particularly in children ([Figure 5-3](#)), and respiratory symptoms  
31 in children with asthma ([Figure 5-2](#); [Table 5-8](#)). Epidemiologic evidence is inconsistent  
32 for SO<sub>2</sub> associations with lung function decrements in adults and children with asthma  
33 ([Table 5-6](#) and [Table 5-7](#)). For the limited results from previous epidemiologic and  
34 controlled human exposure studies on airway responsiveness (i.e., response to  
35 methacholine), an independent effect of SO<sub>2</sub> is unclear. Two controlled human exposure

1 studies demonstrated increased airway responsiveness to subsequent allergen challenge  
2 for at least 48 hours following SO<sub>2</sub> exposure in combination with a copollutant  
3 (i.e., NO<sub>2</sub>). Most epidemiologic studies estimated SO<sub>2</sub> exposure from central site  
4 monitors. A few recent studies aimed to address the uncertainty in exposure estimates and  
5 observed asthma-related effects in association with SO<sub>2</sub> measured or modeled at or near  
6 school or homes. Studies did not statistically correct for measurement error, but in this  
7 new research area, a method has not been reported for short-term SO<sub>2</sub> exposure  
8 ([Section 3.4.4](#)). As in the 2008 ISA for Sulfur Oxides, copollutant confounding is  
9 unresolved in the epidemiologic evidence. Many recent studies continue to indicate that  
10 SO<sub>2</sub> associations with asthma hospital admissions and ED visits remain relatively  
11 unchanged in magnitude in copollutant models, but SO<sub>2</sub> associations with asthma  
12 symptoms and pulmonary inflammation often did not persist after adjustment for PM<sub>2.5</sub>,  
13 EC/BC, or NO<sub>2</sub>. The role of SO<sub>2</sub> in ambient multipollutant mixtures is not clearly  
14 elucidated. Controlled human exposure studies show asthma-related effects when SO<sub>2</sub>  
15 exposure occurs with O<sub>3</sub> or NO<sub>2</sub>, and limited epidemiologic examination shows  
16 associations for multipollutant mixtures that contain SO<sub>2</sub>. However, associations for  
17 mixtures containing SO<sub>2</sub> are similar to those for SO<sub>2</sub>, CO, NO<sub>2</sub>, PM<sub>10</sub>, or PM<sub>2.5</sub> or less  
18 than the sum of single-pollutant effect estimates, indicating an overlap in associations for  
19 copollutants.

20 Expanded evidence for SO<sub>2</sub>-induced allergic inflammation supports an effect of SO<sub>2</sub>  
21 exposure on asthma exacerbation. Epidemiologic findings of SO<sub>2</sub>-associated increases in  
22 pulmonary inflammation are inconsistent, but enhanced allergic inflammation and  
23 allergic responses are demonstrated in a previous controlled human exposure study of  
24 adults with asthma plus atopy and multiple recent studies from a single laboratory in rats  
25 made allergic to ovalbumin and exposed repeatedly to 2 ppm SO<sub>2</sub>. These findings provide  
26 some support for the epidemiologic associations for SO<sub>2</sub> with decreased lung function as  
27 well as increased airway responsiveness, respiratory symptoms, and pulmonary  
28 inflammation observed in most studies of children and adults with asthma plus atopy.

29 Much of the epidemiologic evidence for SO<sub>2</sub>-associated asthma exacerbation is for  
30 24-h avg SO<sub>2</sub> concentrations. Although 24-h avg and 1-h max SO<sub>2</sub> concentrations are  
31 correlated at the same monitor, it is not clear whether this correlation applies across a  
32 community. Some recent studies add evidence for association for asthma symptoms and  
33 ED visits with increases in 1-h max SO<sub>2</sub> concentrations, including SO<sub>2</sub> measured at  
34 schools. For lung function decrements, pulmonary inflammation, and asthma hospital  
35 admission and ED visit studies, several results indicate associations for 3- or 4-day avg  
36 SO<sub>2</sub> concentrations. The evidence for enhanced allergic inflammation, which is seen after  
37 repeated 2 ppm SO<sub>2</sub> exposures and 24 hours after exposure ended, somewhat supports the  
38 biological plausibility of epidemiologic associations with asthma-related outcomes.

1 Moreover, controlled human exposure studies clearly demonstrate that SO<sub>2</sub> exposures of  
2 0.2–0.6 ppm can induce effects related to asthma exacerbation.

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### 5.2.1.3 Allergy Exacerbation

3 The evidence described in the preceding section for SO<sub>2</sub> and allergen coexposure  
4 enhancing inflammation in rodent models of allergic airway disease indicates that SO<sub>2</sub>  
5 exposure may increase the sensitivity of people with allergic asthma to an allergen. This  
6 evidence also suggests the potential for SO<sub>2</sub> exposure to affect respiratory responses in  
7 people with allergy but not asthma. The 2008 ISA for Sulfur Oxides did not make distinct  
8 statements about a relationship with SO<sub>2</sub> exposure, but relevant epidemiologic studies  
9 had inconsistent findings. Recent epidemiologic evidence is also uncertain, including that  
10 for school SO<sub>2</sub> measurements.

#### Lung Function in Populations with Allergy

11 Previous epidemiologic studies examined children or adults with allergy but no asthma,  
12 defined by high serum IgE levels but no bronchial hyperresponsiveness, and did not  
13 indicate associations between short-term increases in ambient SO<sub>2</sub> concentration and  
14 decreases in lung function ([Boezen et al., 2005](#); [Boezen et al., 1999](#)). The same studies  
15 observed associations for groups with asthma plus allergy. Previous findings were based  
16 on 24-h avg SO<sub>2</sub> measured at a single site in each city. The only available recent study  
17 measured SO<sub>2</sub> at children's schools ([Correia-Deur et al., 2012](#)), which may better  
18 represent some component of subjects' exposures. Also, the temporally resolved 2-h avg  
19 metric is more comparable to the exposure durations examined in experimental studies.  
20 In this group of children with allergy in São Paulo, Brazil, SO<sub>2</sub> had an imprecise  
21 association with PEF with a wide 95% CI [–0.82% (95% CI: –1.9, 0.31) per 10-ppb  
22 increase in 2-h avg SO<sub>2</sub>]. Results were similar for allergy defined by high serum IgE  
23 levels alone like previous studies and by multiple criteria (i.e., high IgE levels, positive  
24 skin prick test, and high blood eosinophil levels). There was evidence for an association  
25 among all children (with and without allergy), but that was attenuated in copollutant  
26 models with PM<sub>10</sub>, NO<sub>2</sub>, or CO. Correlations with SO<sub>2</sub> were not reported.

#### Respiratory Symptoms and Physician Visits in Populations with Allergy

27 Limited to epidemiologic studies, evidence for an association between short-term SO<sub>2</sub>  
28 exposure and allergy symptoms is inconsistent. Nonspecific upper and lower respiratory  
29 symptoms were examined in children and adults with high IgE levels but no bronchial

1 hyperresponsiveness, and associations with SO<sub>2</sub> were inconsistent ([Boezen et al., 2005](#);  
2 [Boezen et al., 1999](#)). For symptoms specific to allergy, [Villeneuve et al. \(2006b\)](#)  
3 observed an SO<sub>2</sub>-associated increase in physician visits for allergic rhinitis in older  
4 adults. Recent findings for allergic rhinitis or eczema in children are mixed. However,  
5 inference about an SO<sub>2</sub> effect is weak both for results indicating an association ([Kim et  
6 al., 2016a](#)) and results not indicating an association ([Annesi-Maesano et al., 2012](#);  
7 [Linares et al., 2010](#)). Limitations include cross-sectional design ([Annesi-Maesano et al.,  
8 2012](#); [Linares et al., 2010](#)), analysis of a multipollutant model with NO<sub>2</sub>, O<sub>3</sub>, PM<sub>10</sub>, and  
9 pollen ([Kim et al., 2016a](#); [Annesi-Maesano et al., 2012](#)), lack of consideration of  
10 confounding by meteorological factors ([Kim et al., 2016a](#)), or inclusion of children with  
11 and without allergy in analysis of eczema ([Linares et al., 2010](#)). For results supporting a  
12 relationship with allergy symptoms, associations were observed with same-day (lag 0)  
13 24-h avg SO<sub>2</sub> concentrations. These concentrations were from a single monitor in the  
14 city, and information was not reported on the extent to which the measurements  
15 represented the spatiotemporal variability in SO<sub>2</sub> concentrations in the study area.  
16 Associations were observed with copollutants such as NO<sub>2</sub>, PM<sub>10</sub>, and BS, although these  
17 results were inconsistent as well ([Villeneuve et al., 2006b](#); [Boezen et al., 2005](#); [Boezen et  
18 al., 1999](#)). Correlations with SO<sub>2</sub> concentrations were not reported, and copollutant  
19 models were not analyzed. Thus, the extent to which the supporting findings may indicate  
20 an independent association for SO<sub>2</sub> is unclear.

### **Subclinical Effects Underlying Allergy Exacerbation**

21 In addition to the animal toxicological evidence for SO<sub>2</sub>-enhanced allergic inflammation,  
22 a previous epidemiologic study of children with atopy found an SO<sub>2</sub>-associated decrease  
23 in blood eosinophil number, which was presumed to reflect increased recruitment to the  
24 airways ([Soyseth et al., 1995](#)). Exposure assessment from a monitor 2 km from most  
25 subjects' homes is an uncertainty, as is confounding by PM. The study was conducted in  
26 a European city with an aluminum smelter that emitted SO<sub>2</sub> and PM, and PM was not  
27 examined for association with eosinophils.

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#### **5.2.1.4 Chronic Obstructive Pulmonary Disease Exacerbation**

28 COPD is a lung disease characterized by deterioration of lung tissue and airflow  
29 limitation. Reduced airflow can decrease lung function, and clinical symptoms  
30 demonstrating exacerbation of COPD include cough, dyspnea, sputum production, and  
31 shortness of breath. Severe exacerbation can lead to hospital admissions or ED visits.  
32 This spectrum of outcomes has been evaluated in relation to short-term SO<sub>2</sub> exposure,

1 and evidence across outcomes and disciplines is inconsistent. This applies to the small  
2 body of studies available for the 2008 ISA for Sulfur Oxides ([U.S. EPA, 2008d](#)) as well  
3 as the few available recent studies. Recent findings come from epidemiologic studies, and  
4 most are for hospital admissions and ED visits.

### Lung Function and Respiratory Symptoms

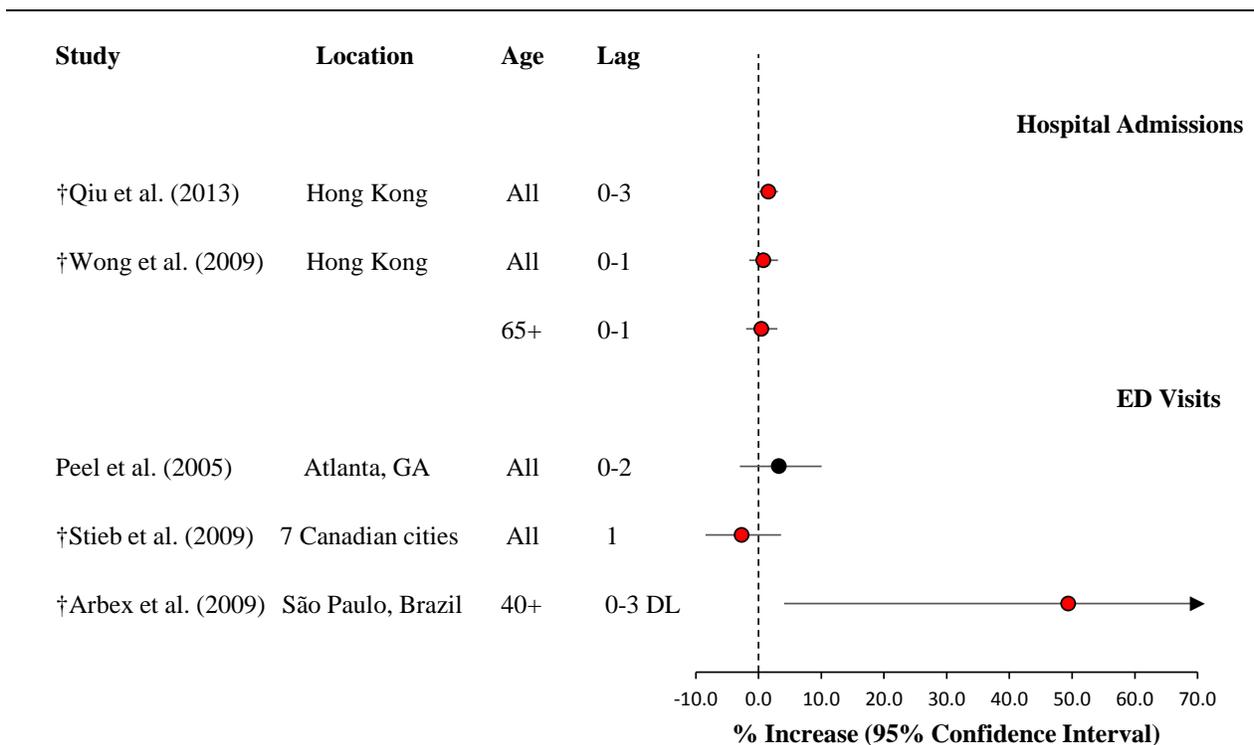
5 Evidence from a controlled human exposure study and epidemiologic studies does not  
6 support an effect of SO<sub>2</sub> exposure on lung function in adults with COPD. Recent  
7 epidemiologic studies add information on respiratory symptoms and mostly do not  
8 indicate an association with ambient SO<sub>2</sub> concentrations.

9 [Linn et al. \(1985a\)](#) reported that a 15-minute exposure to 0.4 and 0.8 ppm SO<sub>2</sub> had no  
10 effect on lung function in older adults with physician-diagnosed COPD. These adults  
11 were much older than the adults with asthma ([Table 5-2](#)) or healthy adults ([Table 5-15](#))  
12 examined in controlled human exposure studies. Also, the level of exercise in adults with  
13 COPD ( $\dot{V}_E = 18$  L/minute) was lower than that of individuals with asthma, which  
14 effectively lowers the SO<sub>2</sub> dose delivered to the lungs ([Section 4.2.2](#)). Neither the  
15 previous nor recent epidemiologic study observed SO<sub>2</sub>-associated decrements in lung  
16 function in adults with COPD ([Peacock et al., 2011](#); [Harre et al., 1997](#)). Both studies  
17 estimated SO<sub>2</sub> exposure from a central site monitor(s), and examined 24-h avg  
18 concentrations lagged 1 day. Whereas previous results were based on a multipollutant  
19 model (with PM<sub>10</sub>, NO<sub>2</sub>, O<sub>3</sub>), which often is unreliable, recent results were based on a  
20 single-pollutant model. Associations were imprecise with wide 95% CIs  
21 [e.g., 0.31 L/minute (95% CI: -0.10, 0.72) change in PEF per 10-ppb increase in SO<sub>2</sub> and  
22 OR 1.01 (95% CI: 0.89, 1.15) for PEF decrement greater than 20%] ([Peacock et al.,](#)  
23 [2011](#)). Mean and 75th percentile SO<sub>2</sub> concentrations were 7.5 and 9.3 ppb, respectively.  
24 SO<sub>2</sub> mostly was not associated with dyspnea, sputum changes, wheeze/tight chest, or  
25 other respiratory symptoms ([Wu et al., 2016](#); [Peacock et al., 2011](#)). [Wu et al. \(2016\)](#)  
26 examined a period of higher SO<sub>2</sub> concentration (median 17 ppb and 75th percentile  
27 27 ppb) and observed dyspnea to increase with an increase in 3- to 6-day avg SO<sub>2</sub> (OR:  
28 1.88 [95% CI: 1.06, 3.34] per 10-ppb increase in 3-day avg SO<sub>2</sub>). However, there was a  
29 wide range of distance from subjects to the monitor (1.6–8.8 km), and associations also  
30 were observed with moderately correlated ( $r = 0.51$ – $0.68$ ) PM<sub>2.5</sub>, PM<sub>10</sub>, and NO<sub>2</sub>.

### Hospital Admissions and Emergency Department Visits

31 Of the studies evaluated in the 2008 SO<sub>x</sub> ISA, only one U.S. or Canadian-based study  
32 examined the association between short-term SO<sub>2</sub> exposure and COPD hospital

1 admissions or ED visits (Figure 5-7). Recent studies add to the initial evidence, which  
 2 generally indicates no association between short-term SO<sub>2</sub> exposures and COPD hospital  
 3 admissions and ED visits. Additionally, most studies averaged SO<sub>2</sub> concentrations over  
 4 multiple monitors and examined 24-h avg exposure metrics, which, may not adequately  
 5 capture the spatial and temporal variability in SO<sub>2</sub> concentrations (Section 3.4.2.). For  
 6 each of the studies evaluated in this section, Table 5-12 presents the air quality  
 7 characteristics of each city or across all cities, the exposure assignment approach used,  
 8 and information on copollutants examined in each COPD hospital admission and ED visit  
 9 study. Other recent studies of COPD hospital admissions and ED visits are not the focus  
 10 of this evaluation because of various study design issues, as initially detailed in  
 11 Section 5.2.1.2, but the full list of these studies, as well as study-specific details, can be  
 12 found in Supplemental Table 5S-5 (U.S. EPA, 2016m).



ED = emergency department.

Note: † and red = recent studies published since the 2008 ISA for Sulfur Oxides; black = U.S. and Canadian studies evaluated in the 2008 ISA for Sulfur Oxides. Corresponding quantitative results are reported in Supplemental Table 5S-6 (U.S. EPA, 2016n).

**Figure 5-7 Percent increase in chronic obstructive pulmonary disease hospital admissions and emergency department visits from U.S. and Canadian studies evaluated in the 2008 SO<sub>x</sub> ISA and recent studies in all-year analyses for a 10-ppb increase in 24-h avg or 40-ppb increase in 1-h max sulfur dioxide concentrations.**

**Table 5-12 Study-specific details and mean and upper percentile concentrations from chronic obstructive pulmonary disease hospital admission and emergency department visit studies conducted in the U.S. and Canada and evaluated in the 2008 SO<sub>x</sub> ISA and studies published since the 2008 SO<sub>x</sub> ISA.**

Study	Location Years	Exposure Assignment	Metric	Mean Concentration ppb	Upper Percentile Concentrations ppb	Copollutants Examined
<b>Hospital admissions</b>						
<a href="#">†(Qiu et al. (2013b); Ko et al. (2007a))</a>	Hong Kong, China (1998–2007)	Average of SO <sub>2</sub> concentrations from 10 monitoring stations	24-h avg	7.4	NR	Correlations ( <i>r</i> ): O <sub>3</sub> : 0.173 Copollutant models: PM <sub>10</sub>
<a href="#">†Wong et al. (2009)</a>	Hong Kong, China (1996–2002)	Average of SO <sub>2</sub> concentrations from eight monitoring stations	24-h avg	6.8	75th: 8.4 Max: 41.8	Correlations ( <i>r</i> ): NR Copollutant models: none
<b>ED visits</b>						
<a href="#">Peel et al. (2005)</a>	Atlanta, GA (1993–2000)	Average of SO <sub>2</sub> concentrations across monitors for several monitoring networks	1-h max	16.5	90th: 39.0	Correlations ( <i>r</i> ): PM <sub>2.5</sub> : 0.17 PM <sub>10</sub> : 0.20 PM <sub>10-2.5</sub> : 0.21 UFP: 0.24 PM <sub>2.5</sub> water soluble metals: 0.00 PM <sub>2.5</sub> sulfate: 0.08 PM <sub>2.5</sub> acidity: -0.03 PM <sub>2.5</sub> OC: 0.18 PM <sub>2.5</sub> EC: 0.20 Oxygenated HCs: 0.14 O <sub>3</sub> : 0.19 CO: 0.26 NO <sub>2</sub> : 0.34 Copollutant models: none

**Table 5-12 (Continued): Study specific details and mean and upper percentile concentrations from chronic obstructive pulmonary disease hospital admission and emergency department visit studies conducted in the U.S. and Canada and evaluated in the 2008 SO<sub>x</sub> ISA and studies published since the 2008 SO<sub>x</sub> ISA.**

Study	Location Years	Exposure Assignment	Metric	Mean Concentration ppb	Upper Percentile Concentrations ppb	Copollutants Examined
†( <a href="#">Stieb et al. (2009)</a> )	Seven Canadian cities (1992–2003)	Average SO <sub>2</sub> concentrations across all monitors in each city. Number of SO <sub>2</sub> monitors in each city ranged from 1–11.	24-h avg	2.6–10.0	75th: 3.3–13.4	Correlations ( <i>r</i> ) only reported by city and season. Copollutant models: none
†( <a href="#">Arbex et al. (2009)</a> )	São Paulo, Brazil (2001–2003)	Average of SO <sub>2</sub> concentrations across 13 monitoring stations	24-h avg	5.3	75th: 6.6 Max: 16.4	Correlations ( <i>r</i> ): PM <sub>10</sub> : 0.77 NO <sub>2</sub> : 0.63 CO: 0.52 Copollutant models: none

CO = carbon monoxide; EC = elemental carbon; HC = hydrocarbon; NR = not reported; O<sub>3</sub> = ozone; OC = organic carbon; NO<sub>2</sub> = nitrogen dioxide; PM<sub>10</sub> = particulate matter with nominal aerodynamic diameter less than or equal to 10 µm; PM<sub>2.5</sub> = particulate matter with nominal aerodynamic diameter less than or equal to 2.5 µm; PM<sub>10-2.5</sub> = particulate matter with a nominal aerodynamic diameter less than or equal to 10 µm and greater than a nominal 2.5 µm; *r* = correlation coefficient; SO<sub>2</sub> = sulfur dioxide; UFP = ultrafine particle.

† = Studies published since the 2008 ISA for Sulfur Oxides.

### **Hospital Admissions**

1 Of the studies evaluated in the 2008 SO<sub>x</sub> ISA, relatively few examined the association  
 2 between short-term SO<sub>2</sub> exposure and COPD hospital admissions, and evidence of an  
 3 association was inconsistent across studies. Although several recent studies assessed the  
 4 relationship between short-term SO<sub>2</sub> exposures and COPD hospital admissions, the  
 5 overall body of evidence remains limited.

6 [Wong et al. \(2009\)](#) in a study that examined the potential modification of the relationship  
 7 between air pollution and respiratory-related hospital admissions by influenza, also  
 8 focused on cause-specific respiratory hospital admissions, including COPD. When  
 9 focusing on the baseline effect of short-term SO<sub>2</sub> exposures on COPD hospital  
 10 admissions, the authors found limited evidence of an association at lag 0–1 days for a  
 11 10-ppb increase in 24-h avg SO<sub>2</sub> concentrations in analyses of both all ages [0.8% (95%  
 12 CI: –1.5, 3.1)] and individuals over the age of 65 [0.5% (95% CI: –2.0, 3.0)].

1 In an additional study conducted in Hong Kong, [Qiu et al. \(2013b\)](#) focused on whether  
2 there is evidence of modification of the air pollution-COPD hospital admissions  
3 relationship by season and humidity. Compared to [Wong et al. \(2009\)](#), [Qiu et al. \(2013b\)](#)  
4 included 5 additional years of recent data through the year 2007. In single-pollutant  
5 models focusing on the association between short-term SO<sub>2</sub> exposures and COPD  
6 hospital admissions, for a multiday lag of 0–3 days, the authors reported a 1.6% increase  
7 (95% CI: 0.1, 3.1) for a 10-ppb increase in 24-h avg SO<sub>2</sub> concentrations. The magnitude  
8 of the SO<sub>2</sub> association was found to differ between [Qiu et al. \(2013b\)](#) and [Wong et al.](#)  
9 [\(2009\)](#), but the reason for the difference remains unclear, considering that similar data  
10 sources were used in each study. It is important to note that neither study conducted  
11 copollutant analyses for the entire study duration nor provided detailed information on  
12 the correlation between the air pollutants examined to help in the assessment of whether  
13 SO<sub>2</sub> has an independent effect on COPD hospital admissions.

### ***Emergency Department Visits***

14 The 2008 SO<sub>x</sub> ISA identified relatively few studies that examined the association  
15 between short-term SO<sub>2</sub> exposure and COPD ED visits, and across studies there was  
16 inconsistent evidence of an association. Although recent studies continued to assess the  
17 relationship between short-term SO<sub>2</sub> exposures and COPD ED visits, the overall body of  
18 evidence remains limited.

19 In the seven Canadian cities study discussed previously, and consistent with the asthma  
20 ED visits results, [Stieb et al. \(2009\)](#) did not find any evidence of associations between  
21 24-h avg SO<sub>2</sub> and COPD ED visits at single-day lags of 0 to 2 days. Additionally, there  
22 was no evidence of consistent associations between any pollutant and COPD ED visits at  
23 subdaily time scales (i.e., 3-h avg of ED visits vs. 3-h avg pollutant concentrations).

24 [Arbex et al. \(2009\)](#) also examined the association between COPD and several ambient air  
25 pollutants, including SO<sub>2</sub>, in a single-city study conducted in São Paulo, Brazil for  
26 individuals over the age of 40 years. The authors examined associations between  
27 short-term SO<sub>2</sub> exposures and COPD ED visits in both at single-day lags (0 to 6 days)  
28 and in a polynomial distributed lag model (0–6 days). The authors found evidence that  
29 the magnitude of the association was larger at multiday lags compared to single-day lags,  
30 with the lag of 0–3 days from the distributed lag model [49.4% (95% CI: 4.1, 113.7) for a  
31 10-ppb increase in 24-h avg SO<sub>2</sub> concentrations] most representative of the pattern of  
32 associations across single-day lags. Although the 0–6-day distributed lag model had the  
33 largest risk estimate, it was not supported by the single-day lag results that showed the  
34 strongest associations at lags of 0 and 1 day. It is important to note that [Arbex et al.](#)  
35 [\(2009\)](#) did not conduct copollutant analyses, but unlike correlations with SO<sub>2</sub> observed in  
36 other locations, SO<sub>2</sub> was highly correlated with PM<sub>10</sub> ( $r = 0.77$ ) and moderately

1 correlated with NO<sub>2</sub> ( $r = 0.63$ ) and CO ( $r = 0.52$ ) in this study. The results of [Arbex et al.](#)  
2 [\(2009\)](#) provide evidence of a potentially prolonged SO<sub>2</sub> effect on COPD ED visits;  
3 however, the results should be viewed with caution because effect estimates are not  
4 precise, time series is short, and there is potential for copollutants confounding.

### **Seasonal Analyses**

5 Traditionally, epidemiologic studies have examined potential seasonal differences in  
6 associations by stratifying by season. In the study of air pollution and COPD hospital  
7 admissions in Hong Kong, [Qiu et al. \(2013b\)](#) examined potential seasonal differences in  
8 associations by this traditional approach but also examined whether the combination of  
9 season and humidity modify the air pollution-health effect association. In seasonal  
10 analyses, the authors found a stronger association at lag 0–3 for a 10-ppb increase in  
11 24-h avg SO<sub>2</sub> concentrations during the cool season (November–April) [2.7% (95% CI:  
12 0.5, 4.9)] compared to the warm season (May–October) [0.6% (95% CI: –1.1, 2.3)]. [Qiu](#)  
13 [et al. \(2013b\)](#) then examined whether the seasonal differences in associations observed  
14 were due to low humidity days (i.e., relative humidity <80%) or high humidity days  
15 (i.e., relative humidity ≥80%) by examining the interaction between the various  
16 combinations of season and humidity. When focusing on the combined effect of season  
17 and humidity, SO<sub>2</sub> concentrations were found to be highest on days with low humidity in  
18 both seasons. In the warm season, there was no evidence of an association regardless of  
19 whether the interaction between season and low or high humidity days were examined. In  
20 the cold season, at lag 0–3 for a 10-ppb increase in 24-h avg SO<sub>2</sub> concentrations, [Qiu et](#)  
21 [al. \(2013b\)](#) reported the strongest association during days with low humidity [5.3% (95%  
22 CI: 2.4, 8.3)] compared to high humidity [0.5% (95% CI: –2.6, 3.7)], suggesting that the  
23 combination of season and humidity plays a role in the relationship between air pollution  
24 and health effects. However, when examining copollutant models with PM<sub>10</sub>, associations  
25 in all season and humidity combinations were attenuated, with only the association in the  
26 cool season and low humidity combination remaining positive, albeit with large  
27 uncertainty estimates [0.8% (95% CI: –2.1, 3.9); lag 0–3 for a 10-ppb increase in  
28 24-h avg SO<sub>2</sub> concentrations]. The results from [Qiu et al. \(2013b\)](#) are consistent with  
29 evidence from controlled human exposure studies demonstrating that SO<sub>2</sub> responses are  
30 exacerbated in colder and dryer conditions ([Section 5.2.1.2](#)). However, these studies  
31 focused on lung function changes in people with asthma and it is unclear how these  
32 results correspond to results from an epidemiologic study of COPD hospital admissions.  
33 Additionally, it is important to note the potential influence of geographic location on the  
34 results from studies that examine the seasonal patterns of associations.

### **Lag Structure of Associations**

1 Only a limited number of studies examined the lag structure of associations for  
2 SO<sub>2</sub>-related COPD hospital admissions and ED visits. [Qiu et al. \(2013b\)](#) in the  
3 examination of air pollution and COPD hospital admissions in Hong Kong conducted  
4 analyses to evaluate associations with SO<sub>2</sub> at both single-day and multiday lags of  
5 0–3 days. The authors found the strongest evidence for an SO<sub>2</sub>-COPD hospital admission  
6 association at a multiday lag of 0–3 days, with additional evidence of positive  
7 associations at single-day lags of 1 day and 3 days.

8 [Arbex et al. \(2009\)](#), when examining associations between SO<sub>2</sub> exposure and COPD ED  
9 visits in São Paulo, Brazil, focused on both single-day lags (0 to 6 days) and a polynomial  
10 distributed lag (0–6 day) model. The authors found evidence that the magnitude of the  
11 association was larger at multiday lags compared to single-day lags, and the magnitude of  
12 the association increased as the number of lag days examined increased, specifically  
13 across lags of 0–1, 0–2, and 0–5 days. However, the 0–5-day distributed lag model  
14 results were not supported by the single-day lag results, which indicated that the effect of  
15 SO<sub>2</sub> on COPD ED visits was rather immediate, occurring in the range of lag 0 and 1 days.  
16 Collectively, the results of [Qiu et al. \(2013b\)](#) and [Arbex et al. \(2009\)](#) provide initial  
17 evidence suggesting a potential prolonged effect of SO<sub>2</sub> on COPD hospital admissions  
18 and ED visits. However, the collective evidence indicating a potential association  
19 between short-term SO<sub>2</sub> exposures and COPD hospital admissions and ED visits remains  
20 relatively small.

### **Summary of Chronic Obstructive Pulmonary Disease Exacerbation**

21 Across disciplines and outcomes, evidence from previous and recent studies does not  
22 clearly support a relationship between short-term SO<sub>2</sub> exposure and COPD exacerbation.  
23 The evidence base is relatively small and mostly comprises epidemiologic studies.  
24 Neither the single controlled human exposure study nor the few epidemiologic studies  
25 indicate SO<sub>2</sub>-related lung function changes in adults with COPD, and recent  
26 epidemiologic studies mostly reported no association with an array of respiratory  
27 symptoms, including sputum changes and dyspnea, which are characteristic of COPD  
28 exacerbation. There is similarly inconsistent evidence for association between short-term  
29 increases in ambient SO<sub>2</sub> concentration and hospital admissions and ED visits for COPD  
30 ([Figure 5-7](#)). Hospital admissions, ED visits, lung function, and symptoms were  
31 examined in relation to 24-h avg SO<sub>2</sub> concentrations, but an association was not observed  
32 with 1-h max SO<sub>2</sub> either. The supporting evidence is limited largely to an association of  
33 COPD hospital admissions and ED visits with same-day and 4-day avg SO<sub>2</sub>  
34 concentrations. All epidemiologic studies estimated SO<sub>2</sub> exposure from central site

1 monitors. SO<sub>2</sub> generally has low to moderate spatial correlations across urban  
2 geographical scales, and the potential error in the exposure estimates in adequately  
3 representing the spatiotemporal variability is uncharacterized in the evidence  
4 ([Section 3.4.2.2](#)). The uncertainty in exposure estimates especially applies to 1-h max  
5 SO<sub>2</sub>. COPD hospital admissions were associated with PM<sub>10</sub>, NO<sub>2</sub>, and O<sub>3</sub>. PM<sub>10</sub> was  
6 highly correlated with SO<sub>2</sub> ( $r = 0.77$ ) or when analyzed in a copollutant model, attenuated  
7 the SO<sub>2</sub> association and produced wide 95% CIs. The copollutant model results have  
8 unclear implication due to uncertainty in the exposure estimates and unreported  
9 SO<sub>2</sub>-PM<sub>10</sub> correlation. Overall, there is inconsistent evidence for an effect of SO<sub>2</sub>  
10 exposure on COPD exacerbation, and for the limited supporting evidence, an effect of  
11 SO<sub>2</sub> exposure that is independent of copollutants is unclear.

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### 5.2.1.5 Respiratory Infection

12 The respiratory tract is protected from exogenous pathogens and particles through various  
13 lung host defense mechanisms that include mucociliary clearance, phagocytosis by  
14 alveolar macrophages, and innate and adaptive immunity. There is a paucity of evidence  
15 related to host defense from animal toxicological experiments using ambient-relevant  
16 concentrations of SO<sub>2</sub>. Several studies of short-term exposure to SO<sub>2</sub> were reported in the  
17 1982 AQCD ([U.S. EPA, 1982a](#)) and discussed in the 2008 SO<sub>x</sub> ISA ([U.S. EPA, 2008d](#)).  
18 Findings of short-term studies included some effects of 0.1–1 ppm SO<sub>2</sub> on the clearance  
19 of labeled particles. No new animal studies of the effects of SO<sub>2</sub> exposure on lung host  
20 defense have been conducted since the previous review. A small number of previous  
21 epidemiologic studies reported SO<sub>2</sub>-associated increases in respiratory infections as  
22 self-reported or indicated by hospital admissions and ED visits. However, many results  
23 were noted as being unreliable because they were based on statistical methods prone to  
24 bias.

25 Recent contributions to the evidence are limited to epidemiologic studies, and the  
26 evaluation of this evidence focuses on hospital admissions and ED visits. There are recent  
27 studies of self-reported infections, and they inconsistently show associations with  
28 ambient SO<sub>2</sub> concentrations, [Supplemental Figure 5S-2 ([U.S. EPA, 2016h](#))]. Results  
29 based on school or home SO<sub>2</sub> exposure estimates are limited by their cross-sectional  
30 design or examination of nonspecific symptoms such as fever. Other studies do not  
31 provide insight over studies of hospital admissions and ED visits on issues such as  
32 exposure measurement error, copollutant confounding, or potentially relevant exposure  
33 durations and concentrations. Recent studies of respiratory infection hospital admissions  
34 and ED visits provide some evidence for association with ambient SO<sub>2</sub> concentrations.  
35 However, copollutant confounding remains an uncertainty.

## Hospital Admissions and Emergency Department Visits

1 The 2008 SO<sub>x</sub> ISA contained limited evidence of an association between short-term SO<sub>2</sub>  
2 concentrations and respiratory conditions other than asthma or COPD. Although some  
3 studies evaluated respiratory infections, including respiratory tract infections and  
4 pneumonia, the majority of studies used generalized additive models with default  
5 convergence criteria in the analysis, and this statistical approach was shown to  
6 inaccurately calculate effect estimates and to underestimate standard errors. Additionally,  
7 of the studies evaluated in the 2008 SO<sub>x</sub> ISA, only one study was conducted in the U.S.  
8 or Canada [i.e., ([Peel et al., 2005](#))]. Recent studies have examined a variety of outcomes  
9 indicative of respiratory infection; however, none have examined the same respiratory  
10 infection outcome. Additionally, most studies averaged SO<sub>2</sub> concentrations over multiple  
11 monitors and examined 24-h avg exposure metrics, which may not adequately capture the  
12 spatial and temporal variability in SO<sub>2</sub> concentrations ([Section 3.4.2](#)). For each of the  
13 studies evaluated in this section, [Table 5-13](#) presents the air quality characteristics of each  
14 city, or across all cities, the exposure assignment approach used, and information on  
15 copollutants examined in each respiratory infection hospital admission and ED visit  
16 study. Other recent studies of respiratory infection hospital admissions and ED visits are  
17 not the focus of this evaluation because of various study design issues, as initially  
18 detailed in [Section 5.2.1.2](#), but the full list of these studies, as well as study specific  
19 details, can be found in Supplemental Table 5S-5 ([U.S. EPA, 2016m](#)).

### ***Hospital Admissions***

20 Although recent studies have continued to examine the association between short-term  
21 SO<sub>2</sub> exposures and respiratory infection hospital admissions, the overall evidence  
22 remains limited, primarily due to the variety of respiratory infection outcomes examined.  
23 In a study conducted in Ho Chi Minh City, Vietnam [Mehta et al. \(2013\)](#) and [HEI \(2012\)](#)  
24 examined the association between short-term air pollution exposures and pediatric (ages  
25 28 days–5 years) hospital admissions for acute lower respiratory infections (ALRI,  
26 including bronchiolitis and pneumonia). In a time-stratified, case-crossover analysis  
27 focusing only on the average of a 1–6 day lag, the study authors reported a positive  
28 association, with large uncertainty estimates, between SO<sub>2</sub> and ALRI hospital admissions  
29 in the all-year analysis [7.0% (95% CI: –3.0, 19.1) for a 10-ppb increase in 24-h avg SO<sub>2</sub>  
30 concentrations]. A larger association was observed in the time-series analysis ([HEI,](#)  
31 [2012](#)) ([Figure 5-8](#)). When examining copollutant models with PM<sub>10</sub> and O<sub>3</sub>, SO<sub>2</sub>  
32 associations increased slightly, with the percent increase ranging from 7.5–8.0%,  
33 respectively. However, in models with NO<sub>2</sub>, the SO<sub>2</sub> association was attenuated, but  
34 remained positive [4.9% (95% CI: –6.0, 17.0) for a 10-ppb increase in 24-h avg SO<sub>2</sub>  
35 concentrations].

**Table 5-13 Study-specific details and mean and upper percentile concentrations from respiratory infection hospital admission and emergency department visit studies conducted in the U.S. and Canada and evaluated in the 2008 SO<sub>x</sub> ISA and studies published since the 2008 SO<sub>x</sub> ISA.**

Study	Location (Years)	Type of Visit (ICD 9/10)	Exposure Assignment	Metric	Mean Concentration ppb	Upper Percentile of Concentrations ppb	Copollutants Examined
<b>Hospital admissions</b>							
† <a href="#">HEI (2012)</a> <a href="#">Mehta et al. (2013)</a>	Ho Chi Minh City, Vietnam (2003–2005)	Acute lower respiratory infection (J13–16, 18, 21)	Average of SO <sub>2</sub> concentrations across nine monitors	24-h avg	8.2	Max: 30.5	Correlations (r): Dry season: PM <sub>10</sub> : 0.32 O <sub>3</sub> : 0.19 NO <sub>2</sub> : 0.29 Rainy season: PM <sub>10</sub> : 0.36 O <sub>3</sub> : 0.65 NO <sub>2</sub> : 0.01 Copollutant models: NO <sub>2</sub> , PM <sub>10</sub> , O <sub>3</sub>
† <a href="#">Ségala et al. (2008)</a>	Paris, France (1997–2001)	Bronchiolitis	Average SO <sub>2</sub> concentrations across 30 monitors	24-h avg	4.0	Max: 27.4	Correlations (r): BS: 0.76 PM <sub>10</sub> : 0.73 NO <sub>2</sub> : 0.78 Copollutant models: none

**Table 5-13 (Continued): Study specific details and mean and upper percentile concentrations from respiratory infection hospital admission and emergency department visit studies conducted in the U.S. and Canada and evaluated in the 2008 SO<sub>x</sub> ISA and studies published since the 2008 SO<sub>x</sub> ISA.**

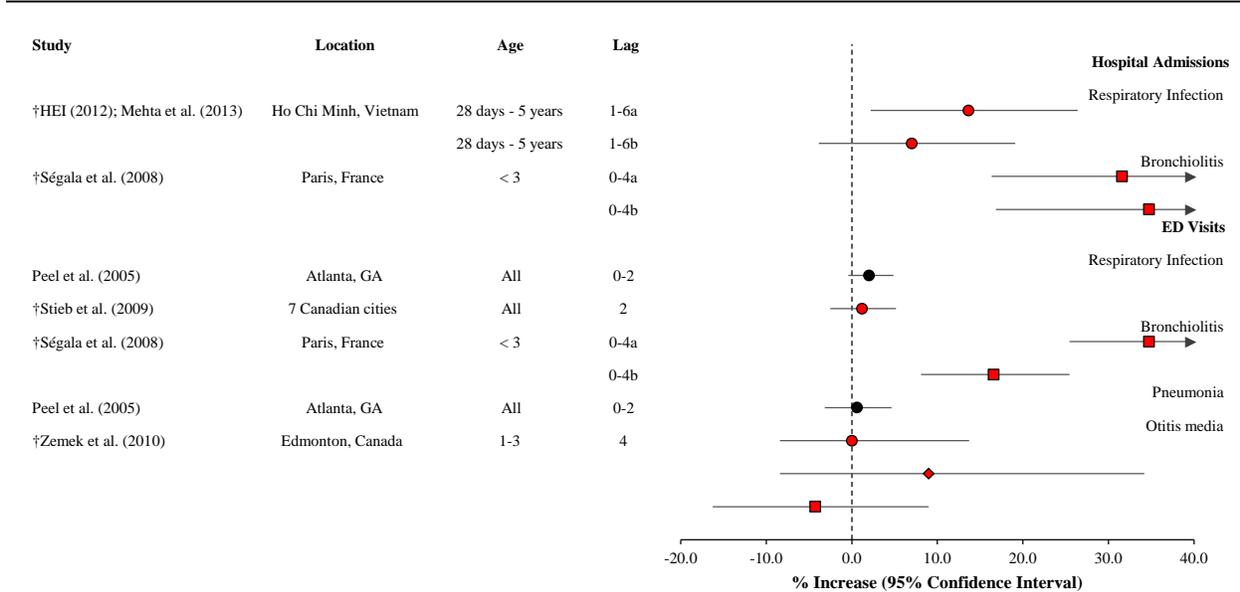
Study	Location (Years)	Type of Visit (ICD 9/10)	Exposure Assignment	Metric	Mean Concentration ppb	Upper Percentile of Concentrations ppb	Copollutants Examined
<b>ED visits</b>							
<a href="#">Peel et al. (2005)</a>	Atlanta, GA (1993–2000)	Pneumonia (480–486)	Average of SO <sub>2</sub> concentrations from monitors for several monitoring networks	1-h max	16.5	90th: 39.0	Correlations ( <i>r</i> ): PM <sub>2.5</sub> : 0.17 PM <sub>10</sub> : 0.20 PM <sub>10-2.5</sub> : 0.21 UFP: 0.24 PM <sub>2.5</sub> water soluble metals: 0.00 PM <sub>2.5</sub> sulfate: 0.08 PM <sub>2.5</sub> acidity: -0.03 PM <sub>2.5</sub> OC: 0.18 PM <sub>2.5</sub> EC: 0.20 Oxygenated HCs: 0.14 O <sub>3</sub> : 0.19 CO: 0.26 NO <sub>2</sub> : 0.34 Copollutant models: none
<a href="#">†Stieb et al. (2009)</a>	Seven Canadian cities (1992–2003)	Respiratory infection (464, 466, 480–487)	Average SO <sub>2</sub> concentrations across all monitors in each city. Number of SO <sub>2</sub> monitors in each city ranged from 1–11.	24-h avg	2.6–10.0	75th: 3.3–13.4	Correlations ( <i>r</i> ) only reported by city and season. Copollutant models: none

**Table 5-13 (Continued): Study specific details and mean and upper percentile concentrations from respiratory infection hospital admission and emergency department visit studies conducted in the U.S. and Canada and evaluated in the 2008 SO<sub>x</sub> ISA and studies published since the 2008 SO<sub>x</sub> ISA.**

Study	Location (Years)	Type of Visit (ICD 9/10)	Exposure Assignment	Metric	Mean Concentration ppb	Upper Percentile of Concentrations ppb	Copollutants Examined
<a href="#">†Ségala et al. (2008)</a>	Paris, France (1997–2001)	Bronchiolitis	Average SO <sub>2</sub> concentrations across 30 monitors	24-h avg	4.0	Max: 27.4	Correlations ( <i>r</i> ): BS: 0.76 PM <sub>10</sub> : 0.73 NO <sub>2</sub> : 0.78 Copollutant models: none
<a href="#">†Zemek et al. (2010)</a>	Edmonton, AB (1992–2002)	Otitis media (382.9)	Average of SO <sub>2</sub> concentrations across three monitors	24-h avg	All-year: 2.6 Warm (Apr–Sep): 2.1 Cold (Oct–Mar): 3.1	All-year 75th: 3.5	Correlations ( <i>r</i> ): NR Copollutant models: none
<b>Outpatient and physician visits</b>							
<a href="#">†Sinclair et al. (2010)</a>	Atlanta, GA (1998–2002)	Upper respiratory infection Lower respiratory infection	SO <sub>2</sub> concentrations collected as part of AIRES at SEARCH Jefferson Street site	1-h max	1998–2000: 19.3 2000–2002: 17.6 1998–2002: 18.3	NR	Correlations ( <i>r</i> ): NR Copollutant models: none

AIRES = Aerosol Research Inhalation Epidemiology Study; BS = black smoke; CO = carbon monoxide; EC = elemental carbon; HC = hydrocarbon; ICD = International Classification of Diseases; ISA = Integrated Science Assessment; NO<sub>2</sub> = nitrogen dioxide; O<sub>3</sub> = ozone; OC = organic carbon; PM = particulate matter; NR = not reported; *r* = correlation coefficient; SEARCH = Southeast Aerosol Research Characterization; SO<sub>2</sub> = sulfur dioxide; UFP = ultrafine particle.

† = studies published since the 2008 ISA for Sulfur Oxides.



ED = emergency department.

Note: † and red = recent studies published since the 2008 ISA for Sulfur Oxides; Black = U.S. and Canadian studies evaluated in the 2008 ISA for Sulfur Oxides; circles = all-year results, diamonds = warm season results, squares = cold season results. Corresponding quantitative results are found in Supplemental Table 5S-7 ([U.S. EPA, 2016k](#)).

**Figure 5-8 Percent increase in respiratory infection hospital admissions and emergency department visits from U.S. and Canadian studies evaluated in the 2008 SO<sub>x</sub> ISA and recent studies in all-year and seasonal analyses for a 10-ppb increase in 24-h avg or 40-ppb increase in 1-h max sulfur dioxide concentrations.**

1 In another study that also examined respiratory infections (i.e., bronchiolitis) in children,  
 2 [Ségala et al. \(2008\)](#) focused on associations with winter (October–January) air pollution  
 3 because that is when respiratory syncytial virus (RSV) activity peaks. It has been  
 4 hypothesized that air pollution exposures may increase the risk of respiratory infections,  
 5 including bronchiolitis due to RSV ([Ségala et al., 2008](#)). Focusing on children <3 years of  
 6 age in Paris, France, the study authors conducted a bidirectional case-crossover analysis  
 7 along with a time-series analysis to examine air pollution associations with bronchiolitis  
 8 hospital admissions and ED visits (see ED visits section below). Although the authors  
 9 specified that the bidirectional case-crossover approach was used to “avoid time-trend  
 10 bias,” it must be noted that the bidirectional approach has been shown to bias results  
 11 ([Ségala et al., 2008](#); [Levy et al., 2001](#)). In the case-crossover analysis, SO<sub>2</sub> was associated  
 12 with bronchiolitis hospital admissions at lag 0–4 days for a 10-ppb increase in 24-h avg  
 13 SO<sub>2</sub> concentrations [34.8% (95% CI: 19.5, 47.8)] with a similar risk estimate observed

1 for the time-series analysis [31.6% (95% CI: 13.7, 51.2)]. Although a positive association  
2 was observed, the authors did not conduct copollutant analyses. This omission  
3 complicates the interpretation of the results because SO<sub>2</sub> was highly correlated with the  
4 other pollutants examined, with correlations ranging from  $r = 0.73$ – $0.87$ .

### ***Emergency Department Visits***

5 Similar to respiratory infection hospital admissions, recent studies have examined  
6 respiratory infection ED visits; however, these studies overall have not consistently  
7 examined the same respiratory infection outcomes ([Figure 5-8](#)). In their study of seven  
8 Canadian cities, [Stieb et al. \(2009\)](#) also examined the association between short-term SO<sub>2</sub>  
9 exposure and respiratory infection ED visits. The authors reported a positive association  
10 at a 2-day lag [1.2% (95% CI: -2.5, 5.2) for a 10-ppb increase in 24-h avg SO<sub>2</sub>  
11 concentrations], but there was uncertainty surrounding this result and there was no  
12 evidence of an association at single-day lags of 0 and 1 days. However, [Ségala et al.](#)  
13 [\(2008\)](#), in addition to examining bronchiolitis hospital admissions, also examined  
14 bronchiolitis ED visits. The authors reported evidence of an association between  
15 short-term SO<sub>2</sub> exposures and bronchiolitis ED visits [34.7% (95% CI: 25.5, 44.5); lag  
16 0–4 for a 10-ppb increase in 24-h avg SO<sub>2</sub> concentrations]. However, as mentioned  
17 previously, the interpretation of these results is complicated by the lack of copollutant  
18 analyses and the high correlation between the pollutants examined ( $r = 0.73$  to  $0.87$ ),  
19 along with the use of a bidirectional case-crossover approach.

20 In an additional study conducted in Edmonton, AB, [Zemek et al. \(2010\)](#) examined a new  
21 outcome for SO<sub>2</sub>, otitis media (i.e., ear infections) ED visits, for ages 1–3 years.  
22 Associations were examined for single-day lags of 0 to 4 days in all-year as well as  
23 seasonal analyses. The authors found no evidence of an association between short-term  
24 SO<sub>2</sub> exposures and increases in ED visits for otitis media at any single-day lag in the  
25 all-year analysis.

### ***Physician/Outpatient Visits***

26 In a study conducted in Atlanta, GA as discussed in [Section 5.2.1.2](#), [Sinclair et al. \(2010\)](#)  
27 examined the association between air pollution and respiratory infection (e.g., upper  
28 respiratory infections, lower respiratory infections) outpatient visits from a managed care  
29 organization. As detailed previously, the authors separated the analysis into two time  
30 periods - the first 25 months of the study period (i.e., August 1998–August 2000) and the  
31 second 28 months of the study period (i.e., September 2000–December 2002).  
32 A comparison of the two time periods indicated that risk estimates across outcomes  
33 tended to be larger in the earlier 25-month period compared to the later 28-month period.  
34 An examination of the respiratory infection outcomes found no evidence of an

1 association for upper respiratory infections at any lag and a positive association for lower  
2 respiratory infections for only lag 0–2.

### ***Multiday Lags***

3 In the case of respiratory infection hospital admission and ED visit studies, none of the  
4 studies evaluated conducted an extensive analysis of the lag structure of associations.  
5 However, [Ségala et al. \(2008\)](#) in a study of acute bronchiolitis examined multiday lags of  
6 0–1 and 0–4 days, which does provide some indication of the lag structure of  
7 associations. The authors found relatively similar associations for both multiday lags, but  
8 the association was slightly larger for lag 0–4 days (i.e., 31.6 vs. 34.8%). These initial  
9 results indicate a potential prolonged effect of SO<sub>2</sub> that could lead to a respiratory  
10 infection hospital admission or ED visit.

### ***Seasonal Analyses***

11 A few of the recent studies that examined respiratory infection-related hospital  
12 admissions and ED visits also examined whether there was evidence of seasonal  
13 differences in associations. It should be noted that interpreting the results from these  
14 studies is complicated by the different geographic locations as well as the respiratory  
15 infection outcome examined in each study. [Mehta et al. \(2013\)](#) in the study of ALRI  
16 hospital admissions in Vietnam examined potential seasonal differences in associations  
17 by dividing the year into the dry (November–April) and rainy seasons (May–October).  
18 Within these seasons, SO<sub>2</sub> concentrations differed drastically, with mean 24-h avg SO<sub>2</sub>  
19 concentrations being 10.1 ppb in the dry season and 5.7 ppb in the rainy season. In  
20 seasonal analyses, [Mehta et al. \(2013\)](#) reported that SO<sub>2</sub> was consistently associated with  
21 ALRI hospital admissions in the dry season [16.1% (95% CI: 1.2, 33.3) for a 10-ppb  
22 increase in 24-h avg SO<sub>2</sub> concentrations, lag 1–6 day avg], with no evidence of an  
23 association in the rainy season. Of the other pollutants that were found to be positively  
24 associated with ALRI hospital admissions during the dry season (i.e., PM<sub>10</sub> and NO<sub>2</sub>),  
25 none were associated during the rainy season. In copollutant analyses for the dry season,  
26 SO<sub>2</sub> was robust to the inclusion of PM<sub>10</sub> and O<sub>3</sub> in the model, with the magnitude of the  
27 effect remaining similar, 15.0 and 15.8%, respectively. However, in models with NO<sub>2</sub>,  
28 the SO<sub>2</sub>-ALRI hospital admission association was attenuated, but remained positive with  
29 large uncertainty estimates [10.0% (95% CI: –4.6, 26.9) for a 10-ppb increase in 24-h avg  
30 SO<sub>2</sub> concentrations, lag 1–6 day avg].

31 Additionally, [Zemek et al. \(2010\)](#) in the study of otitis media ED visits in Alberta,  
32 reported that the magnitude of the association was larger, albeit with wide confidence  
33 intervals, in the warm months (April–September), 9.0% (95% CI: –8.4, 34.2), compared

1 to the cold months, (October–March),  $-4.3\%$  (95% CI:  $-16.30, 9.0$ ) at lag 4 for a 10-ppb  
2 increase in 24-h avg  $\text{SO}_2$  concentrations.

### Summary of Respiratory Infection

3 Recent evidence, which comes from epidemiologic studies, expands on that presented in  
4 the 2008 ISA for Sulfur Oxides and provides some, but not entirely consistent, support  
5 for an association between ambient  $\text{SO}_2$  concentrations and respiratory infection.

6 Whereas cross-sectional studies do not consistently link  $\text{SO}_2$  exposures estimated for  
7 school or home to respiratory infections self-reported by children [Supplemental  
8 Figure 5S-2 ([U.S. EPA, 2016h](#))], some evidence points to an association with hospital  
9 admission and ED visits ([Figure 5-8](#)). Associations are observed for all respiratory  
10 infections combined and bronchiolitis but not pneumonia or otitis media. The lack of  
11 multiple studies examining the same respiratory infection outcome complicates the  
12 interpretation of the collective body of evidence, specifically because the etiologies of  
13 upper and lower respiratory infections are vastly different.

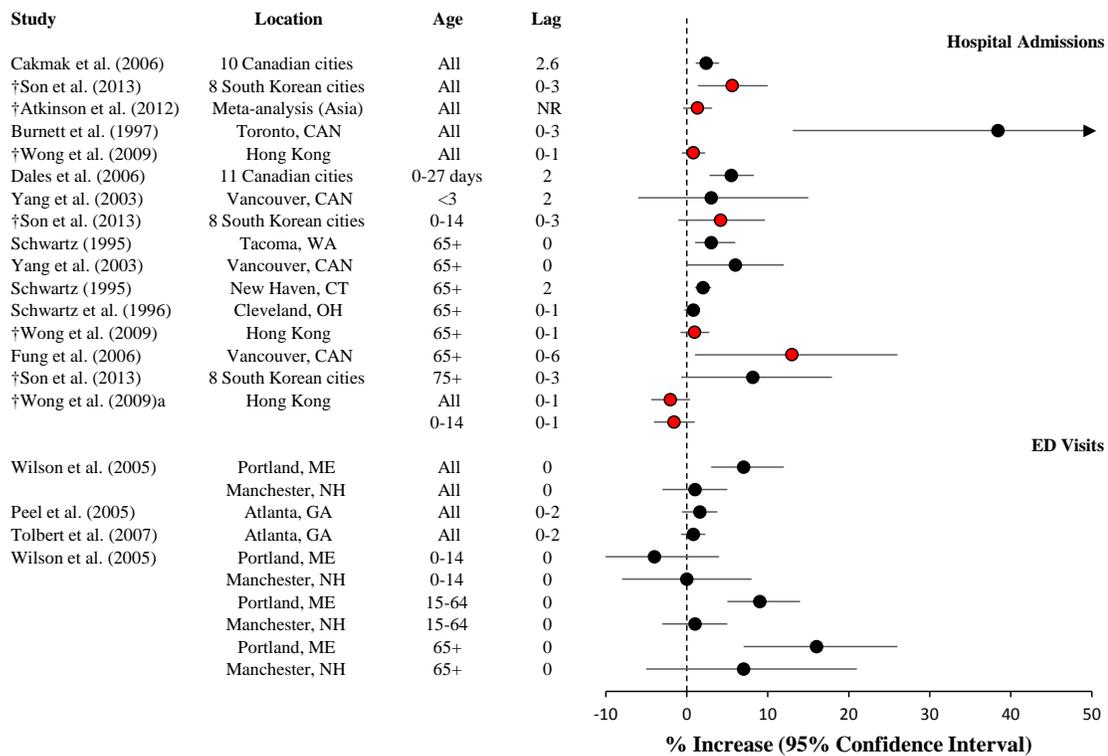
14 Most supporting evidence points to associations with 24-h avg  $\text{SO}_2$  concentrations  
15 averaged over 3 to 7 days, but an association was observed with temporally resolved  
16 1-h max as well. The relatively small number of studies does not provide a strong basis  
17 for drawing inferences about the lag structure of associations with respiratory infection or  
18 potential seasonal differences in associations. An examination of potential factors that  
19 could modify the  $\text{SO}_2$ -respiratory infection hospital admission or ED visit association  
20 finds differences by SES but inconsistent differences by sex ([Chapter 6](#)). Recent studies  
21 continued to rely on central site monitors.  $\text{SO}_2$  generally has low to moderate spatial  
22 correlations across urban geographical scales, which could contribute to some degree of  
23 exposure error ([Section 3.4.2.2](#)). Another uncertainty that persists in the recent evidence  
24 is copollutant confounding. Respiratory infection hospital admissions and ED visits were  
25 associated with  $\text{PM}_{2.5}$ ,  $\text{PM}_{10}$ , BS, and  $\text{NO}_2$ . High  $\text{SO}_2$ -copollutant correlations were  
26 observed ( $r = 0.73\text{--}0.78$ ). Correlations were low in some locations ( $r = 0.17\text{--}0.34$ )  
27 ([Table 5-13](#)), but these may not adequately reflect correlation in exposure due to  
28 differential measurement error, particularly for copollutants with different averaging  
29 times. New information from copollutant models shows an  $\text{SO}_2$  association that is  
30 attenuated and made imprecise with adjustment for  $\text{NO}_2$ , but uncertainty in the exposure  
31 estimates weakens inference about independent associations. Information to assess the  
32 biological plausibility of epidemiologic findings is limited. There is some evidence in  
33 rodents that  $\text{SO}_2$  exposures of 0.1–1 ppm diminish clearance of particles, but responses to  
34 infectious agents have not been examined in relation to ambient-relevant exposures.

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### 5.2.1.6 Aggregated Respiratory Conditions

1 In addition to individual respiratory conditions, epidemiologic studies examined  
2 respiratory effects as an aggregate of multiple respiratory conditions (e.g., asthma,  
3 COPD, respiratory infections). Epidemiologic studies examining the association between  
4 short-term SO<sub>2</sub> exposures and respiratory-related hospital admissions or ED visits,  
5 including those discussed earlier in this chapter, were not available until after the  
6 completion of the 1986 Supplement to the Second Addendum of the 1982 SO<sub>x</sub> AQCD  
7 ([U.S. EPA, 1994](#)). Therefore, the 2008 SO<sub>x</sub> ISA ([U.S. EPA, 2008d](#)) included the first  
8 thorough evaluation of respiratory morbidity in the form of respiratory-related hospital  
9 admissions and ED visits. Of the studies evaluated, the majority consisted of single-city,  
10 time-series studies that primarily examined all respiratory disease or asthma hospital  
11 admissions or ED visits, with a more limited number of studies examining other  
12 respiratory outcomes, as discussed in previous sections. Additionally, most studies  
13 averaged SO<sub>2</sub> concentrations over multiple monitors and examined 24-h avg exposure  
14 metrics, which may not adequately capture the spatial and temporal variability in SO<sub>2</sub>  
15 concentrations ([Section 3.4.2](#)). The studies that examined all respiratory disease hospital  
16 admissions and ED visits generally reported positive associations ([Figure 5-9](#)). These  
17 associations were found to remain generally positive with some evidence of an  
18 attenuation of the association in models with gaseous pollutants (i.e., NO<sub>2</sub> and O<sub>3</sub>) and  
19 particulate matter ([U.S. EPA, 2008d](#)).

20 Since the completion of the 2008 SO<sub>x</sub> ISA, recent studies have examined the association  
21 between short-term exposure to ambient SO<sub>2</sub> and all respiratory disease hospital  
22 admissions and ED visits. For each of the studies evaluated in this section, [Table 5-14](#)  
23 presents the air quality characteristics of each city or across all cities, the exposure  
24 assignment approach used, and information on copollutants examined in each hospital  
25 admission and ED visit study that examined all respiratory diseases. Other recent studies  
26 that have examined all respiratory disease hospital admissions and ED visits are not the  
27 focus of this evaluation because of various study design issues, as initially detailed in  
28 [Section 5.2.1.2](#), but the full list of these studies, as well as study specific details, can be  
29 found in Supplemental Table 5S-5 ([U.S. EPA, 2016m](#)).



ED = emergency department.

Note: † and red = recent studies published since the 2008 ISA for Sulfur Oxides; Black = U.S. and Canadian studies evaluated in the 2008 ISA for Sulfur Oxides. Corresponding quantitative results are found in Supplemental Table 5S-8 ([U.S. EPA, 2016o](#)). a = ([Wong et al., 2009](#)) also presented results for acute respiratory disease hospital admissions, which is a subset of total respiratory hospital admissions.

**Figure 5-9** Percent increase in respiratory disease hospital admissions and emergency department visits from U.S. and Canadian studies evaluated in the 2008 SO<sub>x</sub> ISA and recent studies in all-year and seasonal analyses for a 10-ppb increase in 24-h avg or 40-ppb increase in 1-h max sulfur dioxide concentrations.

**Table 5-14 Study-specific details and mean and upper percentile concentrations from respiratory disease hospital admission and emergency department visit studies conducted in the U.S. and Canada and evaluated in the 2008 SO<sub>x</sub> ISA and studies published since the 2008 SO<sub>x</sub> ISA.**

Study	Location Years	Exposure Assignment	Metric	Mean Concentration (ppb)	Upper Percentile of Concentrations (ppb)	Copollutants Examined
<b>Hospital admissions</b>						
<a href="#">Cakmak et al. (2006)</a>	10 Canadian cities (1993–2000)	Average of SO <sub>2</sub> concentrations across all monitors in each city	24-h avg	4.6	Max: 14–75	Correlations (r): NR Copollutant models: none
<a href="#">Dales et al. (2006)</a>	11 Canadian cities (1986–2000)	Average of SO <sub>2</sub> concentrations across all monitors in each city	24-h avg	4.3 <sup>a</sup>	95th: 3.5–23.5	Correlations (r): PM <sub>10</sub> : –0.09 to 0.61 O <sub>3</sub> : –0.41 to 0.13 NO <sub>2</sub> : 0.20 to 0.67 CO: 0.19 to 0.66 Copollutant models: none
<a href="#">Burnett et al. (1997)</a>	Toronto, ON (1992–1994)	Average of SO <sub>2</sub> concentrations from 4–6 monitors during the course of the study	1-h max	7.9	75th: 11 95th: 18 Max: 26	Correlations (r): H <sup>+</sup> : 0.45 SO <sub>4</sub> : 0.42 PM <sub>10</sub> : 0.55 PM <sub>2.5</sub> : 0.49 PM <sub>10-2.5</sub> : 0.44 COH: 0.50 O <sub>3</sub> : 0.18 NO <sub>2</sub> : 0.46 CO: 0.37 Copollutant models: COH, PM <sub>10</sub> , PM <sub>10-2.5</sub> , PM <sub>2.5</sub>

**Table 5-14 (Continued): Study specific details and mean and upper percentile concentrations from respiratory disease hospital admission and emergency department visit studies conducted in the U.S. and Canada and evaluated in the 2008 SO<sub>x</sub> ISA and studies published since the 2008 SO<sub>x</sub> ISA.**

Study	Location Years	Exposure Assignment	Metric	Mean Concentration ppb)	Upper Percentile of Concentrations ppb)	Copollutants Examined
<a href="#">Fung et al. (2006)</a>	Vancouver, BC (1995–1999)	Average of SO <sub>2</sub> concentrations across all monitors within Vancouver	24-h avg	3.46	Max: 12.5	Correlations ( <i>r</i> ): CO: 0.61 COH: 0.65 O <sub>3</sub> : -0.35 NO <sub>2</sub> : 0.57 PM <sub>10</sub> : 0.61 PM <sub>2.5</sub> : 0.42 PM <sub>10-2.5</sub> : 0.57 Copollutant models: none
<a href="#">Schwartz (1995)</a>	New Haven, CT Tacoma, WA (1988–1990)	Average of SO <sub>2</sub> concentrations across all monitors in each city	24-h avg	New Haven: 29.8 Tacoma: 11.5	New Haven: 75th: 38.2 90th: 60.7 Tacoma: 75th: 21.4 90th: 28.2	Correlations ( <i>r</i> ): NR Copollutant models: PM <sub>10</sub> , O <sub>3</sub>
<a href="#">Schwartz et al. (1996)</a>	Cleveland, OH (1988–1990)	Average of SO <sub>2</sub> concentrations across all monitors	24-h avg	35.0	75th: 45.0 90th: 61.0	Correlations ( <i>r</i> ): NR Copollutant models: none
<a href="#">Yang et al. (2003b)</a>	Vancouver, BC (1986–1998)	Average of SO <sub>2</sub> concentrations across four monitors	24-h avg	4.8	75th: 6.3 Max: 24.0	Correlation ( <i>r</i> ): O <sub>3</sub> : -0.37 Copollutant models: O <sub>3</sub>
† <a href="#">Son et al. (2013)</a>	Eight South Korean cities (2003–2008)	Average of hourly ambient SO <sub>2</sub> concentrations from monitors in each city	24-h avg	3.2–7.3	NR	Correlation ( <i>r</i> ): PM <sub>10</sub> : 0.5 O <sub>3</sub> : -0.1 NO <sub>2</sub> : 0.6 Copollutant models: none
† <a href="#">Atkinson et al. (2012)</a>	Meta-analysis (Asia) (1980–2007)	NR	24-h avg	NR	NR	Correlation ( <i>r</i> ): NR Copollutant models: none

**Table 5-14 (Continued): Study specific details and mean and upper percentile concentrations from respiratory disease hospital admission and emergency department visit studies conducted in the U.S. and Canada and evaluated in the 2008 SO<sub>x</sub> ISA and studies published since the 2008 SO<sub>x</sub> ISA.**

Study	Location Years	Exposure Assignment	Metric	Mean Concentration (ppb)	Upper Percentile of Concentrations (ppb)	Copollutants Examined
<a href="#">†Wong et al. (2009)</a>	Hong Kong, China (1996–2002)	Average of SO <sub>2</sub> concentrations from eight monitoring stations	24-h avg	6.8	75th: 8.4 Max: 41.8	Correlation (r): NR Copollutant models: none
<b>ED visits</b>						
<a href="#">Peel et al. (2005)</a>	Atlanta, GA (1993–2000)	Average of SO <sub>2</sub> concentrations from monitors for several monitoring networks	1-h max	16.5	90th: 39.0	Correlations (r): PM <sub>2.5</sub> : 0.17 PM <sub>10</sub> : 0.20 PM <sub>10-2.5</sub> : 0.21 UFP: 0.24 PM <sub>2.5</sub> water soluble metals: 0.00 PM <sub>2.5</sub> sulfate: 0.08 PM <sub>2.5</sub> acidity: -0.03 PM <sub>2.5</sub> OC: 0.18 PM <sub>2.5</sub> EC: 0.20 Oxygenated HCs: 0.14 O <sub>3</sub> : 0.19 CO: 0.26 NO <sub>2</sub> : 0.34 Copollutant models: none

**Table 5-14 (Continued): Study specific details and mean and upper percentile concentrations from respiratory disease hospital admission and emergency department visit studies conducted in the U.S. and Canada and evaluated in the 2008 SO<sub>x</sub> ISA and studies published since the 2008 SO<sub>x</sub> ISA.**

Study	Location Years	Exposure Assignment	Metric	Mean Concentration (ppb)	Upper Percentile of Concentrations (ppb)	Copollutants Examined
<a href="#">Tolbert et al. (2007)</a>	Atlanta, GA (1993–2004)	Average of SO <sub>2</sub> concentrations from monitors for several monitoring networks	1-h max	14.9	75th: 20.0 90th: 35.0	Correlations ( <i>r</i> ): PM <sub>10</sub> : 0.21 O <sub>3</sub> : 0.21 NO <sub>2</sub> : 0.36 CO: 0.28 PM <sub>10-2.5</sub> : 0.16 PM <sub>2.5</sub> : 0.17 PM <sub>2.5</sub> SO <sub>4</sub> : 0.09 PM <sub>2.5</sub> EC: 0.22 PM <sub>2.5</sub> OC: 0.17 PM <sub>2.5</sub> TC: 0.19 PM <sub>2.5</sub> water soluble metals: 0.06 Organic hydrocarbon: 0.05 Copollutant models: none
<a href="#">Wilson et al. (2005)</a>	Portland, ME Manchester, NH (1996–2000)	SO <sub>2</sub> concentrations from one monitor in each city	24-h avg	Portland: 11.1 Manchester: 16.5	NR	Correlation ( <i>r</i> ): Portland O <sub>3</sub> : 0.05 Manchester O <sub>3</sub> : 0.01 Copollutant models: none

CO = carbon monoxide; COH = coefficient of haze; EC = elemental carbon; H<sup>+</sup> = hydrogen ion; HC = hydrocarbon; OC = organic carbon; NO<sub>2</sub> = nitrogen dioxide; NR = not reported; O<sub>3</sub> = ozone; PM<sub>10</sub> = particulate matter with a nominal aerodynamic diameter less than or equal to 10 µm; PM<sub>2.5</sub> = particulate matter with a nominal aerodynamic diameter less than or equal to 2.5 µm; PM<sub>10-2.5</sub> = particulate matter with a nominal aerodynamic diameter less than or equal to 10 µm and greater than a nominal 2.5 µm; *r* = correlation coefficient; SO<sub>2</sub> = sulfur dioxide; SO<sub>4</sub> = sulfate; TC = total hydrocarbon; UFP = ultrafine particle.

† studies published since the 2008 SO<sub>x</sub> ISA.

## Hospital Admissions

1 A recent multicity study conducted in Korea ([Son et al., 2013](#)) and a single-city study  
2 conducted in Hong Kong ([Wong et al., 2009](#)) provide additional insight into the  
3 relationship between short-term SO<sub>2</sub> exposures and hospital admissions for all respiratory  
4 diseases.

5 [Son et al. \(2013\)](#) examined the association between short-term exposures to air pollution  
6 and respiratory-related hospital admissions in eight South Korean cities. It is important to  
7 note that South Korea has unique demographic characteristics with some indicators more  
8 in line with other developed countries (e.g., life expectancy, percent of population living  
9 in urban areas), but because it represents a rapidly developing Asian country, it is likely  
10 to have different air pollution, social, and health patterns than less industrialized Asian  
11 nations or Western nations that developed earlier ([Son et al., 2013](#)). In a time-series  
12 analysis using a two-stage Bayesian hierarchical model, [Son et al. \(2013\)](#) examined both  
13 single-day lags and multiday lags up to 3 days (i.e., lag 0–3). For a lag of 0–3 days the  
14 authors reported a 5.6% increase (95% CI: 1.4, 10.0) in respiratory disease hospital  
15 admissions for a 10-ppb increase in 24-h avg SO<sub>2</sub> concentrations. The authors did not  
16 conduct copollutant analyses; however, SO<sub>2</sub> was found to be moderately correlated with  
17 PM<sub>10</sub> ( $r = 0.5$ ), NO<sub>2</sub> ( $r = 0.6$ ), and CO ( $r = 0.6$ ). The results of [Son et al. \(2013\)](#) add  
18 additional support to the results from the multicity studies evaluated in the 2008 SO<sub>x</sub> ISA  
19 [i.e., ([Cakmak et al. \(2006\)](#); [Dales et al. \(2006\)](#))] in terms of the lag in which the strongest  
20 associations were observed and the magnitude of the association ([Figure 5-9](#)).

21 A greater degree of variability in the magnitude of the association between short-term  
22 SO<sub>2</sub> exposures and all respiratory hospital admissions was observed when evaluating  
23 single-city studies in the 2008 SO<sub>x</sub> ISA ([Figure 5-9](#)). [Wong et al. \(2009\)](#) in a study  
24 conducted in Hong Kong reported results consistent with these earlier single-city studies  
25 for individuals over the age of 65 [1.0% (95% CI: -0.8, 2.8) for a 10-ppb increase in  
26 24-h avg SO<sub>2</sub> concentrations at lag 0–1]. However, compared to studies that examined all  
27 ages, the magnitude of the association was much smaller [0.8% (95% CI: -0.6, 2.3) for a  
28 10-ppb increase in 24-h avg SO<sub>2</sub> concentrations at lag 0–1]. [Wong et al. \(2009\)](#) also  
29 examined acute respiratory disease, which represents a smaller subset of outcomes within  
30 all respiratory diseases. When focusing on only acute respiratory disease, [Wong et al.](#)  
31 [\(2009\)](#) reported no evidence of an association at a 0–1 day lag for all ages [-2.0% (95%  
32 CI: -4.4, 0.4) for a 10-ppb increase in 24-h avg SO<sub>2</sub> concentrations].

33 The all-respiratory-disease hospital admissions results of [Son et al. \(2013\)](#) and [Wong et](#)  
34 [al. \(2009\)](#) are supported by the results of a meta-analysis conducted by [Atkinson et al.](#)  
35 [\(2012\)](#) that focused on studies conducted in Asian cities since 1980. The six estimates

1 from studies that examined the association between SO<sub>2</sub> and all respiratory hospital  
2 admissions were included in a random effects model, which yielded a 1.3% increase in  
3 respiratory hospital admissions (95% CI: -0.4, 3.2) for a 10-ppb increase in 24-h avg SO<sub>2</sub>  
4 concentrations. However, [Atkinson et al. \(2012\)](#) found some evidence of publication bias  
5 for associations between SO<sub>2</sub> and respiratory hospital admissions.

### Emergency Department Visits

6 The 2008 SO<sub>x</sub> ISA evaluated a few studies that examined the association between  
7 short-term SO<sub>2</sub> exposures and all respiratory ED visits [[Figure 5-9](#), Supplemental  
8 Table 5S-8 ([U.S. EPA, 2016o](#))]. These studies reported evidence of a positive  
9 association, but the magnitude of the association varied across study locations. However,  
10 these studies were limited in that they did not examine copollutant confounding. Recent  
11 studies that examined the association between air pollution and all respiratory ED visits  
12 have not examined associations with SO<sub>2</sub>.

### Model Specification—Sensitivity Analyses

13 A question that often arises when evaluating studies that examine the association between  
14 air pollution and a health effect is whether the statistical model employed adequately  
15 controls for the potential confounding effects of temporal trends and meteorological  
16 conditions. [Son et al. \(2013\)](#), in the study of eight South Korean cities, conducted  
17 sensitivity analyses to identify whether risk estimates changed depending on the df used  
18 to control for temporal trends and meteorological covariates (i.e., temperature, humidity,  
19 and barometric pressure). The authors reported that the association between short-term  
20 SO<sub>2</sub> exposures and all of the respiratory hospital admission outcomes examined (i.e., all  
21 respiratory diseases, allergic disease, and asthma) was sensitive to using less than 7 df per  
22 year, indicating inadequate control for temporal trends, but was stable when using  
23 7–10 df per year. These results suggest that at least 7 df per year are needed to adequately  
24 account for temporal trends when examining the relationship between short-term SO<sub>2</sub>  
25 exposures and respiratory disease hospital admissions. However, additional studies have  
26 not systematically examined this issue for SO<sub>2</sub>.

27 In an additional sensitivity analysis focusing on meteorological covariates  
28 (i.e., temperature, relative humidity, and barometric pressure), [Son et al. \(2013\)](#) examined  
29 whether risk estimates were sensitive to the degree of smoothing used and to the lag  
30 structure. The authors found that when varying the number of df for each covariate from  
31 3 to 6 df and varying the lag structure (i.e., lag 0 and lag 0–3 days), the SO<sub>2</sub> association  
32 remained robust for all respiratory hospital admission outcomes.

## Lag Structure of Associations

1 As stated previously, when examining associations between air pollution and a specific  
2 health outcome, it is informative to assess whether there is a specific exposure window  
3 for SO<sub>2</sub> that results in the strongest association with the health outcome of interest. In the  
4 examination of all respiratory disease hospital admissions, [Son et al. \(2013\)](#) focused on  
5 both single-day and multiday lags to address whether there is evidence of an immediate  
6 or persistent effect of SO<sub>2</sub>. Across single-day lags of 0 to 3 days, positive associations  
7 were observed across each lag with the magnitude of the association being relatively  
8 similar across each lag (i.e., 2.4% for lag 0 and 2.1% for lags 1 to 3 days for a 10-ppb  
9 increase in 24-h avg SO<sub>2</sub> concentrations). When examining multiday lags of 0–1, 0–2,  
10 and 0–3 days, the authors reported an increase in the magnitude of the association as the  
11 length of the multiday lag increased with a 3.5% increase reported at lag 0–1 and a 5.6%  
12 increase reported for lag 0–3 days. Therefore, the limited evidence suggests that SO<sub>2</sub>  
13 effects occur within the first few days after exposure, but also that SO<sub>2</sub> effects on  
14 respiratory disease hospital admissions may persist over several days.

## Examination of Seasonal Differences

15 Of the studies that examined all respiratory disease hospital admissions or ED visits, only  
16 [Son et al. \(2013\)](#) in the analysis of eight South Korean cities examined potential seasonal  
17 differences in SO<sub>2</sub> associations. However, it is important to note the potential influence of  
18 geographic location on the results from studies that examine potential seasonal  
19 differences in associations. For all outcomes examined, including respiratory diseases,  
20 the association with SO<sub>2</sub> was largest in magnitude during the summer, although  
21 confidence intervals were quite large [respiratory diseases: 21.5% (95% CI: –0.7, 48.3),  
22 lag 0–3, for a 10-ppb increase in 24-h avg SO<sub>2</sub> concentrations] with additional evidence  
23 of a positive association in the fall [8.9% (95% CI: –1.4, 20.7), lag 0–3, for a 10-ppb  
24 increase in 24-h avg SO<sub>2</sub> concentrations]. There was no evidence of an association  
25 between short-term SO<sub>2</sub> exposures and respiratory disease hospital admissions in either  
26 the spring or winter seasons. Across the eight cities, mean 24-h avg SO<sub>2</sub> concentrations  
27 were lowest during the summer season (4.4 ppb compared to a range of 4.8 to 7.0 in the  
28 other seasons) as was also the case for NO<sub>2</sub> and CO.

## Summary of Aggregate Respiratory Conditions

29 Recent studies add to the evidence detailed in the 2008 SO<sub>x</sub> ISA that indicated a  
30 generally positive association between short-term SO<sub>2</sub> exposures and respiratory disease  
31 hospital admissions and ED visits ([Figure 5-9](#)). These recent studies provide some insight

1 into previously identified limitations (i.e., model specification, lag structure of  
2 associations, and potential seasonal differences) in the SO<sub>2</sub>-respiratory disease hospital  
3 admission and ED visits relationship. Initial evidence from a limited number of studies  
4 suggests that SO<sub>2</sub> associations are robust to alternative model specifications for weather  
5 covariates and that SO<sub>2</sub> associations are relatively stable in the range of df per year  
6 indicative of reasonable control for temporal trends (i.e., 7–10 df per year); however,  
7 more studies are needed to confirm these findings. Additionally, an examination of the  
8 lag structure of associations is in line with the results reported in studies that focused on  
9 a priori lags [i.e., associations tend to be strongest within the first few days after  
10 exposure, primarily within the range of 0 to 3 days ([Figure 5-9](#))]. The potential seasonal  
11 patterns in SO<sub>2</sub> associations remain unclear due to the variability in SO<sub>2</sub> associations  
12 observed across different geographic locations, as reflected in studies of other respiratory  
13 hospital admission and ED visit outcomes. Some studies have also examined whether  
14 there is evidence that specific factors modify the SO<sub>2</sub>-respiratory disease hospital  
15 admission or ED visit relationship and have found some evidence for potential  
16 differences by lifestage and influenza intensity (see [Chapter 6](#)). Studies of all respiratory  
17 hospital admissions and ED visits have not conducted extensive analyses to examine  
18 potential copollutant confounding. However, studies that reported SO<sub>2</sub> correlations with  
19 other pollutants found low ( $r < 0.4$ ) to moderate ( $r = 0.4$ – $0.7$ ) correlations. Overall, the  
20 results of recent studies are limited in that they do not further inform the understanding of  
21 potential confounding by copollutants on the relationship between short-term SO<sub>2</sub>  
22 concentrations and respiratory disease hospital admissions and ED visits.

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### 5.2.1.7 Respiratory Effects in General Populations and Healthy Individuals

23 The 2008 SO<sub>x</sub> ISA ([U.S. EPA, 2008d](#)) reported respiratory effects of SO<sub>2</sub> in general  
24 populations and healthy individuals but did not make specific conclusions about the  
25 relationship. Respiratory effects were demonstrated in healthy individuals following SO<sub>2</sub>  
26 exposures  $\geq 1.0$  ppm in controlled human exposure studies. Animal toxicological studies  
27 demonstrated bronchoconstriction after a single SO<sub>2</sub> exposure and increased airway  
28 responsiveness and inflammation after repeated SO<sub>2</sub> exposures. Epidemiologic evidence  
29 was weak. The few recent toxicological studies corroborate previous results, but recent  
30 epidemiologic and controlled human exposure studies provide inconsistent results,  
31 including new results for pulmonary inflammation.

## Lung Function Changes in General Populations and Healthy Individuals

1 Compared with evidence for lung function changes in individuals with asthma, evidence  
2 for SO<sub>2</sub>-induced lung function effects in healthy individuals is weak. Most of the  
3 controlled human exposure studies evaluating these effects in healthy individuals were  
4 discussed in the 1982 SO<sub>x</sub> AQCD ([U.S. EPA, 1982a](#)). While some studies showed that  
5 transient decreases in lung function can occur at concentrations of 1.0 ppm SO<sub>2</sub> under  
6 exercising or forced oral breathing conditions, the evidence was more consistent for  
7 exposures >1.0 ppm ([U.S. EPA, 2008d](#)). Epidemiologic associations between ambient  
8 SO<sub>2</sub> concentrations and lung function continue to be inconsistent in children. While  
9 recent results indicate associations in adults, inferences about SO<sub>2</sub> exposure still are weak  
10 because of uncertainty in the exposure estimates and copollutant confounding.

### ***Controlled Human Exposure Studies***

11 Evidence from controlled human exposure studies evaluating SO<sub>2</sub>-induced lung function  
12 changes in healthy adults was extensively discussed in the 1982 AQCD ([U.S. EPA,  
13 1982a](#)). In general, these studies demonstrated respiratory effects such as increased  
14 airway resistance and decreased FEV<sub>1</sub> following exposures to concentrations  
15 >1.0–5.0 ppm, while some studies demonstrated respiratory effects at 1.0 ppm.

16 Lung function changes in response to SO<sub>2</sub> exposure in controlled human exposure studies  
17 have been investigated since the early 1950s. Respiratory effects including increased  
18 respiration rates, decrements in peak flow, bronchoconstriction, and increased airway  
19 resistance have been observed in healthy human volunteers at concentrations ≥1.0 ppm  
20 ([Lawther et al., 1975](#); [Andersen et al., 1974](#); [Snell and Luchsinger, 1969](#); [Abe, 1967](#);  
21 [Frank et al., 1962](#); [Sim and Pattle, 1957](#); [Lawther, 1955](#); [Amdur et al., 1953](#)). Although  
22 bronchoconstriction was observed in healthy subjects exposed to concentrations  
23 ≥5.0 ppm, shallow rapid respiration and increased pulse rate, decreased maximum  
24 expiratory flow from one-half vital capacity, and increased sRaw were observed  
25 following exposures as low as 1.0 ppm ([Lawther et al., 1975](#); [Snell and Luchsinger, 1969](#);  
26 [Amdur et al., 1953](#)). Overall, only these few studies have reported SO<sub>2</sub>-induced  
27 respiratory effects in healthy individuals for 5–10-minute exposures at concentrations  
28 ≥1.0 ppm SO<sub>2</sub>.

29 A limited number of studies examined lung function changes in healthy populations in  
30 response to ≥1 hour exposures to SO<sub>2</sub>. Controlled human exposure studies examining  
31 lung function changes in healthy individuals exposed to SO<sub>2</sub> are summarized in  
32 [Table 5-15](#). [Andersen et al. \(1974\)](#) reported that exposures of up to 6 hours to 1.0 ppm  
33 SO<sub>2</sub> in resting healthy adults induced decreases in FEF<sub>25–75</sub> and to a lesser extent FEV<sub>1</sub>.  
34 Another human exposure study ([van Thriel et al., 2010](#)) reported that healthy subjects

1 exposed to SO<sub>2</sub> concentrations of 0.5, 1.0, or 2.0 ppm for 4 hours while exercising did not  
2 show changes in FEV<sub>1</sub>. However, lung function measurements in this study were not  
3 performed between 40–100 minutes after exercise and more sensitive measures such as  
4 shallow rapid respiration or FEF<sub>25–75</sub> were not reported. Healthy individuals at rest or  
5 exercising exhibited no changes in several measures of lung function following a 1 hour  
6 exposure to 0.2–0.6 ppm SO<sub>2</sub> ([Tunnicliffe et al., 2003](#); [Linn et al., 1987](#)).

7 The interaction of SO<sub>2</sub> exposure with O<sub>3</sub> was reported in two studies. [Hazucha and Bates](#)  
8 [\(1975\)](#) demonstrated that a combined 2 hours exposure to low concentrations of O<sub>3</sub>  
9 (0.37 ppm) and SO<sub>2</sub> (0.37 ppm) has a greater effect on lung function than exposure to  
10 either agent alone in exercising adults. However using a similar study design, [Bedi et al.](#)  
11 [\(1979\)](#) did not observe a greater effect of the combined exposures compared with  
12 exposure to only O<sub>3</sub>; exposure to SO<sub>2</sub> alone had no effect.

### ***Epidemiologic Studies***

13 Previous epidemiologic evidence was inconsistent for an association between ambient  
14 SO<sub>2</sub> concentrations and lung function in healthy adults or children and people recruited  
15 from the general population ([U.S. EPA, 2008d](#)). Studies mostly estimated SO<sub>2</sub> exposure  
16 from central site monitors and did not report whether the measurements well captured the  
17 spatiotemporal variability in the study areas. Some recent studies measured SO<sub>2</sub> at  
18 subjects' locations and observed associations with lung function decrements in adults but  
19 not consistently in children. Most studies examined 24-h avg SO<sub>2</sub> concentrations, which  
20 are much longer than the 5–10 minute exposures inducing lung function decrements in  
21 experimental studies. Inconsistency also is observed among recent results for temporally  
22 resolved metrics such as 1-h max and 1- to 10-h avg SO<sub>2</sub> concentrations, which is similar  
23 to controlled human exposure findings for 1- to 6-hour exposures to SO<sub>2</sub>.

24 **Adults.** Among previous studies, an SO<sub>2</sub>-associated decrease in lung function was  
25 observed in adults in Beijing, China where coal was used for domestic heating ([Xu et al.,](#)  
26 [1991](#)). Recent results are based on much lower SO<sub>2</sub> concentrations [means 7.3–8.6 ppb  
27 vs. 6.8–49 ppb in [Xu et al. \(1991\)](#)]. Associations are observed with lung function  
28 decrements in adults without respiratory disease ([Table 5-16](#)), with some based on  
29 relatively good exposure characterization ([Dales et al., 2013](#)).

**Table 5-15 Study-specific details from controlled human exposure studies of lung function and respiratory symptoms in healthy adults.**

Reference	Disease Status; n; Sex; Age (mean ± SD)	Exposure Details (Concentration; Duration)	Endpoints Examined
<a href="#">Andersen et al. (1974)</a>	Healthy; n = 15; 15 M; 20–28 yr	0, 1, 5, or 25 ppm SO <sub>2</sub> for 6 h at rest	Nasal mucociliary flow Area of the nasal airway Airway resistance (FEV <sub>1</sub> , FEF <sub>25–75%</sub> ) Nasal removal of SO <sub>2</sub> Discomfort level symptoms
<a href="#">Linn et al. (1987)</a>	Healthy; n = 24; 15 M, 9 F; 18–37 yr	0, 0.2, 0.4, or 0.6 ppm SO <sub>2</sub> 1 h exposures 3 × 10-min exercise (bicycle) periods ~40 L/min Exposures were repeated for a total of eight	Lung function measure pre-exposure, ~15 min, and ~55 min into exposure sRaw, FVC, FEV <sub>1</sub> , peak expiratory flow rate, maximal mid expiratory flow rate Continuously EKG Midway-HR Before, during, 1-d after, and 1 wk after-symptom score, self-rated activity Immediately after exposure-bronchial reactivity percent change in FEV induced by 3 min normocapnic hyperpnea with cold, dry air
<a href="#">Raulf-Heimsoth et al. (2010)</a>	Healthy; n = 16; 8 M, 8 F; 19–36 yr	0, 0.5, 1.0, or 2.0 SO <sub>2</sub> for 4 h with exercise for 15 min (bicycle, 75 Watts) two times during each session	Exhaled NO, biomarkers of airway inflammation in EBC and NALF
<a href="#">Tunnicliffe et al. (2003)</a>	Asthma; n = 12 adults, 35.7 yr Healthy; n = 12 adults, 34.5 yr	0 or 0.2 ppm SO <sub>2</sub> for 1 h at rest	Symptoms, FEV <sub>1</sub> , FVC, MMEF, exhaled NO, ascorbic and uric acid in nasal lavage fluid
<a href="#">van Thriel et al. (2010)</a>	Healthy; n = 16; 8 M, 8 F; M: 28.4 ± 3.9 yr, F: 24.3 ± 5.2 yr	0, 0.5, 1.0, or 2.0 ppm SO <sub>2</sub> for 4 h with exercise for 15 min (bicycle, 75 Watts) two times during each session	Symptoms, FEV <sub>1</sub>

EBC = exhaled breath condensate; EKG = electrocardiogram; F = female; FEF<sub>25–75%</sub> = forced expiratory flow at 25–75% of exhaled volume; FEV = forced expiratory volume; FEV<sub>1</sub> = forced expiratory volume in 1 sec; FVC = forced vital capacity; HR = heart rate; M = male; MMEF = maximum midexpiratory flow; n = sample size; NALF = nasal lavage fluid; NO = nitric oxide; SD = standard deviation; SO<sub>2</sub> = sulfur dioxide; sRaw = specific airway resistance.

1 The exposure characterization of [Dales et al. \(2013\)](#) is judged to be good because SO<sub>2</sub>  
2 was measured on site of adults’ scripted exposures near (0.87 km) and away from  
3 (4.5 km at a college campus) a steel plant in Ontario. Another strength was the  
4 well-defined 8-hour exposure duration and lag between exposure and lung function  
5 testing. Higher SO<sub>2</sub> concentrations averaged over 10 hours (8 a.m.–6 p.m.) were

1 associated with decreases in several lung function parameters measured just after  
2 exposure ([Table 5-16](#)). For example, a 10-ppb increase in SO<sub>2</sub> was linked to a -0.50%  
3 FEV<sub>1</sub> change (95% CI: -1.0, 0.05). [Son et al. \(2010\)](#) also examined air pollution from  
4 industry, in this case a petrochemical complex in Ulsan, South Korea. Ambient SO<sub>2</sub>  
5 concentrations across the study area were highly variable. Between-monitor correlation  
6 varied widely (0–0.8), even for those 5 km apart, and the mean decreased from about 0.4  
7 to 0.2 with increasing distance up to 20 km. Investigators aimed to capture this  
8 spatiotemporal variability by combining SO<sub>2</sub> measurements across monitors with inverse  
9 distance weighting or kriging. These metrics and that for the nearest monitor to the  
10 subjects' home, all 24-h avg SO<sub>2</sub>, were associated with FVC but not FEV<sub>1</sub> ([Table 5-16](#)).  
11 The implications overall are unclear because many subjects lived far from a monitor, and  
12 potential confounding by meteorological factors and season were not considered. Both  
13 studies observed associations with copollutants among PM<sub>2.5</sub>, PM<sub>10</sub>, UFP, CO, NO<sub>2</sub>, and  
14 O<sub>3</sub>. Correlations among copollutants and analyses of confounding or interactions were  
15 not reported for personal exposures near the steel plant ([Dales et al., 2013](#)). For the study  
16 near the petrochemical complex, the decrease in FEV<sub>1</sub> for kriged SO<sub>2</sub> was larger after CO  
17 adjustment ([Son et al., 2010](#)) ([Table 5-16](#)). The effect estimate for CO became null, but  
18 the range of between-monitor correlations was 0–0.8. The effect estimate for SO<sub>2</sub> was  
19 attenuated with adjustment for O<sub>3</sub>, which could be influenced by differential exposure  
20 measurement error. Between-monitor correlations were 0.4 to 0.8 for O<sub>3</sub>.

21 Other studies reported SO<sub>2</sub>-associated lung function decrements, but inference about SO<sub>2</sub>  
22 is weaker ([Steinvil et al., 2009](#); [Min et al., 2008a](#)). Associations were observed for SO<sub>2</sub>  
23 after adjustment for NO<sub>2</sub> or CO, but correlations with SO<sub>2</sub> were 0.62–0.70, and  
24 single-pollutant associations for SO<sub>2</sub> were in opposing directions across lags and limited  
25 to lags of 3 or more days ([Steinvil et al., 2009](#)). Associations were observed with 1-h avg  
26 SO<sub>2</sub> concentrations lagged 5–30 hours, but confounding by meteorological factors was  
27 not considered ([Min et al., 2008a](#)). Also, both studies had cross-sectional design and  
28 estimated SO<sub>2</sub> exposure from monitors up to 11 km or unspecified distance from homes.

29 **Children.** Similar to previous studies, many recent studies of children examined  
30 populations with high prevalence (8–35%) of respiratory disease, such as asthma, and  
31 populations outside the U.S. and Canada. As examined in several recent studies, SO<sub>2</sub> at  
32 schools was inconsistently associated with lung function ([Table 5-17](#)). Previously,  
33 1-h max SO<sub>2</sub> concentrations at school were not associated with lung function. Additional  
34 results for temporally resolved SO<sub>2</sub> metrics, both school and central site, are inconsistent.

**Table 5-16 Recent epidemiologic studies of lung function in healthy adults and adults in the general population.**

Study Population and Methodological Details	SO <sub>2</sub> Exposure Estimates (ppb)	SO <sub>2</sub> Averaging Time and Lag Day	Effect Estimate (95% CI) Single-Pollutant Model <sup>a</sup>	Copollutant Examination <sup>a</sup>
<p>†<a href="#">Dales et al. (2013)</a>                      Sault Ste. Marie, ON, May–Aug 2010                      N = 61, mean age 24 yr. 100% healthy.                      Cross-over, with scripted outdoor exposures near and away from steel plant. Five consecutive 8-h days at each site, with 9-d washout period in between. Supervised spirometry. Recruited from university. Required not to live in neighborhood bordering steel plant.</p>	<p>Monitor on site of outdoor exposures                      Mean (SD)                      Near steel plant 7.8 (13)                      College campus 1.6 (4.2)</p>	<p>10-h avg                      (8 a.m.–6 p.m.)                      Lag 0 h</p>	<p>Percent change                      FEV<sub>1</sub>: -0.50 (-1.0, 0.05)                      FVC: -0.45 (-1.1, 0.19)                      FEV<sub>1</sub>/FVC: -0.15 (-0.31, 0.01)                      FEF<sub>25–75%</sub>: -0.44 (-0.74, -0.14)                      Total lung capacity                      -0.42 (-0.70, -0.13)                      Residual volume                      -2.1 (-4.1, -0.18)</p>	<p>No copollutant model                      Associations observed with PM<sub>2.5</sub>, UFP, NO<sub>2</sub>, and O<sub>3</sub>. All pollutants higher at steel plant than at college campus.                      Copollutant correlations NR.</p>
<p>†<a href="#">Son et al. (2010)</a>                      Ulsan, South Korea, 2003–2007                      N = 2,102, ages 7–97 yr. Mean age 45 yr. Mean percent predicted FEV<sub>1</sub> 83%.                      Cross-sectional. Supervised spirometry. Recruited from a meeting of residents near a petrochemical complex. Did not examine confounding by meteorological factors or season.</p>	<p>13 monitors in city                      Mean (SD), 75th percentile, max                      Kriging                      8.3 (4.4), 9.6, 25                      Nearest monitor                      7.3 (5.9), 9.5, 34                      IDW                      8.4 (5.3), 11, 29                      Average of 13 monitors                      8.6 (4.1), 10, 24</p>	<p>24-h avg                      0–2 avg</p>	<p>Change in percent predicted FVC                      Kriging                      -6.2 (-8.2, -4.2)                      IDW                      -5.3 (-7.1, -3.5)                      Nearest monitor                      -5.6 (-7.4, -3.9)                      Average of 13 monitors                      -7.0 (-9.0, -4.8)                      FEV<sub>1</sub>                      Kriging                      -0.08 (-0.76, 0.60)                      IDW                      0.31 (-0.32, 0.95)                      Nearest monitor                      0.35 (-0.21, 0.92)                      Average of 13 monitors                      -0.15 (-0.89, 0.58)</p>	<p>Copollutant model, lag 0–2 avg FVC                      Kriging                      with O<sub>3</sub>: -1.8 (-4.0, 0.46)                      with CO: -8.8 (-11, -6.3)                      O<sub>3</sub> association persists with SO<sub>2</sub> adjustment. CO association attenuated. Association also observed with PM<sub>10</sub> and NO<sub>2</sub> but no copollutant model. PM<sub>2.5</sub> not examined.                      Copollutant correlations NR.</p>

**Table 5-16 (Continued): Recent epidemiologic studies of lung function in healthy adults and adults in the general population.**

Study Population and Methodological Details	SO <sub>2</sub> Exposure Estimates (ppb)	SO <sub>2</sub> Averaging Time and Lag Day	Effect Estimate (95% CI) Single-Pollutant Model <sup>a</sup>	Copollutant Examination <sup>a</sup>
<a href="#">†Steinvil et al. (2009)</a> Tel Aviv, Israel, 2002–2007 N = 2,380, mean age 43 yr. 100% healthy. Cross-sectional. Supervised spirometry. Recruited from ongoing survey of individuals attending health center.	Three monitors within 11 km of home Mean (SD): 2.8 (1.2) 75th percentile: 3.4 Max: 9.4	24-h avg	Change in FEV <sub>1</sub> (mL)	Copollutant model, lag 5, FEV <sub>1</sub> (mL) with O <sub>3</sub> : -220 (-413, -33) with NO <sub>2</sub> : -280 (-527, -33) with CO: -247 (-473, -20) NO <sub>2</sub> and CO association attenuated with SO <sub>2</sub> adjustment. No association with O <sub>3</sub> . SO <sub>2</sub> highly correlated with NO <sub>2</sub> , moderately correlated with CO, weakly correlated with O <sub>3</sub> . <i>r</i> = 0.70, 0.62, -0.24.
		0	93 (-90, 277)	
		5	-300 (-487, -113)	
		0–6 avg	-447 (-750, -143)	
		0	Change in FVC (mL)	
		5	53 (-167, 273)	
		0–6 avg	-373 (-600, -147)	
<a href="#">†Min et al. (2008a)</a> South Korea, 2006 N = 867, ages 20–86 yr. 100% no serious medical conditions. Cross-sectional. Supervised spirometry. Recruitment not described. Did not examine confounding by meteorological factors.	Monitors in city Number and distance NR Mean: 6	1-h avg	Results presented only in figure. No copollutants examined.	
		Lag 1 h	Associations observed only in smokers. FEV <sub>1</sub> and FVC decrease after lag of 5–6 h. No association after 30 h.	
		0	Percent change in FEV <sub>1</sub> /FVC	
		0–6 avg	716 (-6.5, 4,233)	
		5	237 (-79, 2,195)	
		0–6 avg	220 (-217, 657)	

CI = confidence interval; CO = carbon monoxide; FEF<sub>25–75%</sub> = forced expiratory flow at 25–75% of forced vital capacity; FEV<sub>1</sub> = forced expiratory volume in 1 sec; FVC = forced vital capacity; IDW = inverse distance weighting; max = maximum; mL = millilitres; N = sample size; NO<sub>2</sub> = nitrogen dioxide; NR = not reported; *r* = correlation coefficient; O<sub>3</sub> = ozone; PM<sub>2.5</sub> = particulate matter with nominal aerodynamic diameter less than or equal to 2.5 µm; PM<sub>10</sub> = particulate matter with nominal aerodynamic diameter less than or equal to 10 µm; SD = standard deviation; SO<sub>2</sub> = sulfur dioxide, UFP = ultrafine particles.

<sup>a</sup>Effect estimates are standardized to a 10-ppb increase in 1-h to 24-h avg SO<sub>2</sub>.

†Studies published since the 2008 Integrated Science Assessment for Sulfur Oxides.

**Table 5-17 Recent epidemiologic studies of lung function in healthy children and children in the general population.**

Study Population and Methodological Details	SO <sub>2</sub> Exposure Estimates (ppb)	SO <sub>2</sub> Averaging Time and Lag Day	Effect Estimate (95% CI) Single-Pollutant Model <sup>a</sup>	Copollutant Examination <sup>a</sup>
<p><a href="#">†Correia-Deur et al. (2012)</a>            São Paolo, Brazil, Apr–Jul 2004            N = 31, ages 9–11 yr. 100% no allergic sensitization.            Daily measures for 15 d. Supervised spirometry. Recruited from schools.</p>	<p>Monitor at school            Mean (SD): 8.8 (3.3)            75th percentile: 11            90th percentile: 13</p>	<p>2-h avg            0            24-h avg            0</p>	<p>Percent change in PEF            –0.24 (–0.96, 0.49)            –0.20 (–1.4, 0.96)            No association for 3-, 5-, 7-, or 10-d avg</p>	<p>Copollutant model for group that included 65 children with atopy.            SO<sub>2</sub> association near null with adjustment for PM<sub>10</sub>, NO<sub>2</sub>, or CO.            SO<sub>2</sub> highly correlated with PM<sub>10</sub>, moderately correlated with NO<sub>2</sub> &amp; CO. Pearson <i>r</i> = 0.75, 0.60, 0.60</p>
<p><a href="#">†Altuğ et al. (2014)</a>            Eskisehir, Turkey, Feb–Mar 2007            N = 535, ages 9–13 yr            Cross-sectional. Supervised spirometry. Recruited from schools from participants of a larger study.</p>	<p>Monitor at school            Mean and max            Suburban: 21, 29            Urban: 29, 44            Urban-traffic: 22, 27</p>	<p>24-h avg            0–6 avg</p>	<p>Relative ratio for change            Subjects without URS            FVC: 1.00 (0.97, 1.03)            FEV<sub>1</sub>: 1.00 (0.97, 1.03)            PEF: 1.00 (0.97, 1.03)            MMEF: 1.00 (0.92, 1.08)</p> <hr/> <p>Subjects with URS            FVC: 1.00 (0.97, 1.03)            FEV<sub>1</sub>: 1.00 (0.97, 1.03)            PEF: 1.00 (0.97, 1.03)            MMEF: 1.03 (0.95, 1.11)</p>	<p>No copollutant model            No association with O<sub>3</sub> or NO<sub>2</sub>.            PM<sub>2.5</sub> and PM<sub>10</sub> not examined.            SO<sub>2</sub> moderately correlated with NO<sub>2</sub>, negatively correlated with O<sub>3</sub> in winter. <i>r</i> = 0.49, –0.40.</p>

**Table 5-17 (Continued): Recent epidemiologic studies of lung function in healthy children and children in the general population.**

Study Population and Methodological Details	SO <sub>2</sub> Exposure Estimates (ppb)	SO <sub>2</sub> Averaging Time and Lag Day	Effect Estimate (95% CI) Single-Pollutant Model <sup>a</sup>	Copollutant Examination <sup>a</sup>
<p><a href="#">†Altuğ et al. (2013)</a> Eskisehir, Turkey, Jan 2008–Mar 2009 N = 1,880, 9–13 yr. 7% asthma. 11% hay fever Two measures: summer and winter. Supervised spirometry. Recruited from schools. Did not examine confounding by meteorological factors.</p>	<p>Monitor at school Mean and max Summer Suburban: 8.5, 16 Urban: 10, 16 Urban-traffic: 6.3, 8.9 Winter Suburban: 21, 29 Urban: 29, 44 Urban-traffic: 22, 33</p>	<p>24-h avg 0–6 avg</p>	<p>OR for impaired lung function (predicted values &lt;85% for FEV<sub>1</sub> or FVC or &lt;75% for PEF or MMEF) Summer Girls: 1.22 (0.72, 2.09) Boys: 0.83 (0.47, 1.45) Winter Girls: 1.00 (0.76, 1.32) Boys: 0.83 (0.61, 1.11)</p>	<p>Copollutant model, girls, summer with O<sub>3</sub>: 1.08 (0.63, 1.91) with NO<sub>2</sub>: 1.14 (0.65, 1.99) O<sub>3</sub> association persists with SO<sub>2</sub> adjustment. No association for NO<sub>2</sub> overall. PM<sub>2.5</sub> and PM<sub>10</sub> not examined. SO<sub>2</sub> moderately correlated with NO<sub>2</sub> and negatively correlated with O<sub>3</sub> in winter. <i>r</i> = 0.49, -0.40. Summer correlations NR.</p>
<p><a href="#">†Castro et al. (2009)</a> Rio de Janeiro, Brazil, 2004 N = 118, ages 6–15 yr. 18% asthma. Daily measures for 6 wk. Supervised PEF. Recruited from schools.</p>	<p>Monitor at school Mean (SD): 7.1 (6.8) 90th percentile: 16 Max: 37</p>	<p>24-h avg 1 2 3 0–1 avg 0–2 avg</p>	<p>Change in PEF (L/min) -0.73 (-2.5, 0.99) -0.99 (-2.6, 0.61) 0.34 (-1.1, 1.8) -1.8 (-3.8, 0.17) -1.5 (-3.4, 0.46)</p>	<p>No copollutant model Associations observed with PM<sub>10</sub> and CO but not NO<sub>2</sub>. PM<sub>2.5</sub> not examined. Copollutant correlations NR.</p>
<p><a href="#">†Chang et al. (2012b)</a> Taipei, Taiwan, 1996–1997 N = 2,919, ages 12–16 yr. Cross-sectional. Supervised spirometry. Recruited from schools.</p>	<p>Five monitors averaged within 2 km of schools Means across districts 4-h avg (8 a.m.–12 p.m.): 4.6–10 10-h avg (8 a.m.–6 p.m.): 1.8–5.4 1-h max: 5.9–35</p>	<p>4-h avg 0 10-h avg 1 1-h max 0 1</p>	<p>Change in FEV<sub>1</sub> (mL) 0.4 (-32, 33) -117 (-193, -42) 3.6 (-21, 28) -85 (-129, -41)</p>	<p>No copollutant model Associations observed with PM<sub>10</sub>, NO<sub>2</sub>, CO, O<sub>3</sub>. PM<sub>2.5</sub> not examined. Copollutant correlations NR.</p>

**Table 5-17 (Continued): Recent epidemiologic studies of lung function in healthy children and children in the general population.**

Study Population and Methodological Details	SO <sub>2</sub> Exposure Estimates (ppb)	SO <sub>2</sub> Averaging Time and Lag Day	Effect Estimate (95% CI) Single-Pollutant Model <sup>a</sup>	Copollutant Examination <sup>a</sup>
<p>†<a href="#">Linares et al. (2010)</a>                      Salamanca, Mexico, Mar 2004–Feb 2005                      N = 464, ages 6–14 yr. 0.6% asthma.                      Daily measures for 20 d in each season.                      Supervised spirometry. Recruited from schools</p>	<p>Monitors within 2 km of school                      Means spring–winter                      School 1: 12, 12, 10, 9.8                      School 2: 9.1, 8.7, 10, 13</p>	<p>24-h avg                      0</p>	<p>Units not reported                      FVC: -0.06 (-0.13, 0)                      FEV<sub>1</sub>: -0.01 (-0.01, -0.00)                      PEF: -0.03 (-0.05, 0)                      FEV<sub>1</sub>/FVC: -0.07 (-0.18, 0.03)</p>	<p>No copollutant model                      Associations observed with PM<sub>10</sub> and O<sub>3</sub> but not NO<sub>2</sub>. PM<sub>2.5</sub> not examined.                      Copollutant correlations NR.</p>
<p>†<a href="#">Reddy et al. (2012)</a>                      Durban, South Africa, 2004–2005                      N = 129, ages 9–11 yr. 37% asthma.                      Daily measures for 3 wk each season.                      Supervised spirometry. Recruited from schools. Did not examine confounding by meteorological factors except season.</p>	<p>Monitor at school                      Mean (SD): 5.8 (0.2)                      Max: 41</p>	<p>24-h avg                      0–4 avg                      3</p>	<p>Percent change FEV<sub>1</sub> diurnal variability (increase = poorer function)                      By <i>GSTM1</i> gene variant                      Null: -1.2 (-3.0, 0.54)                      Positive: 1.1 (0.45, 2.7)                      By <i>GSTP1</i> gene variant                      AG/GG: 3.1 (1.6, 4.7)                      AA: -0.73 (-2.2, 0.70)</p>	<p>No copollutant model                      Association observed with PM<sub>10</sub> in <i>GSTP1</i> AG/GG group. NO<sub>2</sub> association in AA group. PM<sub>2.5</sub> not examined.                      Copollutant correlations NR.</p>
<p>†<a href="#">Makamure et al. (2016a)</a>                      Durban, South Africa, 2004–2005                      N = 71, ages 9–11 yr. 35% asthma.                      Part of the same cohort as <a href="#">Reddy et al. (2012)</a> above.                      Daily measures for 3 wk each season.                      Supervised spirometry. Recruited from schools. Did not examine confounding by meteorological factors except season.</p>	<p>Monitor at school                      Mean (SD): 5.8 (0.2)                      Max: 41</p>	<p>24-h avg                      1</p>	<p>Percent change FEV<sub>1</sub> diurnal variability (increase = poorer function)                      All subjects: 1.6 (-0.03, 3.3)                      By <i>CD14</i> gene variant                      CC: -1.5 (-3.4, -0.37)                      CT/TT: -3.6 (-7.1, -0.17)</p>	<p>No copollutant model                      Association observed with PM<sub>10</sub> in CD14 CC group. No association with NO<sub>2</sub>. PM<sub>2.5</sub> not examined.                      Copollutant correlations NR.</p>

**Table 5-17 (Continued): Recent epidemiologic studies of lung function in healthy children and children in the general population.**

Study Population and Methodological Details	SO <sub>2</sub> Exposure Estimates (ppb)	SO <sub>2</sub> Averaging Time and Lag Day	Effect Estimate (95% CI) Single-Pollutant Model <sup>a</sup>	Copollutant Examination <sup>a</sup>
<a href="#">†Makamure et al. (2016b)</a> Durban, South Africa, 2004–2005 N = 104, ages 9–11 yr. 39% asthma. Part of the same cohort as <a href="#">Reddy et al. (2012)</a> above. Daily measures for 3 wk each season. Supervised spirometry. Recruited from schools. Did not examine confounding by meteorological factors except season.	Monitor at school Mean (SD): 5.8 (0.2) Max: 41	24-h avg	Percent change FEV <sub>1</sub> diurnal variability (increase = poorer function)	No copollutant model Association observed with NO <sub>2</sub> at lag 1 and NO at lag 2. No association with PM <sub>10</sub> in AA/GA group. PM <sub>2.5</sub> not examined. Copollutant correlations NR.
		1	By <i>TNF-α</i> gene variant AA/GA: 2.3 (–0.29, 5.0) GG: 0.83 (–1.32, 3.0)	
		2	AA/GA: 2.7 (0.52, 4.8) GG: 0.24 (–1.19, 1.68)	
		1-h max	All subjects	No copollutant model Association observed with 24-h avg O <sub>3</sub> measured at central site not PM <sub>10</sub> or NO <sub>2</sub> . PM <sub>2.5</sub> not examined. Copollutant correlations NR.
		0	Percent change post 6-min run 43 (–3,787, 3,873)	
24-h avg	Children without asthma			
<a href="#">†Amadeo et al. (2015)</a> Pointe-à-Pitre, Guadeloupe, 2008–2009 N = 354, ages 8–13 yr. 17% asthma. Cross-sectional. Supervised spirometry. Recruited from schools.	Monitors in city Number and distance NR Mean (SD): 1.8 (1.4) Max: 4.9	0–13 avg	Change in prerun PEF (L/min) 18 (–84, 119) Percent change post 6-min run 4.5 (–24, 33)	

CI = confidence interval; CO = carbon monoxide; FEV<sub>1</sub> = forced expiratory volume in 1 sec; FVC = forced vital capacity; MMEF = maximum midexpiratory flow; N = sample size; NO<sub>2</sub> = nitrogen dioxide; NR = not reported; O<sub>3</sub> = ozone; OR = odds ratio; PEF = peak expiratory flow; PM<sub>2.5</sub> = particulate matter with nominal aerodynamic diameter less than or equal to 2.5 μm; PM<sub>10</sub> = particulate matter with nominal aerodynamic diameter less than or equal to 10 μm; *r* = correlation coefficient; SD = standard deviation; SO<sub>2</sub> = sulfur dioxide; TNF-α = tumor necrosis factor-alpha; URS = upper respiratory symptoms.

<sup>a</sup>Effect estimates are standardized to a 10-ppb increase in 1-h to 24-h avg SO<sub>2</sub> or a 40-ppb increase in 1-h max SO<sub>2</sub>.

†Studies published since the 2008 Integrated Science Assessment for Sulfur Oxides.

1 For SO<sub>2</sub> measured at schools, there is no evidence for association with lung function in  
2 groups of children without respiratory disease or symptoms in Turkey or Brazil ([Altuğ et](#)  
3 [al., 2014](#); [Correia-Deur et al., 2012](#)). [Altuğ et al. \(2014\)](#) examined only 1-wk avg SO<sub>2</sub>,  
4 but [Correia-Deur et al. \(2012\)](#) was noteworthy for examining multiple averaging times  
5 and lags (i.e., 3- to 10-day avg). PEF also was measured at school and analyzed with the  
6 preceding 2-h avg SO<sub>2</sub> concentrations. The association was imprecise [−0.24% change  
7 (95% CI: −1.4, 0.96) in PEF per 10-ppb increase in SO<sub>2</sub>]. Another strength of this study  
8 over similar ones is its repeated-measures design and clinical assessment of children’s  
9 respiratory health status. Among the studies of school SO<sub>2</sub>, an association with lung  
10 function was observed in another cohort of children from Brazil ([Castro et al., 2009](#)).  
11 The impact of the 18% of children with asthma on these results is unknown. The effect  
12 estimate was largest for 2-day avg SO<sub>2</sub> concentrations and imprecise for lag 1 and 2  
13 ([Table 5-17](#)). Missing SO<sub>2</sub> concentration data for 52% of days could be one reason for the  
14 imprecision.

15 Some results for SO<sub>2</sub> measured at children’s schools have more ambiguous implication  
16 ([Makamure et al., 2016a, b](#); [Altuğ et al., 2013](#); [Reddy et al., 2012](#)) ([Table 5-17](#)). For  
17 children in Turkey, lung function was analyzed dichotomously based on a cutpoint of 85  
18 or 75% of the predicted value ([Altuğ et al., 2013](#)). Healthy children may not experience  
19 such decrements, and the 7% of the cohort with asthma may influence results. In a South  
20 African cohort, results were in opposing directions across the many comparisons made  
21 among lung function parameters, pollutants, exposure lags, and gene variants ([Makamure](#)  
22 [et al., 2016a, b](#); [Reddy et al., 2012](#)). For example, an association for SO<sub>2</sub> was found in  
23 children with the GSTP1 variant with reduced oxidative metabolism activity but children  
24 with the GSTM1 variant with normal activity ([Table 5-17](#) and [Section 6.4](#)). Confounding  
25 by meteorology was not considered in either cohort.

26 For exposures estimated from central site monitors, lung function associations were  
27 inconsistent for 1-h max SO<sub>2</sub> ([Amadeo et al., 2015](#); [Chang et al., 2012b](#)), which may be  
28 more variable within a community and subject to greater exposure error. For children in  
29 Taiwan, a 40-ppb increase in 1-h max SO<sub>2</sub> lagged 1 day was associated with a −85 mL  
30 (95% CI: −129, −41) change in FEV<sub>1</sub> ([Chang et al., 2012b](#)). SO<sub>2</sub> concentrations were  
31 averaged from five monitors within 2 km of children’s schools. For children in  
32 Guadeloupe, West Indies, the distance to monitors was not reported. Daily 1-h max SO<sub>2</sub>  
33 concentrations were not associated with PEF ([Amadeo et al., 2015](#)). Although PEF was  
34 measured before and after a 6-minute exercise period, which is akin to procedures in  
35 controlled human exposure studies, the SO<sub>2</sub> metric was not likely matched temporally  
36 with PEF measurements. Lung function in populations of children with low or no  
37 prevalence of asthma was inconsistently associated with 24-h avg SO<sub>2</sub> measured at  
38 central site monitors ([Amadeo et al., 2015](#); [Linares et al., 2010](#)), although the null

1 findings are for 13-day avg SO<sub>2</sub> ([Amadeo et al., 2015](#)). Airway responsiveness increased  
2 with increases in 24-h avg SO<sub>2</sub> in a population of children with 8% asthma and 18%  
3 atopy ([Soyseth et al., 1995](#)). SO<sub>2</sub> exposures were estimated from monitors within 2 km of  
4 homes, which is similar to studies observing associations with 24-h avg and 1-h max SO<sub>2</sub>  
5 ([Chang et al., 2012b](#); [Linares et al., 2010](#)).

6 For the few associations observed for SO<sub>2</sub> with lung function or airway responsiveness,  
7 the potential for copollutant confounding or interactions is not addressed, including the  
8 study conducted near an aluminum smelter that also emitted PM ([Soyseth et al., 1995](#)).  
9 Associations were observed for PM<sub>10</sub>, CO, NO<sub>2</sub>, and O<sub>3</sub> measured at schools and central  
10 site monitors, but neither correlations with SO<sub>2</sub> nor copollutant model results were  
11 reported ([Chang et al., 2012b](#); [Linares et al., 2010](#); [Castro et al., 2009](#)). [Altuğ et al. \(2014\)](#)  
12 reported a moderate correlation with NO<sub>2</sub> of 0.49 and observed no association for either  
13 NO<sub>2</sub> or SO<sub>2</sub>. Copollutant models were analyzed for long-term SO<sub>2</sub>, which was not  
14 associated with lung function decrements in single-pollutant models ([Linares et al.,](#)  
15 [2010](#)). Importantly, none of the studies examined PM<sub>2.5</sub>

### ***Animal Toxicological Studies***

16 Lung function was examined in numerous studies reported in the 1982 SO<sub>x</sub> AQCD ([U.S.](#)  
17 [EPA, 1982a](#)) and the 2008 SO<sub>x</sub> ISA ([U.S. EPA, 2008d](#)). The majority of these were  
18 conducted in naive animals rather than in animal models of allergic airway disease.  
19 Bronchoconstriction, indicated by increased pulmonary resistance, was identified as the  
20 most sensitive indicator of lung function effects of acute SO<sub>2</sub> exposure, based on the  
21 observation of increased pulmonary resistance in guinea pigs that were acutely exposed  
22 to 0.16 ppm SO<sub>2</sub> ([U.S. EPA, 2008d, 1982a](#)). The 2008 SO<sub>x</sub> ISA ([U.S. EPA, 2008d](#))  
23 reported a few additional studies conducted at concentrations below 2 ppm. Animal  
24 toxicological studies examining lung function changes in naive animals exposed to SO<sub>2</sub>  
25 are summarized in [Table 5-18](#). Increased pulmonary resistance and decreased dynamic  
26 compliance were observed in conscious guinea pigs exposed to 1 ppm SO<sub>2</sub> for 1 hour  
27 ([Amdur et al., 1983](#)). Effects were seen immediately after exposure and were not present  
28 1 hour post-exposure. No changes in tidal volume, minute volume, or breathing  
29 frequency were found. These same investigators also exposed guinea pigs to 1 ppm SO<sub>2</sub>  
30 for 3 hours/day for 6 days ([Conner et al., 1985](#)). No changes were observed in lung  
31 function or respiratory parameters (i.e., diffusing capacity for CO, functional reserve  
32 capacity, vital capacity, total lung capacity, respiratory frequency, tidal volume,  
33 pulmonary resistance, or pulmonary compliance). In another study, [Barthelemy et al.](#)  
34 [\(1988\)](#) demonstrated a 16% increase in airway resistance following a 45-minute exposure  
35 of anesthetized rabbits to 0.5 ppm SO<sub>2</sub> via an endotracheal tube. This latter exposure is  
36 more relevant to oronasal than to nasal breathing.

**Table 5-18 Study-specific details from animal toxicological studies of lung function.**

Study	Species (Strain); n; Sex; Lifestage/Age or Weight	Exposure Details (Concentration; Duration)	Endpoints Examined
<a href="#">Amdur et al. (1983)</a>	Hartley guinea pig; n = 8-23/group; M; age NR; 200-300 g;	≈1 ppm (2.62 mg/m <sup>3</sup> ); head only for 1 h	Endpoints examined during exposure and up to 1 h post-exposure. Lung function—pulmonary resistance, dynamic compliance, breathing frequency, tidal volume, and min volume
<a href="#">Conner et al. (1985)</a>	Hartley guinea pig; n ≤ 18/group/time point; M; age NR; 250-320 g;	1 ppm (2.62 mg/m <sup>3</sup> ); nose only for 3 h/d for 6 d	Endpoints examined 1, 24, and 48 h after the sixth exposure. Lung function—residual volume, functional residual capacity, vital capacity, total lung capacity, respiratory frequency, tidal volume, pulmonary resistance, pulmonary compliance, diffusing capacity for CO, and alveolar volume
<a href="#">Barthelemy et al. (1988)</a>	Rabbit; n = 5-9/group; sex NR; adult; mean 2.0 kg; rabbits were mechanically ventilated	0.5 ppm (1.3 mg/m <sup>3</sup> ) for 45 min; intratracheal	Endpoints examined 5 min before and up to 1 h post-exposure. Lung function—pulmonary resistance
<a href="#">Amdur et al. (1988)</a>	Guinea pig; n = 8	1 ppm for 1 h	Endpoints examined 2 h following exposure Airway responsiveness to acetylcholine
<a href="#">Riedel et al. (1988)</a>	Guinea pigs (Perlbright-White); n = 5-14; M; age NR; 300-350 g	0.1, 4.3, and 16.6 ppm whole body; 8 h/d for 5 d Animals were sensitized to ovalbumin (ovalbumin aerosol) on the last 3 d of exposure Bronchial provocation every other day with aerosolized 0.1% ovalbumin began at 1 wk after the last exposure to SO <sub>2</sub> and continued for 14 d 4 groups: Control 0.1 ppm SO <sub>2</sub> 4.3 ppm SO <sub>2</sub> 16.6 ppm SO <sub>2</sub>	Bronchial obstruction determined by examination of the respiratory loop measured by whole-body plethysmography in spontaneously breathing animals after each bronchial provocation.

**Table 5-18 (Continued): Study specific details from animal toxicological studies of lung function.**

Study	Species (Strain); n; Sex; Lifestage/Age or Weight	Exposure Details (Concentration; Duration)	Endpoints Examined
<a href="#">Park et al. (2001)</a>	Guinea pigs (Dunkin-Hartley); n = 7–12/group; M; age NR; 250–350 g	0.1 ppm whole body; 5 h/d for 5 d Animals were sensitized to ovalbumin (0.1% ovalbumin aerosol) on the last 3 d of exposure Bronchial challenge with 1% ovalbumin aerosol occurred at 1 wk after the last exposure to SO <sub>2</sub> 4 groups: Control Ovalbumin	Bronchial obstruction—measurement of Penh by whole-body plethysmography

CO = carbon monoxide; n = sample size; NR = not reported; M = male; Penh = enhanced pause; SD = standard deviation; SO<sub>2</sub> = sulfur dioxide.

1 The 2008 SO<sub>x</sub> ISA ([U.S. EPA, 2008d](#)) also described studies that examined airway  
2 responsiveness following SO<sub>2</sub> exposure. In several different animal species, a single  
3 exposure to SO<sub>2</sub> at a concentration up to 10 ppm failed to increase airway responsiveness  
4 to a challenge agent. These studies were mainly conducted in naive animals rather than in  
5 models of allergic airways disease. Only one was conducted at a SO<sub>2</sub> concentration of  
6 less than 2 ppm. This study found no change in airway responsiveness to acetylcholine  
7 measured 2 hours following a 1-hour exposure in guinea pigs to 1 ppm SO<sub>2</sub> ([Amdur et  
8 al., 1988](#)). However, two toxicological studies ([Park et al., 2001](#)) ([Riedel et al., 1988](#))  
9 described in the 2008 SO<sub>x</sub> ISA ([U.S. EPA, 2008d](#)), provide evidence that repeated SO<sub>2</sub>  
10 exposure of guinea pigs to concentrations as low as 0.1 ppm enhanced AHR following  
11 subsequent sensitization and challenge with ovalbumin.

***Summary of Lung Function Changes in General Populations and  
Healthy Individuals***

12 Across disciplines, there is limited evidence that short-term SO<sub>2</sub> exposure induces lung  
13 function changes in healthy people. Evidence from controlled human exposure studies of  
14 healthy individuals shows that transient decreases in lung function can occur at  
15 concentrations of 1.0 ppm SO<sub>2</sub> under exercising or forced oral breathing conditions, but  
16 the evidence is more consistent for exposures >1.0 ppm. Animal toxicological studies  
17 demonstrated that acute exposure of guinea pigs to 0.16–1.0 ppm SO<sub>2</sub> results in increased  
18 airway resistance and repeated exposure of guinea pigs to concentrations of SO<sub>2</sub> as low as  
19 0.1 ppm led to an enhancement of AHR following sensitization and challenge with an  
20 allergen. Epidemiologic studies do not clearly indicate SO<sub>2</sub>-associated decreases in lung  
21 function in healthy adults or children or groups from the general population with varying

1 prevalence of respiratory disease. Results are mixed for SO<sub>2</sub> measured at subjects'  
2 locations and at central site monitors. Similar to experimental studies in healthy humans  
3 and animals without allergen challenge plus 1- to 6-hour SO<sub>2</sub> exposures, epidemiologic  
4 findings are mixed for temporally resolved metrics such as 1-h max or 1- to 4-h avg SO<sub>2</sub>.  
5 Associations were observed for populations living in locations with steel, aluminum, or  
6 petrochemical industry or coal heating, but SO<sub>2</sub> was one of many pollutants implicated.

## **Respiratory Symptoms in General Populations and Healthy Individuals**

7 Respiratory symptoms in relation to short-term SO<sub>2</sub> exposure have been investigated in a  
8 limited number of studies of general populations or healthy individuals. The 2008 SO<sub>x</sub>  
9 ISA ([U.S. EPA, 2008d](#)) described some controlled human exposure and epidemiologic  
10 studies of respiratory symptoms among children or adults without asthma. Most  
11 controlled human exposure studies reported no respiratory symptoms at concentrations up  
12 to 2.0 ppm. Evidence from both previous and recent epidemiologic studies is  
13 inconsistent.

### ***Controlled Human Exposure Studies***

14 Controlled human exposure studies examining respiratory symptoms in healthy  
15 individuals exposed to SO<sub>2</sub> are summarized in [Table 5-15](#). Briefly, [Tunnicliffe et al.](#)  
16 [\(2003\)](#) found no association between respiratory symptoms (i.e., throat irritation, cough,  
17 and wheeze) and 1-hour exposures at rest to 0.2 ppm SO<sub>2</sub> in either healthy adults or those  
18 with asthma. Similarly, [Andersen et al. \(1974\)](#) reported no change in respiratory  
19 symptoms in resting adults exposed to 1.0 ppm SO<sub>2</sub> for 6 hours. A more recent study in  
20 which exercising healthy adults were exposed to SO<sub>2</sub> concentrations as high as 2.0 ppm  
21 for 4 hours confirms these null findings ([van Thriel et al., 2010](#)).

### ***Epidemiologic Studies***

22 Associations for ambient SO<sub>2</sub> with respiratory symptoms in populations of healthy adults  
23 and children are inconsistent. Most results are from Europe and Asia. There are more  
24 studies of children than adults, but studies of adults focus on healthy individuals. Many  
25 previous studies of children examined populations with 5–81% chronic wheeze, asthma,  
26 or atopy, although results were inconsistent for healthy children as well ([Boezen et al.,](#)  
27 [1999](#); [Neas et al., 1995](#)). Some recent studies examine populations of children with low  
28 (0.6–4%) prevalence of respiratory disease, but like previous studies do not consistently  
29 associate increases in SO<sub>2</sub> concentrations with respiratory symptoms ([Table 5-19](#)).  
30 Previous results were largely based on 24-h avg SO<sub>2</sub> concentrations measured at central  
31 site monitors. Many recent studies have improved exposure assessment, examining  
32 temporally resolved 1-hour SO<sub>2</sub> concentrations for adults or SO<sub>2</sub> concentrations at

1 children's schools. These associations with respiratory symptoms also are inconsistent.  
2 Other uncertainties include confounding by meteorological factors and copollutants.

3 For adults, a study on Miyakejima Island, Japan 5 years after a volcano eruption provided  
4 information on effects related to SO<sub>2</sub> concentrations and durations comparable to those  
5 examined in experimental studies ([Ishigami et al., 2008](#)). Incidence of many symptoms  
6 increased at 1-h avg SO<sub>2</sub> concentrations above 100 ppb and 1-h max concentrations  
7 above 600 ppb than concentrations less than 10 ppb (reference category) ([Table 5-19](#)).  
8 Although temporally resolved metrics were analyzed, inference about an SO<sub>2</sub> effect is  
9 weak. SO<sub>2</sub> concentrations were measured within 2 km of volunteer workers' home and  
10 work site, no other air pollutants or other potential confounders were examined, and 80%  
11 of concentrations were in the reference category. Results linking long-term air pollution  
12 from volcanoes to respiratory symptoms also are uncertain because they are based on  
13 ecological comparisons of areas with low and high air pollution mixtures in which SO<sub>2</sub> is  
14 one constituent ([Section 5.2.2.1](#)).

15 For children, associations with SO<sub>2</sub> concentrations were inconsistent within studies  
16 among the array of symptoms examined ([Table 5-19](#)). Results across studies were  
17 consistent for wheeze, an asthma symptom that is less likely to be experienced by healthy  
18 children. A study in South Korea has many limitations including estimating SO<sub>2</sub> exposure  
19 from central site monitors at an unspecified distance from children and observing only a  
20 few isolated associations among the numerous pollutants, symptoms, exposure lags, and  
21 cities examined ([Moon et al., 2009](#)). Other studies had cross-sectional design and  
22 measured SO<sub>2</sub> at school or within 2 km from school ([Altuğ et al., 2014](#); [Linares et al.,  
23 2010](#); [Zhao et al., 2008](#)). A study in China examined high SO<sub>2</sub> concentrations similar to  
24 those in the Japanese volcano study. Mean school SO<sub>2</sub> concentrations were 101 ppb  
25 indoors and 271 ppb outdoors. Indoor, but not outdoor, 1-wk avg SO<sub>2</sub> concentrations  
26 were associated with symptoms ([Zhao et al., 2008](#)) ([Table 5-19](#)). Temporal mismatch is  
27 likely between current SO<sub>2</sub> measurements and symptoms at any time in the preceding  
28 12 months. The other study with 1-wk avg school SO<sub>2</sub> measures, conducted in Turkey,  
29 observed an association with any shortness of breath or wheeze in the previous 7 days but  
30 not throat symptoms, runny nose, or medication use concurrently or in the previous  
31 7 days ([Altuğ et al., 2014](#)). It is not clear whether the single positive association applied  
32 to the entire population, the 7% with asthma, or 27% with hay fever. Among mostly  
33 healthy children (0.6% asthma) in Mexico, lag 0 SO<sub>2</sub> concentration was associated with  
34 wheeze, but SO<sub>2</sub> was measured up to 2 km from children's schools ([Linares et al., 2010](#)).  
35 SO<sub>2</sub> concentrations were not associated with runny nose or difficulty breathing.

**Table 5-19 Recent epidemiologic studies of respiratory symptoms in healthy adults and children and groups in the general population.**

Study Population and Methodological Details	SO <sub>2</sub> Exposure Estimates (ppb)	SO <sub>2</sub> Averaging Time and Lag Day	Effect Estimate (95% CI) Single-Pollutant Model <sup>a</sup>	Copollutant Examination
<b>Adults</b>				
<a href="#">†Ishigami et al. (2008)</a> Miyakejima Island, Japan, 2005 N = 611, ages ≥15 yr, 100% healthy Daily diaries for 1–15 d. Recruited from volunteers working on an active volcanic island 5 yr after eruption. Did not examine potential confounding factors.	Monitors within 2 km of residence/work area Means across monitors 0–3,550 Max across monitors 3,790–10,320	1-h avg	Cough crude incidence rate, males < 10 ppb: 4.8, 10–20 ppb: 1.4, 20–30 ppb: 2.9, 30–100 ppb: 6.6, > 100 ppb: 19.3. p for trend < 0.01	No copollutant model No copollutants examined.
		1-h max	< 10 ppb: 4.7, 10–20 ppb: 4.3, 20–60 ppb: 8.1, 60–2,000 ppb: 16.4, > 2,000 ppb: 58.3. p for trend < 0.01	
<b>Children</b>				
<a href="#">†Zhao et al. (2008)</a> Taiyuan, China, Dec 2004 N = 1,993, ages 11–15 yr. 2% asthma. 4% with furry pet or pollen allergy. Cross-sectional. Recruited from schools. Likely temporal mismatch between current SO <sub>2</sub> concentrations and symptoms assessed as any occurrence in preceding 12 mo.	Monitor at school Mean (SD) and max Outdoor: 271 (72), 386 Indoor: 101 (53), 244	24-h avg	Outdoor SO <sub>2</sub> Wheeze OR: 1.01 (0.98, 1.04) Daytime attacks of breathlessness OR: 0.99 (0.97, 1.01) Nocturnal attacks of breathlessness OR: 1.01 (0.96, 1.06)	No copollutant model Indoor NO <sub>2</sub> and formaldehyde associated with symptoms. PM <sub>2.5</sub> not examined. SO <sub>2</sub> highly correlated with NO <sub>2</sub> . <i>r</i> = 0.74.
		0–6 avg	Indoor SO <sub>2</sub> Wheeze OR: 1.04 (1.01, 1.08) Daytime attacks of breathlessness OR: 1.02 (0.99, 1.04) Nocturnal attacks of breathlessness OR: 1.07 (1.01, 1.13)	

**Table 5-19 (Continued): Recent epidemiologic studies of respiratory symptoms in healthy adults and children and groups in the general population.**

Study Population and Methodological Details	SO <sub>2</sub> Exposure Estimates (ppb)	SO <sub>2</sub> Averaging Time and Lag Day	Effect Estimate (95% CI) Single-Pollutant Model <sup>a</sup>	Copollutant Examination
<p>†<a href="#">Altuğ et al. (2014)</a> Eskisehir, Turkey, Feb–Mar 2007 N = 605, ages 9–13 yr. 7% asthma, 44% eczema. Cross-sectional. Recruited from schools from participants of a larger study.</p>	<p>Monitor at school Mean and max Suburban: 21, 29 Urban: 29, 44 Urban-traffic: 22, 27</p>	<p>24-h avg 0–6 avg</p>	<p>Complaints of the throat in last 7 d RR: 0.83 (0.59, 1.15) Complaints of the throat at the moment RR: 1.03 (0.72, 1.47) Runny nose in last 7 d RR: 0.95 (0.74, 1.22) Runny nose at the moment RR: 0.92 (0.69, 1.23) Shortness of breath/wheeze in last 7 d RR: 1.72 (1.05, 2.81) Medication for shortness of breath/wheeze in last 7 d RR: 1.44 (0.69, 2.99) Shortness of breath/wheeze today RR: 1.79 (0.90, 3.58) Medication for shortness of breath/wheeze today RR: 0.74 (0.16, 3.33)</p>	<p>No copollutant model O<sub>3</sub> and NO<sub>2</sub> not associated with symptoms. PM<sub>2.5</sub> not examined. SO<sub>2</sub> weakly correlated with O<sub>3</sub>, moderately correlated with NO<sub>2</sub>. <i>r</i> = 0.40, 0.49.</p>
<p>†<a href="#">Linares et al. (2010)</a> Salamanca, Mexico, Mar 2004–Feb 2005 N = 464, ages 6–14 yr. 0.6% asthma. Cross-sectional. Recruited from schools.</p>	<p>Monitors within 2 km of school Means spring–winter School 1: 12, 12, 10, 9.8 School 2: 9.1, 8.7, 10, 13</p>	<p>24-h avg 0</p>	<p>Wheezing OR: 1.06 (1.00, 1.11) Rhinorrhoea OR: 0.98 (0.92, 1.05) Dyspnea OR: 1.02 (0.97, 1.07)</p>	<p>No copollutant model PM<sub>10</sub> and O<sub>3</sub> but not NO<sub>2</sub> associated with symptoms. PM<sub>2.5</sub> not examined. Copollutant correlations NR.</p>
<p>†<a href="#">Moon et al. (2009)</a> Seoul, Incheon, Busan, Jeju, South Korea, 2003 N = 696, ages &lt; 13 yr Daily diaries for 2 mo. Recruited from schools.</p>	<p>Monitors in city Number and distance NR Means NR Max: 38</p>	<p>24-h avg 0</p>	<p>LRS OR: 1.00 (0.93, 1.08) URS OR: 1.11 (1.03, 1.20)</p>	<p>No copollutant model PM<sub>10</sub> and CO associated with symptoms. PM<sub>2.5</sub> not examined. Copollutant correlations NR.</p>

CI = confidence interval; CO = carbon monoxide; LRS = lower respiratory symptoms; N = sample size; NO<sub>2</sub> = nitrogen dioxide; NR = not reported; O<sub>3</sub> = ozone; OR = odds ratio; PM<sub>2.5</sub> = particulate matter with a nominal aerodynamic diameter less than or equal to 2.5 μm; PM<sub>10</sub> = particulate matter with a nominal aerodynamic diameter less than or equal to 10 μm; *r* = correlation coefficient; RR = relative risk or ratio; SD = standard deviation; SO<sub>2</sub> = sulfur dioxide; URS = upper respiratory symptoms.

<sup>a</sup>Effect estimates are standardized to a 10-ppb increase in 1-h avg and 24-h avg SO<sub>2</sub> and a 40-ppb increase in 1-h max SO<sub>2</sub>.

†Studies published since the 2008 Integrated Science Assessment for Sulfur Oxides.

1 For the few observations of SO<sub>2</sub>-associated increases in respiratory symptoms in healthy  
2 adults and children, the potential for copollutant confounding was not examined. PM<sub>10</sub>,  
3 CO, and formaldehyde were also associated with symptoms; PM<sub>2.5</sub> was not examined  
4 ([Table 5-19](#)). Most studies did not report copollutant correlations, and none examined  
5 copollutant models. Symptoms were not associated with outdoor NO<sub>2</sub> ([Altuğ et al., 2014](#);  
6 [Linares et al., 2010](#); [Zhao et al., 2008](#)), but an association was observed with indoor NO<sub>2</sub>  
7 ([Zhao et al., 2008](#)). Indoor school SO<sub>2</sub> and NO<sub>2</sub> were highly correlated ( $r = 0.74$ ), and it  
8 is not clear the extent to which the association with breathlessness can be attributed  
9 independently to SO<sub>2</sub> or NO<sub>2</sub> or to a combined effect of those and other copollutants.

### ***Summary of Respiratory Symptoms in General Populations and Healthy Individuals***

10 There is little evidence for an effect of short-term SO<sub>2</sub> exposure on respiratory symptoms  
11 in healthy individuals. Controlled human exposure studies of healthy adults did not  
12 demonstrate effects for 1- to 6-hour SO<sub>2</sub> exposures up to 2 ppm, and epidemiologic  
13 findings are inconsistent for healthy adults and children. For epidemiologic studies, there  
14 is uncertain representativeness of SO<sub>2</sub> exposures estimated from central site monitors.  
15 However, as shown in recent studies, respiratory symptoms are also inconsistently  
16 associated with SO<sub>2</sub> measured at children's schools. A biological explanation for  
17 associations observed with 1-wk avg SO<sub>2</sub> concentrations is unclear. For associations  
18 observed with 1-h avg or max concentrations and the evidence overall, potential for  
19 confounding by PM<sub>2.5</sub>, PM<sub>10</sub>, NO<sub>2</sub>, CO, and formaldehyde is not addressed.

### **Subclinical Respiratory Effects in Healthy Individuals**

20 Pulmonary inflammation is a key subclinical effect in the pathogenesis of asthma and  
21 other respiratory diseases. It consists of both acute and chronic responses and involves  
22 the orchestrated interplay of the respiratory epithelium and both the innate and adaptive  
23 immune system. The immunohistopathologic features of chronic inflammation involve  
24 the infiltration of inflammatory cells such as eosinophils, lymphocytes, mast cells, and  
25 macrophages and the release of inflammatory mediators such as cytokines and  
26 leukotrienes. The 2008 ISA for Sulfur Oxides described limited evidence from animal  
27 toxicological studies for SO<sub>2</sub>-induced pulmonary inflammation and allergic sensitization  
28 in rodents exposed to allergen. Recent controlled human exposure and epidemiologic  
29 studies add to the evidence base and do not clearly support SO<sub>2</sub>-related pulmonary  
30 inflammation in healthy populations.

### ***Controlled Human Exposure Studies***

1 A recent controlled human exposure study examined eNO and other biomarkers of  
2 pulmonary inflammation in the NALF and EBC after exposures to 0, 0.5, 1, and 2 ppm  
3 SO<sub>2</sub> for 4 hours in exercising healthy adults ([Raulf-Heimsoth et al., 2010](#)). Data  
4 demonstrated no statistically significant changes in eNO; leukotriene B<sub>4</sub>, prostaglandin  
5 E<sub>2</sub>, and 8-iso-prostaglandin F<sub>2</sub> alpha in EBC; or substance P, interleukin-8 (IL-8), and  
6 brain derived neurotrophic factor in NALF after SO<sub>2</sub> exposures, compared to air.

### ***Epidemiologic Studies***

7 Unlike the study reviewed in the 2008 ISA for Sulfur Oxides ([Adamkiewicz et al., 2004](#)),  
8 recent studies measured SO<sub>2</sub> near subjects' homes, schools, or work. SO<sub>2</sub> concentrations  
9 at a site within 1 km of most homes were not associated with pulmonary inflammation in  
10 a population of children with high prevalence (33%) of asthma or atopy ([Chen et al.,  
11 2012a](#)). Previous results were similar for a population of older adults that included people  
12 with respiratory disease. Recent examination of healthy adults and children in Beijing,  
13 China indicates SO<sub>2</sub>-associated increases in pulmonary inflammation or oxidative stress.  
14 These recent studies were conducted before, during, and after the 2008 Olympics ([Roy et  
15 al., 2014](#); [Lin et al., 2011b](#)). Concentrations of SO<sub>2</sub> and other pollutants were lower  
16 during the Olympics than before or after (e.g., mean 24-h avg 3.0 vs. 7.5 and 6.8 ppb).  
17 During a winter 2007 period, mean 24-h avg SO<sub>2</sub> concentrations were 45 ppb ([Lin et al.,  
18 2011b](#)). Pollutants were measured 0.65 km from the school that study children attended  
19 and the hospital where most of the study adults worked. A 10-ppb increase in lag 0  
20 24-h avg SO<sub>2</sub> was associated with a 7.6% (95% CI: 5.9, 9.3) increase in eNO of children  
21 ([Lin et al., 2011b](#)) and, in adults, a 0.67 standard deviation (95% CI: 0.48, 0.86) increase  
22 in an index of pulmonary inflammation and oxidative stress combining eNO and EBC  
23 markers ([Roy et al., 2014](#)). Associations were also observed with PM<sub>2.5</sub>, sulfate, EC/BC,  
24 CO, NO<sub>2</sub>, and OC. Copollutant models were analyzed for children, in which SO<sub>2</sub> effect  
25 estimates remained positive but decreased substantially with adjustment for PM<sub>2.5</sub> or BC  
26 ([Lin et al., 2011b](#)). Conversely, the effect estimate for BC was robust to adjustment for  
27 SO<sub>2</sub>. Correlations with SO<sub>2</sub> concentrations were not reported, but inference from  
28 copollutant models is likely better for pollutants measured close to school than at central  
29 site monitors due to more comparable exposure measurement error. Confounding by  
30 other copollutants was not examined.

### ***Animal Toxicological Studies***

31 The 2008 SO<sub>x</sub> ISA ([U.S. EPA, 2008d](#)) described several animal toxicological studies that  
32 examined the effects of repeated exposure to SO<sub>2</sub> on inflammation. These and other  
33 animal toxicological studies examining inflammation in naive animals exposed to SO<sub>2</sub>

1 are summarized in [Table 5-20](#). Repeated exposure to SO<sub>2</sub> was found to promote allergic  
2 sensitization and enhanced allergen-induced bronchial obstruction in guinea pigs. In the  
3 first of these studies, [Riedel et al. \(1988\)](#) examined the effect of SO<sub>2</sub> exposure on local  
4 bronchial sensitization to inhaled antigen. Guinea pigs were exposed by inhalation to 0.1,  
5 4.3, and 16.6 ppm SO<sub>2</sub> for 8 hours/day for 5 days. During the last 3 days, SO<sub>2</sub> exposure  
6 was followed by exposure to nebulized ovalbumin for 45 minutes. Following bronchial  
7 provocation with inhaled ovalbumin (0.1%) 1 week later, bronchial obstruction was  
8 measured by examining the respiratory loop obtained by whole-body plethysmography.  
9 In addition, specific antibodies against ovalbumin were measured in serum and BALF.  
10 Results showed significantly higher bronchial obstruction in animals exposed to both  
11 SO<sub>2</sub>, at all concentration levels, and ovalbumin compared with animals exposed only to  
12 ovalbumin. In addition, significant increases in anti-ovalbumin IgG antibodies were  
13 detected in BALF of animals exposed to 0.1, 4.3, and 16.6 ppm SO<sub>2</sub> and in serum from  
14 animals exposed to 4.3 and 16.6 ppm SO<sub>2</sub> and ovalbumin compared with controls  
15 exposed only to ovalbumin. These results demonstrated that repeated exposure to SO<sub>2</sub>  
16 enhanced allergic sensitization and bronchial obstruction in the guinea pig at a  
17 concentration as low as 0.1 ppm.

18 In the second study, guinea pigs were exposed to 0.1 ppm SO<sub>2</sub> for 5 hours/day for 5 days  
19 and sensitized with 0.1% ovalbumin aerosols for 45 minutes on days 4 and 5 ([Park et al.,  
20 2001](#)). One week later, animals were subjected to bronchial challenge with 0.1%  
21 ovalbumin and lung function was evaluated 24 hours later by whole-body  
22 plethysmography. The results demonstrated a significant increase in enhanced pause  
23 (Penh), a measure of airway obstruction, in animals exposed to both SO<sub>2</sub> and ovalbumin  
24 but not in animals treated with ovalbumin or SO<sub>2</sub> alone. In animals treated with both SO<sub>2</sub>  
25 and albumin, increased numbers of eosinophils were found in lavage fluid. In addition,  
26 infiltration of inflammatory cells, bronchiolar epithelial cell damage, and plugging of the  
27 airway lumen with mucus and cells were observed in bronchial tissues. These cellular  
28 changes were not observed in animals treated with ovalbumin or SO<sub>2</sub> alone. Results  
29 indicate that repeated exposure to near-ambient levels of SO<sub>2</sub> may play a role in allergic  
30 sensitization and in exacerbating allergic inflammatory responses in the guinea pig.  
31 Furthermore, increases in bronchial obstruction suggest that SO<sub>2</sub> exposure induced an  
32 increase in airway responsiveness in the animals subsequently made allergic to  
33 ovalbumin.

**Table 5-20 Study-specific details from animal toxicological studies of subclinical effects.**

Study	Species (strain); n; Sex; Lifestage/Age or Weight	Exposure Details (Concentration; Duration)	Endpoints Examined
<a href="#">Conner et al. (1989)</a>	Guinea pigs (Hartley); n = 4; M; age NR; 250–300 g;	1 ppm nose only; 3 h/d for 1–5 d	BAL performed each day. BALF—total and differential cell counts
<a href="#">Riedel et al. (1988)</a>	Guinea pigs (Perlbright-White); n = 5–14/group; M; age NR; 300–350 g;	0.1, 4.3, and 16.6 ppm whole body; 8 h/d for 5 d Animals were sensitized to ovalbumin (ovalbumin aerosol) on the last 3 d of exposure Bronchial provocation every other day with 0.1% ovalbumin aerosol began at 1 wk after the last exposure to SO <sub>2</sub> and continued for 14 d Four groups: Control 0.1 ppm SO <sub>2</sub> 4.3 ppm SO <sub>2</sub> 16.6 ppm SO <sub>2</sub>	Endpoints examined 48 h after the last provocation. Serum—anti IgG levels BALF—anti IgG levels
<a href="#">Park et al. (2001)</a>	Guinea pigs (Dunkin-Hartley); n = 7–12/group; M; age NR; 250–350 g;	0.1 ppm whole body; 5 h/d for 5 d Animals were sensitized to ovalbumin (0.1% ovalbumin aerosol) on the last 3 d of exposure Bronchial challenge with 1% ovalbumin aerosol occurred at 1 wk after the last exposure to SO <sub>2</sub> Four groups: Control Ovalbumin SO <sub>2</sub> Ovalbumin/SO <sub>2</sub>	Endpoints examined 24 h after the bronchial challenge. BALF—differential cell counts cells Lung and bronchial tissue—histopathology
<a href="#">Li et al. (2007)</a>	Rats (Wistar); n = 6/group; M; age NR	2 ppm SO <sub>2</sub> for 1 h/d for 7 d	Endpoints examined 24 h following the last exposure BALF—inflammatory cell counts Lung—histopathology and immunohistochemistry Lung and tracheal tissue—mRNA and protein levels of MUC5AC and ICAM-1

**Table 5-20 (Continued): Study specific details from animal toxicological studies of subclinical effects.**

Study	Species (strain); n; Sex; Lifestage/Age or Weight	Exposure Details (Concentration; Duration)	Endpoints Examined
<a href="#">Li et al. (2014)</a>	Rats (Wistar); n = 6/group; M; age NR; 180–200 g	2 ppm SO <sub>2</sub> for 1 h/d for 7 d	Endpoints examined BALF—inflammatory cell counts and cytokines IL-4, IFN-γ, TNFα, IL-6 Serum—IgE Lung—histopathology, Lung and tracheal tissue—mRNA and protein levels NFκB, IκBα, IKKβ, IL-6, IL-4, TNFα, FOXP3, EMSA NFκB binding activity

BAL = bronchoalveolar lavage; BALF = bronchoalveolar lavage fluid; EMSA = electrophoretic mobility shift assay; FOXP3 = forkhead box p3; ICAM-1 = intercellular adhesion molecule 1; IFN-γ = interferon gamma; IgE = immunoglobulin E; IgG = immunoglobulin G; IKKβ = inhibitor of nuclear factor kappa-B kinase subunit beta; IL-4 = interleukin-4; IL-6 = interleukin-6; IκBα = nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha; i.p. = intraperitoneal; M = male; MUC5AC = mucin 5AC glycoprotein; n = sample size; NFκB = nuclear factor kappa-light-chain-enhancer of activated B cells; NR = not reported; SD = standard deviation; SO<sub>2</sub> = sulfur dioxide; TNFα = tumor necrosis factor alpha.

1                    [Park et al. \(2001\)](#) demonstrated that repeated exposure of guinea pigs to 0.1 ppm SO<sub>2</sub>  
2                    alone did not lead to allergic inflammation or morphologic changes in the lung although  
3                    it enhanced the allergic inflammation due to subsequent sensitization and challenge with  
4                    ovalbumin. [Conner et al. \(1989\)](#) found no changes in total cells and neutrophils in BALF  
5                    from guinea pigs exposed repeatedly to 1 ppm SO<sub>2</sub>. In contrast, found that repeated  
6                    exposure of rats to 2 ppm SO<sub>2</sub> resulted in mild pathologic changes in the lung, including  
7                    inflammatory cell influx and smooth muscle hyperplasia ([Li et al., 2014](#); [Li et al., 2007](#)).  
8                    Several other indicators of inflammation and immune response were not changed by  
9                    exposure to SO<sub>2</sub> alone.

***Summary of Subclinical Respiratory Effects in Healthy Individuals***

10                   There is limited evidence for inflammatory and other subclinical respiratory effects in  
11                   healthy populations following short-term exposure to SO<sub>2</sub>, primarily from animal  
12                   toxicological studies involving allergen sensitization. As newly informed by recent  
13                   studies, SO<sub>2</sub> is not clearly related to pulmonary inflammation in healthy populations in  
14                   controlled human exposure or epidemiologic studies. Associations were observed in  
15                   some epidemiologic studies, but confounding by PM<sub>2.5</sub>, sulfate, BC, or NO<sub>2</sub> is not well  
16                   addressed. Studies in animals demonstrated that repeated exposure of guinea pigs to 0.1  
17                   or 1 ppm SO<sub>2</sub> had no effect on inflammation. However, when followed by sensitization  
18                   with an allergen, exposure of guinea pigs to 0.1 ppm SO<sub>2</sub> enhanced allergic sensitization,  
19                   allergic inflammatory responses, and airway responsiveness to that allergen. These results

1 point to the potential for SO<sub>2</sub> exposure to increase sensitivity to an allergen, which differ  
2 from the inflammatory responses examined in healthy humans. In addition, repeated  
3 exposure of rats to 2 ppm SO<sub>2</sub> resulted in inflammation and smooth muscle hyperplasia,  
4 early indicators of airway remodeling.

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### 5.2.1.8 Respiratory Mortality

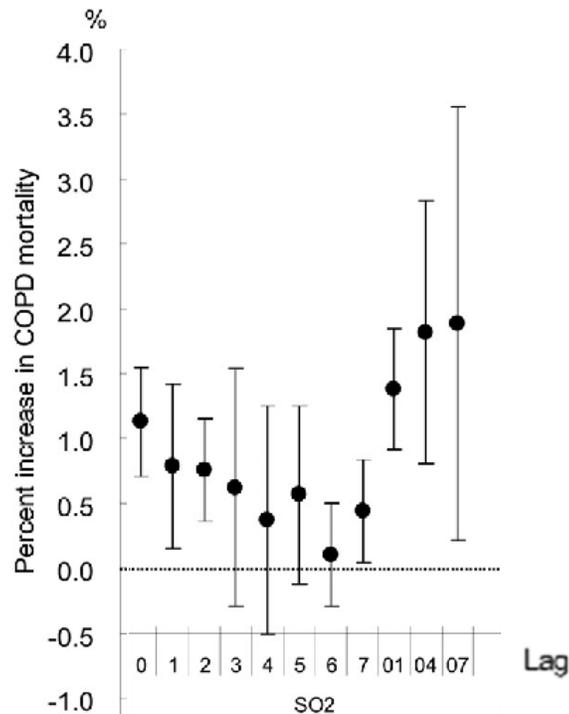
5 Studies evaluated in the 2008 SO<sub>x</sub> ISA that examined the association between short-term  
6 SO<sub>2</sub> exposure and cause-specific mortality found consistent positive associations with  
7 respiratory mortality using a 24-h avg exposure metric with some evidence indicating that  
8 the magnitude of the association was larger compared to all-cause and cardiovascular  
9 mortality. Recent multicity studies conducted in Asia ([Chen et al., 2012b](#); [Kan et al.,  
10 2010b](#)) and Italy ([Bellini et al., 2007](#)), a meta-analysis of studies conducted in Asia  
11 ([Atkinson et al., 2012](#)), and a four-city study conducted in China that focused specifically  
12 on COPD mortality ([Meng et al., 2013](#)) add to the initial body of evidence indicating  
13 larger respiratory mortality effects ([Section 5.5.1.3, Figure 5-18](#)).

14 Studies evaluated in and prior to the 2008 SO<sub>x</sub> ISA that examined the association  
15 between short-term SO<sub>2</sub> exposures and respiratory mortality focused exclusively on  
16 single-pollutant analyses. Therefore, questions arose regarding the independent effect of  
17 SO<sub>2</sub> on respiratory mortality, and whether associations remained robust in copollutant  
18 models. A few recent multicity studies conducted in China ([Meng et al., 2013](#); [Chen et  
19 al., 2012b](#)) and multiple Asian cities ([Kan et al., 2010b](#)) examined both of these  
20 questions. [Chen et al. \(2012b\)](#) found that the SO<sub>2</sub>-respiratory mortality association was  
21 attenuated, but remained positive in copollutant models with PM<sub>10</sub> [2.03% (95% CI: 0.89,  
22 3.17) for a 10-ppb increase in 24-h avg SO<sub>2</sub> concentrations at lag 0–1 days] and NO<sub>2</sub>  
23 [1.16% (95% CI: -0.03, 2.37) for a 10-ppb increase in 24-h avg SO<sub>2</sub> concentrations at lag  
24 0–1 days]. These results are similar to what the authors reported when examining the  
25 SO<sub>2</sub>-total mortality association in models with PM<sub>10</sub> (i.e., ~40% reduction), but more  
26 attenuation was observed in models with NO<sub>2</sub> (i.e., ~80% reduction for total mortality  
27 and 65% reduction for respiratory mortality) ([Section 5.5.1.4, Kan et al. \(2010b\)](#)), as part  
28 of the Public Health and Air Pollution in Asia (PAPA) study, also examined the effect of  
29 copollutants (i.e., NO<sub>2</sub>, PM<sub>10</sub>, and O<sub>3</sub>), but only in each city individually. The study  
30 authors found that although the SO<sub>2</sub>-respiratory mortality association remained positive  
31 in copollutant models, there was evidence of an attenuation of the association in models  
32 with PM<sub>10</sub> and more so in models with NO<sub>2</sub> ([Figure 5-10, Meng et al. \(2013\)](#)) in a  
33 four-city analysis of COPD mortality in China reported evidence consistent with [Chen et  
34 al. \(2012b\)](#) and [Kan et al. \(2010b\)](#). The authors observed a 3.7% (95% CI: 2.4, 4.9)  
35 increase in COPD mortality for a 10-ppb increase in 24-h avg SO<sub>2</sub> concentrations at lag

1 0–1 days. However, compared to the results for respiratory mortality from copollutant  
2 models reported in [Chen et al. \(2012b\)](#), [Meng et al. \(2013\)](#) found a larger degree of  
3 attenuation in models with PM<sub>10</sub>, ~50% reduction [1.9% (95% CI: 0.3, 3.5)] and NO<sub>2</sub>,  
4 ~99% reduction [0.0% (95% CI: -1.8, 1.9)] compared to the SO<sub>2</sub> results from the single  
5 pollutant model. The larger degree of attenuation of the SO<sub>2</sub>-COPD mortality association  
6 in [Meng et al. \(2013\)](#), compared to respiratory mortality in [Chen et al. \(2012b\)](#) could be a  
7 reflection of the smaller sample size and smaller number of cities included in the  
8 analysis. Overall, the studies that examined the potential confounding effects of  
9 copollutants on the SO<sub>2</sub>-respiratory mortality relationship show results consistent with  
10 what has been observed for total mortality. However, the overall assessment of potential  
11 copollutant confounding remains limited, and it is unclear how the results observed in  
12 Asia translate to other locations, specifically due to the unique air pollution mixture and  
13 higher concentrations observed in Asian cities.

14 Of the studies evaluated, only [Bellini et al. \(2007\)](#) (in a multicity study conducted in  
15 Italy) examined potential seasonal differences in the SO<sub>2</sub>-cause-specific mortality  
16 relationship. [Bellini et al. \(2007\)](#) reported that risk estimates for respiratory mortality  
17 were dramatically increased in the summer from 4.1 to 12.0% for a 10-ppb increase in  
18 24-h avg SO<sub>2</sub> concentrations at lag 0–1, respectively, with the all-year and winter results  
19 being similar. These results are consistent with the seasonal pattern of SO<sub>2</sub> associations  
20 observed in [Bellini et al. \(2007\)](#) for total and cardiovascular mortality. However, it  
21 remains unclear whether this seasonal pattern of SO<sub>2</sub>-respiratory mortality associations is  
22 observed in other locations.

23 An uncertainty that often arises when examining the relationship between short-term air  
24 pollution exposures and cause-specific mortality is whether the lag structure of  
25 associations and the C-R relationship is consistent with what is observed for total  
26 mortality. [Meng et al. \(2013\)](#) addressed both the lag structure of associations and the C-R  
27 relationship in a study of short-term air pollution exposures and COPD mortality in four  
28 Chinese cities. Although not explicitly part of the China Air Pollution and Health Effects  
29 Study (CAPES) study, [Meng et al. \(2013\)](#) focused on four CAPES cities over the same  
30 time period as [Chen et al. \(2012b\)](#). In comparison to [Chen et al. \(2012b\)](#), who found a  
31 steady decline in risk estimates at single-day lags of 0 to 7 days with the largest effect at  
32 lag 0–1, [Meng et al. \(2013\)](#) observed a steady decline over single lag days, but some  
33 indication of larger associations, although highly uncertain, at longer multiday lags  
34 (i.e., 0–4 and 0–7 days) ([Figure 5-10](#)). Note that [Chen et al. \(2012b\)](#) did not examine  
35 multiday lags longer than 0–1 days, but the magnitude of the association for all  
36 respiratory mortality [3.3% (95% CI: 2.1, 4.6) for a 10-ppb increase in 24-h avg SO<sub>2</sub>  
37 concentrations] is similar to that reported in [Meng et al. \(2013\)](#) for COPD [3.7% (95%  
38 CI: 2.4, 4.9)].

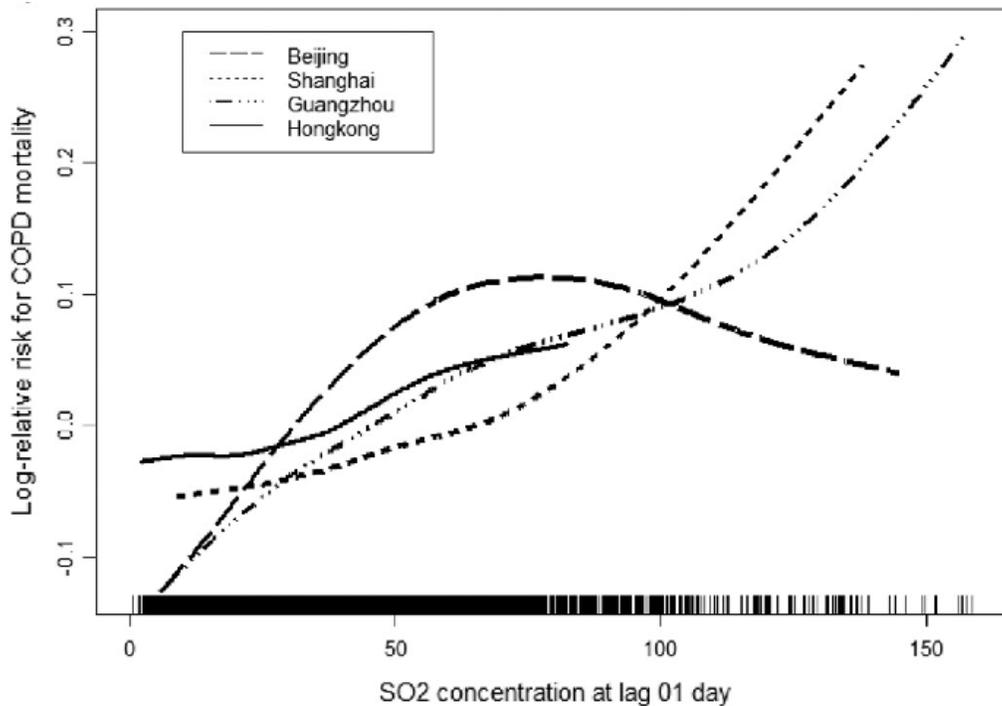


COPD = chronic obstructive pulmonary disease; SO<sub>2</sub> = sulfur dioxide.

Source: Adapted from [Meng et al. \(2013\)](#).

**Figure 5-10** Percent increase in chronic obstructive pulmonary disease mortality associated with a 10 µg/m<sup>3</sup> (3.62 ppb) increase in 24-h avg sulfur dioxide concentrations at various single and multiday lags.

1 [Meng et al. \(2013\)](#) also examined the shape of the SO<sub>2</sub>-COPD mortality C-R relationship.  
 2 To examine the assumption of linearity, the authors modeled the relationship between air  
 3 pollution exposures and COPD mortality using a natural spline with 3 df. [Meng et al.](#)  
 4 [\(2013\)](#) then computed the difference between the deviance of the linear and spline  
 5 models to assess whether there was evidence of nonlinearity in the SO<sub>2</sub>-COPD  
 6 relationship. As depicted in [Figure 5-11](#), the authors found no evidence that the spline  
 7 model resulted in a better fit of the SO<sub>2</sub>-mortality relationship compared to the linear  
 8 model. However, the authors did not present confidence intervals for each of the C-R  
 9 curves, which complicates the interpretation of the results.



COPD = chronic obstructive pulmonary disease; SO<sub>2</sub> = sulfur dioxide.

Source: Adapted from [Meng et al. \(2013\)](#).

**Figure 5-11 City-specific concentration-response curves for short-term sulfur dioxide exposures and daily chronic obstructive pulmonary disease mortality in four Chinese cities.**

1 Overall, recent multicity studies report evidence of consistent positive associations  
 2 between short-term SO<sub>2</sub> concentrations and respiratory mortality, which is consistent  
 3 with those studies evaluated in the 2008 SO<sub>x</sub> ISA. Unlike studies evaluated in the 2008  
 4 SO<sub>x</sub> ISA, recent studies examined whether copollutants confound the relationship  
 5 between short-term SO<sub>2</sub> concentrations and respiratory mortality. Overall, these studies  
 6 reported evidence that the SO<sub>2</sub>-respiratory mortality association was attenuated in models  
 7 with NO<sub>2</sub> and PM<sub>10</sub>, but the analyses are limited to Asian cities where the air pollution  
 8 mixture and concentrations are different than those reported in other areas of the world.  
 9 Additional analyses focusing on seasonal patterns of associations, lag structure of  
 10 associations, and the C-R relationship are limited in number, but suggest evidence of:  
 11 larger associations in the summer/warm season, larger and more precise associations at  
 12 shorter lag periods (in the range of 0 and 1 days), and a linear, no threshold C-R  
 13 relationship, respectively. However, for both total and cause-specific mortality, the  
 14 overall assessment of linearity in the C-R relationship is based on a very limited  
 15 exploration of alternatives.

---

### 5.2.1.9 Summary and Causal Determination

1 Strong evidence indicates that there is a causal relationship between short-term SO<sub>2</sub>  
2 exposure and respiratory effects, particularly for respiratory effects in the at-risk  
3 population of individuals with asthma. This determination is based on the consistency of  
4 SO<sub>2</sub>-induced bronchoconstriction in exercising individuals with asthma in controlled  
5 human studies, coherence of asthma-related effects among multiple lines of evidence, and  
6 biological plausibility for effects specifically related to asthma exacerbation. There is  
7 limited support for a relationship between short-term SO<sub>2</sub> exposure and other respiratory  
8 effects, including exacerbation of COPD, allergy exacerbation, respiratory infection,  
9 respiratory effects in healthy populations, and respiratory mortality. The limited and  
10 inconsistent evidence for these nonasthma-related respiratory effects does not contribute  
11 heavily to the causal determination.

12 The determination of a causal relationship is the same as the conclusion of the 2008 SO<sub>x</sub>  
13 ISA ([U.S. EPA, 2008d](#)). The evidence for this conclusion was heavily based on  
14 controlled human exposure studies that showed lung function decrements and respiratory  
15 symptoms in adult individuals with asthma exposed to SO<sub>2</sub> for 5–10 minutes under  
16 increased ventilation conditions. These findings are consistent with the current  
17 understanding of biological plausibility described in the mode of action section  
18 ([Section 4.3.6](#)). Previous epidemiologic studies provided supporting evidence indicating  
19 associations between short-term increases in ambient SO<sub>2</sub> concentration and  
20 respiratory-related ED visits and hospital admissions as well as respiratory symptoms.  
21 The evidence for a causal relationship is detailed below using the framework described in  
22 the [Preamble](#) to the ISAs ([U.S. EPA, 2015b](#)). While new evidence adds to the existing  
23 body of evidence, the determination remains largely based on previous controlled human  
24 exposure studies. The key evidence as it relates to the causal framework is presented in  
25 [Table 5-21](#).

#### Evidence for Asthma Exacerbation

26 A causal relationship between short-term SO<sub>2</sub> exposure and respiratory effects is  
27 primarily supported by evidence from controlled human exposure studies of respiratory  
28 effects in adults with asthma. These studies consistently demonstrated that the majority of  
29 individuals with asthma experience a moderate or greater decrement in lung function, as  
30 defined by a  $\geq 100\%$  increase in sRaw or  $\geq 15\%$  decrease in FEV<sub>1</sub>. This decrement is  
31 frequently accompanied by respiratory symptoms following exposures of 5–10 minutes,  
32 with elevated ventilation rates at concentrations of 0.4–0.6 ppm ([Johns et al., 2010](#); [Linn  
33 et al., 1990](#); [Linn et al., 1988](#); [Balmes et al., 1987](#); [Linn et al., 1987](#); [Horstman et al.,  
34 1986](#); [Linn et al., 1983b](#)). A fraction of the population with asthma (~5–30%) has also

1 been observed to have decrements in lung function at lower SO<sub>2</sub> concentrations  
2 (0.2–0.3 ppm) ([Linn et al., 1990](#); [Linn et al., 1988](#); [Linn et al., 1987](#); [Bethel et al., 1985](#)).  
3 Although the degree of lung function decrements are considered moderate, they are less  
4 likely to be accompanied by respiratory symptoms at these lower concentrations ([Linn et  
5 al., 1990](#); [Linn et al., 1988](#); [Linn et al., 1987](#); [Roger et al., 1985](#); [Linn et al., 1983b](#)).  
6 A group of responders (defined as having ≥15% decrease in FEV<sub>1</sub> after exposure to 0.6 or  
7 1.0 ppm SO<sub>2</sub>) showed statistically significant decrements in FEV<sub>1</sub> following 5–10 minute  
8 exposure to 0.3 ppm SO<sub>2</sub> ([Johns et al., 2010](#)) ([Table 5-3](#)). While SO<sub>2</sub>-induced respiratory  
9 effects have been examined in individuals classified as having mild and moderate asthma,  
10 these individuals are relatively healthy. Thus, extrapolating to individuals with severe  
11 asthma is difficult because such individuals cannot be tested in an exposure chamber due  
12 to the severity of their disease. Therefore, it is unknown whether people with severe  
13 asthma are at increased risk to respiratory effects due to short-term SO<sub>2</sub> exposure.  
14 The same may be said about children with asthma. There are no laboratory studies of  
15 children exposed to SO<sub>2</sub>, but a number of studies have assessed airway responsiveness of  
16 children and adults exposed to the bronchoconstrictive stimuli methacholine. Based  
17 largely on those studies, school-aged children, particularly boys and perhaps obese  
18 children, would be expected to have greater responses (i.e., larger decrements in lung  
19 function) following exposure to SO<sub>2</sub> than adolescents and adults.

20 The coherence of epidemiologic findings ([Section 5.2.1.2](#)) is supporting evidence for a  
21 causal relationship. Epidemiologic evidence for lung function changes in adults and  
22 children with asthma is inconsistent. However, short-term increases in ambient SO<sub>2</sub>  
23 concentration are associated with increases in asthma hospital admissions and ED visits  
24 among all ages, children (i.e., <18 years of age) and older adults (i.e., 65 years of age and  
25 older) ([Figure 5-3](#)), as well as asthma symptoms in children ([Velická et al., 2015](#); [Spira-  
26 Cohen et al., 2011](#)). Epidemiologic associations between short-term increases in ambient  
27 SO<sub>2</sub> concentration and respiratory mortality provide support for a potential continuum of  
28 effects between respiratory morbidity and respiratory mortality.

29 Most epidemiologic studies indicating associations between short-term SO<sub>2</sub> exposures  
30 and asthma exacerbation assigned exposure using SO<sub>2</sub> concentrations measured at central  
31 site monitors. The use of central site monitors to assign exposure, particularly to 1-h max  
32 SO<sub>2</sub>, may introduce exposure measurement error if the spatiotemporal variability in SO<sub>2</sub>  
33 concentrations is not captured. Studies did not statistically correct for measurement error,  
34 but in this new research area, a method has not been reported for short-term SO<sub>2</sub> exposure  
35 ([Section 3.4.4](#)). A few recent results reduce the uncertainty with SO<sub>2</sub> measured or  
36 modeled at or near children's school or home ([Velická et al., 2015](#); [Spira-Cohen et al.,  
37 2011](#)). Additional uncertainty exists regarding potential copollutant confounding. In  
38 many studies, SO<sub>2</sub> was moderately to highly correlated with PM<sub>2.5</sub>, larger sized PM,

1 EC/BC, NO<sub>2</sub>, and VOCs ( $r = 0.4$ – $0.9$ ). The few available results show association with  
2 sulfate. A small number of studies examined copollutant models. Some associations were  
3 relatively unchanged in magnitude after adjustment for a copollutant; others did not  
4 persist. However, inference from copollutant models is limited given potential differences  
5 in exposure measurement error for SO<sub>2</sub> compared to NO<sub>2</sub>, CO, PM, and O<sub>3</sub> and in many  
6 cases, high copollutant correlations. Copollutant interactions are not well studied. Some  
7 controlled human exposure studies demonstrate increased asthma-related effects with  
8 coexposure to SO<sub>2</sub> and NO<sub>2</sub> or O<sub>3</sub>. Limited epidemiologic evidence shows increased  
9 asthma-related effects with joint increases in SO<sub>2</sub> and copollutants but does not clearly  
10 show a joint association that is greater than a single-pollutant association.

11 There is supportive evidence for a relationship between short-term SO<sub>2</sub> exposure and  
12 airway responsiveness and pulmonary inflammation. Limited epidemiologic evidence  
13 points to associations with increased airway responsiveness in adults with asthma plus  
14 atopy ([Taggart et al., 1996](#)). [Gong et al. \(2001\)](#) demonstrated an increase in airway  
15 eosinophils in adults with asthma 2 hours after a 10-minute exposure to 0.75 ppm SO<sub>2</sub>.  
16 This effect, along with bronchoconstriction, was attenuated by pretreatment with a  
17 leukotriene receptor antagonist. Other pharmacologic studies have demonstrated the  
18 importance of inflammatory mediators in mediating SO<sub>2</sub> exposure-induced  
19 bronchoconstriction in people with asthma ([Section 4.3.1](#)). Further support for an  
20 important role of airway inflammation, including allergic inflammation, is provided by  
21 animal toxicological studies of repeated SO<sub>2</sub> exposure in allergic animals that are used to  
22 model the asthmatic phenotype ([Li et al., 2014](#); [Li et al., 2007](#)). In addition, repeated  
23 exposure of naive animals promoted allergic sensitization and enhanced allergic  
24 inflammation and airway responsiveness to an allergen ([Park et al., 2001](#); [Riedel et al.,](#)  
25 [1988](#)). These latter studies point to a possible increased sensitivity to allergens following  
26 SO<sub>2</sub> exposure.

### **Evidence for Other Respiratory Effects**

27 Epidemiologic studies demonstrate some associations of ambient SO<sub>2</sub> concentrations  
28 with hospital admissions and ED visits for all respiratory causes combined ([Figure 5-9](#)).  
29 While these results suggest that the respiratory effects of short-term SO<sub>2</sub> exposure could  
30 extend beyond exacerbation of asthma, evidence across disciplines is inconsistent and/or  
31 lacks biological plausibility for conditions such as allergy exacerbation ([Section 5.2.1.3](#)),  
32 COPD exacerbation ([Section 5.2.1.4](#)), and respiratory infection ([Section 5.2.1.5](#)). Where  
33 epidemiologic associations were found, potential copollutant confounding is uncertain.  
34 For COPD exacerbation, a controlled human exposure study demonstrated no effect of  
35 SO<sub>2</sub> exposure, and epidemiologic associations are inconsistent for lung function,  
36 respiratory symptoms, hospital admissions, and ED visits. Some evidence supports

1 SO<sub>2</sub>-associated increases in hospital admissions and ED visits due to respiratory  
2 infections. However, the lack of multiple studies examining the same respiratory  
3 infection outcome, inconsistent findings for self-reported infections in children, and the  
4 lack of evidence from controlled human exposure and animal toxicological studies  
5 produces uncertainty as to whether a relationship exists. Controlled human exposure  
6 studies in healthy individuals provide evidence for transient decreases in lung function  
7 with  $\geq 1$  ppm SO<sub>2</sub> exposures for 5–10 minutes under exercising or a forced oral breathing  
8 condition with no evidence for increased respiratory symptoms. Epidemiologic evidence  
9 is inconsistent for SO<sub>2</sub> associations with lung function, respiratory symptoms, and  
10 pulmonary inflammation in healthy children and adults.

### **Conclusion**

11 The evidence integrated across disciplines supports a causal relationship between  
12 short-term SO<sub>2</sub> exposure and respiratory effects, particularly asthma exacerbation. This  
13 determination is primarily based on decreased lung function and increased respiratory  
14 symptoms observed in controlled human exposure studies in adults with asthma.  
15 Epidemiologic studies of asthma hospital admissions and ED visits and asthma symptoms  
16 in children provide supporting evidence. Supportive evidence for a relationship between  
17 short-term SO<sub>2</sub> exposure and pulmonary inflammation and AHR, is provided by  
18 controlled human exposure, epidemiologic, and toxicological studies. Evidence for an  
19 effect of SO<sub>2</sub> exposure on allergy exacerbation, COPD exacerbation, respiratory  
20 infection, respiratory effects in healthy populations, and respiratory mortality is  
21 inconsistent within and across disciplines and outcomes, and there is uncertainty related  
22 to potential confounding by copollutants. The limited and inconsistent evidence for these  
23 nonasthma-related respiratory effects does not contribute heavily to the causal  
24 determination.

**Table 5-21 Summary of evidence for a causal relationship between short-term sulfur dioxide exposure and respiratory effects.**

Rationale for Causal Determination <sup>a</sup>	Key Evidence <sup>b</sup>	Key References <sup>b</sup>	SO <sub>2</sub> Concentrations Associated with Effects <sup>c</sup>
<b>Asthma exacerbation</b>			
Consistent evidence from multiple, high-quality controlled human exposure studies rules out chance, confounding, and other biases	Decreased lung function following exposures of 5–10 min in exercising individuals with asthma	<a href="#">Section 5.2.1.2</a> <a href="#">Table 5-2</a>	400–600 ppb
	A group of responders (defined as having ≥15% decrease in FEV <sub>1</sub> after exposure to 0.6 or 1.0 ppm SO <sub>2</sub> ) showed statistically significant decrements in FEV <sub>1</sub> following 5-10 min of exposure to 0.3 ppm SO <sub>2</sub>	<a href="#">Section 5.2.1.2</a> <a href="#">Table 5-3</a>	300 ppb
	Decreased lung function following exposures of 5-10 min in 5-30% of exercising individuals with asthma	<a href="#">Section 5.2.1.2</a> <a href="#">Table 5-2</a>	200–300 ppb
	Increased respiratory symptoms following exposure of 5–10 min in exercising individuals with asthma	<a href="#">Section 5.2.1.2</a> <a href="#">Table 5-2</a>	400–1,000 ppb
Generally supporting evidence from multiple epidemiologic studies at relevant SO <sub>2</sub> concentrations	Increase in asthma hospital admissions and ED visits in single- and multi-city studies, among all ages, children and older adults	<a href="#">Section 5.2.1.2</a>	1-h max: 9.6–10.8 ppb 24-h avg: 1.03–36.9 ppb
	Limited evidence for respiratory symptoms in children with asthma with school and/or home SO <sub>2</sub> exposure estimates	<a href="#">†Spira-Cohen et al. (2011)</a> , <a href="#">†Velická et al. (2015)</a> <a href="#">Section 5.2.1.2</a>	24-h avg: median 4.0 ppb
Uncertainty regarding exposure measurement error	SO <sub>2</sub> exposures estimated from central site monitors may not capture spatiotemporal variability of SO <sub>2</sub> across a community	<a href="#">Section 3.4.2</a>	
Uncertainty regarding potential copollutant confounding	Some SO <sub>2</sub> associations were relatively unchanged in magnitude in copollutant models with NO <sub>2</sub> , PM <sub>2.5</sub> , or PM <sub>10</sub> . Others were attenuated. Differential exposure measurement error limits inference. SO <sub>2</sub> showed a wide correlation with copollutants across studies ( $r = 0.4$ – $0.9$ ).	Attenuated: <a href="#">†Spira-Cohen et al. (2011)</a> <a href="#">Section 5.2.1.2</a> , <a href="#">Section 3.4.3</a>	
		Neural reflexes and/or inflammation lead to bronchoconstriction.	<a href="#">Section 4.3.6</a>

**Table 5-21 (Continued): Summary of evidence for a causal relationship between short-term sulfur dioxide exposure and respiratory effects.**

Rationale for Causal Determination <sup>a</sup>	Key Evidence <sup>b</sup>	Key References <sup>b</sup>	SO <sub>2</sub> Concentrations Associated with Effects <sup>c</sup>
Evidence for key events in proposed mode of action	Increased airway eosinophils in adults with asthma exposed to SO <sub>2</sub> Enhanced allergic inflammation in rats previously sensitized with an allergen and then repeatedly exposed to SO <sub>2</sub> .	<a href="#">Gong et al. (2001)</a> , <a href="#">Li et al. (2007)</a> , <a href="#">†Li et al. (2014)</a>	750–2,000 ppb
	Enhancement of allergic sensitization, allergic inflammation and airway responsiveness in guinea pigs exposed to SO <sub>2</sub> repeatedly over several days and subsequently sensitized and challenged with an allergen	<a href="#">Park et al. (2001)</a> , <a href="#">Riedel et al. (1988)</a>	100 ppb
	Allergic inflammation leads to increased airway responsiveness. Association with airway responsiveness among adults with asthma plus atopy	<a href="#">Taggart et al. (1996)</a>	24-h avg: max 39 ppb
<b>Other respiratory effects</b>			
Limited and inconsistent evidence across disciplines and outcomes	Inconsistent evidence for allergy exacerbation, COPD exacerbation, respiratory infection, respiratory diseases, hospital admissions and ED visits, and respiratory effects in healthy individuals	<a href="#">Section 5.2.1.3</a> , <a href="#">Section 5.2.1.4</a> , <a href="#">Section 5.2.1.5</a> , <a href="#">Section 5.2.1.6</a> , and <a href="#">Section 5.2.1.7</a>	
<b>Respiratory mortality</b>			
Consistent epidemiologic evidence from multiple studies at relevant SO <sub>2</sub> concentrations	Increases in respiratory mortality in multicity studies conducted in the U.S., Canada, Europe, and Asia	<a href="#">Section 5.2.1.8</a> and <a href="#">Section 5.5.1.3</a> <a href="#">Figure 5-8</a> and <a href="#">Figure 5-16</a>	Mean 24-h avg: U.S., Canada, Europe: 0.4–28.2 <sup>d</sup> ppb Asia: 0.7–>200 ppb <a href="#">Table 5-39</a>
Uncertainty regarding potential confounding by copollutants	No copollutant models with PM <sub>2.5</sub> . SO <sub>2</sub> associations remained positive but decreased in magnitude with adjustment for PM <sub>10</sub> or NO <sub>2</sub> , suggesting confounding. Studies limited to areas with high SO <sub>2</sub> concentrations, which complicates the interpretation of independent association for SO <sub>2</sub> .	<a href="#">Section 5.2.1.8</a> , <a href="#">Section 3.4.3</a>	

**Table 5-21 (Continued): Summary of evidence for a causal relationship between short-term sulfur dioxide exposure and respiratory effects.**

Rationale for Causal Determination <sup>a</sup>	Key Evidence <sup>b</sup>	Key References <sup>b</sup>	SO <sub>2</sub> Concentrations Associated with Effects <sup>c</sup>
Uncertainty regarding exposure measurement error	SO <sub>2</sub> exposures estimated from central site monitors may not capture spatiotemporal variability of SO <sub>2</sub> across a community.	<a href="#">Section 3.4.2</a>	

COPD = chronic obstructive pulmonary disease; ED = emergency department; NO<sub>2</sub> = nitrogen dioxide; PM<sub>10</sub> = particulate matter with a nominal aerodynamic diameter less than or equal to 10 µm; PM<sub>2.5</sub> = particulate matter with a nominal aerodynamic diameter less than or equal to 2.5 µm; *r* = correlation coefficient; SO<sub>2</sub> = sulfur dioxide.

<sup>a</sup>Based on aspects considered in judgments of causality and weight of evidence in causal framework in Table I and Table II of the [Preamble](#) to the ISAs ([U.S. EPA, 2015b](#)).

<sup>b</sup>Describes the key evidence and references, supporting or contradicting, contributing most heavily to causal determination and, where applicable, to uncertainties or inconsistencies. References to earlier sections indicate where the full body of evidence is described.

<sup>c</sup>Describes the SO<sub>2</sub> concentrations with which the evidence is substantiated (for experimental studies, below 2,000 ppb).

<sup>d</sup>The value of 28.2 represents the median concentration from [Katsouyanni et al. \(1997\)](#).

†Studies published since the 2008 Integrated Science Assessment for Sulfur Oxides.

## 5.2.2 Long-Term Exposure

1 The 2008 SO<sub>x</sub> ISA ([U.S. EPA, 2008d](#)) reviewed the epidemiologic and toxicological  
2 evidence for long-term exposure to SO<sub>2</sub> and respiratory effects and concluded that the  
3 evidence was inadequate to infer a causal relationship. Although some positive  
4 associations with asthma prevalence, bronchitis, symptoms, and lung function were  
5 observed among children, uncertainties made it difficult at that time to assess the  
6 evidence as a whole. Uncertainties related to assessing the consistency of findings across  
7 a diverse set of respiratory outcomes, the potential for exposure measurement error to  
8 influence results, and the lack of information available to assess the impact of copollutant  
9 confounding were cited in the document. The studies of long-term exposure to SO<sub>2</sub> and  
10 respiratory morbidity that were considered in the last review are found in Supplemental  
11 Table 5S-9 ([U.S. EPA, 2015f](#)). Animal toxicological studies of the effects of long-term  
12 exposure to SO<sub>2</sub>, which were reviewed in the 2008 SO<sub>x</sub> ISA ([U.S. EPA, 2008d](#)),  
13 examined lung function, morphology, and host defense. Most of these studies involved  
14 SO<sub>2</sub> concentrations well above 2 ppm. Recent toxicological studies add to this database.

15 Both older and more recent epidemiologic and toxicological studies that evaluate the  
16 relationship between long-term SO<sub>2</sub> exposure and asthma ([Section 5.2.2.1](#)), allergy  
17 ([Section 5.2.2.2](#)), lung function ([Section 5.2.2.3](#)), respiratory infection ([Section 5.2.2.4](#)),  
18 other respiratory diseases ([Section 5.2.2.5](#)), and respiratory mortality ([Section 5.2.2.6](#)) are  
19 discussed below. Recent cohort studies of asthma incidence ([Nishimura et al., 2013](#);  
20 [Clark et al., 2010](#)) use a longitudinal design, a methodological enhancement over the

1 cross-sectional studies of asthma prevalence available in the 2008 SO<sub>x</sub> ISA ([U.S. EPA, 2008d](#)). A recent study ([Ierodiakonou et al., 2015](#)) using a longitudinal design provides  
2 the first epidemiological report relating SO<sub>2</sub> exposure to AHR in human subjects with  
3 asthma. Uncertainties related to exposure estimates based on IDW concentrations or other  
4 estimates based on monitors (see [Section 3.3.1](#)) may limit the inferences that can be made  
5 for these recent studies. The majority of other recent and earlier epidemiologic studies  
6 used cross-sectional designs evaluating prevalence. Results were generally positive,  
7 although the strength of the associations varied across studies. The designs used  
8 (i.e., ecological, cross-sectional) limit the contribution of these studies to possible  
9 inferences about causality of relationships between long-term SO<sub>2</sub> exposure and  
10 respiratory effects. The caution expressed in the 2008 SO<sub>x</sub> ISA ([U.S. EPA, 2008d](#))  
11 related to the limitation of attributing an independent effect to SO<sub>2</sub> (due to the  
12 relationship of SO<sub>2</sub> levels to PM levels) is still a concern. The evidence base does not  
13 include studies evaluating concentration-responses, and few studies provide copollutant  
14 model analyses. The 2008 SO<sub>x</sub> ISA ([U.S. EPA, 2008d](#)) found that animal toxicological  
15 studies did not provide sufficient evidence to assess the effects of long-term SO<sub>2</sub>  
16 exposure on lung function, morphology, or host defense. The one new subchronic animal  
17 toxicological study that is discussed in this review found effects of SO<sub>2</sub> exposure on  
18 airway responsiveness, airway remodeling, and allergic inflammation. Short-term  
19 toxicological studies also provide some evidence for these responses to SO<sub>2</sub> exposure.  
20

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### 5.2.2.1 Development and Severity of Asthma

#### Development of Asthma

21 Asthma is described by the National Heart, Lung, and Blood Institute ([NHLBI NAEP, 2007](#)) as a chronic inflammatory disease of the airways that develops over time.  
22 Pulmonary inflammation can induce AHR, resulting in bronchoconstriction (bronchial  
23 smooth muscle contraction), and in turn, episodes of shortness of breath, coughing,  
24 wheezing, and chest tightness. When asthma advances in its development to the stage  
25 when the symptoms lead people to seek medical treatment, a diagnosis of asthma can  
26 result. Epidemiologic studies of SO<sub>2</sub> used self- or parental report of a diagnosis to define  
27 asthma. Epidemiologic studies reviewed in the 2008 SO<sub>x</sub> ISA ([U.S. EPA, 2008d](#)) were  
28 limited to those with cross-sectional designs [Supplemental Table 5S-9 ([U.S. EPA, 2015f](#))].  
29 The majority of these studies reported positive associations of long-term SO<sub>2</sub>  
30 exposure with asthma prevalence. A few recent longitudinal epidemiologic studies  
31 support associations with asthma incidence and provide coherent evidence for  
32 associations with respiratory symptoms in healthy populations. Uncertainty remains in  
33

1 the adequacy of SO<sub>2</sub> exposure estimates and copollutant confounding. However, some  
2 support for an effect of SO<sub>2</sub> exposure comes from a recent toxicological study showing  
3 SO<sub>2</sub>-induced AHR.

### ***Epidemiologic Studies***

4 A strength of recent epidemiologic studies of asthma development is their longitudinal  
5 design (see [Table 5-22](#)). The follow-up of children over time to mark the first record of a  
6 physician diagnosis with no prior record of diagnosis can better characterize the temporal  
7 sequence between SO<sub>2</sub> exposure and the incidence of asthma. In this regard, longitudinal  
8 studies can better distinguish between onset of asthma and the exacerbation of asthma. In  
9 a large multicity study (N = 4,320 from Chicago, IL, Bronx, NY, Houston, TX, San  
10 Francisco Bay Area, CA, and the territory of Puerto Rico), [Nishimura et al. \(2013\)](#)  
11 observed that for SO<sub>2</sub> exposures during the first year of life the OR and 95% CI for  
12 asthma incidence was 0.95 (0.59–1.47) per 5 ppb change. SO<sub>2</sub> exposure during the first  
13 3 years of life produced an OR and 95% CI for asthma incidence of 1.16 (0.73–1.84) per  
14 5 ppb SO<sub>2</sub>. SO<sub>2</sub> exposures were estimated using the IDW average of the four monitors  
15 within 50 km of the subject's residence. Selection bias due to differential loss to  
16 follow-up is not an issue given the retrospective design.

17 In a study of the British Columbia Birth Cohort (n =3,394 asthma cases), [Clark et al.](#)  
18 [\(2010\)](#) used IDW estimate-based concentrations from the three closest monitors within  
19 50 km of the participants postal code to estimate SO<sub>2</sub> exposure. These authors observed  
20 an adjusted OR (95% CI) per 5 ppb of 1.48 (1.3–1.9) due to average exposures both  
21 during pregnancy and the first year of life. Conducted in Southwest British Columbia, the  
22 study had 14 SO<sub>2</sub> monitors available to provide data. [Clark et al. \(2010\)](#) conducted a  
23 quartile analysis to explore the exposure-response relationship and observed that the  
24 trend across quartiles was not linear (i.e., for the first-year exposure model the second  
25 quartile was smaller, negative with confidence intervals less than 1.0, than the positive  
26 first and last quartiles), lessening the strength of the association. In this nested  
27 case-control study (n = 37,401), medical records of children ages 3–4 years (born  
28 1999–2000) were reviewed for asthma diagnosis ([Clark et al., 2010](#)). Selection bias due  
29 to differential loss to follow-up is not an issue, because of the records-based analysis  
30 used.

**Table 5-22 Selected epidemiologic studies of long-term exposure to SO<sub>2</sub> and the development of asthma and intervention studies/natural experiments.**

Study/Population	Location (Years)	Mean SO <sub>2</sub> ppb	Exposure Assessment	Selected Effect Estimates (95% CI) <sup>a</sup>
<b>Longitudinal studies of the development of asthma</b>				
† <a href="#">Nishimura et al. (2013)</a> GALA II and SAGE II cohorts (Latinos and African Americans 8–21 yr) N = 4,320	Chicago, IL; Bronx, NY; Houston, TX; San Francisco Bay Area, CA; and the territory of Puerto Rico (2006–2011)	4.0	IDW avg of monitors within 50 km of residence; annual avg and concentration during first 3 yr of life.  Copolutant correlations: NR	0.95 (0.59–1.47)—annual avg 1.16 (0.74–1.84)—early life exposure  Covariate adjustment: age, sex, ethnicity, and composite SES.
† <a href="#">Clark et al. (2010)</a> British Columbia Birth Cohort (N = 37,401)	Southwest British Columbia 1999–2000	In utero Controls: 5.11 Cases: 5.22 1st yr of life: Controls: 5.22 Cases: 5.37	IDW avg of three monitors within 50 km of postal code centroid. Concentrations for in utero and 1st yr of life estimated.  Copolutant correlations: NR	1.47 (1.30–1.89) (both in utero/1st yr of life) Covariate adjustment: native status, breast-feeding, maternal smoking, income quartile, birth weight, and gestational length.

**Table 5-22 (Continued): Selected epidemiologic studies of long term exposure to SO<sub>2</sub> and the development of asthma and intervention studies/natural experiments.**

Study/Population	Location (Years)	Mean SO <sub>2</sub> ppb	Exposure Assessment	Selected Effect Estimates (95% CI) <sup>a</sup>
<p>†(Chiang et al. (2016a), 2016b))</p> <p>Recruited 587 children aged between 11 and 14 yr from junior high schools in each of 9 townships.</p> <p>N = 587</p> <p>Incidence rates for asthma (ICD-9; 493) were obtained from the Taiwan Health Insurance Database.</p>	<p>Taiwan, near a petrochemical complex which yields a diverse pollution mix.</p> <p>1999 to 2010</p>	<p>The three-year average of the 99th percentage of SO<sub>2</sub> levels in high and low exposure areas after 2003 was 137.3 ppb and 32.0 ppb in the HE and LE areas respectively between 2003 and 2006. From 2003 to 2010, There were 138 h with hourly SO<sub>2</sub> concentrations above 75 ppb each year in the HE areas and 2 hours in LE areas.</p>	<p>Two air quality monitoring stations, part of the Taiwan Environmental Protection Administration (TEPA), provided the SO<sub>2</sub> levels in the HE and LE areas. One is located 8.1 km south of the complex, and the other 16.2 km east and south of the complex. Three exposure periods were reported since opening of the complex.</p> <p>Copollutant correlations NR.</p>	<p>The incidence rate of asthma in the HE group (18.5%) was significantly higher than that in the LE group (11.0%) in the first 4 yr after the complex began its operations. A difference in the incidence of asthma between the two groups emerged after 12 mo, and the maximum difference appeared at 40 mo. The hazard ratios of the incidences of asthma, during the different study periods were adjusted for group, age, gender, living near roads, incense burning and passive smoking exposure. In example for the third study period (1999–2010), HR (CI): 1.29 (0.91 to 1.83) for the difference between Hi and Low exposure areas.</p>
<p><b>Intervention studies and natural experiments</b></p>				
<p>Peters et al. (1996b)</p> <p>Children</p> <p>N = 3,521</p>	<p>Hong Kong, China (Kwai Tsing and Southern districts)</p> <p>Period of study: 1989–1991</p>	<p>Annual avg (µg/m<sup>3</sup>):</p> <p>Southern</p> <p>1989: 11</p> <p>1990: 8</p> <p>1991: 7</p> <p>Kwai Tsing</p> <p>1989: 111</p> <p>1990: 67</p> <p>1991: 23</p>	<p>Pre- and post-regulation concentrations compared in natural experiment; SO<sub>2</sub> emissions were reduced by 80% post-regulation.</p>	<p>Associations between respiratory symptoms and living in polluted areas observed and greater decline in symptoms post-regulation.</p> <p>Covariate adjustment: age, gender, environmental tobacco smoking in the family home, housing and father's education.</p>
<p>†Wong et al. (1998)</p> <p>Children (9–12 yr)</p> <p>N = 423</p>	<p>Hong Kong, China (Kwai Tsing and Southern districts)</p> <p>Period of study: 1989–1991</p>	<p>Annual avg (µg/m<sup>3</sup>):</p> <p>Southern</p> <p>1989: 11</p> <p>1990: 8</p> <p>1991: 7</p> <p>Kwai Tsing</p> <p>1989: 111</p> <p>1990: 67</p> <p>1991: 23</p>	<p>Pre- and post-regulation concentrations compared in natural experiment; SO<sub>2</sub> emissions were reduced by 80% post-regulation.</p>	<p>Decreased bronchial responsiveness observed post-intervention.</p>

**Table 5-22 (Continued): Selected epidemiologic studies of long term exposure to SO<sub>2</sub> and the development of asthma and intervention studies/natural experiments.**

Study/Population	Location (Years)	Mean SO <sub>2</sub> ppb	Exposure Assessment	Selected Effect Estimates (95% CI) <sup>a</sup>
<p><a href="#">†Iwasawa et al. (2009)</a> Miyake adults (N= 823)</p>	<p>Miyakejima Island, Japan, near Mt. Oyama volcano 2004–2006</p>	<p>31, post volcano (range: 19–45) Inhabited areas were classified into one lower SO<sub>2</sub> and three higher SO<sub>2</sub> areas to gauge exposure.</p>	<p>Seven monitors in residential areas used to estimate 2 yr avg; Natural experiment comparing symptom prevalence pre- and post-volcano eruption. Copollutant correlations: NR</p>	<p>Minor health effects on the respiratory system observed. Phlegm higher in higher exposure areas. Note: no consistent differences in lung function observed. Logistic regression model used. Covariate adjustment: sex, age, current smoking status, residential area, and hyper-susceptibility.</p>
<p><a href="#">†Iwasawa et al. (2015)</a> 120 Miyake school children</p>	<p>Feb. 2005 to Nov. 2011</p>	<p>Average concentrations (ppb) of SO<sub>2</sub> decreased year-by-year and ranged from 11.3 to 2.47 in low area, from 32.2 to 12.2 in high area-1, and from 75.1 to 12.1 in high area-2.</p>	<p>Six monitors in residential areas used to estimate post-volcano eruption concentrations in different residential areas. Other volcanic gases were measured and considered to be unlikely to cause the health effects seen in the study.</p>	<p>Prevalence of respiratory symptoms (cough, phlegm, wheeze, shortness of breath) was increased in areas with higher post-volcano SO<sub>2</sub> concentrations compared to areas with lower concentrations. Exposure-dependent increases in symptoms observed (no effects observed at concentrations lower than 30 ppb). Logistic regression model used. Covariate adjustment: age, sex, and hyper-susceptibility.</p>
<p><a href="#">†Longo et al. (2008)</a> <a href="#">†Longo (2009)</a> Adults (≥20 yr) N = 115 exposed N = 110 unexposed</p>	<p>Kilauea volcano, Hawaii Apr. to Jun. 2004</p>	<p>24.5 (exposed) 0.7 (unexposed). The emission pattern of the volcanic plume is carried over the exposed by the Pacific trade winds. The unexposed area is located at the extreme end of the island from the volcano.</p>	<p>Ambient and indoor SO<sub>2</sub> concentrations measured using a network of 70 passive samplers over a 3 wk sample period. Copollutant correlations: NR</p>	<p>Cough on most days for 3 consecutive months or more (acute bronchitis) per year increased in areas with higher levels. Note: associations with other symptoms also reported. Logistic regression model used. Covariate adjustment: age, sex, race, smoking, dust and body mass index.</p>

**Table 5-22 (Continued): Selected epidemiologic studies of long term exposure to SO<sub>2</sub> and the development of asthma and intervention studies/natural experiments.**

Study/Population	Location (Years)	Mean SO <sub>2</sub> ppb	Exposure Assessment	Selected Effect Estimates (95% CI) <sup>a</sup>
† <a href="#">Tam et al. (2016)</a> 1,836 4th/5th graders mean age 10,1 yr	Kilauea volcano, Hawaii 2002 to 2005	SO <sub>2</sub> , PM <sub>2.5</sub> , and particulate acid in four exposure zones. Mean (SD) SO <sub>2</sub> across zones ranged from 0.3 to 10.1 ppb.	SO <sub>2</sub> measured by passive diffusion for 1- to 4-wk intervals to determine zone levels at representative sites in each zone.	Strongly acidic respirable particulates associated with cough. SO <sub>2</sub> not evaluated specifically but included in the area mix which was not related to cough.  Cross-sectional study with adjustments for age, race, sex, sitting height, BMI, premature birth, maternal smoking during pregnancy, current smokers in the home, and visible mold in the home.

BMI = body mass index; CI = confidence interval; FEV<sub>1</sub> = forced expiratory volume in 1 second; FVC = forced vital capacity; IDW = inverse distance weighting; N = population number; NR = not reported; PM<sub>2.5</sub> = particulate matter with a nominal aerodynamic diameter less than or equal to 2.5 µm; SD = standard deviation; SES = socioeconomic status; SO<sub>2</sub> = sulfur dioxide.

<sup>a</sup>Effect estimates are standardized per 5-ppb increase in SO<sub>2</sub> concentrations unless otherwise noted.

†Studies published since the 2008 ISA for Sulfur Oxides.

1 Asthma incidence for school children from the Taiwan Health Insurance Database was  
2 evaluated contrasting high and low air pollution areas near a petrochemical complex for  
3 three time periods after the opening of the complex. The areas were indexed by 3-year  
4 annual average levels of the 99<sup>th</sup> % of SO<sub>2</sub> levels and periods above 75 ppb ([Chiang et al.,  
5 2016a, b](#)). The HRs were positive with wide confidence intervals for the three periods.  
6 Caution is required in inferences about an SO<sub>2</sub> effect because the areas examined  
7 represent complicated mixes from petrochemical complexes, the uncertainty for exposure  
8 error is high to include area comparisons rather than individual level comparisons, and  
9 the absence of evaluation for potential asthma risk factors.

10 The use of questionnaires in these studies to ascertain parents' report of  
11 physician-diagnosed asthma, a strength of the study design ([Burr, 1992](#); [Ferris, 1978](#)),  
12 adds to the strength of inference about associations with SO<sub>2</sub>. A limitation of these  
13 longitudinal studies include the potential for measurement error related to the use of IDW  
14 for SO<sub>2</sub> exposure estimates and comparison of high and low concentration areas (see  
15 [Section 3.3.2](#)). Validation of SO<sub>2</sub> exposures was not discussed for these studies.  
16 The standard increment used in the current ISA, 5 ppb for an annual average, is larger  
17 than the mean exposures in these studies, especially so for [Clark et al. \(2010\)](#) where the  
18 mean exposure and SD are 1.98 (0.97) ppb. Additionally, the strongest associations  
19 observed in both studies were with NO<sub>2</sub> concentration. Correlations between pollutant

1 concentrations were not reported by ([Chiang et al. \(2016a\)](#); [Nishimura et al. \(2013\)](#)),  
2 while [Clark et al. \(2010\)](#) noted that correlations between pollutant concentrations were  
3 generally high, but did not provide quantitative data. These studies suggest the potential  
4 for a relationship between long-term SO<sub>2</sub> exposure and the development of asthma.  
5 However, these results do little to reduce uncertainty related to potential copollutant  
6 confounding.

7 These studies considered confounding by asthma risk factors, which may be related to  
8 PM<sub>2.5</sub> exposure. All used information on maternal smoking. [Clark et al. \(2010\)](#) and  
9 [Nishimura et al. \(2013\)](#) examined parental education level. [Nishimura et al. \(2013\)](#)  
10 considered family history of allergy. These are key risk factors for asthma ([Paaso et al.,](#)  
11 [2014](#)). Other potentially important risk factors that do not appear to have been considered  
12 in these studies include respiratory infections, dampness, gas stove, pets, and daycare  
13 attendance ([Gehring et al., 2010](#)). Obesity identified as a potential risk factor for asthma  
14 in children ([Gilliland et al., 2003](#); [Gold et al., 2003](#)) was not evaluated in these studies.  
15 However [Borrell et al. \(2013\)](#) examined obesity in the cohorts studied by [Nishimura et al.](#)  
16 [\(2013\)](#) in a nonpollution study.

17 Several recent studies presented in Supplemental Table 5S-10 ([U.S. EPA, 2016p](#)) also  
18 examine the association of long-term exposure to SO<sub>2</sub> with the prevalence of asthma in  
19 cross-sectional designs with various SO<sub>2</sub> exposure estimates as discussed in the table.  
20 While these studies involve uncertainties, most ([Liu et al., 2016](#); [Deng et al., 2015a](#); [Liu](#)  
21 [et al., 2014a](#); [Dong et al., 2013c](#); [Dong et al., 2013b](#); [Kara et al., 2013](#); [Deger et al., 2012](#);  
22 [Portnov et al., 2012](#); [Akinbami et al., 2010](#); [Sahsuvaroglu et al., 2009](#)), but not all  
23 ([Portnov et al., 2012](#)), reported positive associations. These studies are consistent with  
24 similar studies in the 2008 SO<sub>x</sub> ISA ([U.S. EPA, 2008d](#)). [Deng et al. \(2015a\)](#) used  
25 multipollutant models and reported that adjusting SO<sub>2</sub> for PM<sub>10</sub> only slightly changes  
26 asthma risk. However, adjusting SO<sub>2</sub> for NO<sub>2</sub> substantially changed the SO<sub>2</sub> result. In  
27 addition, [Liu et al. \(2016\)](#) found that adjusting the effect in the single adjusted model for  
28 SO<sub>2</sub> was attenuated when further adjusted for NO<sub>2</sub> and PM<sub>10</sub>. No longitudinal study of  
29 asthma incidence evaluates copollutant models. Thus, within the recent epidemiologic  
30 evidence base, studies provide limited new data to reduce the uncertainty related to  
31 whether the effect was from SO<sub>2</sub> or another pollutant. Studies of asthma incidence  
32 strengthen the inference by addressing the temporality of exposure and response.

33 Supportive evidence for a relationship between long-term SO<sub>2</sub> exposure and the  
34 development of asthma is provided by cross-sectional studies of respiratory symptoms  
35 related to asthma. In the 2008 SO<sub>x</sub> ISA ([U.S. EPA, 2008d](#)), studies examining an array of  
36 respiratory symptoms related to SO<sub>2</sub> exposure are presented in Supplemental Table 5S-11  
37 ([U.S. EPA, 2016q](#)) and others are noted in the text of the 2008 SO<sub>x</sub> ISA ([U.S. EPA,](#)

1 [2008d](#); [Ware et al., 1986](#); [Chapman et al., 1985](#); [Dodge et al., 1985](#)). These  
2 cross-sectional studies used fixed site monitors for the SO<sub>2</sub> exposure estimate. While  
3 associations were generally positive, some inverse or null associations were also  
4 observed. Recent studies evaluating the relationship between long-term SO<sub>2</sub> exposure and  
5 the prevalence of asthma symptoms [Supplemental Table 5S-10 ([U.S. EPA, 2016p](#))] also  
6 found positive associations ([Altuğ et al., 2013](#); [Pan et al., 2010](#); [Arnedo-Pena et al.,](#)  
7 [2009](#)).

8 Additional epidemiologic evidence for a link between long-term exposure to SO<sub>2</sub> and the  
9 development of asthma may come from intervention or natural experiment studies (see  
10 [Table 5-22](#)). Physicians diagnose asthma, in part, based on the occurrence or  
11 exacerbation of asthma symptoms, such as cough and wheeze, and the level of bronchial  
12 hyperreactivity (BHR) in the subjects. Decline in such symptoms and BHR in relation to  
13 a decline of a pollutant level may support a relationship between asthma development  
14 and exposure to pollutants such as SO<sub>2</sub>. Decreases in respiratory symptoms, including  
15 any wheeze or asthmatic symptoms, wheezing, and cough and sore throat, in  
16 3,521 healthy children (mean age of 9.51 years) were associated with decreases in SO<sub>2</sub>  
17 concentrations in Hong Kong due to a government restriction of sulfur content of fuels as  
18 discussed in the 2008 SO<sub>x</sub> ISA [see [Peters et al. \(1996b\)](#), within [U.S. EPA \(2008d\)](#)].  
19 During the same period, [Wong et al. \(1998\)](#) examined the effect of the same decrease in  
20 SO<sub>2</sub> concentrations on BHR in children aged 9–12 who were non-wheezing and did not  
21 have asthma at study entry. In the cohort analysis, which compared measurements made  
22 before the intervention and 1 year afterwards, BHR declined. The subjective health  
23 measures seen in [Peters et al. \(1996b\)](#) were corroborated by the objective data of the  
24 histamine challenge test in [Wong et al. \(1998\)](#). These results should be interpreted with  
25 caution given the uncertainty of whether changes in BHR and respiratory symptoms were  
26 independently related to SO<sub>2</sub> in light of the concomitant decline in sulfate respirable  
27 suspended particles (RSP) (<10 μm). Over the study period, SO<sub>2</sub> declined about 80%  
28 (from about 111 to 23 μg/m<sup>3</sup> while annual mean sulfate concentrations in RSP fell from  
29 12.5 to 7.7 μg/m<sup>3</sup>. It is difficult to determine whether one was more important than the  
30 other. However, these studies add to the information base relating long-term SO<sub>2</sub>  
31 exposure and asthma-related outcomes.

32 Recent cross-sectional studies that estimated long-term SO<sub>2</sub> exposure from volcano  
33 emissions in Japan and Hawaii were conducted ([Table 5-22](#)). [Iwasawa et al. \(2009\)](#)  
34 observed increased frequencies of phlegm and minor effects on the respiratory system  
35 among both adults and children residing near the Mt. Ōyama volcano in Japan across four  
36 inhabitant areas with varying SO<sub>2</sub> levels. [Iwasawa et al. \(2015\)](#) further followed the  
37 children yearly from 2006 to 2011, finding the prevalence of respiratory symptoms  
38 (cough, phlegm, wheeze, shortness of breath) to be related to the higher SO<sub>2</sub> exposure.

1 Studies conducted near the Kīlauea volcano in Hawaii observed an adjusted increase in  
2 cough on most days for 3 consecutive months or more per year in children and adults  
3 ([Longo, 2009](#); [Longo and Yang, 2008](#); [Longo et al., 2008](#)). [Tam et al. \(2016\)](#) related  
4 cough to a mixture containing acidic respirable particulates, but not to SO<sub>2</sub> exposure  
5 directly, in children near the Kilauea volcano. As a whole, these studies are supportive of  
6 a link between SO<sub>2</sub> exposure and respiratory symptoms. However, such studies compare  
7 areas of high volcano emissions to areas of lower emissions (indexed by SO<sub>2</sub>  
8 concentration) and thus, results may be confounded by copollutant exposures.

### 9 **Severity of Asthma**

10 [NHLBI NAEPP \(2007\)](#) identifies stages of asthma such as mild, moderate,  
11 moderate-persistent, and severe. When going from mild to severe, the likelihood of acute  
12 exacerbations increases. Stages of worsening of asthma are usually based on severity  
13 scores as used in the following studies [Supplemental Table 5S-10, ([U.S. EPA, 2016p](#))].  
14 [Rage et al. \(2009\)](#) examined severity of asthma in adults. Long-term SO<sub>2</sub> exposure was  
15 correlated with a higher asthma severity score. Ozone showed the strongest relationship  
16 while NO<sub>2</sub> was unrelated. In 17--year-old male military recruits, [Greenberg et al. \(2016\)](#)  
17 related asthma severity to SO<sub>2</sub> measured as low, intermediate, and high. The observed  
18 associations between asthma severity and air pollution support the notion that air  
19 pollutants may increase asthma severity. However, the uncertainty related to these effects  
20 potentially being influenced by short-term exposure needs to be examined. [Deger et al.](#)  
21 [\(2012\)](#) examined the prevalence of active and poor asthma control in children and  
22 observed an association with long-term SO<sub>2</sub> exposure among children with active asthma  
23 and a more marked association among children with poor asthma control. No other  
24 pollutants were examined. Adjusting for child's age and sex, parental atopy and  
25 environmental tobacco smoke exposure slightly decreased the association, and  
26 stratification according to age (<6 years and ≥6 years) showed that associations with SO<sub>2</sub>  
27 were mainly observed in the older age group. Adjusting for socioeconomic status  
28 (i.e., household income and maternal educational level) had limited influence on the  
29 results of the analyses (<5%).

30 AHR is a key component of asthma. In a recent study, long-term exposures to SO<sub>2</sub> were  
31 associated with increased methacholine responsiveness determined by FEV<sub>1</sub> decreasing  
32 by 20% or more [provocative concentration 20 (PC<sub>20</sub>)] ([Ierodiakonou et al., 2015](#)), but  
33 results have uncertain inference because exposures were estimated from monitors up to  
34 50 km from subjects' ZIP code centroid. Further, a very large number of comparisons  
35 were made among pollutants, exposure lags, lung function parameters, cities, and asthma  
36 medication groups, and there is higher probability that the few associations observed are  
37 due to chance. The PC<sub>20</sub> percent change per interquartile range (2 ppb 4-month moving

1 average) was -6% (95% CI, -11% to -1.5%) in 2,661 observations in the Childhood  
2 Asthma Management Program (CAMP), a randomized clinical trial involving eight cities  
3 in North America. The PC<sub>20</sub> standardized to per 5 ppb is -15% (-27.5 to -3.75%).  
4 Four-month average SO<sub>2</sub> was not associated with changes in lung function measured  
5 before or after bronchodilator treatment. Health outcome results for 1-day and 1-week  
6 exposure periods are discussed earlier in [Section 5.2.1.2](#); only the 4-month moving  
7 average results are discussed here. The original health study, a longitudinal prospective  
8 cohort study with repeated measures but without a pollution component, was designed to  
9 examine the long-term safety and effectiveness of daily inhaled anti-inflammatory  
10 medication in children with mild to moderate asthma diagnosed and was sponsored by  
11 the NHLB. The children were 5 to 12 years of age and hyperresponsive to methacholine  
12 at study entry. Recruitment occurred from late December 1993 to early September 1995  
13 ([CAMP Research Group, 1999](#); [Cherniack et al., 1999](#)) at two HMO's and six academic  
14 institutions.

15 Monitoring data on 24-h avg concentrations of pollutants ozone, CO, NO<sub>2</sub>, and SO<sub>2</sub> were  
16 obtained for each metropolitan area from the Aerometric Information Retrieval System  
17 for the U.S. cities and from the Air Quality and Reporting Unit for Toronto were linked  
18 to the ZIP code of the subject's address at study entry. There is uncertainty in the  
19 measurement estimate and a potential for measurement error. Distance or proximity of  
20 sites to subjects is not known. For long-term studies bias can go in either direction. Thus,  
21 the evidence base for a relationship between long-term SO<sub>2</sub> exposure and AHR is limited.

### **Animal Toxicological Studies**

22 A single animal study of chronic SO<sub>2</sub> exposure-related effects on lung morphology was  
23 discussed in the 2008 SO<sub>x</sub> ISA ([U.S. EPA, 2008d](#)). Study characteristics are summarized  
24 in [Table 5-23](#). [Smith et al. \(1989\)](#) found that rats exposed to 1 ppm of SO<sub>2</sub> had an  
25 increased incidence of bronchiolar epithelial hyperplasia and increased numbers of  
26 nonciliated epithelial cells after 4 months of exposure. However, these effects were not  
27 present at 8 months of exposure, suggesting that repair and/or adaptation may have taken  
28 place.

**Table 5-23 Study-specific details from animal toxicological studies.**

Study	Species (strain); n; Sex; Lifestage/Age	Exposure Details (Concentration; Duration)	Endpoints Examined
<a href="#">Smith et al. (1989)</a>	Rats (Sprague-Dawley); n = 12–15 per data point; M; young adult; normal or elastase-impaired	1 ppm (2.62 mg/m <sup>3</sup> ) SO <sub>2</sub> whole body; 5 h/d, 5 d/wk for 4 or 8 mo 8-mo exposure group sacrificed immediately or 3 mo after exposure ended	Endpoints examined prior to sacrifice Lung function—residual volume, functional residual capacity, quasi-static compliance, residual volume/total lung capacity, N <sub>2</sub> washout Morphological effects Lung function—residual volume, functional residual capacity, quasi-static compliance, residual volume/total lung capacity, N <sub>2</sub> washout Endpoints examined after sacrifice Morphology
<a href="#">Song et al. (2012)</a>	Rats (Sprague-Dawley); n = 10/group; M; 4 wk old neonates	Sensitization by i.p. injection of 10 mg ovalbumin followed by booster injection of 10 mg ovalbumin after 7 d Challenge with 1% ovalbumin aerosol for 30 min daily for 4 wk beginning at 15 d Exposure to 2 ppm SO <sub>2</sub> for 4 h/d for 4 wk beginning at 15 d Exposure groups: (1) Control (2) SO <sub>2</sub> alone (3) Ovalbumin alone (4) Ovalbumin + SO <sub>2</sub>	Endpoints examined 24 h after challenge Lung function—whole body plethysmography (MCh challenge) BALF-IL-4, IFN-γ Serum-IL-4, IFN-γ Lung—histopathology In vitro culture of airway smooth muscle cells from experimentally treated animals—stiffness and contractility

BALF = bronchoalveolar lavage fluid; IFN-γ = interferon gamma; IL-4 = interleukin-4; i.p. = intraperitoneal; M = male; MCh = methacholine; n = sample size; N<sub>2</sub> = nitrogen; SD = standard deviation; SO<sub>2</sub> = sulfur dioxide.

1 No studies on airway responsiveness or pulmonary inflammatory responses to long-term  
 2 exposure to SO<sub>2</sub> concentrations of 2 ppm and lower were discussed in the 2008 SO<sub>x</sub> ISA  
 3 ([U.S. EPA, 2008d](#)). One new animal toxicological study of subchronic SO<sub>2</sub> exposure has  
 4 become available since the last review. Key findings are discussed here, and study  
 5 characteristics are summarized in [Table 5-23](#). [Song et al. \(2012\)](#) found that airway  
 6 responsiveness was enhanced in a model of allergic airways disease using rats that were  
 7 first sensitized and challenged with ovalbumin and then exposed to 2 ppm SO<sub>2</sub> for  
 8 4 hours/day for 28 days. Airway responsiveness was not changed with exposure to SO<sub>2</sub>  
 9 alone in naive rats. However, [Song et al. \(2012\)](#) observed hyperemia in the lung

1 parenchyma and inflammation in the airways of naive rats exposed only to SO<sub>2</sub>. SO<sub>2</sub>  
2 exposure also increased the inflammatory responses in rats made allergic to ovalbumin.  
3 Airway remodeling was found in ovalbumin-treated rats with and without exposure to  
4 SO<sub>2</sub>. A more pronounced increase in the airway smooth muscle layer was found in the  
5 ovalbumin/SO<sub>2</sub> group compared to the ovalbumin group. The authors concluded that the  
6 effects of SO<sub>2</sub> on airway responsiveness and airway remodeling were dependent on  
7 ovalbumin sensitization and challenge. [Song et al. \(2012\)](#) also measured concentrations  
8 of IL-4 and IFN- $\gamma$  in the BALF and serum of rats exposed to SO<sub>2</sub>, with and without prior  
9 sensitization and challenge with ovalbumin. Concentrations of IL-4 in the BALF were  
10 increased in the ovalbumin and the SO<sub>2</sub> groups, with the greatest increase occurring in  
11 the combined ovalbumin/SO<sub>2</sub> group. An increase in IL-4 in serum occurred only in the  
12 ovalbumin/SO<sub>2</sub> group. Concentrations of IFN- $\gamma$  in the BALF were decreased in the  
13 ovalbumin, SO<sub>2</sub>, and ovalbumin/SO<sub>2</sub> groups. A decrease in serum IFN- $\gamma$  was observed in  
14 the ovalbumin and ovalbumin/SO<sub>2</sub> groups. IL-4 is a Th2 cytokine associated with allergic  
15 responses, while IFN- $\gamma$  is a Th1 cytokine. An increase in the ratio of Th2 to Th1  
16 cytokines indicates Th2 polarization (or possibly a Type 2 immune response mediated by  
17 group 2 innate lymphoid cells), a key step in allergic sensitization. As discussed in prior  
18 sections, these findings provide evidence that repeated SO<sub>2</sub> exposure enhances allergic  
19 responses, airway remodeling, and airway responsiveness in this model of allergic airway  
20 disease. Furthermore, repeated SO<sub>2</sub> exposure in naive rats increased levels of the Th2  
21 cytokine IL-4, decreased levels of the Th1 cytokine IFN- $\gamma$  in the BALF, and increased  
22 airway inflammation suggesting that SO<sub>2</sub> exposure may on its own induce allergic  
23 sensitization. Because allergic sensitization, airway remodeling, and AHR are key events  
24 (or endpoints) in the proposed mode of action for the development of asthma  
25 ([Section 4.3.6](#)), these results suggest that long-term exposure to SO<sub>2</sub> may lead to the  
26 development of an asthma-like phenotype in this animal model involving newborn rats.

### **Summary of Asthma Development and Severity**

27 Recent epidemiologic evidence from a limited number of longitudinal studies report  
28 associations between asthma incidence among children and long-term SO<sub>2</sub> exposures.  
29 Additional supportive evidence for a link between long-term SO<sub>2</sub> exposure and the  
30 development of asthma is provided by cross-sectional studies of asthma prevalence.  
31 The longitudinal studies help reduce the uncertainty associated with the temporality of  
32 exposure and response that is inherent in cross-sectional study designs. This evidence is  
33 coherent with animal toxicological evidence of inflammation, allergic sensitization and  
34 other allergic responses, airway remodeling, and AHR, which are key events (or  
35 endpoints) in the proposed mode of action for the development of asthma ([Section 4.3.6](#)).  
36 The animal toxicological evidence provides support for an independent effect of SO<sub>2</sub> and

1 strengthens the link between long-term exposure to SO<sub>2</sub> and the development of asthma  
2 in children. Additional evidence supportive of this link comes from cross-sectional  
3 studies of respiratory symptoms and respiratory allergies among children and from  
4 natural experiments. Thus, multiple lines of evidence suggest that long-term SO<sub>2</sub>  
5 exposure results in a coherent and biologically plausible sequence of events that  
6 culminates in the development of asthma, especially allergic asthma, in children.

7 The potential for a relationship between long-term SO<sub>2</sub> exposure and severity of asthma  
8 has been examined in a few studies. One study in adults correlated exposure with higher  
9 asthma severity scores. A study in children found a more marked association in those  
10 with poor asthma control. AHR, measured as PC<sub>20</sub>, worsened with long-term SO<sub>2</sub>  
11 exposure in a multicity cohort of children. Thus, evidence of asthma control and  
12 increased AHR provides suggestive but limited support for this relationship.

---

### 5.2.2.2 Development of Allergy

13 There is some evidence for a potential relationship between long-term SO<sub>2</sub> exposure and  
14 indicators or respiratory allergies and inflammation among children. Several recent  
15 cross-sectional studies examined the prevalence of respiratory allergies using different  
16 markers for respiratory allergies including IgE antibodies, rhinitis, eczema, sensitization  
17 to pollen, and hay fever related to long-term SO<sub>2</sub> exposure ([Liu et al., 2016](#); [Chan et al.,  
18 2013](#); [Bhattacharyya and Shapiro, 2010](#); [Penard-Morand et al., 2010](#); [Parker et al., 2009](#);  
19 [Nordling et al., 2008](#)) [see Supplemental Table 5S-11 ([U.S. EPA, 2016q](#))]. Positive  
20 results were observed for children using these various indicators of allergy. Further, a  
21 very weak relationship was found [Dales et al. \(2008\)](#) between long-term SO<sub>2</sub> exposure  
22 and eNO, an indicator of inflammation [see Supplemental Table 5S-11 ([U.S. EPA,  
23 2016q](#))].

24 Recent studies examine two-pollutant models for allergic rhinitis prevalence. Results for  
25 allergic rhinitis prevalence based on responses from ISAAC questionnaire data in  
26 Changsha China ([Chan et al., 2013](#)) did not find an association for SO<sub>2</sub> for site-specific  
27 background SO<sub>2</sub> and allergic rhinitis in children 3–6 year old, but did find an association  
28 for age-related accumulative exposure in a single pollutant model using the closest  
29 monitor to kindergartens. The two-pollutant model with PM<sub>10</sub> was attenuated. For SO<sub>2</sub>  
30 exposures during the first year of life in Shanghai, China, [Liu et al. \(2016\)](#) found an  
31 association with allergic rhinitis in children at age 6 which was attenuated when adjusted  
32 for other pollutants using district monitors. These findings suggest the possibility that  
33 chronic exposure to SO<sub>2</sub> may play a role in the development of allergic conditions based  
34 on results for various allergic markers. The cross-sectional design of these studies makes

1 these relationships uncertain and the exposure estimates from monitors is subject to the  
2 possibility of measurement error and uncertainties informing the representativeness of the  
3 exposure estimates in the studies as discussed in [Section 3.4.2](#). Thus, the evidence base  
4 for a relationship between long-term SO<sub>2</sub> exposure and allergic rhinitis response is  
5 limited and two-pollutant model begin to characterize the role of SO<sub>2</sub> exposure.

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### 5.2.2.3 Lung Function

#### Epidemiologic Studies

6 Longitudinal epidemiologic studies examine associations between long-term SO<sub>2</sub>  
7 exposure and decrements in lung function. Lung function grows through early adulthood  
8 with growth and development, then declines with aging ([Stanojevic et al., 2008](#); [Zeman  
9 and Bennett, 2006](#); [Thurlbeck, 1982](#)). Thus, a relationship between long-term SO<sub>2</sub>  
10 exposure and decreased lung function over time in school-age children into early  
11 adulthood would be an indicator of decreased lung development.

12 As discussed in the 2008 SO<sub>x</sub> ISA ([U.S. EPA, 2008d](#)), earlier cross-sectional studies  
13 ([Dockery et al., 1989](#); [Schwartz, 1989](#)) found no association between long-term SO<sub>2</sub>  
14 exposure and lung function in U.S. children. A longitudinal cohort study ([Frischer et al.,  
15 1999](#)) reported that long-term SO<sub>2</sub> exposure was associated with decrements in lung  
16 function in the summer but not in the winter. In Poland, a prospective cohort study of  
17 children ([Jedrychowski et al., 1999](#)) found decrements in lung function growth related to  
18 a polluted area where concentrations of both TSP and SO<sub>2</sub> were high compared to a  
19 cleaner area where concentrations of both TSP and SO<sub>2</sub> were low, thus not providing  
20 results specifically for SO<sub>2</sub>. In a cross-sectional study in adults in Switzerland,  
21 [Ackermann-Lieblich et al. \(1997\)](#) observed an association between SO<sub>2</sub> concentration  
22 and lung function, but after controlling for PM<sub>10</sub>, this association was no longer evident.  
23 In the former East Germany from 1992 to 1999, [Frye et al. \(2003\)](#) reported improvements  
24 in lung function associated with declines in SO<sub>2</sub> concentrations in 2,493 children over  
25 three cross-sectional surveys. These studies are presented in Supplemental Table 5S-9  
26 ([U.S. EPA, 2015f](#)).

27 Recent studies in children and adults add to this evidence base [see Supplemental  
28 Table 5S-12 ([U.S. EPA, 2016r](#))]. In a repeated measure prospective study of the TCHS  
29 cohort, [Hwang et al. \(2015a\)](#) examined lung function growth for a 2 year period from age  
30 12 to 14 years. No association was found for SO<sub>2</sub> exposure and FEV<sub>1</sub> or FVC for boys  
31 and girls, but a deficit was observed for boys for FEF<sub>25-75</sub>. A single measure longitudinal  
32 study in several U.S. cites observed for first year of life exposures a suggestive

1 association for SO<sub>2</sub> and FEV<sub>1</sub>. [Neophytou et al. \(2016\)](#) examined the same cohort that  
2 [Nishimura et al. \(2013\)](#) did as discussed earlier in this section for asthma incidence in the  
3 same cities with the same SO<sub>2</sub> exposure method evaluating the same confounding factors  
4 plus obesity. For each 1 ppb increase of SO<sub>2</sub> percent change in FEV<sub>1</sub> and the 95% CI  
5 were -1.01 (-3.25, 1.27).

6 In a cross-sectional, longitudinal repeated-measures study of children, [Linares et al.](#)  
7 [\(2010\)](#) reported a decline in FEV<sub>1</sub> related to long-term SO<sub>2</sub> exposure in the entire study  
8 group. This study included children from two schools in different locations relative to a  
9 petrochemical zone. In an analysis of the children by sex, in one- and two-pollutant  
10 analysis of PM<sub>10</sub> and O<sub>3</sub>, the outcome was attenuated. In a cross-sectional study of  
11 children in 14 communities in Taiwan, [Lee et al. \(2011c\)](#) found a reduction in FEV<sub>1</sub>  
12 related to long-term SO<sub>2</sub> exposure with larger reductions related to NO<sub>2</sub> and CO  
13 exposure. [Yogev-Baggio et al. \(2010\)](#) related the effect of the interaction, NO<sub>x</sub> × SO<sub>2</sub>  
14 “event,” to reduction in FEV<sub>1</sub> in children in Israel near a coal-fired power plant. In a  
15 cross-sectional study of 32,712 adults in England, [Forbes et al. \(2009c\)](#) related FEV<sub>1</sub>  
16 effects to exposure to SO<sub>2</sub>, PM<sub>10</sub>, and NO<sub>2</sub>, but not O<sub>3</sub>. A U.K. study of  
17 alpha-1-antitrypsin deficiency and COPD ([Wood et al., 2010](#)) found reduced FEV<sub>1</sub> in  
18 relation to SO<sub>2</sub> concentration but a more rapid decline in relation to PM<sub>10</sub> concentration.  
19 [Dales et al. \(2008\)](#) found a weak decline in FEV<sub>1</sub> and FVC related to long-term SO<sub>2</sub>  
20 exposure in school children in Windsor, ON using a cross-sectional prevalence design.

21 The majority of the recent studies and earlier studies used cross-sectional designs. Some  
22 studies took into account potentially confounding covariates detailed in the Supplemental  
23 Table 5S-12 ([U.S. EPA, 2016r](#)). [Neophytou et al. \(2016\)](#) controlled for age, height, and  
24 calendar time, allowing for nonlinear effects, indicator variables for sex, race/ethnicity,  
25 and continuous variables for SES (composite score variable), and numbers of smokers in  
26 the household and also assessed effect modification by sex, obesity, SES, atopy, and  
27 parental asthma. The designs used in most of the recent studies (i.e., ecological,  
28 cross-sectional, single measure) limit the possible inferences about the relationship  
29 between long-term SO<sub>2</sub> exposure and lung function. The evidence does not include  
30 studies evaluating concentration-responses. The one study conducting a copollutant  
31 analysis found attenuation of the effect with adjustment for PM<sub>10</sub>. Thus, recent studies do  
32 not add information that changes conclusions made in the 2008 SO<sub>x</sub> ISA ([U.S. EPA,](#)  
33 [2008d](#)) that there is not clear evidence that long-term SO<sub>2</sub> exposure is related to lung  
34 function changes.

## Animal Toxicological Studies

1 A single long-term study with SO<sub>2</sub> exposure concentrations at or below 2 ppm was  
2 discussed in the 2008 SO<sub>x</sub> ISA ([U.S. EPA, 2008d](#)). Study characteristics are summarized  
3 in [Table 5-23](#). [Smith et al. \(1989\)](#) found that rats exposed to 1 ppm SO<sub>2</sub> for 4 months had  
4 decreased residual volume and quasi-static compliance when treated with saline (control).  
5 Rats treated with elastase (a model of emphysema) and exposed to 1 ppm SO<sub>2</sub> for  
6 4 months had a decreased ratio of residual volume to total lung capacity and decreased  
7 alveolar plateau of the single-breath nitrogen (N<sub>2</sub>) washout (N<sub>2</sub>-slope), indicating a  
8 worsening of the emphysema. However, [Smith et al. \(1989\)](#) concluded that the effects of  
9 SO<sub>2</sub> on lung function measurements were very minor in the saline (control) group and  
10 likely due to chance alone (residual volume) or to unusually high control values  
11 (quasi-static compliance).

## Summary of Lung Function

12 Several studies evaluated the relationship between long-term SO<sub>2</sub> exposure and  
13 decrements in lung function. Evidence supporting this relationship is limited because  
14 associations were inconsistent and because both PM and SO<sub>2</sub> were at high concentrations  
15 in the same areas, which does not allow determination of individual SO<sub>2</sub> effects. Potential  
16 confounding of long-term SO<sub>2</sub> exposure-related decrements in lung function and lung  
17 development by other pollutants, especially PM, was evaluated in only one study. This  
18 study found an attenuation of the effect in copollutant analyses. No changes in lung  
19 function were found in long-term animal toxicological studies at relevant SO<sub>2</sub>  
20 concentrations. The recent studies support conclusions of no association between  
21 long-term SO<sub>2</sub> exposure and lung function in children made in the 2008 SO<sub>x</sub> ISA ([U.S.](#)  
22 [EPA, 2008d](#)).

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### 5.2.2.4 Respiratory Infection

#### Epidemiologic Studies

23 Studies have also examined the association of long-term exposure to SO<sub>2</sub> with infant  
24 bronchiolitis, otitis media, and pneumonia in children, hospital admission for  
25 community-acquired pneumonia in adults aged 65 years or more, and tuberculosis in  
26 adults. Infant bronchiolitis was examined in British Columbia by [Karr et al. \(2009\)](#).  
27 These authors observed an association with lifetime exposure to SO<sub>2</sub> after adjustment for  
28 an array of confounders [Supplemental Table 5S-11 ([U.S. EPA, 2016q](#))]. The largest  
29 associations were observed with NO<sub>2</sub> and CO concentrations. [MacIntyre et al. \(2011\)](#)

1 found no increased risk for otitis media in relation to long-term SO<sub>2</sub> exposure in a study  
2 of children up to the age of 2 in British Columbia, while [Bhattacharyya and Shapiro](#)  
3 [\(2010\)](#) found a strong relationship with long-term SO<sub>2</sub> exposure in the U.S. National  
4 Health Interview Survey of 126,060 children ages 3–6 years. [Lu et al. \(2014\)](#) observed  
5 that the prevalence of pneumonia in children 3 to 6 year old was related to long-term SO<sub>2</sub>  
6 exposure. [Liu et al. \(2016\)](#) reported that doctor-diagnosed pneumonia in children  
7 4–6 years old was related to SO<sub>2</sub> exposure during the first year of life. [Neupane et al.](#)  
8 [\(2010\)](#) estimated long-term SO<sub>2</sub> exposure at the residence for both the case and control  
9 subjects with bicubic splined (SPL) and IDW methods for the 2-yr avg for 2001 and  
10 2002, obtaining means of 4.65 ppb and 5.80 ppb, respectively, but with a twofold greater  
11 range for SPL. Adjusted estimates of associations for SO<sub>2</sub> with hospitalization from  
12 community-acquired pneumonia were positive for SPL but not for IDW. The incidence of  
13 tuberculosis was associated with an increase of SO<sub>2</sub> in adult males ([Hwang et al., 2014](#))  
14 but not in a study in California ([Smith et al., 2016](#)). Although limited in number, by  
15 inconsistency, and by their cross-sectional design, these studies suggest a potential  
16 relationship between long-term exposure to SO<sub>2</sub> and respiratory infections due to various  
17 infectious agents.

### **Animal Toxicological Studies**

18 No new animal studies of the effects of long-term SO<sub>2</sub> exposure on lung host defense  
19 have been conducted since the previous review. Several studies of short- and long-term  
20 exposure to SO<sub>2</sub> were reported in the 1982 AQCD ([U.S. EPA, 1982a](#)) and discussed in  
21 the 2008 SO<sub>x</sub> ISA ([U.S. EPA, 2008d](#)). Short-term exposure studies found some effects of  
22 0.1–1 ppm SO<sub>2</sub> on the clearance of labeled particles. Long-term exposure studies found  
23 decreased tracheal mucus flow at a concentration of 1 ppm SO<sub>2</sub>, but no effects on  
24 susceptibility to bacterial infection or alterations in the pulmonary immune system at  
25 concentrations of 2 ppm or less.

### **Summary of Respiratory Infection**

26 Evidence for prevalence of infant bronchiolitis and/or respiratory infections consists of  
27 generally positive associations found in cross-sectional studies. Thus, they provide a  
28 limited evidence base in number and design. While some animal toxicological studies  
29 reported alterations in specific host defense mechanisms, there is no evidence to support  
30 increases in bacterial or viral infections in animals exposed to SO<sub>2</sub> at relevant  
31 concentrations.

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### 5.2.2.5 Development of Other Respiratory Diseases: Chronic Bronchitis, Chronic Obstructive Pulmonary Disease, and Acute Respiratory Distress Syndrome

1 Chronic bronchitis consists of symptoms, including daily cough and/or congestion or  
2 phlegm for 3 months in a row. While these symptoms may have started with acute  
3 exacerbation, they are likely to represent chronic indolent symptoms. As discussed in the  
4 2008 SO<sub>x</sub> ISA ([U.S. EPA, 2008d](#)), earlier cross-sectional studies observed positive  
5 relationships between long-term SO<sub>2</sub> exposure estimates derived from fixed site monitors  
6 and chronic bronchitis as presented in Supplemental Table 5S-11 ([U.S. EPA, 2016q](#)).  
7 Recent cross-sectional studies of the association of long-term exposure to SO<sub>2</sub> with the  
8 prevalence of bronchitis also observed positive relationships after adjustment for  
9 potential confounders. In addition, a recent COPD incidence study in a national English  
10 cohort ([Atkinson et al., 2015](#)), discussed in Supplemental Table 5S-11 ([U.S. EPA,](#)  
11 [2016q](#)), reported a positive association in an adjusted HR model with SO<sub>2</sub> exposure  
12 averaged over 3 years determined by dispersion models. Assessment of model validity  
13 using national network sites and separate verification sites yielded poor *R*<sup>2</sup> values for SO<sub>2</sub>  
14 of 0 and 0.39, respectively. Other limitations of this study include a short follow-up time  
15 and the failure to confirm the 36% of incident hospital admissions for COPD by a general  
16 practitioner diagnosis.

17 A relationship between Acute Respiratory Distress Syndrome (ARDS) and long-term SO<sub>2</sub>  
18 exposure has recently been studied ([Ware et al., 1986](#)) as discussed in Supplementary  
19 Table 5S-11 ([U.S. EPA, 2016q](#)). SO<sub>2</sub> and PM<sub>2.5</sub> were not associated with ARDS.

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### 5.2.2.6 Respiratory Mortality

20 Recent studies provide some evidence that respiratory mortality may be more  
21 consistently associated with long-term exposure to SO<sub>2</sub> than other causes of death  
22 ([Section 5.5.2](#) and [Figure 5-27](#)). There is uncertainty in the small, positive associations  
23 between long-term exposure to SO<sub>2</sub> and respiratory mortality observed in these studies,  
24 because the exposure assessment and statistical methods are not adequate for studying a  
25 highly spatially and temporally heterogeneous pollutant like SO<sub>2</sub>. Additionally, there is  
26 little evidence of respiratory health effects in adults in relation to long-term SO<sub>2</sub> exposure  
27 that could provide coherence with the observed associations with respiratory mortalities.

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### 5.2.2.7 Summary and Causal Determination

28 Overall, the evidence is suggestive of, but not sufficient to infer, a causal relationship  
29 between long-term SO<sub>2</sub> exposure and respiratory effects, mainly the development of

1 asthma in children. This conclusion represents a change from “inadequate to infer a  
2 causal association” for respiratory effects as stated in the 2008 SO<sub>x</sub> ISA ([U.S. EPA,  
3 2008d](#)).

4 Recent epidemiologic evidence from a limited number of longitudinal studies report  
5 associations between asthma incidence among children and long-term SO<sub>2</sub> exposures.  
6 The longitudinal studies address the temporality of exposure and response and help to  
7 reduce the uncertainty associated with temporality that is inherent in cross-sectional study  
8 designs. The evidence from longitudinal studies is coherent with animal toxicological  
9 evidence of allergic sensitization, airway remodeling, and enhanced airway  
10 responsiveness, which are key events (or endpoints) in the proposed mode of action for  
11 the development of asthma. The animal toxicological evidence provides support for an  
12 independent effect of SO<sub>2</sub> and a possible relationship between long-term exposure to SO<sub>2</sub>  
13 and the development of asthma in children. Some evidence of a link between long-term  
14 exposure to SO<sub>2</sub> and respiratory symptoms and/or respiratory allergies among children  
15 further supports this relationship. The potential for SO<sub>2</sub> to serve as an indicator for other  
16 pollutants or mixture related to PM is an uncertainty that applies to the new body of  
17 epidemiologic evidence across the respiratory effects examined.

18 The key evidence supporting the causal determination is detailed below using the  
19 framework described in Table I of the [Preamble](#) to the ISAs ([U.S. EPA, 2015b](#)) and is  
20 presented in [Table 5-24](#).

### **Evidence for the Development of Asthma**

21 A limited number of longitudinal studies demonstrate associations between ambient SO<sub>2</sub>  
22 concentrations measured in the first year of life and/or over the first 3 years of life in  
23 children and asthma incidence such as ([Clark et al., 2010](#)) and ([Nishimura et al., 2013](#))  
24 ([Section 5.5.2.1](#)). Results are fairly consistent between studies with one based on several  
25 different locations across the U.S., another over a large area in Canada, and one in  
26 Taiwan, involving a large number of participants. Uncertainties and the potential for  
27 measurement error related to the use of IDW and area comparisons in these studies may  
28 limit inferences that can be made ([Section 3.4.2](#)). Additional supportive evidence for a  
29 link between long-term SO<sub>2</sub> exposure and the development of asthma is provided by  
30 cross-sectional studies of asthma prevalence, respiratory symptoms, and markers of  
31 respiratory allergies among children ([Section 5.2.2.2](#)). Findings of studies evaluating  
32 respiratory symptoms are supportive of the development of asthma; however, they may  
33 also reflect other respiratory conditions. Intervention and natural experiment studies also  
34 indicate a possible relationship between long-term exposure to SO<sub>2</sub> and the development  
35 of asthma.

**Table 5-24 Summary of evidence for a suggestive of, but not sufficient to infer, a causal relationship between long-term sulfur dioxide exposure and respiratory effects.**

Rationale for Causal Determination <sup>a</sup>	Key Evidence <sup>b</sup>	Key References <sup>b</sup>	SO <sub>2</sub> Concentrations Associated with Effects <sup>c</sup>
<b>Development and severity of asthma</b>			
Evidence from epidemiologic studies is generally supportive but not entirely consistent	Evidence for increases in asthma incidence in cohorts of children in U.S. and Canada. Adequate adjustment for confounding by asthma risk factors. Some inconsistency regarding time window	<a href="#">Nishimura et al. (2013)</a> <a href="#">Clark et al. (2010)</a>	Mean (SD) across five cities 4.0 (3.4) ppb 1.98 (0.97) ppb
	Supporting cross-sectional studies of asthma prevalence among children but uncertainty regarding the temporal sequence between exposure and the development of asthma	<a href="#">Section 5.2.2.1</a>	
	Supporting evidence for respiratory symptoms and markers of respiratory allergies among children in cross-sectional studies	<a href="#">Section 5.2.2.1 and Section 5.2.2.2</a>	
	Supporting evidence from intervention studies and natural experiments	<a href="#">Section 5.2.2.1</a>	
	Evidence for increases in asthma severity as indicated by asthma severity score, degree of asthma control, and AHR	<a href="#">Section 5.2.2.1</a>	
Uncertainty regarding potential for measurement error in exposure estimates	Use of IDW in asthma incidence studies and fixed monitoring sites in cross-sectional studies	<a href="#">Section 3.4.2</a>	
Uncertainty regarding potential confounding by copollutants	No copollutant models analyzed in asthma incidence studies; limited evidence from cross-sectional studies that observed effects are robust to copollutant adjustment	<a href="#">Section 3.4.3</a> <a href="#">(Liu et al. (2016); Deng et al. (2015a))</a>	

**Table 5-24 (Continued): Summary of evidence for a suggestive of, but not sufficient to infer, a causal relationship between long term sulfur dioxide exposure and respiratory effects.**

Rationale for Causal Determination <sup>a</sup>	Key Evidence <sup>b</sup>	Key References <sup>b</sup>	SO <sub>2</sub> Concentrations Associated with Effects <sup>c</sup>
Limited animal toxicological evidence provides coherence and biological plausibility	Th2 polarization (or other Type 2 immune responses) and airway inflammation following repeated exposure of naive newborn rats for 28 d  Evidence for enhanced inflammation, airway remodeling and AHR following repeated exposure of allergic newborn rats for 28 d	<a href="#">Song et al. (2012)</a>	2,000 ppb
Coherence with evidence from short-term animal toxicological studies	Inflammation and morphologic responses indicative of airway remodeling following repeated exposures of naive rats over several days	<a href="#">Li et al. (2007)</a> <a href="#">Li et al. (2014)</a>	2,000 ppb
	Enhancement of allergic sensitization, allergic inflammation, airway responsiveness in guinea pigs exposed repeatedly over several days and subsequently sensitized and challenged with an allergen	<a href="#">Riedel et al. (1988)</a> <a href="#">Park et al. (2001)</a>	100 ppb 100 ppb
	Enhanced inflammation and allergic responses in rats previously sensitized with an allergen and then repeatedly exposed	<a href="#">Li et al. (2007)</a> <a href="#">Li et al. (2014)</a>	2,000 ppb
Some evidence for key events in proposed mode of action	Inflammation, allergic sensitization, AHR, airway remodeling	<a href="#">Section 4.3.6</a>	
<b>Development of allergy</b>			
Limited epidemiologic evidence but uncertainty regarding SO <sub>2</sub> independent effects	Generally positive associations with different markers for allergies in cross-sectional studies in children. Uncertainty in temporality and exposures estimated from central site monitors; copollutant confounding examined on a limited basis remains uncertain	<a href="#">Section 5.2.2.2</a>	
<b>Lung function</b>			
Inconsistent epidemiologic evidence among children from quality studies and uncertainty regarding SO <sub>2</sub> independent effects	In cohort studies, associations inconsistent with adjustment for PM and by season	<a href="#">Neophytou et al. (2016)</a> <a href="#">Jedrychowski et al. (1999)</a> <a href="#">Frischer et al. (1999)</a>	
	Inconsistent results from cross-sectional studies	<a href="#">Dockery et al. (1989)</a> <a href="#">Schwartz (1989)</a> <a href="#">Ackermann-Lieblich et al. (1997)</a> <a href="#">Frye et al. (2003)</a>	

**Table 5-24 (Continued): Summary of evidence for a suggestive of, but not sufficient to infer, a causal relationship between long term sulfur dioxide exposure and respiratory effects.**

Rationale for Causal Determination <sup>a</sup>	Key Evidence <sup>b</sup>	Key References <sup>b</sup>	SO <sub>2</sub> Concentrations Associated with Effects <sup>c</sup>
<b>Respiratory infection</b>			
Limited epidemiologic evidence; uncertainty regarding SO <sub>2</sub> independent effects	Generally positive associations in cross-sectional studies. Uncertainty in temporality, exposures estimated from monitors in the community, and copollutant confounding	<a href="#">Section 5.2.2.4</a>	
Limited animal toxicological evidence	Altered clearance of particles and decreased tracheal mucus flow	<a href="#">U.S. EPA (1982a)</a>	0.1–1 ppm
Lack of evidence for key events in proposed mode of action	Changes in specific host defense mechanisms but no evidence of greater infectivity		
<b>Development of other respiratory diseases</b>			
Limited epidemiologic evidence but uncertainty regarding SO <sub>2</sub> independent effects	Generally positive associations for chronic bronchitis in cross-sectional studies. Uncertainty in temporality, exposures estimated from monitors in the community, and copollutant confounding	<a href="#">Section 5.2.2.5</a>	
<b>Respiratory mortality</b>			
Generally consistent epidemiologic evidence	Small, positive associations between long-term exposure to SO <sub>2</sub> and respiratory mortality in several cohorts, even after adjustment for common potential confounders	<a href="#">Hart et al. (2011)</a> , <a href="#">Nafstad et al. (2004)</a> , <a href="#">Elliott et al. (2007)</a> , <a href="#">Cao et al. (2011)</a> , <a href="#">Carey et al. (2013)</a> , <a href="#">Dong et al. (2012)</a> , <a href="#">Katanoda et al. (2011)</a>	2.4–41.4
No coherence between respiratory morbidity in and respiratory mortality	No evidence for a relationship between long-term exposure and respiratory mortality to support the observed associations with respiratory morbidity	<a href="#">Section 5.2.2.6</a>	

AHR = airway hyper-responsiveness; IDW = inverse distance weighting; PM = particulate matter; SD = standard deviation; SO<sub>2</sub> = sulfur dioxide.

<sup>a</sup>Based on aspects considered in judgments of causality and weight of evidence in causal framework in Table I and Table II of the [Preamble](#) to the ISAs ([U.S. EPA, 2015b](#)).

<sup>b</sup>Describes the key evidence and references, supporting or contradicting, contributing most heavily to causal determination, and where applicable, to uncertainties or inconsistencies. References to earlier sections indicate where the full body of evidence is described.

<sup>c</sup>Describes the SO<sub>2</sub> concentrations with which the evidence is substantiated (for experimental studies, ≤2,000 ppb).

1 Epidemiologic studies of asthma development in children have not clearly characterized  
2 potential confounding by other pollutants or mixtures of pollutants. This uncertainty was  
3 present in the previous review, and there is no new information from incidence studies to  
4 help reduce this uncertainty. No studies of asthma incidence have evaluated copollutant  
5 models to address copollutant confounding, making it difficult to evaluate the  
6 independent effect of SO<sub>2</sub> within the epidemiologic evidence base for incidence.  
7 A limited number of recent cross-sectional studies of asthma prevalence involving  
8 two-pollutant models provide preliminary information to characterize the role of  
9 long-term SO<sub>2</sub> exposure. In studies that examined both SO<sub>2</sub> and PM<sub>2.5</sub>, positive  
10 associations were observed between PM<sub>2.5</sub> concentrations and asthma development; the  
11 effects were similar in magnitude to those for SO<sub>2</sub> ([Nishimura et al., 2013](#); [Clark et al.,  
12 2010](#)). Correlations between SO<sub>2</sub> and PM<sub>2.5</sub> were not reported in these studies. Thus,  
13 results from these two studies do not reduce the uncertainty related to potential  
14 copollutant confounding.

15 The uncertainties in the epidemiologic evidence base is reduced, in part, by the biological  
16 plausibility provided by findings from experimental studies that demonstrate  
17 SO<sub>2</sub>-induced effects on key events or endpoints that are part of the proposed mode of  
18 action for development of asthma [i.e., allergic sensitization, airway remodeling and  
19 AHR ([Section 4.3.6](#))]. An experimental study in newborn rats, which were not previously  
20 sensitized and challenged with an allergen (i.e. naive animals), found that repeated acute  
21 SO<sub>2</sub> exposures over several weeks led to airway inflammation and Th2 polarization (or  
22 other Type 2 immune responses), important steps in allergic sensitization [([Song et al.,  
23 2012](#)); (see [Section 5.2.2.1](#))]. Repeated SO<sub>2</sub> exposure in the newborn rats, which were  
24 previously sensitized and challenged with an allergen (i.e., allergic animals), resulted in  
25 enhanced allergic airway inflammation and some evidence of airway remodeling and  
26 AHR. Additional evidence comes from experimental studies in adult animals involving  
27 short-term exposure to SO<sub>2</sub> over several days. In naive rats, airway inflammation and  
28 morphologic responses indicative of airway remodeling were seen ([Section 5.2.1.7](#)).  
29 Furthermore, enhancement of allergic sensitization and other inflammatory responses  
30 were observed along with AHR in guinea pigs exposed repeatedly to SO<sub>2</sub> for several days  
31 and subsequently sensitized and challenged with an allergen ([Section 5.2.1.7](#)). Similarly,  
32 SO<sub>2</sub> exposure enhanced airway inflammation in rats previously sensitized with an  
33 allergen ([Section 5.2.1.2](#)).

### **Evidence for the Severity of Asthma**

34 A few studies provide evidence for a potential relationship between long-term SO<sub>2</sub>  
35 exposure and the severity of asthma, as indicated by asthma severity scores, asthma  
36 control, and AHR ([Section 5.2.2.1](#)).

## Evidence for the Development of Allergies

1 Epidemiologic evidence from a few long-term studies provides a link between long-term  
2 SO<sub>2</sub> exposure and respiratory allergies and allergic rhinitis among children  
3 ([Section 5.2.2.2](#)). However, uncertainties remain given the cross-sectional design of these  
4 studies. Two pollutant models have begun to address the role of SO<sub>2</sub> exposure in the  
5 development of allergic rhinitis.

## Evidence for Lung Function

6 Several studies evaluated the relationship between long-term SO<sub>2</sub> exposure and  
7 decrements in lung function ([Section 5.2.2.3](#)). Evidence supporting this relationship is  
8 limited because associations were inconsistent and because both PM and SO<sub>2</sub> were at  
9 high concentrations in the same areas, precluding determination of individual SO<sub>2</sub> effects.  
10 Potential confounding of long-term SO<sub>2</sub> exposure-related decrements in lung function  
11 and lung development by other pollutants, especially PM, was evaluated in only one  
12 study. This study found an attenuation of the effect in two-pollutant analyses. No changes  
13 in lung function were found in long-term animal toxicological studies at relevant SO<sub>2</sub>  
14 concentrations. The recent studies support conclusions made in the 2008 SO<sub>x</sub> ISA ([U.S.  
15 EPA, 2008d](#)) that the available evidence was inadequate to infer a causal relationship  
16 between long-term exposure to SO<sub>2</sub> at ambient concentrations and changes in lung  
17 function.

## Evidence for Respiratory Infection

18 Respiratory infection related to long-term SO<sub>2</sub> exposure is discussed in [Section 5.2.2.4](#).  
19 A limited number of the cross-sectional studies examined indicate associations between  
20 long-term SO<sub>2</sub> exposure and bronchitis or respiratory infection due to various infectious  
21 agents; findings were generally positive. While some animal toxicological studies  
22 reported alterations in specific host defense mechanisms, there is no evidence to support  
23 increases in bacterial or viral infections in animals exposed to SO<sub>2</sub> at relevant  
24 concentrations.

## Evidence for the Development of Other Respiratory Diseases

25 Evidence for prevalence of bronchitis and/or COPD consists of generally positive  
26 associations found in cross-sectional studies ([Section 5.2.2.5](#)).

## Evidence for Respiratory Mortality

1 Small positive associations between long-term exposure to SO<sub>2</sub> and respiratory mortality  
2 among adults were found in several cohort studies after adjustment for common potential  
3 confounders ([Section 5.2.2.6](#)). There is little evidence of respiratory health effects in  
4 adults in relation to long-term SO<sub>2</sub> exposure that could provide coherence with the  
5 observed associations with respiratory mortality among adults.

## Conclusion

6 Taken together, epidemiologic and animal toxicological studies provide evidence that is  
7 suggestive of, but not sufficient to infer, a causal relationship between long-term SO<sub>2</sub>  
8 exposure and respiratory effects (see [Table 5-24](#)). The strongest evidence is provided by  
9 coherence of findings of epidemiologic studies showing associations between long-term  
10 SO<sub>2</sub> exposure and increases in asthma incidence among children and findings of animal  
11 toxicological studies that provide a pathophysiologic basis for the development of  
12 asthma. These latter studies demonstrated that repeated SO<sub>2</sub> exposure over several weeks  
13 resulted in Th2 polarization (or other Type 2 immune responses) and airway  
14 inflammation, key steps in allergic sensitization, in naive newborn animals. In addition,  
15 repeated SO<sub>2</sub> exposure over several weeks resulted in enhanced airway inflammation and  
16 some evidence of airway remodeling and AHR in allergic newborn animals.

17 Toxicological studies involving repeated exposure to SO<sub>2</sub> over several days provide  
18 additional evidence of these effects. However, because the animal toxicological evidence  
19 is limited, particularly for long-term exposure, some uncertainty remains regarding an  
20 independent effect of long-term SO<sub>2</sub> exposure on the development of asthma. In addition,  
21 potential confounding by other pollutants is unexamined, and largely unavailable, for  
22 epidemiologic studies of asthma among children. However, multiple lines of evidence  
23 suggest that long-term SO<sub>2</sub> exposure results in a coherent and biologically plausible  
24 sequence of events that culminates in the development of asthma, especially allergic  
25 asthma, in children.

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## 5.3 Cardiovascular Effects

### 5.3.1 Short-Term Exposure

#### 5.3.1.1 Introduction

1 The 2008 ISA for Sulfur Oxides ([U.S. EPA, 2008d](#)) reviewed studies published through  
2 2006 and concluded that “the evidence as a whole is inadequate to infer a causal  
3 relationship” between short-term exposure to SO<sub>2</sub> and cardiovascular health effects.  
4 Specifically, the 2008 ISA for Sulfur Oxides found a lack of consistency with regard to  
5 short-term exposure to SO<sub>2</sub> and markers of HRV, cardiac repolarization, discharges of  
6 implantable cardioverter defibrillators (ICDs), blood pressure, blood markers of  
7 cardiovascular disease risk, the triggering of a myocardial infarction, or ED visits or  
8 hospital admission for cardiovascular diseases. This section reviews the published studies  
9 pertaining to the cardiovascular effects of short-term exposure (i.e., up to 1 month) to  
10 SO<sub>2</sub> in humans and animals. There are no toxicological studies evaluating cardiovascular  
11 effects following 5–10 minute exposures to SO<sub>2</sub>. With few exceptions, most  
12 epidemiologic studies model the association of 24-h avg SO<sub>2</sub> concentration with  
13 cardiovascular outcomes. With the existing body of evidence serving as the foundation,  
14 emphasis has been placed on studies published since the 2008 ISA for Sulfur Oxides  
15 ([U.S. EPA, 2008d](#)).

16 To clearly characterize the evidence underlying causality, the discussion of the evidence  
17 is organized into groups of related outcomes [myocardial infarction and ischemic heart  
18 disease ([Section 5.3.1.2](#)), arrhythmia and cardiac arrest ([Section 5.3.1.3](#)), cerebrovascular  
19 disease ([Section 5.3.1.4](#)), hypertension ([Section 5.3.1.5](#)), venous thromboembolism  
20 ([Section 5.3.1.6](#)), heart failure ([Section 5.3.1.7](#)), aggregated cardiovascular disease  
21 ([Section 5.3.1.8](#)), and cardiovascular mortality ([Section 5.3.1.9](#))]. Evidence for  
22 subclinical effects (e.g., heart rate variability, blood biomarkers of cardiovascular effects)  
23 of short-term exposure to SO<sub>2</sub> that potentially underlie the triggering or indication of  
24 various clinical events are discussed in [Section 5.3.1.10](#), and may provide biological  
25 plausibility for multiple outcomes. When considered with the evidence reviewed in the  
26 2008 ISA for Sulfur Oxides, recent epidemiologic studies add to the evidence for effects  
27 of SO<sub>2</sub> exposure on a broader array of cardiovascular effects and mortality. Still,  
28 substantial uncertainties remain concerning exposure measurement error, the lack of  
29 mechanistic evidence to describe a role for SO<sub>2</sub> in the initiation of key events in a  
30 proposed mode of action, and potential confounding by copollutants. The majority of the

1 recent evidence is from epidemiologic studies, which examined the association of SO<sub>2</sub>  
2 exposure with MI, cerebrovascular disease and other cardiovascular effects.

3 The previous ISA included a small number of animal toxicological studies of blood  
4 pressure ([Section 5.3.1.5](#)), HR and HRV ([Section 5.3.1.10](#)), and arrhythmia frequency  
5 ([Section 5.3.1.3](#)) and controlled human exposure studies that examined effects on the  
6 autonomic nervous system ([Section 5.3.1.10](#)) from short-term exposure to SO<sub>2</sub>. Since the  
7 2008 ISA for Sulfur Oxides ([U.S. EPA, 2008d](#)), no controlled human exposure studies  
8 and few animal toxicological studies have investigated the effects of short-term SO<sub>2</sub>  
9 exposure on the cardiovascular system. Results from the experimental studies included in  
10 the past and current reviews that evaluated cardiovascular effects of short-term SO<sub>2</sub>  
11 exposures of less than 2,000 ppb are summarized in the relevant outcome section and  
12 additional study details are summarized in Supplemental Table 5S-13 ([U.S. EPA, 2016s](#)).

13 Studies examining cardiovascular effects of sulfite exposure (via i.p., i.v., etc.) are not  
14 included in this section because these studies generally involve exposures to sulfite that  
15 are higher than what is expected to occur following inhalation of SO<sub>2</sub> at ambient relevant  
16 concentrations. Some studies using prolonged exposures to 300 ppb and higher  
17 concentrations of SO<sub>2</sub> reported measurable changes in the concentrations of  
18 sulfite/S-sulfonate in plasma and tissues. A positive correlation was found between the  
19 concentration of inhaled SO<sub>2</sub> and plasma sulfite/S-sulfonate levels in humans exposed  
20 continuously to SO<sub>2</sub> (300–6,000 ppb) ([Gunnison and Palmes, 1974](#)). Similarly, a recent  
21 report in mice exposed to 5,000–20,000 ppb SO<sub>2</sub> for 7 days found a  
22 concentration-dependent increase in sulfite/S-sulfonate levels in lung, heart, and brain  
23 compared to controls ([Meng et al., 2005b](#)). These studies suggest that prolonged exposure  
24 to SO<sub>2</sub> at concentrations higher than typically found in ambient air may increase  
25 circulating sulfite, but these changes would be expected to be far less following ambient  
26 exposures of shorter duration. The literature on the distribution and metabolism of sulfite  
27 is discussed in [Section 4.2.3](#) and [Section 4.2.4](#). The potential role of sulfite in the  
28 induction of systemic effects, such as effects of the cardiovascular system, is discussed in  
29 [Section 4.3.4](#).

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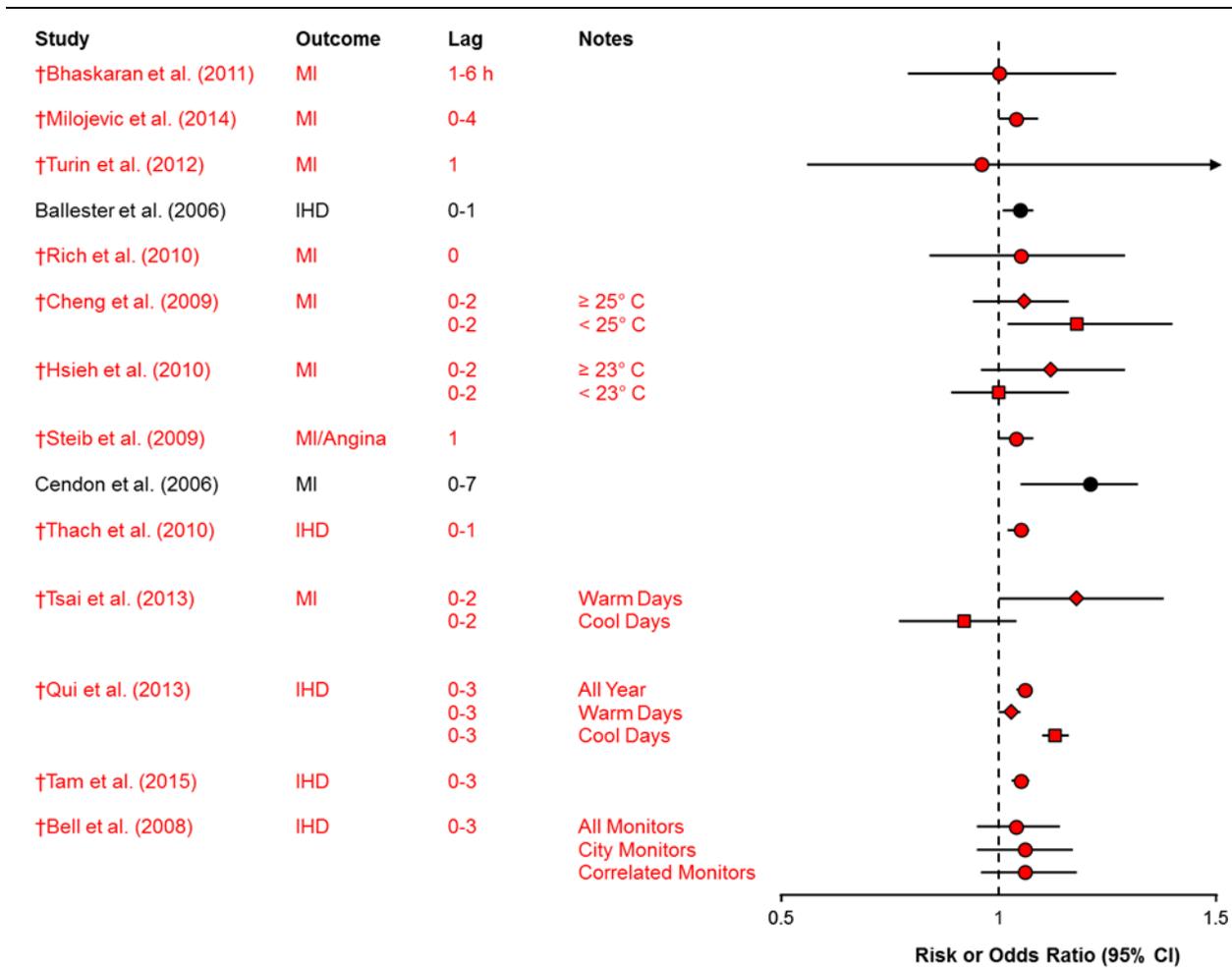
### 5.3.1.2 Myocardial Infarction and Ischemic Heart Disease

30 Several lines of evidence are discussed in evaluating the relationship between short-term  
31 SO<sub>2</sub> exposure and MI. An MI, or heart attack, occurs as a consequence of IHD, resulting  
32 in insufficient blood flow to the heart that overwhelms myocardial repair mechanisms  
33 and leads to muscle tissue death. ICD codes for MI are classified within the group of  
34 IHDs, thus studies in which IHD is evaluated will include any patients diagnosed with an

1 MI. Finally, acute MI may be characterized by ST-segment depression, a nonspecific  
2 marker of myocardial ischemia. The evaluation of evidence supporting a relationship  
3 between short-term SO<sub>2</sub> exposure and the triggering of an MI includes hospitalization and  
4 ED visits for MI or IHD and ST-segment amplitude changes.

5 The epidemiologic data available for review by the 2008 ISA for Sulfur Oxides ([U.S.  
6 EPA, 2008d](#)) did not indicate an association between SO<sub>2</sub> and risk of MI. A number of  
7 additional studies based on administrative data of hospital admissions or ED visits or on  
8 clinical data are now available in [Figure 5-12](#). The air quality characteristics of the city,  
9 or across all cities, and the exposure assignment approach used in each MI-related  
10 hospital admission and ED visit study evaluated in this section are presented in  
11 [Table 5-25](#). The recent clinical registry studies provide inconsistent evidence for an  
12 association between MI and ambient SO<sub>2</sub>, while multicity and single-city hospital  
13 admission and ED visit studies provide generally consistent evidence of an association.  
14 However, potential copollutant confounding and limited mechanistic evidence are still  
15 key uncertainties that make it difficult to interpret the results of these studies.  
16 Additionally, most studies examined 24-h avg exposure metrics for SO<sub>2</sub>, which may not  
17 adequately capture the spatial and temporal variability in SO<sub>2</sub> concentrations  
18 ([Section 3.4.2](#)).

19 Some studies rely on clinical registries, which are generally less susceptible to  
20 misclassification of the outcome. Using data from the Myocardial Ischaemia National  
21 Audit Project (MINAP) clinical registry, [Bhaskaran et al. \(2011\)](#) reported that hourly  
22 ambient SO<sub>2</sub> concentrations were not associated with risk of MI in a case-crossover study  
23 of 15 conurbations in England and Wales between 2003 and 2006. While no associations  
24 were reported in the population overall, there was some evidence of an association in  
25 subgroup analyses within older age groups (60–69, 70–79, and 80+) at inconsistent lag  
26 times. This study is unique because it included detailed data on the timing of MI onset in  
27 more than 79,000 patients, which allowed examination of the association with ambient  
28 SO<sub>2</sub> in the hours preceding MI. [Milojevic et al. \(2014\)](#) also used data from MINAP, from  
29 2003 to 2009, and observed stronger evidence of an association between SO<sub>2</sub>  
30 concentrations and MI [4.3% (95% CI: –0.25, 8.8%) increase in risk of MI per 10-ppb  
31 increase in 24-h avg SO<sub>2</sub> at lag 0–4]. [Turin et al. \(2012\)](#) did not observe any association  
32 using data from the Takashima County Stroke and Acute Myocardial Infarction Registry  
33 in central Japan, although this study was likely underpowered to detect an association of  
34 the expected magnitude. None of the clinical registry studies examined copollutant  
35 models.



CI = confidence interval.

- 1 Note: Studies in red are recent studies. Studies in black were included in the 2008 ISA for Sulfur Oxides. All-year
- 2 associations = circles; summer/warm-days associations = diamonds; winter/cold-days associations = squares.
- 3 Relative risks are standardized to a 10-ppb or 40-ppb increase in sulfur dioxide for 24-h avg and 1-h max metrics,
- 4 respectively. Lag times are reported in days, unless otherwise noted. Corresponding quantitative results are reported
- 5 in Supplemental Table 5S-14 ([U.S. EPA, 2016t](#)). All results are from single pollutant models.

**Figure 5-12 Results of studies of short-term sulfur dioxide exposure and hospital admissions for ischemic heart disease.**

**Table 5-25 Mean and upper percentile concentrations of sulfur dioxide from ischemic heart disease hospital admission and emergency department visit studies.**

Study	Location Years	Exposure Assignment	Metric	Mean/Median Concentration ppb	Upper Percentile of Concentrations ppb
<a href="#">†Bhaskaran et al. (2011)</a>	15 conurbations in England and Wales (2003–2006)	Central site monitor from each conurbation (aggregated when more than one monitor)	1-h max	Mean: 1.9	75th: 3.4
<a href="#">†Milojevic et al. (2014)</a>	230 acute hospitals in England and Wales (2003–2009)	Nearest monitor within 50-km distance from residence location	24-h avg	Median: 1.2	75th: 2.3
<a href="#">†Turin et al. (2012)</a>	Takashima County, Japan (1988–2004)	Nearest monitor to Takashima County (20 km)	24-h avg	Mean: 3.9	75th: 4.8
<a href="#">Ballester et al. (2006)</a>	14 Spanish cities (1995–1999)	Citywide average for each city	24-h avg	Mean: 2.9–15.6 across cities	90th: 4.8–28.8 across cities
<a href="#">†Rich et al. (2010)</a>	New Jersey (2004–2006)	Closest of 14 monitor (those >10 km from monitor excluded)	24-h avg	NR	NR
<a href="#">†Cheng et al. (2009)</a>	Kaohsiung, Taiwan (1996–2006)	Average across six monitoring stations	24-h avg	Mean: 9.33	75th: 11.69 Max: 31.26
<a href="#">†Hsieh et al. (2010)</a>	Taipei, Taiwan (1996–2006)	Average across six monitoring stations	24-h avg	Mean: 4.36	75th: 5.48 Max: 17.82
<a href="#">†Stieb et al. (2009)</a>	Seven Canadian cities (1992–2003)	Citywide average for each city	24-h avg	Mean: 2.6–10.0 across cities	75th: 3.3–13.4 across cities
<a href="#">Cendon et al. (2006)</a>	São Paulo, Brazil (1998–1999)	Average across 13 monitoring stations	24-h avg	Mean: 5.6	95th: 12.1
<a href="#">†Thach et al. (2010)</a>	Hong Kong, China (1996–2002)	Average across eight monitoring stations	24-h avg	Mean: 6.8	NR
<a href="#">†Tsai et al. (2012)</a>	Taipei, Taiwan (1999–2009)	Average across six monitoring stations	24-h avg	Mean: 3.94	75th: 5.01 Max: 12.7

**Table 5-25 (Continued): Mean and upper percentile concentrations of sulfur dioxide from ischemic heart disease hospital admission and emergency department visit studies.**

Study	Location Years	Exposure Assignment	Metric	Mean/Median Concentration ppb	Upper Percentile of Concentrations ppb
<a href="#">†Qiu et al. (2013a)</a>	Hong Kong, China (1998, 2007)	Average across 14 monitoring stations	24-h avg	Mean: 7.4	NR
<a href="#">†San Tam et al. (2015)</a>	Hong Kong, China (2001–2010)	Average across 13 monitoring stations	24-h avg	Mean: 7.6	75th: 9.3 Max: 51.9
<a href="#">†Bell et al. (2008)</a>	Taipei, Taiwan (1995–2002)	Average across 13 monitoring stations; 5 within city limits; or 6 with correlations >0.75	24-h avg	Mean: 4.7	Max: 26.9

NR = not reported.

†Studies published since the 2008 ISA for Sulfur Oxides.

1 One prominent study from the previous 2008 ISA for Sulfur Oxides ([U.S. EPA, 2008d](#))  
2 was conducted in 14 cities across Spain and found a 4.5% (95% CI: 1.3, 8.1%) increase  
3 in hospital admissions per 10-ppb shift in SO<sub>2</sub> for the composite endpoint of IHD,  
4 arrhythmias, and heart failure ([Ballester et al., 2006](#)). This association was still positive,  
5 but attenuated and no longer statistically significant after adjustment for CO or NO<sub>2</sub>. It  
6 was lessened in magnitude, but more precise, with adjustment for TSP or O<sub>3</sub> in  
7 copollutant models (no quantitative results; results presented graphically). Several  
8 additional ED visit and hospital admission studies are now available. In a study of  
9 hospitalization in New Jersey, [Rich et al. \(2010\)](#) did not report strong evidence for an  
10 association between SO<sub>2</sub> and risk of hospital admissions for MI [OR: 1.05 (95% CI: 0.84,  
11 1.29) per 10-ppb increase in 24-h avg SO<sub>2</sub> on the same day]. The inclusion of PM<sub>2.5</sub> in a  
12 copollutant model did not reveal a positive association for SO<sub>2</sub> [OR: 0.91 (95% CI: 0.69,  
13 1.21)]. In Kaohsiung, Taiwan, [Cheng et al. \(2009\)](#) reported an association between SO<sub>2</sub>  
14 concentrations and hospital admissions for MI, but only on days when the mean ambient  
15 temperature was <25°C. However, in copollutant models adjusting for PM<sub>10</sub>, NO<sub>2</sub>, or CO,  
16 SO<sub>2</sub> was no longer associated with increased admissions. Conversely, in Taipei, Taiwan,  
17 [Hsieh et al. \(2010\)](#) only observed an association between SO<sub>2</sub> and MI on warm days  
18 (≥23°C). Similar to the findings of [Cheng et al. \(2009\)](#), this association was no longer  
19 positive after adjustment for PM<sub>10</sub>, NO<sub>2</sub>, O<sub>3</sub>, or CO in copollutants models. Most other  
20 studies have not considered copollutant models.

21 A study using data from 14 hospitals in seven Canadian cities found a 4.2% (95% CI: 0.4,  
22 8.0%) increase in risk of ED visits for the composite endpoint of acute MI or angina per

1 10-ppb increase in SO<sub>2</sub> on the previous day ([Stieb et al., 2009](#)). Most ([San Tam et al.,](#)  
2 [2015](#); [Qiu et al., 2013a](#); [Tsai et al., 2012](#); [Thach et al., 2010](#); [Cendon et al., 2006](#); [Martins](#)  
3 [et al., 2006](#)) but not all ([Bell et al., 2008](#)) studies using data from individual cities have  
4 found associations between SO<sub>2</sub> concentrations and risk of hospital admissions or ED  
5 visits for ischemic heart disease or MI. None of the single-city studies evaluated potential  
6 copollutant confounding, and all of the studies in this section used fixed site monitors to  
7 measure ambient SO<sub>2</sub>. The limitations of these monitors in capturing spatial variation in  
8 SO<sub>2</sub> has been noted previously ([Section 3.4.2](#)).

### ST-Segment Changes

9 ST-segment changes (either ST-segment elevation or depression) on the  
10 electrocardiogram are considered a nonspecific marker of myocardial ischemia. While  
11 the 2008 ISA for Sulfur Oxides did not review any epidemiologic studies of ambient SO<sub>2</sub>  
12 concentrations and markers of myocardial ischemia, one subsequent study reported an  
13 association. [Chuang et al. \(2008\)](#) conducted a repeated-measures study in adults with a  
14 history of coronary heart disease (CHD) and examined the association between ambient  
15 pollutants and ST-segment level changes. This study found an odds ratio of 3.0 (95% CI:  
16 1.8, 5.5) for ST-segment depression of  $\geq 0.1$  mm per 10-ppb increase in SO<sub>2</sub> over the  
17 previous 24 hours. This finding was generally unchanged after additional control for  
18 PM<sub>2.5</sub> and BC in copollutant models.

### Summary of Ischemic Heart Disease and Myocardial Infarction

19 In summary, while evidence from epidemiologic studies suggests a potential association  
20 between ambient SO<sub>2</sub> concentrations and rates of hospital admissions or ED visits for MI  
21 or ischemic heart diseases in single-pollutant models, these associations may be the result  
22 of confounding by other pollutants. While three studies based on clinical data report  
23 inconsistent evidence regarding associations between ambient SO<sub>2</sub> concentrations and  
24 risk of MI, the majority of studies relying on MI hospital admission and ED visit data  
25 observed either seasonal or year-round associations with SO<sub>2</sub>. However, some of these  
26 associations were either attenuated or no longer present after controlling for potential  
27 copollutant confounding ([Hsieh et al., 2010](#); [Cheng et al., 2009](#); [Ballester et al., 2006](#)),  
28 leaving uncertainties regarding the independent effect of short-term SO<sub>2</sub> exposure. In  
29 congruence with the evidence from hospital admission and ED visit studies, there was  
30 limited evidence from a single study indicating that SO<sub>2</sub> may be associated with  
31 ST-segment changes on the electrocardiogram in patients with a history of coronary heart  
32 disease. Most studies examined 24-h avg exposure metrics for SO<sub>2</sub>, which may not  
33 adequately capture the spatial and temporal variability in SO<sub>2</sub> concentrations

1 (Section 5.2.1.2). No experimental studies have been conducted to evaluate measures of  
2 ischemic heart disease or MI following short-term SO<sub>2</sub> exposure. Overall, despite some  
3 epidemiologic evidence of an association between short-term exposure to SO<sub>2</sub> and  
4 hospital admissions and ED visits for ischemic heart disease and MI, uncertainties  
5 regarding copollutant confounding continue to impede the determination of an  
6 independent SO<sub>2</sub> effect.

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### 5.3.1.3 Arrhythmias and Cardiac Arrest

7 The 2008 ISA for Sulfur Oxides ([U.S. EPA, 2008d](#)) concluded that the evidence available  
8 at the time did not suggest that SO<sub>2</sub> has an effect on cardiac arrhythmias. There continues  
9 to be essentially no epidemiologic or toxicological evidence suggestive of such a  
10 relationship.

11 [Metzger et al. \(2007\)](#) examined 518 patients with ICDs with 6,287 tachyarrhythmic  
12 event-days over a 10-year period in Atlanta, Georgia and found no association between  
13 SO<sub>2</sub> concentrations and the risk of tachyarrhythmias, either overall or in analyses limited  
14 to more severe tachyarrhythmic events, or stratified by season or the presence of a recent  
15 past arrhythmic event (results for this study and other studies in this section can be found  
16 in [Table 5-26](#)). A similar study in London, England also found limited evidence of an  
17 association between SO<sub>2</sub> concentrations and arrhythmic risk ([Anderson et al., 2010](#)).  
18 [Anderson et al. \(2010\)](#) reported an increase in risk of ICD activations corresponding to an  
19 increase in ambient SO<sub>2</sub>, but the association was imprecise [OR: 1.35 (95% CI: 0.75,  
20 2.41) per 10-ppb increase in SO<sub>2</sub> at lag days 0–1]. Similarly, a study in Boston,  
21 Massachusetts observed an association between ambient SO<sub>2</sub> and ICD activations that  
22 was even more imprecise [32.0% (95% CI: –48.5, 336.2%) increase in ICD activations  
23 per 10-ppb increase in SO<sub>2</sub> concentrations at lag 1] ([Link et al., 2013](#)). Additionally, a  
24 multicity study in Canada ([Stieb et al., 2009](#)) and a large single-city study in Taipei,  
25 Taiwan ([Tsai et al., 2009](#)) have reported finding no association between SO<sub>2</sub> and ED  
26 visits for arrhythmias, while a large single-city study in Shanghai, China reported a  
27 positive association that was attenuated and no longer positive in a copollutant model  
28 adjusted for NO<sub>2</sub> ([Zhao et al., 2014](#)).

**Table 5-26 Epidemiologic studies of arrhythmia and cardiac arrest.**

Study	Location and Years (Sample Size)	Mean and Upper Concentration SO <sub>2</sub> (ppb)	Exposure Assessment	Selected Effect Estimates <sup>a</sup> (95% CI)
<a href="#">†Metzger et al. (2007)</a>	Atlanta, GA 1993–2002 (n = 518)	1-h max: 15.5 90th percentile: 36 Max: 149	Central monitor	All tachyarrhythmic events (OR); year round Lag 0: 1.00 (0.94, 1.08) Warm season Lag 0: 1.06 (0.98, 1.25) Cold season Lag 0: 0.97 (0.91, 1.05) Cardiac pacing or defibrillation (OR): Lag 0: 0.98 (0.88, 1.09) Defibrillation (OR): Lag 0: 1.01 (0.98, 1.24)
<a href="#">†Anderson et al. (2010)</a>	London, U.K. 1995–2003 [n = 705 (5,462 device activations)]	24-h avg: 1.03 75th percentile: 1.15 Max: 2.67	Citywide avg	ICD activations (OR); Lag 01: 1.35 (0.75, 2.41) Lag 05: 1.71 (0.69, 4.27) Correlations: PM <sub>10</sub> : 0.48, PM <sub>2.5</sub> : 0.42, BS: 0.35, SO <sub>4</sub> <sup>2-</sup> : 0.19, PNC: 0.29, NO <sub>2</sub> : 0.60, NO: 0.44, NO <sub>x</sub> : 0.49, O <sub>3</sub> : -0.36
<a href="#">†Link et al. (2013)</a>	Boston, MA 2006–2010 [n = 176 (328 atrial fibrillation episodes ≥30 sec)]	24-h avg: 3.2 75th percentile: 4	Citywide avg	ICD activations (percent change); Lag 1: 32.0 (-48.5, 336.2) Correlations: CO: -0.06 to 0.75, NO <sub>2</sub> : 0.05 to 0.69, O <sub>3</sub> : -0.52 to -0.18, PM <sub>10</sub> : 0.27 to 0.55, PM <sub>2.5</sub> : 0.01 to 0.67
<a href="#">†Stieb et al. (2009)</a>	Seven Canadian cities 1992–2003 (n = 45,160 ED visits)	24-h avg: 2.6 to 10 across cities 75th percentile: 3.3 to 13.4 across cities	Citywide avg for each city	Dysrhythmia ED visits (percent change); Lag 0: -1.4 (-6.0, 3.4) Lag 1: 0.8 (-6.4, 8.6) Lag 2: -5.0 (-9.2, -0.6) Correlations: PM <sub>10</sub> : 0.52, NO <sub>2</sub> : 0.43, CO: 0.24, O <sub>3</sub> : 0.09
<a href="#">†Tsai et al. (2009)</a>	Taipei, Taiwan 2000–2006 (n = 21,581 ED visits)	24-h avg: 3.93 75th percentile: 5.02 Max: 12.7	Citywide avg	Arrhythmia ED visits (OR); ≥23°C: 1.04 (0.88, 1.23) <23°C: 1.04 (0.88, 1.27) Correlations: PM <sub>10</sub> : 0.52, NO <sub>2</sub> : 0.43, CO: 0.24, O <sub>3</sub> : 0.09
<a href="#">†Zhao et al. (2014)</a>	Shanghai, China 2010–2011 (n = 56,940 outpatient visits)	24-h avg: 11.1 75th percentile: 14.1 Max: 49.6	Central monitor	Arrhythmia outpatient visits (percent change); Lag 0: 1.06 (1.04, 1.07)

**Table 5-26 (Continued): Epidemiologic studies of arrhythmia and cardiac arrest.**

Study	Location and Years (Sample Size)	Mean and Upper Concentration SO <sub>2</sub> (ppb)	Exposure Assessment	Selected Effect Estimates <sup>a</sup> (95% CI)
<a href="#">†Dennekamp et al. (2010)</a>	Melbourne, Australia 2003–2006 (n = 8,434 OHCA)	24-h avg: 0.49 75th percentile: 0.76	Central monitor	OHCA (percent change); Lag 0: -10.0 (-40.3, 64.0) Lag 1: 6.9 (-34.9, 75.6) Lag 2: 0.8 (-39.0, 66.7) Lag 01: -0.7 (-34.9, 75.6)
<a href="#">†Silverman et al. (2010)</a>	New York City, NY 2003–2006 (n = 8,216 OHCA)	24-h avg: 6.3 (median) 75th percentile: 9.6 95th percentile: 18	Citywide avg	No quantitative results; results presented graphically. Null association between OHCA and year-round SO <sub>2</sub> concentrations. OHCA positively but imprecisely (i.e., wide 95% CI) associated with ambient SO <sub>2</sub> during the warm season
<a href="#">†Straney et al. (2014)</a>	Perth, Australia 2000–2010 (n = 8,551 OHCA)	1-h avg: 0.4 (median) 75th percentile: 0.9 95th: 3.5	Nearest monitor	OHCA (OR); Lag 0: 0.91 (0.71, 1.17)
<a href="#">†Rosenthal et al. (2013)</a>	Helsinki, Finland 1998–2006 (n = 2,134 OHCA)	24-h avg: 1.5	Citywide avg	OHCA (OR); Lag 0: 0.93 (0.58, 1.44) Lag 1: 0.68 (0.42, 1.08) Lag 2: 1.08 (0.68, 1.66) Lag 3: 1.00 (0.63, 1.55) Lag 03: 0.86 (0.42, 1.55)
<a href="#">†Kang et al. (2016)</a>	Seoul, South Korea 2006–2013 (n = 28,315 OHCA)	24-h avg: 2.1 75th percentile: 2.5 Max: 8.1		No quantitative results; results presented graphically. Positive, statistically significant associations at single day lags 0 through 3. Null associations at lags 4 and 5.

BS = black smoke; CI = confidence interval; CO = carbon monoxide; ED = emergency department; ICD = implantable cardioverter defibrillators; n = sample size; NO = nitric oxide; NO<sub>2</sub> = nitrogen dioxide; NO<sub>x</sub> = the sum of NO and NO<sub>2</sub>; O<sub>3</sub> = ozone; OHCA = out-of-hospital cardiac arrhythmias; OR = odds ratio; PM<sub>10</sub> = particulate matter with a nominal aerodynamic diameter less than or equal to 10 μm; PM<sub>2.5</sub> = particulate matter with a nominal aerodynamic diameter less than or equal to 2.5 μm; PNC = particle number concentration; SO<sub>2</sub> = sulfur dioxide; SO<sub>4</sub><sup>2-</sup> = sulfate.

All Lag times are in days, unless otherwise noted.

†Studies published since the 2008 ISA for Sulfur Oxides.

<sup>a</sup>Effect estimates are standardized to a 10-ppb or 40-ppb increase in SO<sub>2</sub> concentration for 24-h avg and 1-h max metrics, respectively.

1 The majority of out-of-hospital cardiac arrests (OHCA) are due to cardiac arrhythmias.  
 2 [Dennekamp et al. \(2010\)](#) considered the association between ambient pollutants and  
 3 OHCA among 8,434 cases identified through the Victorian Cardiac Arrest Registry in  
 4 Melbourne, Australia and found null and/or imprecise associations (e.g., wide 95% CIs)  
 5 between SO<sub>2</sub> concentrations and risk of OHCA. A similar approach was used by  
 6 [Silverman et al. \(2010\)](#) with data from 8,216 OHCA in New York City. Quantitative

1 results for SO<sub>2</sub> were not provided, but graphs showed a null association between OHCA  
2 and year-round SO<sub>2</sub> concentrations. [Silverman et al. \(2010\)](#) also presented  
3 season-specific analyses graphically, demonstrating that out-of-hospital cardiac arrests  
4 were positively but imprecisely (i.e., wide 95% CI) associated with SO<sub>2</sub> concentrations  
5 during the warm season. Two additional case-crossover studies of OHCA in Perth,  
6 Australia ([Straney et al., 2014](#)) and Helsinki, Finland ([Rosenthal et al., 2013](#)) observed  
7 null associations with ambient SO<sub>2</sub>. In contrast, [Kang et al. \(2016\)](#) observed an  
8 association between 24-h avg SO<sub>2</sub> and OHCA in Seoul, South Korea at individual lag  
9 days 0 through 3 (no quantitative results; results presented graphically).

10 One animal toxicological study ([Nadziejko et al., 2004](#)) evaluated arrhythmia frequency  
11 in rats following short-term SO<sub>2</sub> exposure and reported no significant changes in  
12 spontaneous arrhythmias (irregular, delayed, or premature beats).

13 In summary, studies of patients with implantable cardioverter defibrillators, hospital  
14 admissions for arrhythmias, and out of hospital cardiac arrest do not provide evidence to  
15 support the presence of an association between ambient SO<sub>2</sub> concentrations and  
16 arrhythmias. Most of these studies have been focused on other pollutants and therefore  
17 have not explored whether such an association might exist in certain subgroups.  
18 Additionally, the majority of studies used central site monitors to estimate ambient SO<sub>2</sub>  
19 exposure, which have noted limitations in capturing spatial variation in SO<sub>2</sub> that generally  
20 lead to attenuation and loss of precision in the effect estimates ([Section 3.4.4](#)). One  
21 toxicological study also found no evidence for arrhythmias following short-term SO<sub>2</sub>  
22 exposure.

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#### 5.3.1.4 Cerebrovascular Diseases and Stroke

23 Results among the studies reviewed in the 2008 ISA for Sulfur Oxides were inconsistent  
24 with regard to the association between ambient SO<sub>2</sub> concentrations and hospital  
25 admissions or ED visits for cerebrovascular diseases or stroke (a specific form of  
26 cerebrovascular disease). Many additional studies are now available for consideration  
27 (study details and results presented in [Table 5-27](#) and [Figure 5-13](#)). In Edmonton, AB,  
28 [Szyszkowicz \(2008\)](#) reported that risk of ED visits for ischemic stroke was linked to SO<sub>2</sub>  
29 concentrations, but this association was observed only in subgroup analyses stratified by  
30 sex, season, and age. A subsequent study in Vancouver, BC, found that SO<sub>2</sub> was  
31 associated with risk of ED visits for ischemic stroke in the population overall [OR: 2.09  
32 (95% CI: 1.23, 3.52) per 10-ppb increase in SO<sub>2</sub> at lag 3] ([Szyszkowicz et al., 2012a](#)).  
33 The association was generally unchanged after adjustment for O<sub>3</sub> in a copollutant model,  
34 and attenuated, although still positive, after adjustment for CO [OR: 1.73 (95% CI: 1.00,

1 3.10)]. [Chen et al. \(2014b\)](#) also observed an association between SO<sub>2</sub> and ischemic stroke  
2 at longer lags in Edmonton, AB. In Brazil, [Costa Nascimento et al. \(2012\)](#) observed a  
3 7.8% (95% CI: 0.0, 16.5%) increase in risk of hospital admissions of stroke per 10-ppb  
4 increase in 24-h avg SO<sub>2</sub> at lag 0. [Zheng et al. \(2013\)](#) reported a small but precise  
5 association between SO<sub>2</sub> concentrations and risk of hospital admission for  
6 cerebrovascular disease [1.7% increase (95% CI: 0.5, 2.8%) per 10-ppb increase in  
7 24-h avg SO<sub>2</sub> at lag 2] in Lanzhou, a heavily polluted city in China with a high observed  
8 mean daily concentration of SO<sub>2</sub> (30.19 ppb) over the 5-year study period.  
9 The association was as strong, or stronger, after adjustment for PM<sub>10</sub> [1.8% increase  
10 (95% CI: 0.4, 3.2%)] or NO<sub>2</sub> [2.6% increase (95% CI: 1.4, 3.7%)] in copollutant models.  
11 In central Japan, [Turin et al. \(2012\)](#) found that the risk of hemorrhagic stroke was  
12 associated with SO<sub>2</sub> concentrations, but found no association with other types of stroke.  
13 However, the 95% CI for the hemorrhagic stroke association was wide, indicating an  
14 imprecise association, and copollutant confounding was not considered.

15 In contrast to the studies that reported some evidence of an association between SO<sub>2</sub>  
16 concentrations and cerebrovascular disease, a number of studies observed null or  
17 imprecise associations. In an effort to reduce uncertainty related to the use of central site  
18 monitors, [Bell et al. \(2008\)](#) estimated SO<sub>2</sub> exposure over the entire Taipei, Taiwan area  
19 (average of 13 monitors), within Taipei City only (average of 5 monitors), and using a  
20 subset of monitors where all pairs of monitors had SO<sub>2</sub> correlations greater than 0.75  
21 (6 monitors). Using three exposure metrics, the authors did not observe an association  
22 between SO<sub>2</sub> and risk of hospital admission for cerebrovascular diseases. Contrary to  
23 other studies that reported associations between SO<sub>2</sub> concentrations and hospital  
24 admissions and ED visits for stroke in Canada ([Chen et al., 2014b](#); [Szyszkowicz et al.,](#)  
25 [2012a](#); [Szyszkowicz, 2008](#)), [Villeneuve et al. \(2012\)](#) reported null and/or imprecise  
26 associations between SO<sub>2</sub> and all stroke, ischemic stroke, and hemorrhagic stroke in  
27 Edmonton, AB. Studies in Hong Kong ([Thach et al., 2010](#)), Dijon, France ([Henrotin et](#)  
28 [al., 2007](#)), and Lyon, France ([Mechtouff et al., 2012](#)) also observed null associations  
29 between SO<sub>2</sub> concentrations and rates of hospital admission for stroke.

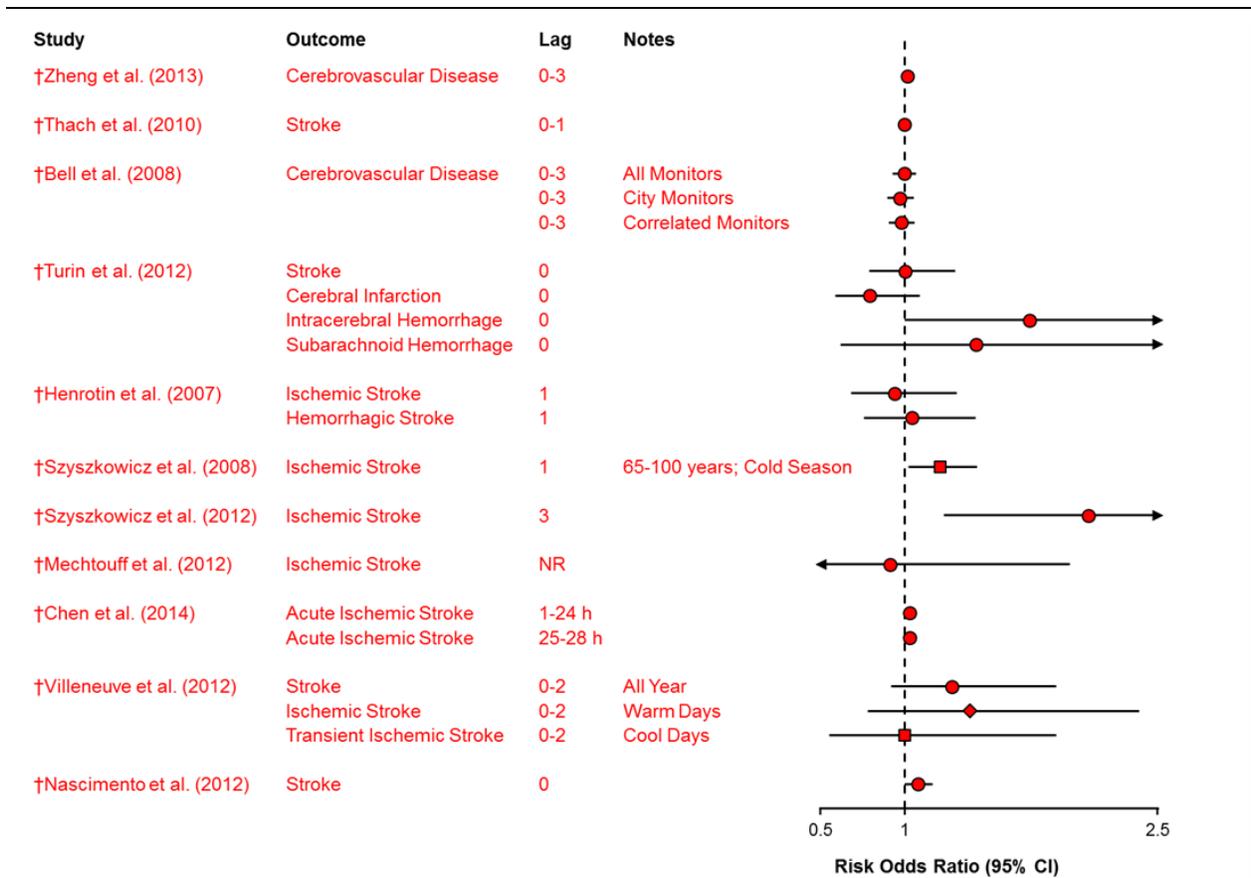
30 Thus, findings for the association between SO<sub>2</sub> and cerebrovascular diseases continue to  
31 be inconsistent across studies. As for other outcomes, associations reported from single  
32 pollutant models in some locations may be at least partly due to confounding by other  
33 pollutants.

**Table 5-27 Mean and upper percentile concentrations of sulfur dioxide from cerebrovascular disease and stroke-related hospital admission and emergency department visit studies.**

Study	Location Years	Exposure Assignment	Metric	Mean/Median Concentration ppb	Upper Percentile of Concentrations ppb
<a href="#">†Zheng et al. (2013)</a>	Lanzhou, China (2001–2005)	Average across four monitoring stations	24-h avg	Mean: 30.19	75th: 40.46 Max: 141.60
<a href="#">†Thach et al. (2010)</a>	Hong Kong, China (1996–2002)	Average across eight monitoring stations	24-h avg	Mean: 6.79	NR
<a href="#">†Bell et al. (2008)</a>	Taipei, Taiwan (1995–2002)	Average across 13 monitoring stations; 5 within city limits; or 6 with correlations >0.75	24-h avg	Mean: 4.7	Max: 26.9
<a href="#">†Turin et al. (2012)</a>	Takashima County, Japan (1988–2004)	Nearest monitor to Takashima county (20 km)	24-h avg	Mean: 3.9	75th: 4.8
<a href="#">Henrotin et al. (2007)</a>	Dijon, France (1994–2004)	Central site monitor	24-h avg	Mean: 2.63	75th: 3.44 Max: 24.81
<a href="#">†Szyszkowicz (2008)</a>	Edmonton, AB (1992–2002)	Average across three monitoring stations	24-h avg	Mean: 2.6	NR
<a href="#">†Szyszkowicz et al. (2012a)</a>	Vancouver, BC (1999–2003)	Average across 11 monitoring stations	24-h avg	Mean: 2.5	NR
<a href="#">†Mechtouff et al. (2012)</a>	Lyon, France (2006–2007)	Average across five monitoring stations	24-h avg	Mean: 2.02	75th: 2.67 Max: 22.52
<a href="#">†Chen et al. (2014b)</a>	Edmonton, AB (1998–2002)	Average across three monitoring stations	1-h avg	Mean: 2.0	95th: 6.7
<a href="#">†Villeneuve et al. (2012)</a>	Edmonton, AB (2003–2009)	Average across three monitoring stations	24-h avg	Mean: 1.5	75th: 1.9
<a href="#">†Costa Nascimento et al. (2012)</a>	São Paulo, Brazil (2007–2008)	Central site monitor	24-h avg	NR	NR

NR = not reported.

†Studies published since the 2008 ISA for Sulfur Oxides.



CI = confidence interval.

1 Note: Studies in red are recent studies. Studies in black were included in the 2008 ISA for Sulfur Oxides. All-year  
2 associations = circles; summer/warm-days associations = diamonds; winter/cold-days associations = squares.  
3 Relative risks are standardized to a 10-ppb or 40-ppb increase in sulfur dioxide for 24-h avg and 1-h max metrics,  
4 respectively, but not standardized for other metrics [e.g., (Chen et al., 2014b)]. Lag times are reported in days,  
5 unless otherwise noted. Corresponding quantitative results are reported in Supplemental Table 5S-15 (U.S. EPA,  
6 2016u). All results are from single pollutant models.

**Figure 5-13 Results of studies of short-term sulfur dioxide exposure and hospital admissions for cerebrovascular disease and stroke.**

### 5.3.1.5 Blood Pressure and Hypertension

7 Based on the data available at the time, the 2008 ISA for Sulfur Oxides (U.S. EPA,  
8 2008d) concluded that the overall evidence was insufficient to determine that SO<sub>2</sub> has an  
9 effect on blood pressure. Recent evidence provides limited and inconsistent evidence for  
10 changes in blood pressure associated with short-term exposure to SO<sub>2</sub>.

## Epidemiologic Studies

1 A number of longitudinal studies measured BP in subjects in Beijing before, during, and  
2 after the 2008 Beijing Olympics when citywide air pollution control measures  
3 substantially reduced ambient levels of most criteria pollutants. [Huang et al. \(2012\)](#)  
4 measured blood pressure repeatedly on up to four occasions in 40 participants with  
5 pre-existing cardiovascular disease in Beijing, including one measurement during the  
6 2008 Beijing Olympics when citywide air pollution control measures reduced ambient  
7 SO<sub>2</sub> concentrations by up to 50%. [Huang et al. \(2012\)](#) found a small decrement in  
8 diastolic blood pressure per IQR (NR) increase in prior 30-minute exposure to SO<sub>2</sub>  
9 [-0.9 mm Hg (95% CI: -2.0, 0.2 mm Hg)], but observed a null association between  
10 ambient SO<sub>2</sub> and systolic blood pressure. Focusing on healthy young adults, [Rich et al.](#)  
11 [\(2012\)](#) and [Zhang et al. \(2013\)](#) observed associations between SO<sub>2</sub> and blood pressure in  
12 repeated-measures studies conducted before, during, and after the 2008 Beijing Olympics  
13 (no quantitative results; results presented graphically). Using the same protocol, [Zhang et](#)  
14 [al. \(2013\)](#) and [Rich et al. \(2012\)](#) observed a positive association between 24-h avg SO<sub>2</sub>  
15 and systolic blood pressure, but an inverse association between 24-h avg SO<sub>2</sub> and  
16 diastolic blood pressure. The negative association between SO<sub>2</sub> and diastolic blood  
17 pressure was relatively unchanged after adjustment for PM<sub>2.5</sub>, EC, or sulfate, while the  
18 association between SO<sub>2</sub> and systolic blood pressure was also robust to sulfate, but  
19 attenuated, although still positive, after adjustment for PM<sub>2.5</sub> or EC ([Zhang et al., 2013](#)).

20 In another repeated measures study, [Kim et al. \(2016b\)](#) observed positive associations  
21 between short-term SO<sub>2</sub> concentrations and systolic blood pressure, diastolic blood  
22 pressure, and mean arterial pressure among 560 older adults living in Seoul, South Korea.  
23 A pair of cross-sectional studies reported conflicting evidence of an association.  
24 Examining data from 7,578 participants in the Taiwanese Survey on Prevalence of  
25 Hyperglycemia, Hyperlipidemia, and Hypertension, [Chuang et al. \(2010\)](#) concluded that  
26 there is “no significant association” between SO<sub>2</sub> concentrations and blood pressure (no  
27 quantitative results presented). However, in a cross-sectional analysis of data from  
28 9,238 participants in the Taiwan Community-based Integrated Screening program, [Chen](#)  
29 [et al. \(2012d\)](#) found a 4.0 mm Hg (95% CI: 3.0 to 5.0 mm Hg) increase in diastolic blood  
30 pressure per 10-ppb increase in SO<sub>2</sub> concentrations 2 days earlier, and a 1.6 mm Hg (95%  
31 CI: 0.15, 3.1 mm Hg) decrease in systolic blood pressure related to SO<sub>2</sub> concentrations  
32 3 days earlier.

33 In addition to longitudinal and cross-sectional studies, a few new studies examined ED  
34 visits for hypertension. In Beijing, [Guo et al. \(2010\)](#) observed a 10.0% (95% CI: 1.1,  
35 19.7%) increase in risk of ED visits for hypertension per 10-ppb increase in 24-h avg SO<sub>2</sub>  
36 on the same day. The association was attenuated, but still positive, in a copollutant model

1 adjusting for PM<sub>10</sub> [6.7% (95% CI: -3.4, 17.9%) increase at lag 0] and no longer present  
2 in a copollutant model adjusting for NO<sub>2</sub> [-0.8% (95% CI: -12.8, 13.0%) change at  
3 lag 0]. Inconsistent results were reported in two studies of ED visits for hypertension in  
4 Canada. In a case-crossover study in Calgary and Edmonton, [Brook and Kousha \(2015\)](#)  
5 reported positive associations between ED visits for hypertension and 24-h avg SO<sub>2</sub>  
6 concentrations for males [OR: 2.50 (95% CI: 1.00, 5.87) per 10-ppb increase] and  
7 females [OR: 2.59 (95% CI: 1.12, 5.61) per 10-ppb increase]. Conversely, in Edmonton,  
8 [Szyszkowicz et al. \(2012b\)](#) observed that ED visits for hypertension were both positively  
9 and negatively associated with SO<sub>2</sub> depending on the lag time examined.

### **Experimental Studies**

10 Several experimental studies examined hypertension and blood pressure following SO<sub>2</sub>  
11 exposure. Study characteristics are summarized in Supplemental Table 5S-13 ([U.S. EPA,](#)  
12 [2016s](#)). One controlled human exposure study reported no change in mean arterial  
13 pressure following SO<sub>2</sub> exposure ([Routledge et al., 2006](#)). Two animal toxicological  
14 studies have examined blood pressure following SO<sub>2</sub> exposure ([Halinen et al., 2000b](#);  
15 [Halinen et al., 2000a](#)). In both studies, SO<sub>2</sub> was administered intratracheally to  
16 hyperventilated guinea pigs in cold, dry air. These studies reported increases in blood  
17 pressure following cold, dry air exposure with and without SO<sub>2</sub> and did not determine  
18 whether there were any effects on blood pressure caused by SO<sub>2</sub> that may not be  
19 attributable to cold, dry air exposure.

### **Summary of Blood Pressure**

20 In summary, epidemiologic studies evaluating the association between ambient SO<sub>2</sub>  
21 concentrations and blood pressure remain inconsistent with most relying on central site  
22 monitors and few examining the potential for copollutant confounding. Experimental  
23 studies provide no additional evidence for SO<sub>2</sub>-induced changes in blood pressure.  
24 The most informative studies to date found no evidence of within-person changes in  
25 blood pressure despite relatively large changes in SO<sub>2</sub> concentrations during the Beijing  
26 Olympics. Experimental studies do not demonstrate effects of SO<sub>2</sub> on blood pressure. As  
27 such, the current evidence does not support the presence of an association between  
28 ambient SO<sub>2</sub> and blood pressure.

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### 5.3.1.6 Venous Thromboembolism

1 Venous thromboembolism (VTE) is a term that includes both deep vein thrombosis  
2 (DVT) and pulmonary embolism (PE). DVT occurs when a blood clot develops in the  
3 deep veins, most commonly in the lower extremities. A part of the clot can break off and  
4 travel to the lungs, causing a PE, which can be life threatening.

5 There were no epidemiologic studies of VTE available for the 2008 ISA for Sulfur  
6 Oxides. One recent study covering the metropolitan region of Santiago, Chile, found a  
7 10.8% (95% CI: 3.3, 15.7%) and 8.5% (95% CI: 4.0, 13.2%) increased rate of hospital  
8 admission for venous thrombosis and pulmonary embolism, respectively, per 10-ppb  
9 increase in 24-h avg SO<sub>2</sub> concentrations ([Dales et al., 2010](#)). Copollutant models were not  
10 evaluated. Given the limited epidemiologic evidence, the association between ambient  
11 SO<sub>2</sub> concentrations and venous thromboembolism is unclear.

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### 5.3.1.7 Heart Failure

12 Results among the studies reviewed in the 2008 ISA for Sulfur Oxides ([U.S. EPA,](#)  
13 [2008d](#)) were inconsistent with regard to the association between ambient SO<sub>2</sub>  
14 concentrations and hospital admissions or ED visits for heart failure. A small number of  
15 additional studies are now available, including a multicity study of seven Canadian cities  
16 ([Stieb et al., 2009](#)). [Stieb et al. \(2009\)](#) observed an imprecise association (i.e., wide 95%  
17 CI) between 24-h avg SO<sub>2</sub> concentrations on the previous day and ED visits for heart  
18 failure [3.0% (95% CI: -1.9, 8.2%) increase in risk of ED visits per 10-ppb increase in  
19 SO<sub>2</sub>]. Similarly, in Guangzhou, China, [Yang et al. \(2014a\)](#) observed a 14.5% increase  
20 (95% CI: 6.1, 23.2%) in emergency ambulance dispatches for heart failure per 10-ppb  
21 increase in 24-h avg SO<sub>2</sub> concentrations on the same day. This association was slightly  
22 attenuated, but still positive and statistically significant in copollutant models adjusting  
23 for PM<sub>10</sub> [13.1% (95% CI: 3.3, 23.4%)] and NO<sub>2</sub> [11.3% (95% CI: 1.7, 21.5%)]. In  
24 contrast, [Yang \(2008\)](#) did not observe evidence of a positive association between ambient  
25 SO<sub>2</sub> exposure and heart failure in Taipei, Taiwan.

26 In summary, the available epidemiologic evidence is limited and inconsistent, and  
27 therefore does not support the presence of an association between ambient SO<sub>2</sub>  
28 concentrations and hospital admissions or ED visits for heart failure.

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### 5.3.1.8 Aggregated Cardiovascular Disease

1 Many epidemiologic studies consider the composite endpoint of all cardiovascular  
2 diseases, which typically includes all diseases of the circulatory system (e.g., heart  
3 diseases and cerebrovascular diseases). This section summarizes the results of  
4 epidemiologic studies evaluating the association between ambient SO<sub>2</sub> concentrations  
5 and ED visits or hospitalizations for all cardiovascular diseases. [Table 5-28](#) presents  
6 study details and air quality characteristics of the city, or across all cities, from the U.S.  
7 and Canadian cardiovascular-related hospital admission and ED visit studies evaluated in  
8 the 2008 ISA for Sulfur Oxides and those more recent.

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**Table 5-28 Mean and upper percentile concentrations of sulfur dioxide from cardiovascular-related hospital admission and emergency department visit studies: U.S. and Canadian studies from the 2008 ISA for Sulfur Oxides and recent studies.**

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Study	Location (Years)	Type of Visit (ICD 9/10)	Metric	Mean Concentration ppb	Upper Percentile of Concentrations ppb
<b>U.S.</b>					
<a href="#">Gwynn et al. (2000)</a>	Buffalo and Rochester, NY (1988–1990)	Hospital admissions: circulatory (401–405, 410–417)	24-h avg	12.2	Max: 37.7
<a href="#">†Ito et al. (2011)</a>	New York City, NY (2000–2006)	Hypertensive diseases (402, I11); MI (410, I21–I22); IHD (414, I25); dysrhythmias (427, I48); heart failure (428, I50); and stroke (430–439, I60–I69)	24-h avg	7.4	
<a href="#">Koken et al. (2003)</a>	Denver, CO (1993–1997)	Discharge data from Agency for Healthcare Research and Quality database: Acute MI (410.00–410.92), atherosclerosis (414.00–414.05), pulmonary heart failure (416.0–416.9), dysrhythmia (427.0–427.9), CHF (428.0)	24-h avg	5.7	Max: 18.9

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**Table 5-28 (Continued): Mean and upper percentile concentrations of sulfur dioxide from cardiovascular related hospital admission and emergency department visit studies: U.S. and Canadian studies from the 2008 ISA for Sulfur Oxides and recent studies.**

Study	Location (Years)	Type of Visit (ICD 9/10)	Metric	Mean Concentration ppb	Upper Percentile of Concentrations ppb
<a href="#">Low et al. (2006)</a>	New York City, NY (1995–2003)	Ischemic stroke (433–434), undetermined stroke (436); monitored intake in 11 hospitals (ED or clinic visits). Excluded stroke patients admitted for rehabilitation	24 h avg	10.98	Max: 96.0
<a href="#">Metzger et al. (2004)</a>	Atlanta, GA (1993–2000)	ED visits: IHD (410–414); acute MI (410); dysrhythmias (427); cardiac arrest (427.5); CHF (428); peripheral and cerebrovascular disease (433–437, 440, 443–444, 451–453); atherosclerosis (440); stroke (436)	1-h max:	11.0 (median)	90th: 39
<a href="#">Michaud et al. (2004)</a>	Hilo, HI (1997–2001)	ED visits Heart (410–414, 425–429)	24-h avg	1.92 (all hourly measurements)	Max: 447 (all hourly measurements)
<a href="#">Moolgavkar (2003)</a> <a href="#">Moolgavkar (2000)</a>	Cook County, IL; Los Angeles County, CA; Maricopa County, AZ (1987–1995)	Hospital admissions: CVD (390–429); cerebrovascular disease (430–448)	24-h avg	Cook: 6 (median) Los Angeles: 2 (median) Maricopa: 2 (median)	Cook: Max: 36 Los Angeles: Max: 16 Maricopa: Max: 14
<a href="#">Morris et al. (1995)</a>	Los Angeles, CA; Chicago, IL; Philadelphia, PA; New York City, NY; Detroit, MI; Houston, TX; Milwaukee, WI (1986–1989)	Hospital admissions: CHF (428)	1-h max	Los Angeles: 10 Chicago: 25 Philadelphia: 29 New York City: 32 Detroit: 25 Houston: 18 Milwaukee: 17	NR

**Table 5-28 (Continued): Mean and upper percentile concentrations of sulfur dioxide from cardiovascular related hospital admission and emergency department visit studies: U.S. and Canadian studies from the 2008 ISA for Sulfur Oxides and recent studies.**

Study	Location (Years)	Type of Visit (ICD 9/10)	Metric	Mean Concentration ppb	Upper Percentile of Concentrations ppb
<a href="#">Peel et al. (2007)</a>	Atlanta, GA (1993–2000)	ED visits: IHD (410–414), dysrhythmia (427), CHF (428), peripheral vascular and cerebrovascular disease (433–437, 440, 443, 444, 451–453)	1-h max	16.5 (17.1)	90th: 39
<a href="#">†Rich et al. (2010)</a>	New Jersey (2004–2006)	Hospital Admissions: transmural infarction (410.0, 410.1, 410.2, 410.3, 410.4, 410.5, 410.6), nontransmural infarction (410.7)	24-h avg	NR	NR
<a href="#">Schwartz and Morris (1995)</a>	Detroit, MI (1986–1989)	Hospital discharge: IHD (410–414), CHF (428), dysrhythmia (427)	24-h avg	25.4	90th: 44.0
<a href="#">Schwartz (1997)</a>	Tuscon, AZ (1988–1990)	Hospital discharge: CVD (390–429)	24-h avg	4.6	90th: 10.1
<a href="#">Tolbert et al. (2007)</a>	Atlanta, GA (1993–2004)	ED visits: CVD (410–414, 427, 428, 433–437, 440, 443–445, 451–453)	1-h max	14.9	Max: 149.0
<a href="#">Ulirsch et al. (2007)</a>	Southeast Idaho (1994–2000)	Hospital admissions and medical visits: CVD (390–429)	NR	3.0	90th: 7.9, 7.7 Max: 30.3, 30.3 (two time series examined)
<a href="#">Wellenius et al. (2005b)</a>	Birmingham, AL; Chicago, IL; Cleveland, OH; Detroit, MI; Minneapolis, MN; New Haven, CT; Pittsburgh, PA; Seattle, WA (1986–1999)	Hospital admissions: ischemic stroke, primary diagnosis of acute but ill-defined cerebrovascular disease or occlusion of the cerebral arteries; HS, primary diagnosis of intracerebral hemorrhage. (ICD codes not provided)	24-h avg	6.22 (median)	90th: 16.17

**Table 5-28 (Continued): Mean and upper percentile concentrations of sulfur dioxide from cardiovascular related hospital admission and emergency department visit studies: U.S. and Canadian studies from the 2008 ISA for Sulfur Oxides and recent studies.**

Study	Location (Years)	Type of Visit (ICD 9/10)	Metric	Mean Concentration ppb	Upper Percentile of Concentrations ppb
<a href="#">Wellenius et al. (2005a)</a>	Allegheny County, PA (1987–1999)	Hospital admissions: CHF (428)	24-h avg	14.78 (9.88)	95th: 33.93
<b>Canada</b>					
<a href="#">Burnett et al. (1997)</a>	Metropolitan Toronto (East York, Etobicoke, North York, Scarborough, Toronto, York) (1992–1994)	Hospital discharge: IHD (410–414); cardiac dysrhythmias (427); heart failure (428); all cardiac (410–414, 427, 428)	1-h max	7.9	Max: 26
<a href="#">Burnett et al. (1999)</a>	Metropolitan Toronto (East York, Etobicoke, North York, Scarborough, Toronto, York) (1980–1994)	IHD (410–414); cardiac dysrhythmias (427); CHF (428); all cardiac (410–414, 427, 428)	24-h avg	5.35	Max: 57
<a href="#">Fung et al. (2005)</a>	Windsor, ON (1995–2000)	CHF (428), IHD (410–414), dysrhythmias (427) and all cardiac	1-h max	27.5 (16.5)	Max: 129
<a href="#">Stieb et al. (2000)</a>	Saint John, NB (1992–1996)	ED visits: angina pectoris, MI, dysrhythmia/conduction disturbance, CHF, all cardiac	24-h avg	6.7 (5.6)	95th: 18 Max: 60
<a href="#">†Szyszkowicz (2008)</a>	Edmonton, AB (1992–2002)	ED visits: acute ischemic stroke (434 and 436)	24-h avg	2.6	NR
<a href="#">†Szyszkowicz et al. (2012a)</a>	Vancouver, BC (1999–2003)	ED visits (discharge diagnosis): transient ischemic attack, cerebrovascular incident, seizure	24-h avg	2.5	NR
<a href="#">†Szyszkowicz et al. (2012b)</a>	Edmonton, AB (1992–2002)	ED visits: hypertension (401.9)	24 h avg	2.6	Max: 16.3

**Table 5-28 (Continued): Mean and upper percentile concentrations of sulfur dioxide from cardiovascular related hospital admission and emergency department visit studies: U.S. and Canadian studies from the 2008 ISA for Sulfur Oxides and recent studies.**

Study	Location (Years)	Type of Visit (ICD 9/10)	Metric	Mean Concentration ppb	Upper Percentile of Concentrations ppb
<a href="#">Villeneuve et al. (2006a)</a>	Edmonton, AB (1992–2002)	ED visits: stroke	24-h avg	All year: 2.6 (1.9)	All year 75th: 4.0

CHF = congestive heart failure; CVD = cardiovascular disease; ED = emergency department; HS = hemorrhagic stroke; ICD = International Classification of Diseases; IHD = ischemic heart disease; MI = myocardial infarction; NR = not reported; SO<sub>2</sub> = sulfur dioxide.

†Studies published since the 2008 ISA for Sulfur Oxides.

1 The majority of epidemiologic studies reviewed in the 2008 ISA for Sulfur Oxides ([U.S.](#)  
2 [EPA, 2008d](#)) found a positive association between ambient SO<sub>2</sub> concentrations and rates  
3 of hospital admission or ED visits for all cardiovascular diseases. One prominent study  
4 from the previous ISA was a study conducted in 14 cities across Spain, which observed a  
5 3.5% (95% CI: 0.5, 6.7%) increased risk of hospital admission for all cardiovascular  
6 diseases per 10-ppb increase in SO<sub>2</sub> at lag 0–1 [([Ballester et al., 2006](#)) study details and  
7 results for this and other studies in this section are presented in [Table 5-29](#), and  
8 [Figure 5-14](#)]. The authors indicate (results not reported) that the association with SO<sub>2</sub> was  
9 attenuated after adjustment for CO or NO<sub>2</sub> in copollutant models. Most studies published  
10 since the 2008 ISA for Sulfur Oxides also observed positive associations between SO<sub>2</sub>  
11 and ED visits or hospitalizations for all CVD, although only a few considered potential  
12 copollutant confounding. For example, a case-crossover study in Beijing found that SO<sub>2</sub>  
13 averaged over eight monitoring sites was associated with risk of ED visits for all  
14 cardiovascular diseases in a single-pollutant model [OR: 1.04 (95% CI: 1.01, 1.06) per  
15 10-ppb increase in SO<sub>2</sub> on the same day] ([Guo et al., 2009](#)). The association remained  
16 comparable in copollutant models adjusting for either PM<sub>2.5</sub> [OR: 1.03 (95% CI: 0.99,  
17 1.06)] or NO<sub>2</sub> [OR: 1.03 (95% CI: 1.00, 1.07)]. Similarly, in Shanghai, [Chen et al.](#)  
18 [\(2010b\)](#) reported a small, but precise increase in risk of hospital admissions for CVD per  
19 10-ppb increase in 24-h avg SO<sub>2</sub> at lag 5 [1.7% (95% CI: 0.5, 3.0%)] and lag 0–6 [1.3%  
20 (5% CI: 0.0, 3.2%)]. The association at lag 5 was similar after adjusting for NO<sub>2</sub> or PM<sub>10</sub>,  
21 while copollutant models for lag 0–6 were not presented.

**Table 5-29 Mean and upper percentile concentrations of sulfur dioxide from cardiovascular-related hospital admission and emergency department visit studies.**

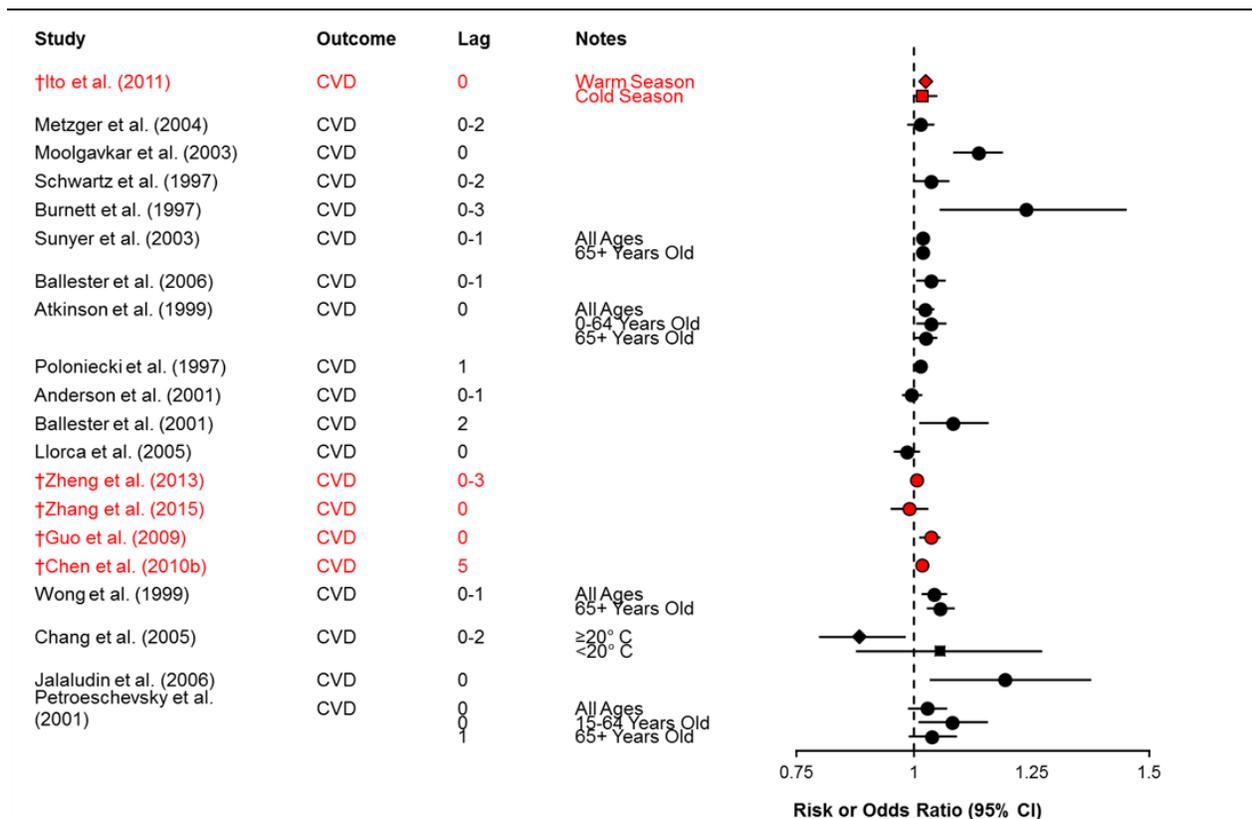
Study	Location (Years)	Exposure Assignment	Metric	Mean/Median Concentration ppb	Upper Percentile of Concentrations ppb
<a href="#">†Ito et al. (2011)</a>	New York City, NY (2000–2006)	Average across five monitoring sites	24-h avg	Mean: 7.4	NR
<a href="#">Metzger et al. (2004)</a>	Atlanta, GA (1993–2000)	Central site monitor	1-h max	Median: 11	90th: 39
<a href="#">Moolgavkar (2003)</a>	Los Angeles, CA (1987–1995)	Central site monitor	24-h avg	NR	NR
<a href="#">Schwartz (1997)</a>	Tuscon, AZ (1998–1990)	Central site monitor	24-h avg	Mean: 4.6	75th: 5.9 90th: 10.1
<a href="#">Burnett et al. (1997)</a>	Toronto (summer 1992–1994)	Average across four to six monitoring sites	1-h max	Mean: 7.9	75th: 11 Max: 26
<a href="#">Sunyer et al. (2003)</a>	Seven European cities (1990–1996)	Central site monitors in each city	24-h avg	Median: 1.9–8.0 across cities	90th: 5.3–29.4 across cities
<a href="#">Ballester et al. (2006)</a>	14 Spanish cities (1995–1999)	Citywide average for each city	24-h avg	Mean: 2.9–15.6 across cities	90th: 4.8–28.8 across cities
<a href="#">Atkinson et al. (1999)</a>	London, England (1992–1994)	Average across five monitoring sites	24-h avg	Mean: 8.1	90th: 11.8 Max: 31.4
<a href="#">Poloniecki et al. (1997)</a>	London, England (1987–1994)	Central site monitor	24-h avg	Median: 6	90th: 21 Max: 114
<a href="#">Anderson et al. (2001)</a>	Birmingham, England (1994–1996)	Average across five monitoring sites	24-h avg	Mean: 7.2	90th: 12.3 Max: 59.8
<a href="#">Ballester et al. (2001)</a>	Valencia, Spain (1994–1996)	Average across 14 monitoring sites	24-h avg	Mean: 9.8	Max: 26.1

**Table 5-29 (Continued): Mean and upper percentile concentrations of sulfur dioxide from cardiovascular related hospital admission and emergency department visit studies.**

Study	Location (Years)	Exposure Assignment	Metric	Mean/Median Concentration ppb	Upper Percentile of Concentrations ppb
<a href="#">Llorca et al. (2005)</a>	Torrelavega, Spain (1992–1995)	Average across three monitoring sites	24-h avg	Mean: 5.1	NR
† <a href="#">Filho et al. (2008)</a>	São Paulo, Brazil (2001–2003)	Average across 13 monitoring sites	24-h avg	Mean: 5.3	Max: 16.4
† <a href="#">Martins et al. (2006)</a>	São Paulo, Brazil (1996–2001)	Average across six monitoring sites	24-h avg	Mean: 6.5	Max: 28.7
† <a href="#">Zheng et al. (2013)</a>	Lanzhou, China (2001–2005)	Average across four monitoring sites	24-h avg	Mean: 30.2	75th: 40.5 Max: 141.6
† <a href="#">Zhang et al. (2015b)</a>	Beijing, China (2009–2011)	Average across 11 monitoring stations	24-h avg	Mean: 10.7	75th: 13.4 Max: 89.5
† <a href="#">Guo et al. (2009)</a>	Beijing, China (2004–2006)	Average across eight monitoring sites	24-h avg	Mean: 18.8	75th: 23.7 Max: 111.8
† <a href="#">Chen et al. (2010b)</a>	Shanghai, China (2005–2007)	Average across six monitoring sites	24-h avg	Mean: 21.4	75th: 27.5 Max: 89.7
<a href="#">Wong et al. (1999)</a>	Hong Kong, China (1994–1995)	Average across seven monitoring sites	24-h avg	Median: 6.5	75th: 9.5 Max: 26.1
<a href="#">Chang et al. (2005)</a>	Taipei, Taiwan (1997–2001)	Average across six monitoring sites	24-h avg	Mean: 4.3	75th: 5.5 Max: 14.6
<a href="#">Jalaludin et al. (2006)</a>	Sydney, Australia (1997–2001)	Average across 14 monitoring sites	24-h avg	Mean: 1.07	75th: 1.39 Max: 3.94
<a href="#">Petroeshevsky et al. (2001)</a>	Brisbane, Australia (1987–1994)	Average across two monitoring sites	24-h avg	Mean: 13.9	Max: 49.7

NR = not reported.

†Studies published since the 2008 ISA for Sulfur Oxides.



CI = confidence interval; CVD = cardiovascular disease.

Note: Studies in red are recent studies. Studies in black were included in the 2008 ISA for Sulfur Oxides. All-year associations = circles; summer/warm-days associations = diamonds; winter/cold-days associations = squares. Relative risks are standardized to a 10-ppb or 40-ppb increase in sulfur dioxide for 24-h avg and 1-h max metrics, respectively. Lag times are reported in days, unless otherwise noted. Corresponding quantitative results are reported in Supplemental Table 5S-16 ([U.S. EPA, 2016](#))<sup>cc</sup>. All results are from single pollutant models.

**Figure 5-14 Studies of hospital admissions and emergency department visits for all cardiovascular disease.**

1 A number of other studies considering single-pollutant models also reported generally  
 2 consistent associations between SO<sub>2</sub> concentrations and hospital admissions or ED visits  
 3 for CVD. A study in New York City ([Ito et al., 2011](#)) observed an association between  
 4 SO<sub>2</sub> concentrations that was stronger and more precise in the warm season [OR: 1.026  
 5 (95% CI: 1.021, 1.031) per 10-ppb increase in 24-h avg SO<sub>2</sub>] than in the cold season  
 6 [OR: 1.018 (95% CI: 0.998, 1.049)]. Two studies in São Paulo, Brazil ([Filho et al., 2008](#);  
 7 [Martins et al., 2006](#)) also found associations in single pollutant models (no quantitative  
 8 results; results presented graphically). Another study found an increase in the risk of daily  
 9 hospital admissions per IQR increase in 24-h avg SO<sub>2</sub> in the heavily polluted city of

1 Lanzhou, China ([Zheng et al., 2013](#)). However, this association was less clinically  
2 relevant when standardized to a 10-ppb increase in 24-h avg SO<sub>2</sub>. In contrast, a large  
3 study in Beijing, China reported that CVD ED visits were not associated with SO<sub>2</sub>  
4 concentrations on the same day ([Zhang et al., 2015b](#)). The authors also examined a  
5 number of other single-day lags and cumulative lags and found little evidence of an  
6 association.

7 Overall, consistent associations between ambient SO<sub>2</sub> concentrations and rates of hospital  
8 admissions or ED visits for all cardiovascular diseases have been observed. Although  
9 associations are evident in single-pollutant models in many locations, there was limited  
10 assessment of potential copollutant confounding. Therefore, this association may at least  
11 partly be the result of confounding by correlated pollutants. Additionally, most studies  
12 examined 24-h avg exposure metrics for SO<sub>2</sub>, which may not adequately capture the  
13 spatial and temporal variability in SO<sub>2</sub> concentrations ([Section 5.2.1.2](#)).

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### 5.3.1.9 Cardiovascular Mortality

14 Studies evaluated in the 2008 SO<sub>x</sub> ISA that examined the association between short-term  
15 SO<sub>2</sub> exposure and cause-specific mortality found consistent positive associations with  
16 cardiovascular mortality using a 24-h avg exposure metric. Across studies, there was  
17 evidence that the magnitude of the SO<sub>2</sub>-cardiovascular mortality relationship was similar  
18 or slightly larger than total mortality. Recent multicity studies conducted in Asia ([Chen et  
19 al., 2012b](#); [Kan et al., 2010b](#)) and Italy ([Bellini et al., 2007](#)), and a meta-analysis of  
20 studies conducted in Asia ([Atkinson et al., 2012](#)) provide evidence that is consistent with  
21 those studies evaluated in the 2008 SO<sub>x</sub> ISA ([Section 5.5.1.3, Figure 5-18](#)).

22 The associations between short-term SO<sub>2</sub> concentrations and cardiovascular mortality are  
23 further supported by studies focusing on stroke mortality ([Yang et al., 2014b](#); [Chen et al.,  
24 2013](#)). In a study conducted in eight of the CAPES cities, [Chen et al. \(2013\)](#) reported  
25 associations for SO<sub>2</sub> and stroke similar to those for all cardiovascular mortality across all  
26 of the CAPES cities ([Section 5.5.1.3, Figure 5-18](#)). The magnitude of the association for  
27 stroke mortality observed in [Chen et al. \(2013\)](#) is supported by multiple systematic  
28 reviews and meta-analyses of stroke mortality ([Shah et al., 2015](#); [Yang et al., 2014b](#)).

29 Both studies reported similar results, with [Yang et al. \(2014b\)](#) reporting a 2.5% increase  
30 in stroke mortality (95% CI: 1.8, 3.1) for a 10-ppb increase in 24-h avg SO<sub>2</sub>  
31 concentrations in a meta-analysis of mortality studies conducted in Asia, Europe, and  
32 North America and [Shah et al. \(2015\)](#) reporting a 2.2% increase in stroke mortality (95%  
33 CI: 1.4, 3.1) for a 10-ppb increase in SO<sub>2</sub> concentrations (averaging time was not  
34 reported) in a meta-analysis of studies conducted worldwide. However, when interpreting  
35 the results of [Yang et al. \(2014b\)](#), it is important to note that when examining regional

1 associations in SO<sub>2</sub>-related stroke (i.e., Asia vs. Europe and North America), which  
2 combined both mortality and hospital admission outcomes, the magnitude of the  
3 association was much smaller, 0.8% (95% CI: -0.2, 1.7), than those observed in studies  
4 conducted in Asia, 2.1% (95% CI: 1.2, 3.2). This could be attributed to the relatively low  
5 variability and overall low SO<sub>2</sub> concentrations observed in both Europe and North  
6 America compared to Asia ([Section 5.5.1.3](#), [Table 5-39](#)).

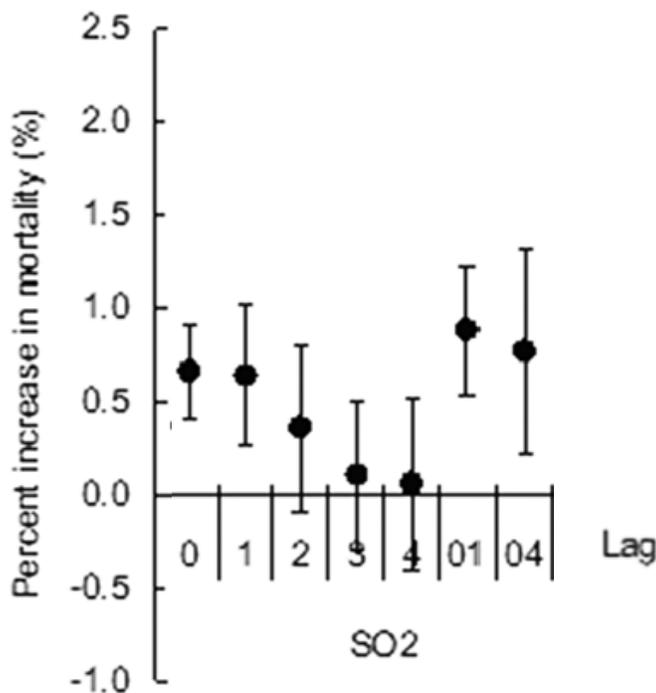
7 Previous studies evaluated in and prior to the 2008 SO<sub>x</sub> ISA that examined the  
8 association between short-term SO<sub>2</sub> exposures and cardiovascular mortality focused  
9 exclusively on single-pollutant analyses. Therefore, questions arose with regard to the  
10 independent effect of SO<sub>2</sub> on cardiovascular mortality and whether associations remained  
11 robust in copollutant models. A few recent multicity studies conducted in China ([Chen et  
12 al., 2012b](#)) and across Asia ([Kan et al., 2010b](#)) examined both of these questions. [Chen et  
13 al. \(2012b\)](#) found that the SO<sub>2</sub>-cardiovascular mortality association was attenuated, but  
14 remained positive in copollutant models with PM<sub>10</sub> [1.0% (95% CI: 0.08, 1.9) for a  
15 10-ppb increase in 24-h avg SO<sub>2</sub> concentrations at lag 0–1] and NO<sub>2</sub> [0.5% (95% CI:  
16 -0.5, 1.4)]. These results are similar to those reported by [Chen et al. \(2012b\)](#) when  
17 examining the SO<sub>2</sub>-total mortality association in models with NO<sub>2</sub> (i.e., ~80% reduction),  
18 but a larger degree of attenuation was observed in models with PM<sub>10</sub> for cardiovascular  
19 mortality (i.e., ~40% reduction for total mortality and 50% reduction for cardiovascular  
20 mortality) ([Section 5.5.1.4](#)). [Kan et al. \(2010b\)](#), as part of the PAPA study, also examined  
21 potential copollutant confounding (i.e., NO<sub>2</sub>, PM<sub>10</sub>, and O<sub>3</sub>) but only in each city  
22 individually. The authors found that, although the SO<sub>2</sub>-cardiovascular mortality  
23 association remained positive in copollutant models, there was evidence of an attenuation  
24 of the association in models with PM<sub>10</sub> and NO<sub>2</sub> ([Figure 5-19](#)). In an analysis of stroke  
25 mortality in eight of the CAPES cities, [Chen et al. \(2013\)](#) reported pattern of associations  
26 similar to that of [Chen et al. \(2012b\)](#) and [Kan et al. \(2010b\)](#) in copollutant models with  
27 PM<sub>10</sub> and NO<sub>2</sub>. In single-pollutant models, the authors reported a 2.3% (95% CI: 1.4, 3.2)  
28 increase in stroke mortality for a 10 ppb increase in 24-h avg SO<sub>2</sub> concentrations at  
29 lag 0–1. However, in copollutant models, [Chen et al. \(2013\)](#) observed that SO<sub>2</sub>-stroke  
30 mortality associations were attenuated in models with PM<sub>10</sub>, ~40% reduction [1.9% (95%  
31 CI: 0.3, 3.5)] and NO<sub>2</sub>, ~80% reduction [0.0% (95% CI: -1.8, 1.9)]. Overall, the studies  
32 that examined potential copollutant confounding on the SO<sub>2</sub>-cardiovascular mortality  
33 relationship report results consistent with what was observed for total mortality.  
34 However, the overall assessment of copollutant confounding remains limited, and it is  
35 unclear how the results observed in Asia translate to other locations, specifically due to  
36 the unique air pollution mixture and higher concentrations observed in Asian cities.

37 Of the multicity studies evaluated, potential seasonal differences in SO<sub>2</sub>-cardiovascular  
38 mortality associations were only assessed in a study conducted in Italy ([Bellini et al.,](#)

1 [2007](#)) with additional information from U.S.-based single-city studies conducted in  
2 Philadelphia ([Sacks et al., 2012](#)) and New York City ([Ito et al., 2011](#)). In a study of  
3 15 Italian cities, [Bellini et al. \(2007\)](#) reported larger SO<sub>2</sub>-cardiovascular mortality  
4 associations in the summer [9.4% increase (April–September)], compared to both winter  
5 [1.6% increase (October–March)] and all-year analyses (92.9% increase), which are  
6 consistent with the pattern of associations observed for total and respiratory mortality.  
7 These results are supported by [Ito et al. \(2011\)](#) in a study conducted in New York City  
8 that found that when examining single-day lags of 0 to 3 days, the SO<sub>2</sub>-cardiovascular  
9 mortality association was consistently positive during the warm season, ranging from a  
10 1.2 to 3.5% increase across lags. The authors reported no evidence of an association in  
11 winter and all-year analyses. Within this analysis, [Ito et al. \(2011\)](#) reported rather poor  
12 monitor-to-monitor temporal correlations for SO<sub>2</sub>, which would indicate potential  
13 exposure error and subsequently attenuation and imprecision in the risk estimate  
14 ([Section 3.4.2](#), [Section 3.4.4](#)). [Sacks et al. \(2012\)](#) provide additional support to the limited  
15 evidence indicating differences in the seasonal pattern of SO<sub>2</sub>-cardiovascular mortality  
16 associations. However, as detailed in [Section 5.5.1.4](#), [Sacks et al. \(2012\)](#) demonstrated  
17 that across models that use various approaches to control for seasonality and the potential  
18 confounding effects of weather, the magnitude of seasonal SO<sub>2</sub>-cardiovascular mortality  
19 associations may vary depending on the modeling approach employed. Therefore,  
20 although [Bellini et al. \(2007\)](#) and [Ito et al. \(2011\)](#) provide initial evidence indicating  
21 potentially larger cardiovascular mortality associations in the summer, the results of  
22 [Sacks et al. \(2012\)](#) suggest that the evidence remains unclear whether the seasonal pattern  
23 of SO<sub>2</sub>-cardiovascular mortality associations is consistent across statistical modeling  
24 choices and study locations.

25 An uncertainty that often arises when evaluating studies that examine the relationship  
26 between short-term air pollution exposures and cause-specific mortality is whether  
27 analyses of statistical modeling parameters, the lag structure of associations, and the C-R  
28 relationship provide results that are consistent with what is observed for total mortality.  
29 [Chen et al. \(2013\)](#) examined each of these issues in a study of stroke mortality, with  
30 additional supporting evidence from the full CAPES study ([Chen et al., 2012b](#)). When  
31 examining alternative approaches to controlling for seasonality, [Chen et al. \(2013\)](#) found  
32 that increasing the df employed from 4 to 10 df per year did not substantially change the  
33 SO<sub>2</sub>-stroke mortality association. However, [Chen et al. \(2012b\)](#) when altering the lag  
34 structure of the temperature term included to control for the potential confounding effects  
35 of weather, reported an attenuation of the association, although it did remain positive.  
36 However, as detailed in [Section 5.5.1.4](#), this could be the result of including only one  
37 temperature term in the model.

1 When examining the lag structure of associations, [Chen et al. \(2013\)](#) reported results for  
2 stroke mortality that are consistent with those observed for all cardiovascular mortality.  
3 As depicted in [Figure 5-15](#) there is evidence of a steady decline in the SO<sub>2</sub>-stroke  
4 mortality association at longer individual lag days, with the strongest association  
5 occurring for a moving average of lag 0–1 days. A similar pattern of associations was  
6 observed for cardiovascular mortality by [Chen et al. \(2012b\)](#) in the full CAPES study  
7 ([Figure 5-20](#)), as well as the PAPA study ([Kan et al., 2010b](#)) ([Figure 5-20](#)). These results  
8 are further confirmed in a systematic review and meta-analysis of studies of stroke  
9 mortality conducted by [Yang et al. \(2014b\)](#), which found the strongest associations at  
10 lag 0 and 1 in a subgroup analysis of single-day lags of 0 to 2 days.



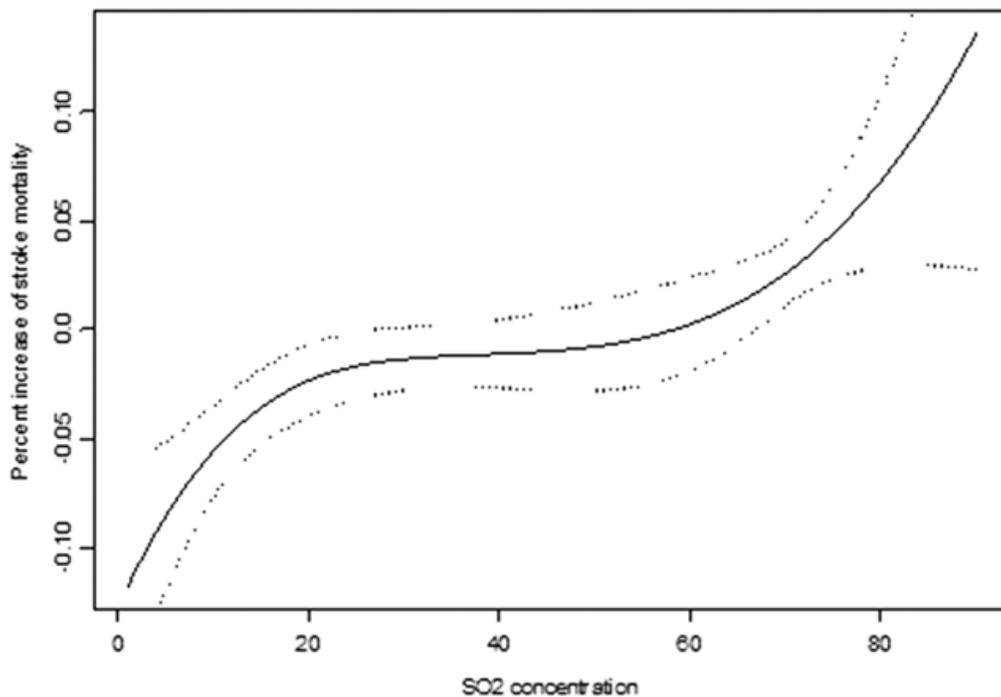
SO<sub>2</sub> = sulfur dioxide.

Source: Adapted from [Chen et al. \(2013\)](#).

**Figure 5-15** Percent increase in stroke mortality associated with a 10 µg/m<sup>3</sup> (3.62 ppb) increase in sulfur dioxide concentrations using different lag structures.

11 [Chen et al. \(2013\)](#) also examined the shape of the SO<sub>2</sub>-stroke mortality C-R relationship.  
12 To examine the assumption of linearity, the authors fit both a linear and spline model to  
13 the SO<sub>2</sub>-stroke mortality relationship. [Chen et al. \(2013\)](#) then computed the deviance

1 between the two models to determine any evidence of nonlinearity. An examination of  
2 the deviance did not indicate that the spline model improved the overall fit of the  
3 SO<sub>2</sub>-stroke mortality relationship (Figure 5-16).



SO<sub>2</sub> = sulfur dioxide.

Note: The solid line represents the mean estimate and the dotted lines are 95% confidence intervals.

Source: Adapted from [Chen et al. \(2013\)](#).

**Figure 5-16 Pooled concentration-response curves for sulfur dioxide and daily stroke mortality in eight Chinese cities for a 10 µg/m<sup>3</sup> (3.62 ppb) increase in 24-h avg concentrations at lag 0–1 days.**

4 Overall, recent multicity studies report evidence of consistent positive associations  
5 between short-term SO<sub>2</sub> concentrations and cardiovascular mortality, which is consistent  
6 with those studies evaluated in the 2008 SO<sub>x</sub> ISA. Unlike studies evaluated in the 2008  
7 SO<sub>x</sub> ISA, recent studies examined whether copollutants confound the relationship  
8 between short-term SO<sub>2</sub> concentrations and cardiovascular mortality. Overall, these  
9 studies reported evidence that the SO<sub>2</sub>-respiratory mortality association was attenuated in  
10 models with NO<sub>2</sub> and PM<sub>10</sub>, but the analyses are limited to Asian cities where the air  
11 pollution mixture and concentrations are different than those reported in other areas of

1 the world. A few studies examined potential seasonal patterns in associations, and found  
2 initial evidence of larger SO<sub>2</sub>-cardiovascular mortality associations in the summer/warm  
3 season. However, seasonal associations may be influenced by study location and the  
4 statistical modeling choice employed. Limited analyses of model specification, the lag  
5 structure of associations, and the C-R relationship suggest that: (1) associations remain  
6 robust when alternating the df used to control for seasonality; (2) associations are larger  
7 and more precise within the first few days after exposure in the range of 0 and 1 days;  
8 and (3) there is a linear, no threshold C-R relationship, respectively. However, for both  
9 total and cause-specific mortality, the overall assessment of linearity in the C-R  
10 relationship is based on a very limited exploration of alternatives.

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### 5.3.1.10 Subclinical Effects Underlying Cardiovascular Effects

11 The following subsections review studies of subclinical effects that serve as useful  
12 measures of physiological and biochemical responses that could provide mechanistic  
13 evidence to describe a role for SO<sub>2</sub> in the manifestation of cardiovascular diseases. These  
14 subclinical effects are not widely validated markers of specific clinical cardiovascular  
15 outcomes, but could potentially underlie the development, progression, or indication of  
16 various clinical events and provide biological plausibility for multiple outcomes.

#### Heart Rate and Heart Rate Variability

17 The 2008 ISA for Sulfur Oxides concluded that the overall evidence available at the time  
18 was insufficient to conclude that SO<sub>2</sub> has an effect on cardiac autonomic control as  
19 assessed by indices of HRV. HRV provides a noninvasive marker of cardiac autonomic  
20 nervous system function. The rhythmic variation in the intervals between heart beats can  
21 be quantified in either the time domain or the frequency domain ([TFESC and NASPE,  
22 1996](#)). Common time-domain measures of HRV include the standard deviation of all  
23 normal-to-normal intervals (SDNN, an index of total HRV) and the root-mean-square of  
24 successive differences (rMSSD, an index influenced mainly by the parasympathetic  
25 nervous system). In the frequency domain, HRV is usually divided into the high  
26 frequency (HF) and low frequency (LF) components, as well as the ratio of the LF to HF  
27 components (LF:HF) ([TFESC and NASPE, 1996](#)). Decreases in indices of HRV have  
28 been associated with increased risk of cardiovascular events in prospective cohort studies  
29 ([La Rovere et al., 2003](#); [Kikuya et al., 2000](#); [Tsuji et al., 1996](#); [Tsuji et al., 1994](#)).

## ***Epidemiology***

1 A number of additional epidemiologic studies are now available for review. In a  
2 cross-sectional study in South Korea, [Min et al. \(2009\)](#) reported negative associations  
3 between ambient SO<sub>2</sub> concentrations and indices of HRV (SDNN, and the LF and HF  
4 components) among 256 smokers, but no association among the 767 nonsmokers (no  
5 quantitative results; result presented graphically). In another cross-sectional study, [Min et  
6 al. \(2008b\)](#) reported a -7.6% (95% CI: -14.7, 0.1%) change in SDNN and a -23.1%  
7 (95% CI: -35.4, -6.5%) change in LF per 10-ppb increase in 24-h avg SO<sub>2</sub> among  
8 1,349 participants in South Korea. The amount of overlapping participants between these  
9 two studies is unclear.

10 The above studies are limited by their cross-sectional approach that compares measures  
11 of HRV across individuals assessed on different days. In contrast, longitudinal or  
12 repeated-measure study provide an estimate of the average association between SO<sub>2</sub> and  
13 measures of HRV within individuals. [Huang et al. \(2012\)](#) measured HRV repeatedly in  
14 40 participants with pre-existing cardiovascular disease in Beijing in the summer of 2007  
15 and again in the summer of 2008, including one measurement period during the 2008  
16 Beijing Olympics when citywide air pollution control measures substantially reduced  
17 ambient concentrations of most criteria pollutants. In this study, SO<sub>2</sub> concentrations  
18 during the Olympics were reduced by nearly 30% versus the previous month and nearly  
19 50% versus the same period the previous summer ([Huang et al., 2012](#)). Despite these  
20 large changes in SO<sub>2</sub> concentrations, overall only small associations were observed  
21 between SO<sub>2</sub> concentrations and HRV indices, limited to a 4.8% reduction (95% CI:  
22 -9.1, -0.3%) in the LF component and an unexpected 4.1% increase (95% CI: -2.2,  
23 10.9%) in the HF component of HRV per interquartile range (NR) increase in SO<sub>2</sub> in the  
24 previous 12 hours ([Huang et al., 2012](#)). In subgroup analyses, SDNN was significantly  
25 positively associated with SO<sub>2</sub> concentrations among those with higher levels of  
26 C-reactive protein (CRP; a marker of inflammation), those with diabetes, and males.  
27 These results are difficult to understand given that a higher SDNN is generally thought to  
28 be associated with lower risk of cardiovascular events. The findings were also  
29 inconsistent with another study that observed a negative association between SDNN and  
30 ambient SO<sub>2</sub> concentrations. A repeated measure study in Shanghai, China reported a  
31 4.36% reduction (95% CI: -5.85, -2.86%) in SDNN per IQR increase (NR) in 4-hour  
32 moving average exposure to SO<sub>2</sub> ([Sun et al., 2015](#)). This association was attenuated, but  
33 still statistically significant in copollutant models adjusting for BC [-2.91% (95% CI:  
34 -4.66, -1.13%)] and O<sub>3</sub> [-3.24% (95% CI: -4.83, -1.62%)], and attenuated and no  
35 longer statistically significant, but still negative in copollutant models adjusting for NO<sub>2</sub>  
36 [-0.56% (95% CI: -2.38, 1.30%)] and CO [-1.25% (95% CI: -3.02, 0.55%)]. In another  
37 study in Beijing before, during, and after the 2008 Olympics, [Rich et al. \(2012\)](#) observed

1 small but statistically significant increases in heart rate associated with ambient SO<sub>2</sub>  
2 concentrations on the previous day (no quantitative results; result presented graphically).  
3 In expanded results from the same protocol, [Zhang et al. \(2013\)](#) found that the association  
4 was similar in copollutants models adjusting for CO, NO<sub>2</sub>, O<sub>3</sub>, EC, or OC, but was  
5 attenuated and no longer positive after adjustment for PM<sub>2.5</sub> or SO<sub>4</sub><sup>2-</sup>. [Zhang et al. \(2013\)](#)  
6 also reported a strong association between LF:HF and ambient SO<sub>2</sub> concentrations on the  
7 previous day. This association was relatively unchanged after adjustment for CO, NO<sub>2</sub>,  
8 O<sub>3</sub>, EC, OC, or PM<sub>2.5</sub> in copollutant models, and attenuated but still positive after  
9 adjustment for SO<sub>4</sub><sup>2-</sup>. In contrast, a panel study in Taipei, Taiwan used Holter monitors to  
10 continuously monitor HRV in 46 participants, and observed no associations between  
11 ambient SO<sub>2</sub> and SDNN, r-MSSD, LF component, or HF component (quantitative results  
12 not reported) ([Chuang et al., 2007](#)). Although new studies are available, findings are  
13 mixed and they do not support the presence of an association between ambient SO<sub>2</sub> and  
14 measures of HRV.

### ***Experimental Studies***

15 Several experimental studies examined heart rate and HRV following SO<sub>2</sub> exposure.  
16 Study characteristics are summarized in Supplemental Table 5S-13. ([U.S. EPA, 2016s](#))  
17 Animal studies have reported no changes in heart rate following SO<sub>2</sub> exposures of  
18 1,000–5,000 ppb in guinea pigs and 1,200 ppb in rats ([Nadziejko et al., 2004](#); [Halinen et](#)  
19 [al., 2000b](#); [Halinen et al., 2000a](#)).

20 Controlled human exposure studies have reported changes in heart rate following SO<sub>2</sub>  
21 exposure but not during exposure. [Tunnicliffe et al. \(2001\)](#) reported no change in heart  
22 rate in healthy adults or adults with asthma during exposure to 200 ppb SO<sub>2</sub> for 1 hour at  
23 rest. However, in a similar study design, [Routledge et al. \(2006\)](#) reported a decrease in  
24 heart rate measured by the RR interval from electrocardiographic (ECG) recordings  
25 4 hours after SO<sub>2</sub> exposure in healthy adults. This change in heart rate was not observed  
26 in SO<sub>2</sub>-exposed older adults with stable angina and coronary artery disease during or  
27 immediately after exposure. Both studies found no change in heart rate during or  
28 immediately following similar exposure conditions. [Tunnicliffe et al. \(2001\)](#) did not  
29 obtain ECG measures following exposure and thus may have been unable to capture the  
30 decrease in heart rate reported by [Routledge et al. \(2006\)](#).

31 [Tunnicliffe et al. \(2001\)](#) and [Routledge et al. \(2006\)](#) reported changes in different  
32 measures of HRV in adults following SO<sub>2</sub> exposure. [Tunnicliffe et al. \(2001\)](#) reported  
33 that HF power, LF power, and total power were higher with SO<sub>2</sub> exposures compared to  
34 air exposure in the healthy subjects, but that these indices were reduced during SO<sub>2</sub>  
35 exposure in the subjects with asthma (statistical significance only in total power in  
36 healthy adults). The LF:HF ratios were unchanged in both groups. [Routledge et al. \(2006\)](#)

1 reported a reduction in SDNN, rMSSD, percentage of successive RR interval differences  
2 exceeding 50 ms (pNN<sub>50</sub>), and HF power (not statistically significant) in healthy adults  
3 4 hours after SO<sub>2</sub> exposure. Baroreflex sensitivity was also reduced 4 hours after SO<sub>2</sub>  
4 exposure determined by changes in  $\alpha$ -HF and  $\alpha$ -LF. There were no changes in HRV  
5 among the patients with coronary heart disease; however, this lack of response may be  
6 due to a drug treatment effect because a large portion of these patients were taking  
7 beta-blockers. The changes in HRV observed in [Tunnicliffe et al. \(2001\)](#) and [Routledge  
8 et al. \(2006\)](#) indicate the potential for SO<sub>2</sub> to affect the autonomic nervous system (see  
9 [Section 4.3.1](#)).

### ***Summary of Heart Rate and Heart Rate Variability***

10 The current epidemiologic evidence does not support the presence of an association  
11 between ambient SO<sub>2</sub> and measures of HRV. No changes in heart rate were observed in  
12 experimental animal studies while changes in HRV observed in human clinical studies  
13 may indicate the potential for SO<sub>2</sub> to affect the autonomic nervous system (see  
14 [Section 4.3.1](#)). Overall, studies evaluating the effect of ambient SO<sub>2</sub> concentrations and  
15 measures of HRV and heart rate remain limited.

### **QT Interval Duration**

16 The QT interval provides an electrocardiographic marker of ventricular repolarization.  
17 Prolongation of the QT interval is associated with increased risk of life-threatening  
18 ventricular arrhythmias. In an analysis of data from the Boston-area Normative Aging  
19 Study, [Baja et al. \(2010\)](#) observed a small and imprecise (i.e., wide confidence intervals)  
20 association between heart-rate-corrected QT interval and 10-hour moving average of SO<sub>2</sub>  
21 concentrations among older, generally white men (no quantitative results; result  
22 presented graphically). The only prior study available for comparison from the 2008 ISA  
23 for Sulfur Oxides ([U.S. EPA, 2008d](#)) also found that SO<sub>2</sub> concentrations were positively  
24 associated with increased QT interval duration amongst a small sample of 56 men in  
25 Erfurt, Germany [3.75 ms increase (95% CI: 1.21, 6.28 ms) per 0.61-ppb increase in  
26 24-h avg SO<sub>2</sub>] ([Henneberger et al., 2005](#)). There was little variability between daily  
27 measured SO<sub>2</sub> concentrations, so the effect estimate is not standardized to prevent  
28 inflation of the confidence interval.

29 The two reviewed studies provide limited evidence of association between short-term  
30 SO<sub>2</sub> exposure and markers of ventricular repolarization. Neither of these studies  
31 evaluated potential copollutant confounding and coherence for an association between  
32 SO<sub>2</sub> exposure and arrhythmias is not provided by experimental studies ([Section 5.5.1.3](#)).

## Insulin Resistance

1 There were no epidemiologic studies of diabetes or insulin deficiency available for the  
2 2008 ISA for Sulfur Oxides. Recent studies reported contrasting findings regarding  
3 short-term associations between air pollutants and measures of insulin resistance and  
4 fasting glucose, which play key roles in the development of Type II diabetes mellitus. In  
5 a panel study of older adults in Korea, [Kim and Hong \(2012\)](#) observed 0.94 (95% CI:  
6 -0.02, 1.88) and 0.94 (95% CI: 0.01, 1.81) mean increases in the homeostatic model  
7 assessment index of insulin resistance [fasting insulin  $\times$  (fasting glucose  $\div$  22.5)] per  
8 10-ppb increase in 24-h avg SO<sub>2</sub> at lags 3 and 4, respectively. There were imprecise  
9 (i.e., wide 95% CI) or null associations at all other individual lag days examined, from 0  
10 to 10. Another panel study, conducted in the heavily polluted Tangshan, China, reported  
11 an association between 24-h avg SO<sub>2</sub> concentrations and fasting glucose levels ([Chen et  
12 al., 2015b](#)). However, this association is unlikely to be clinically relevant when  
13 standardized to a 10-ppb increase in 24-h avg SO<sub>2</sub> [0.045 mmol/L (95% CI: 0.039, 0.050  
14 mmol/L) increase at lag 0–3]. Conversely, [Kelishadi et al. \(2009\)](#) reported the lack of an  
15 association between 24-h avg SO<sub>2</sub> and insulin resistance in a cross-sectional study of  
16 374 Iranian children aged 10–18 years.

17 In summary, the available epidemiologic evidence is limited and inconsistent, and does  
18 not support the presence of an association between ambient SO<sub>2</sub> concentrations and  
19 measures of insulin resistance.

## Biomarkers of Cardiovascular Risk

20 Several epidemiologic and toxicological studies have explored the potential relationship  
21 between SO<sub>2</sub> and biomarkers of cardiovascular risk. In particular, markers of  
22 inflammation have been evaluated in a number of epidemiologic and toxicological  
23 studies published since the 2008 ISA for Sulfur Oxides ([U.S. EPA, 2008d](#)) ([Table 5-30](#)).  
24 Relatively few studies have evaluated the potential link between SO<sub>2</sub> and other  
25 circulating markers of cardiovascular risk, including markers of coagulation, vascular  
26 injury, or lipid oxidation.

**Table 5-30 Epidemiologic studies of biomarkers of cardiovascular effects.**

Study	Location and Years (Sample Size)	Mean and Upper Concentration SO <sub>2</sub> (ppb)	Exposure Assessment	Selected Effect Estimates <sup>a</sup> (95% CI)
<a href="#">†Dubowsky et al. (2006)</a>	St. Louis, MO Mar–Jun 2002 (n = 44)	24-h avg: 6.7 75th percentile: 7.4 Max: 27	Central site	CRP (percent change) Lag 04: -36.1 (-65.2, -2.8) IL-6 (percent change) Lag 04: -16.5 (-38.7, 6.5) White blood cells (cells/μL) Lag 04: 10.0 (0.4, 19.6)
<a href="#">†Steinvil et al. (2008)</a>	Tel Aviv, Israel 2002–2006 (n = 3,659)	24-h avg: 2.8 75th percentile: 3.5	Citywide avg	CRP (percent change) men; women Lag 0: 0 (-38, 38); -13 (56, 28) Lag 1: -19 (-50, 25); -13 (-63, 38) Lag 2: 6 (-38, 44); -25 (-69, 31) Fibrinogen (mg/dL) men; women Lag 0: -20.0 (-40.0, 0.6); -23.8 (-51.3, 3.8) Lag 1: -21.3 (-42.5, 0.0); -13.1 (-41.3, 14.4) Lag 2: -15.0 (-37.5, 6.9); 17.5 (-11.9, 46.9) WBC (cells/μL) men; women Lag 0: 231 (-419, 875); -169 (-1,000, 656) Lag 1: 44 (-631, 713); -544 (-1,381, 294) Lag 2: -125 (-819, 563); -481 (-1,356, 388)
<a href="#">†Thompson et al. (2010)</a>	Toronto, ON 1999–2003 (n = 45)	24-h avg: 3.57	Central site	No quantitative results; results presented graphically. Increase in IL-6 associated with 4- and 5-d moving avg SO <sub>2</sub> concentrations. Null association between SO <sub>2</sub> and fibrinogen Correlations: CO: 0.43, NO <sub>2</sub> : 0.44, O <sub>3</sub> : -0.19, PM <sub>2.5</sub> : 0.45
<a href="#">†Gandhi et al. (2014)</a>	Piscataway, NJ 2005–2009 (n = 49)	24 h avg: 2.4 75th percentile: 3.2 Max: 13.8	Central site	Change in plasma nitrate (nM): Lag 0: 53.6 (-4.5, 111.4) Lag 1: 45.0 (0.9, 90.9) Lag 2: 48.2 (-13.2, 110.0)

**Table 5-30 (Continued): Epidemiologic studies of biomarkers of cardiovascular effects.**

Study	Location and Years (Sample Size)	Mean and Upper Concentration SO <sub>2</sub> (ppb)	Exposure Assessment	Selected Effect Estimates <sup>a</sup> (95% CI)
<a href="#">†Lee et al. (2011b)</a>	Allegheny County, PA 1997–2001 (n = 1,696)	7-d avg: 8.4 75th percentile: 10.1 Max: 25.4	Citywide avg	No quantitative results presented. "...SO <sub>2</sub> ... associations (with CRP) were negligible for both the entire population and nonsmokers only."
<a href="#">†Hildebrandt et al. (2009)</a>	Erfurt, Germany 2001–2002 (n = 38)	24-h avg: 1.35 Max: 14.2	Central site	No quantitative results presented. "No significant associations" between SO <sub>2</sub> and inflammatory (fibrinogen, E-selectin) or coagulation (D-dimer, prothrombin) markers.
<a href="#">Baccarelli et al. (2007a)</a>	Lombardia, Italy 1995–2005 (n = 1,218)	24-h avg median: 2.4 75th percentile: 4.5 Max: 96.7	Citywide avg	Effect estimates not provided. SO <sub>2</sub> not correlated with anticoagulation proteins (plasma fibrinogen, functional AT, functional protein C, protein C antigen, functional protein S, or free protein S).
<a href="#">Baccarelli et al. (2007b)</a>	Lombardia, Italy 1995–2005 (n = 1,213)	24-h avg Median: 2.4 75th percentile: 4.5 Max: 96.7	Citywide avg	Homocysteine difference, fasting (percent change). Lag 24 h: 0.2 (–6.3, 6.7) Lag 0–6 d: 0.2 (–4.3, 4.7) Homocysteine difference, post-methionine-load (percent change) Lag 24 h: 2.6 (–3.2, 8.6) Lag 0–6 d: 2.6 (–1.5, 6.7)
<a href="#">Wellenius et al. (2007)</a>	Boston, MA 2002–2003 (n = 28)	24-h avg: 4.8	Citywide avg	No quantitative results presented. "No significant associations were observed between (NO <sub>2</sub> ) and B-type natriuretic peptide levels at any of the lags examined."
<a href="#">†Goldberg et al. (2008)</a>	Montreal, QC 2002–2003 (n = 31)	NR	Central site	Oxygen saturation (mean difference) Lag 0: –0.104 (–0.320, 0.110) Lag 1: –0.277 (–0.497, –0.058) Lag 0–2: –0.210 (–0.536, 0.116)
<a href="#">†Brüske et al. (2011)</a>	Augsburg, Germany 2003–2004 (n = 200)	24-h avg: 1.15 75th percentile: 1.26 Max: 2.4	Central site	No quantitative results; results presented graphically. Inverse associations were observed for SO <sub>2</sub> with Lp-PLA <sub>2</sub> at Lag days 2 and 3 and positive associations were estimated with Lp-PLA <sub>2</sub> Lag days 4 and 5. Correlations: PNC: 0.77, PM <sub>2.5</sub> : 0.42, PM <sub>10</sub> : 0.43, CO: 0.63, NO <sub>2</sub> : 0.51, NO: 0.60, O <sub>3</sub> : –0.45.

**Table 5-30 (Continued): Epidemiologic studies of biomarkers of cardiovascular effects.**

Study	Location and Years (Sample Size)	Mean and Upper Concentration SO <sub>2</sub> (ppb)	Exposure Assessment	Selected Effect Estimates <sup>a</sup> (95% CI)
† <a href="#">Zhang et al. (2013)</a>	Beijing, China Jun–Oct, 2008 (n = 125)	24-h avg Before: 7.45 During: 2.97 After: 6.81	Central site	No quantitative results; results presented graphically. Positive association between SO <sub>2</sub> and fibrinogen (lag 6). Inverse association between SO <sub>2</sub> and WBC count (lag 5).
† <a href="#">Lin et al. (2015)</a>	Beijing, China 2007–2008 (n = 36 school children)	NR	Monitor located nearby school	<i>Urinary 8-oxodG</i> (Geometric mean ratio by SO <sub>2</sub> exposure percentile) <30th (<2.1 ppb): referent 30th–60th (2.1–6.4 ppb): 1.26 (0.93, 1.70) 60th–90th (6.4–49.1 ppb): 1.66 (1.15, 2.41) >90th (>49.1 ppb): 2.31 (1.54, 3.46)  <i>Urinary Malondialdehyde</i> <30th: referent 30th–60th: 1.21 (1.05, 1.40) 60th–90th: 1.40 (1.15, 1.69) >90th: 1.40 (1.08, 1.83)
† <a href="#">Khafaie et al. (2013)</a>	Pune City, India 2005–2007 (n = 1,392)	24-h avg: 8.3	Citywide avg	No quantitative results; results presented graphically. SO <sub>2</sub> was associated with increases in CRP at lags 0, 1, 2, 4, 5, 0–7, 0–14, and 0–30.

AT = atascadero; CI = confidence interval; CO = carbon monoxide; CRP = C-reactive protein; IL-6 = interleukin-6; Lp-PLA<sub>2</sub> = lipoprotein-associated phospholipase A<sub>2</sub>; n = sample size; NO = nitric oxide; NO<sub>2</sub> = nitrogen dioxide; NR = not reported; O<sub>3</sub> = ozone; PM<sub>2.5</sub> = particulate matter with a nominal aerodynamic diameter less than or equal to 2.5 µm; PM<sub>10</sub> = particulate matter with a nominal aerodynamic diameter less than or equal to 10 µm; PNC = particle number concentration; SO<sub>2</sub> = sulfur dioxide; WBC = white blood cell.

†Studies published since the 2008 ISA for Sulfur Oxides.

Note: All lag times are in days, unless otherwise noted.

<sup>a</sup>Effect estimates are standardized to a 10-ppb or 40-ppb increase in SO<sub>2</sub> concentration for 24-h avg and 1-h max metrics, respectively.

### ***Epidemiologic Studies***

- 1 The epidemiologic data available for review by the 2008 ISA for Sulfur Oxides ([U.S.](#)
- 2 [EPA, 2008d](#)) did not suggest a consistent link between SO<sub>2</sub> and biomarkers of
- 3 cardiovascular risk, including markers of inflammation and coagulation. Results from
- 4 more recent studies continue to be inconsistent. [Dubowsky et al. \(2006\)](#) investigated

1 associations between ambient pollutants and markers of systemic inflammation in a panel  
2 (repeated-measures) study of 44 seniors in St. Louis, MO and found that higher ambient  
3 SO<sub>2</sub> concentrations were associated with lower levels of CRP and white blood cells, but  
4 not IL-6 (results for this study, and other studies in this section can be found in  
5 [Table 5-30](#)). Similarly, during the Beijing Olympics, SO<sub>2</sub> was inversely associated with  
6 white blood cell counts, although positively associated with fibrinogen ([Zhang et al.,  
7 2013](#)). The negative associations observed in these two studies are unexpected and  
8 difficult to explain. In contrast, among 45 nonsmoking adults, [Thompson et al. \(2010\)](#)  
9 found a positive association between SO<sub>2</sub> and IL-6, but not fibrinogen. In another panel  
10 study examining pollutant levels before, during, and after the Beijing Olympics, [Lin et al.  
11 \(2015\)](#) reported positive associations between SO<sub>2</sub> concentrations and urinary markers of  
12 oxidative stress, malondialdehyde and 8-oxodG, in children.

13 In a cross-sectional analysis of data from a panel study of 49 young adults in New Jersey,  
14 [Gandhi et al. \(2014\)](#) observed that plasma nitrite levels, a marker for endothelial  
15 dysfunction, were associated with an increase in 24-h avg SO<sub>2</sub> concentrations on the  
16 same day. [Khafaie et al. \(2013\)](#) observed a positive association between SO<sub>2</sub> and CRP in  
17 a cross-sectional study of Type II diabetes patients in Pune City, India, whereas a study  
18 of 1,696 pregnant women ([Lee et al., 2011b](#)), and one of 38 male patients with chronic  
19 pulmonary disease ([Hildebrandt et al., 2009](#)) observed null associations between SO<sub>2</sub> and  
20 CRP. In a cross-sectional analysis of 3,659 participants in Tel-Aviv, [Steinvil et al. \(2008\)](#)  
21 observed inconsistent and/or imprecise associations between SO<sub>2</sub> and CRP, white blood  
22 cells, or fibrinogen among men and women. Observed associations were both positive  
23 and negative depending on the length of the lags, making interpretation of the results  
24 difficult.

25 Ambient SO<sub>2</sub> concentrations are reportedly not associated with blood coagulation  
26 ([Baccarelli et al., 2007a](#)), plasma homocysteine ([Baccarelli et al., 2007b](#)), markers of  
27 vascular injury ([Hildebrandt et al., 2009](#)), or markers of functional status in patients with  
28 heart failure ([Wellenius et al., 2007](#)). Conversely, SO<sub>2</sub> concentrations were inversely  
29 associated with blood oxygen saturation in patients with heart failure ([Goldberg et al.,  
30 2008](#)) and positively associated with lipoprotein-associated phospholipase A2 (Lp-PLA2)  
31 in survivors of myocardial infarction ([Brüske et al., 2011](#)).

### ***Experimental Studies***

32 Several experimental studies examined biomarkers of cardiovascular risk following SO<sub>2</sub>  
33 exposure, including markers of inflammation, coagulation, and oxidative injury. A recent  
34 study examined the effect of exposure to SO<sub>2</sub> on the mitochondrial function of the heart.  
35 Study characteristics are summarized in Supplemental Table 5S-13 ([U.S. EPA, 2016s](#)).

1 No changes were reported in serum C-reactive protein or markers of coagulation  
2 (fibrinogen, D-dimer, platelet aggregation, blood count, or differential white cell count)  
3 in healthy humans and patients with stable angina and coronary artery disease exposed to  
4 SO<sub>2</sub> ([Routledge et al., 2006](#)). An animal toxicological study examined the hematological  
5 effects of short-term SO<sub>2</sub> exposure on blood biomarkers. Acute exposure of rats to  
6 870 ppb SO<sub>2</sub> for 24 hours resulted in increased hematocrit, sulfhemoglobin, and osmotic  
7 fragility as well as decreased whole blood and packed cell viscosities ([Baskurt, 1988](#)).  
8 These results indicate a systemic effect of inhaled SO<sub>2</sub> and are consistent with an  
9 oxidative injury to red blood cells.

10 A recent study reported mitochondrial dysfunction in cardiac muscles following SO<sub>2</sub>  
11 inhalation in adult rats exposed to 1,340 ppb and greater concentrations (2,670 and  
12 5,340 ppb) of SO<sub>2</sub> for 4 hours/day for 30 days ([Qin et al., 2016](#)). Inhalation of SO<sub>2</sub>  
13 (1,340 ppb) resulted in mitochondrial ultrastructural changes in cardiac myocytes,  
14 including swollen mitochondria and reduced amounts of cristae. In addition to the  
15 structural changes, SO<sub>2</sub> exposure decreased cytochrome c oxidase activity, mitochondrial  
16 membrane potential, ATP contents, mtDNA content, mRNA expression of subunits that  
17 are synthesized in the mitochondria (complex IV and V), and mitochondrial transcription  
18 factors (TFAM, NRF1, and PGC-1a). Mechanistic studies conducted in vitro suggest  
19 reactive oxygen species contribute to the mitochondrial dysfunction leading to the  
20 observed decrease in cardiomyocyte energy status and metabolic activity. In addition to  
21 this study in the heart, a study has reported similar changes in the brain ([Qin et al., 2012](#)).  
22 Further discussion of these mechanisms are found in [Section 4.3.4](#).

### ***Summary of Blood Markers of Cardiovascular Risk***

23 There is inconsistent evidence regarding any potential link between SO<sub>2</sub> and other  
24 circulating markers of cardiovascular risk. Studies of markers of inflammation or  
25 oxidative stress in experimental animals are limited. Overall, evidence from available  
26 studies does not support an effect of ambient SO<sub>2</sub> concentrations and markers of  
27 cardiovascular disease including inflammation.

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#### **5.3.1.11 Summary and Causal Determination**

28 Overall, the available evidence is inadequate to infer the presence or absence of a causal  
29 relationship between short-term exposure to SO<sub>2</sub> and cardiovascular health effects.  
30 Multiple epidemiologic studies report positive associations between short-term ambient  
31 SO<sub>2</sub> concentrations and cardiovascular outcomes; however, uncertainty remains regarding  
32 the biological plausibility of the effects observed in epidemiologic studies. The limited  
33 experimental evidence in humans or animals is not coherent with the positive associations

1 observed in the epidemiologic studies and fails to provide evidence to propose a potential  
2 mode of action. The observed associations in epidemiologic studies are generally  
3 attenuated after adjustment for copollutants, complicating the determination of an  
4 independent SO<sub>2</sub> effect.

5 This determination is consistent with that of the 2008 ISA for Sulfur Oxides ([U.S. EPA,](#)  
6 [2008d](#)). The majority of epidemiologic studies reviewed in the 2008 ISA for Sulfur  
7 Oxides examined hospital admissions or ED visits for aggregated categories of  
8 cardiovascular disease or for mortality from cardiovascular causes. These studies  
9 generally reported positive associations in single pollutant models but analyses designed  
10 to assess copollutant confounding were limited. Relatively few studies evaluated specific  
11 cardiovascular outcomes such as MI, arrhythmia, cerebrovascular disease, and heart  
12 failure, and those that were available did not support an association with short-term SO<sub>2</sub>  
13 exposure. Controlled human exposure studies demonstrated the potential for SO<sub>2</sub>  
14 exposure to exert an effect on the autonomic nervous system but there was a lack of  
15 supporting animal toxicological data. The available animal toxicological studies did not  
16 report effects on HR, HRV, arrhythmia, or blood pressure following short-term SO<sub>2</sub>  
17 exposures [Table 5S-6 ([U.S. EPA, 2016m](#))]. In addition, limited and inconsistent  
18 mechanistic evidence, including evidence pertaining to key events in a proposed mode of  
19 action, failed to describe a role for SO<sub>2</sub> in the triggering of cardiovascular diseases.  
20 Although multiple epidemiologic studies add to the evidence available for the current  
21 review, the additional studies do not substantially reduce uncertainties related to  
22 copollutant confounding. Moreover, there continues to be a lack of experimental  
23 evidence to provide biological plausibility to strengthen the inference of causality for  
24 SO<sub>2</sub>-related cardiovascular effects.

25 The evidence for cardiovascular effects, with respect to the causal determination for  
26 short-term exposure to SO<sub>2</sub> is detailed below using the framework described in the  
27 [Preamble](#) to the ISAs [([U.S. EPA, 2015b](#)), Table I and Table II]. The key evidence,  
28 supporting or contradicting, as it relates to the causal framework is summarized in  
29 [Table 5-31](#).

**Table 5-31 Summary of evidence, which is inadequate to infer a causal relationship between short-term sulfur dioxide exposure and cardiovascular effects.**

Rationale for Causal Determination <sup>a</sup>	Key Evidence <sup>b</sup>	Key References <sup>b</sup>	SO <sub>2</sub> Concentrations Associated with Effects <sup>c</sup>
<b>Triggering a myocardial infarction</b>			
Although most epidemiologic studies examining MI or all CVD report positive associations, results are generally attenuated after adjustment for copollutant confounding.	Increases in hospital admissions and ED visits for IHD, MI, and all CVD in adults in multiple studies, including multicity studies  However, a number of studies report associations with ED visits and hospital admissions were attenuated after adjustment with CO, NO <sub>2</sub> , or PM <sub>10</sub> .	<a href="#">Section 5.3.1.2</a> <a href="#">Section 5.3.1.8</a>  Supplemental figures 5S-3, 5S-4, and 5S-5 ( <a href="#">U.S. EPA, 2016b, c, d</a> )	24-h avg: 1.2–15.6 ppb 24-h avg: 1.9–30.2 ppb
Uncertainty due to lack of coherence with other lines of evidence	Lack of evidence from epidemiologic panel studies and experimental studies for clinical cardiovascular effects		
Lack of evidence to identify key events in the proposed mode of action	Lack of mechanistic evidence for key events leading to extrapulmonary effects	<a href="#">Section 4.3</a>	
	Limited and inconsistent evidence of increased systemic inflammation in epidemiologic studies	<a href="#">Section 5.3.1.10</a>	
<b>Other cardiovascular effects</b>			
Inconclusive evidence from epidemiologic, controlled human exposure and toxicological studies	Epidemiologic studies report generally null associations between SO <sub>2</sub> and risk of cardiac arrest and arrhythmias. One experimental study provides no evidence of arrhythmia.	<a href="#">Section 5.3.1.3</a>	
	Inconsistent epidemiologic evidence for an association between SO <sub>2</sub> and risk of cerebrovascular disease and stroke, and increased blood pressure and hypertension	<a href="#">Section 5.3.1.4</a> and <a href="#">Section 5.3.1.5</a>	
	Insufficient quantity of studies evaluating decompensation of heart failure and venous thrombosis and pulmonary embolism	<a href="#">Section 5.3.1.6</a> and <a href="#">Section 5.3.1.7</a>	

**Table 5-31 (Continued): Summary of evidence, which is inadequate to infer a causal relationship between short term sulfur dioxide exposure and cardiovascular effects.**

Rationale for Causal Determination <sup>a</sup>	Key Evidence <sup>b</sup>	Key References <sup>b</sup>	SO <sub>2</sub> Concentrations Associated with Effects <sup>c</sup>
	Changes in HR and HRV reported in controlled human exposure but coherence with animal toxicological and epidemiologic studies is lacking	<a href="#">Tunncliffe et al. (2001)</a> <a href="#">Routledge et al. (2006)</a> Section <a href="#">5.3.1.10</a>	200 ppb, 1 h at rest (humans)
Some evidence to identify key events in the proposed mode of action	Some evidence for activation of neural reflexes in humans leading to altered HRV	Section <a href="#">4.3.1</a> Figure <a href="#">4-2</a>	
<b>Cardiovascular mortality</b>			
Consistent epidemiologic evidence but uncertainty regarding SO <sub>2</sub> independent effect	Multicity studies consistently observe associations with cardiovascular mortality, including stroke with 24-h avg SO <sub>2</sub> at lags primarily of 0–1 d.  Analysis of potential confounding by copollutants primarily limited to PM <sub>10</sub> and NO <sub>2</sub> reported evidence of attenuation of associations. No studies included copollutant analyses with PM <sub>2.5</sub> .	Section <a href="#">5.3.1.9</a> <a href="#">Chen et al. (2012b)</a> <a href="#">Chen et al. (2013)</a> <a href="#">Kan et al. (2010b)</a> <a href="#">Bellini et al. (2007)</a> <a href="#">Atkinson et al. (2012)</a>	24-h avg: 2.5–38.2

CO = carbon monoxide; CVD = cardiovascular disease; ED = emergency department; HR = heart rate; HRV = heart rate variability; IHD = ischemic heart disease; MI = myocardial infarction; NO<sub>2</sub> = nitrogen dioxide; PM<sub>10</sub> = particulate matter with a nominal aerodynamic diameter less than or equal to 10 μm; SO<sub>2</sub> = sulfur dioxide.

<sup>a</sup>Based on aspects considered in judgments of causality and weight of evidence in causal framework in Table I and Table II of the Preamble to the ISAs ([U.S. EPA, 2015b](#)).

<sup>b</sup>Describes the key evidence and references, supporting or contradicting, that contribute most heavily to causal determination. References to earlier sections indicate where full body of evidence is described.

<sup>c</sup>Describes the SO<sub>2</sub> concentrations with which the evidence is substantiated.

1                   Recent epidemiologic studies of specific cardiovascular outcomes add to the overall  
 2                   evidence for the effect of short-term SO<sub>2</sub> exposure on the cardiovascular system with a  
 3                   number of these studies evaluating effects related to triggering an MI ([Section 5.3.1.2](#)).  
 4                   Several recent epidemiologic studies of MI hospitalizations and ED visits consistently  
 5                   report associations in single pollutant models but associations are not always robust in  
 6                   copollutant models indicating that the associations may be due to confounding ([Hsieh et](#)  
 7                   [al., 2010](#); [Cheng et al., 2009](#); [Ballester et al., 2006](#)). The small number of studies based  
 8                   on clinical MI data, rather than hospitalizations, report inconsistent evidence regarding  
 9                   associations between ambient SO<sub>2</sub> concentrations and risk of MI ([Milojevic et al., 2014](#);  
 10                   [Turin et al., 2012](#); [Bhaskaran et al., 2011](#)). The only study that examined the association  
 11                   of hourly ambient SO<sub>2</sub> concentrations prior to MI onset reported no association, although  
 12                   there was some evidence of a positive association in a sensitivity analysis of older adults

1 [\(Bhaskaran et al., 2011\)](#). Although [Chuang et al. \(2008\)](#) reported an association between  
2 short-term SO<sub>2</sub> exposure and ST-segment changes, a nonspecific marker of myocardial  
3 ischemia, in patients with a history of coronary heart disease that generally remained  
4 unchanged after additional control for PM<sub>2.5</sub> and BC in copollutant models; the evidence  
5 overall, was not generally consistent.

6 Findings from recent studies of the association of short-term exposure to SO<sub>2</sub> with  
7 hospital admissions or ED visits for cerebrovascular diseases or stroke are inconsistent  
8 and, associations reported from single pollutant models in some locations may be due to  
9 confounding by copollutants ([Section 5.3.1.4](#)). Epidemiologic studies evaluating the  
10 association between ambient SO<sub>2</sub> concentrations and blood pressure remain inconsistent  
11 with most relying on centrally located monitors that do not capture the spatial variability  
12 of SO<sub>2</sub> and few examining the potential for copollutant confounding ([Section 5.3.1.5](#)).  
13 Although a small number of studies were conducted to examine the association of  
14 short-term SO<sub>2</sub> exposure with other clinical outcomes, including heart failure  
15 ([Section 5.3.1.7](#)) and VTE ([Section 5.3.1.6](#)), findings from these studies do not support an  
16 effect of short-term exposure to SO<sub>2</sub>. There is also a lack of epidemiologic evidence  
17 supporting an effect of short-term SO<sub>2</sub> exposure on arrhythmia ([Section 5.3.1.3](#)),  
18 although associations between short-term SO<sub>2</sub> exposure and markers of ventricular  
19 repolarization abnormalities that are risk factors for arrhythmia have been observed ([Baja](#)  
20 [et al., 2010](#); [Henneberger et al., 2005](#)) ([Section 5.3.1.10](#)).

21 Consistently positive associations have been reported in epidemiologic studies of  
22 short-term SO<sub>2</sub> exposure and cardiovascular mortality ([Section 5.3.1.9](#)). These include  
23 studies reviewed in the 2008 ISA for Sulfur Oxides and recent multicity studies that  
24 generally report an association similar or slightly larger in magnitude for cardiovascular  
25 mortality compared to total mortality. Studies that report results from copollutants models  
26 generally report attenuation of the association between short-term SO<sub>2</sub> exposure and  
27 cardiovascular mortality after adjustment for PM<sub>10</sub> and NO<sub>2</sub>.

28 Few experimental studies have evaluated the effects of SO<sub>2</sub> exposure on the  
29 cardiovascular system. There is some evidence from controlled human exposure studies,  
30 for which copollutant confounding is not a concern, that short-term exposure to SO<sub>2</sub> can  
31 affect the autonomic nervous system of healthy adults and adults with asthma ([Routledge](#)  
32 [et al., 2006](#); [Tunncliffe et al., 2001](#)) ([Section 5.3.1.10](#)). These studies report changes in  
33 HR and HRV following SO<sub>2</sub> exposure in adults. However, coherence with these findings  
34 is not provided by epidemiologic or experimental animal studies, which have not  
35 observed an effect of short-term SO<sub>2</sub> exposure on HR or HRV. In addition, uncertainty  
36 remains regarding a potentially biologically plausible mechanism for short-term exposure  
37 to SO<sub>2</sub> leading to cardiovascular disease. Cardiovascular effects following SO<sub>2</sub> exposure

1 could be mediated through activation of neural reflexes or oxidative stress; however,  
2 uncertainty remains ([Section 4.3](#)). Diffusion of sulfite into the circulation and tissues  
3 following exposure to SO<sub>2</sub> has been reported and could play a role in the induction of  
4 systemic effects; however, these studies generally involve prolonged exposure to SO<sub>2</sub> at  
5 concentrations higher than is typically found in ambient air ([Section 4.3.4](#)). Overall, the  
6 limited evidence available from these experimental studies in humans and animals are not  
7 coherent with the positive associations observed in the epidemiologic studies and do not  
8 support a potential mode of action.

9 Despite numerous additional epidemiologic studies reporting positive associations  
10 between short-term SO<sub>2</sub> exposure and cardiovascular effects, a key uncertainty that  
11 remains since the 2008 ISA for Sulfur Oxides is the potential for confounding by other  
12 pollutants, specifically those from a common source that are highly correlated with SO<sub>2</sub>.  
13 The majority of hospital admission or ED visit studies have not evaluated whether the  
14 reported associations with SO<sub>2</sub> are robust to adjustment for other pollutants. Those  
15 studies that do examine associations with SO<sub>2</sub> adjusted for PM [Figure 5S-3, ([U.S. EPA,](#)  
16 [2016b](#)) and Table 5S-17 ([U.S. EPA, 2016v](#))], NO<sub>2</sub> [Figure 5S-4, ([U.S. EPA, 2016c](#)) and  
17 Table 5S-18 ([U.S. EPA, 2015g](#))], or other correlated pollutants [Figure 5S-5; ([U.S. EPA,](#)  
18 [2016d](#)) and Table 5S-19 ([U.S. EPA, 2015h](#))] report that, in general, associations were  
19 either attenuated or no longer present after controlling for potential copollutant  
20 confounding ([Hsieh et al., 2010](#); [Cheng et al., 2009](#); [Ballester et al., 2006](#)). A limited  
21 number of studies examined copollutant confounding on the SO<sub>2</sub>-cardiovascular  
22 mortality relationship, which included analyses on stroke mortality, and provided  
23 evidence that the SO<sub>2</sub> association was reduced in copollutant models with NO<sub>2</sub> and PM<sub>10</sub>  
24 ([Chen et al., 2013](#); [Chen et al., 2012b](#); [Kan et al., 2010b](#)). Finally, while copollutant  
25 models are a common statistical tool used to evaluate the potential for copollutant  
26 confounding, their interpretation can be limited ([Section 5.1.2](#)). Without consistent and  
27 reproducible experimental evidence that is coherent with the effects observed in  
28 epidemiologic studies, uncertainty still exists concerning the role of correlated pollutants  
29 in the associations observed with SO<sub>2</sub>. Thus, uncertainty remains regarding the extent to  
30 which SO<sub>2</sub> exposure is independently associated with cardiovascular outcomes or if SO<sub>2</sub>  
31 is a marker for the effects of another correlated pollutant or mix of pollutants.

32 In conclusion, the evidence overall is inadequate to infer the presence or absence of a  
33 causal relationship between short-term SO<sub>2</sub> exposure and cardiovascular health effects.  
34 This conclusion does not represent a change from the conclusion of the 2008 ISA for  
35 Sulfur Oxides ([U.S. EPA, 2008d](#)). Multiple epidemiologic studies report positive  
36 associations between short-term ambient SO<sub>2</sub> concentrations and cardiovascular  
37 outcomes, but these associations are generally attenuated after adjustment for  
38 copollutants. There is limited experimental evidence in humans or animals evaluating

1 exposure to SO<sub>2</sub> and the results of these studies do not provide coherence for the positive  
2 associations observed in the epidemiologic studies. Further, the available experimental  
3 studies do not provide evidence to propose a potential mode of action; consequently,  
4 uncertainty remains regarding the biological plausibility of effects observed in  
5 epidemiologic studies. The combined evidence from epidemiologic and experimental  
6 studies lacks coherence and is of insufficient consistency, and thus, is inadequate to infer  
7 the presence or absence of a causal relationship between short-term SO<sub>2</sub> exposure and  
8 cardiovascular effects.

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## 5.3.2 Long-Term Exposure

### 5.3.2.1 Introduction

9 Studies of the effects of long-term exposure to SO<sub>2</sub> on the cardiovascular system were not  
10 available for inclusion in the 1982 AQCD ([U.S. EPA, 1982a](#)). The 2008 ISA for Sulfur  
11 Oxides ([U.S. EPA, 2008d](#)) reviewed a limited body of toxicological and epidemiologic  
12 studies published through 2006 and concluded that the available evidence was “too  
13 limited to make any conclusions” between the effects of long-term exposure to SO<sub>2</sub> and  
14 cardiovascular health.

15 The 2008 ISA for Sulfur Oxides included one epidemiologic study, which reported an  
16 increased risk of cardiovascular events in association with long-term exposure to SO<sub>2</sub> in  
17 post-menopausal women (50–79 years old) without previous CVD from 36 U.S.  
18 metropolitan areas. In this study, [Miller et al. \(2007\)](#) found that PM<sub>2.5</sub> was most strongly  
19 associated with cardiovascular events (MI, revascularization, angina, CHF, CHD death),  
20 compared to the other pollutants evaluated [hazard ratio (HR): 1.24 (95% CI: 1.04, 1.48)  
21 per 10 µg/m<sup>3</sup>], followed by SO<sub>2</sub> [1.07 (95% CI: 0.95, 1.20) per 5 ppb]. Exposures to air  
22 pollution were estimated by assigning the annual (for the year 2000) mean air pollutant  
23 concentration measured at the monitor nearest to the subject’s five-digit residential ZIP  
24 code centroid. The effect estimate for SO<sub>2</sub> was strengthened in a multipollutant model  
25 that was adjusted for several other pollutants including PM<sub>2.5</sub>. However, correlations  
26 among pollutants were not described and exposure measurement error may have  
27 introduced a bias ([Section 3.4.2](#)). Consequently, the extent to which this study supports  
28 an independent effect of SO<sub>2</sub> on the cardiovascular system is limited. Several recent  
29 epidemiologic studies of the association of long term SO<sub>2</sub> exposure with subclinical and  
30 clinical cardiovascular outcomes add to the available body of evidence. These recent  
31 studies do not change the conclusion from the 2008 ISA for Sulfur Oxides ([U.S. EPA,  
32 2008d](#)).

1 Experimental animal studies with long-term exposures below 2,000 ppb were not  
2 available for inclusion in the 2008 ISA for Sulfur Oxides. Although a small number of  
3 studies using exposures above 2,000 ppb were included, they did not contribute heavily  
4 to conclusions because the concentrations of SO<sub>2</sub> used in these studies were unlikely to  
5 be relevant to ambient concentrations of SO<sub>2</sub>. No new toxicological studies in humans or  
6 animals have been published since the 2008 ISA for Sulfur Oxides. Overall, the  
7 biological plausibility and independence of the effects observed in epidemiologic studies  
8 remains an important uncertainty.

9 This section reviews the published studies of the cardiovascular effects of long-term  
10 exposure to SO<sub>2</sub> (i.e., longer than 1 month). To clearly characterize the evidence  
11 underlying causality, the discussion of the evidence is organized into groups of related  
12 outcomes [ischemic heart disease and myocardial infarction ([Section 5.3.2.2](#)),  
13 cerebrovascular disease and stroke ([Section 5.3.2.3](#)), hypertension ([Section 5.3.2.4](#)), other  
14 cardiovascular effects ([Section 5.3.2.5](#)), and cardiovascular mortality ([Section 5.3.2.6](#))].  
15 Evidence for subclinical effects (e.g., blood biomarkers of cardiovascular effects) of  
16 long-term exposure to SO<sub>2</sub> are discussed in [Section 5.3.2.7](#) and serve to inform biological  
17 plausibility across multiple clinical cardiovascular events and outcomes.

18 Similar to [Section 5.3.1](#), studies examining cardiovascular effects of sulfite exposure (via  
19 i.p., i.v., etc.) are not included in this section because these studies generally involve  
20 exposures to sulfite that are higher than what is expected to occur following inhalation of  
21 SO<sub>2</sub> at ambient relevant concentrations. Studies in humans and animals suggest that  
22 prolonged exposure to SO<sub>2</sub> may result in measurable changes in the concentrations of  
23 sulfite in plasma and tissues, but these changes would be expected to be far less following  
24 concentrations of SO<sub>2</sub> typically found in ambient air. The literature describing the  
25 distribution and metabolism of sulfite is discussed in [Section 4.2.3](#) and [Section 4.2.4](#).  
26 The potential role of sulfite in the induction of systemic effects, such as effects of the  
27 cardiovascular system, is discussed in [Section 4.2.4](#).

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### 5.3.2.2 Ischemic Heart Disease and Myocardial Infarction

28 IHD generally develops due to a buildup of plaques in the arterial walls  
29 (i.e., atherosclerosis) that impede the blood flow and oxygen delivery to the heart. This  
30 restricted oxygen delivery or ischemia from excess plaque, plaque rupture and clot  
31 formation can lead to an MI. Several epidemiologic studies provide evidence of a  
32 relationship between long-term exposure to SO<sub>2</sub> and ischemic heart disease and incident  
33 or fatal MI ([Table 5-32](#)). However, uncertainty remains regarding the influence of  
34 exposure measurement error on the effect estimates observed in epidemiologic studies

1 (Section 3.4.2) and the ability of these studies to distinguish the independent effect of  
 2 long-term SO<sub>2</sub> exposure from the effect of correlated copollutant exposures  
 3 (Section 3.4.3).

**Table 5-32 Epidemiologic studies of the association of long-term exposure to sulfur dioxide with cardiovascular disease.**

Study	Cohort, Location, and Study Period	Mean ppb	Exposure Assessment	Effect Estimates (95% CI) <sup>a</sup>
<a href="#">†Lipsett et al. (2011)</a>	California Teachers Study Cohort N = 124,614 California Jun 1996– Dec 2005	SO <sub>2</sub> IQR: 0.43 mean: 1.72	Geocoded residential address linked to pollutant surface developed using IDW (fixed site monitors concentrations from 1995–2005 used to model exposure as a time-dependent function)  Correlation of SO <sub>2</sub> with: ozone, $r = -0.17$ PM <sub>2.5</sub> , $r = 0.02$ PM <sub>10</sub> , $r = 0.54$ NO <sub>2</sub> , $r = 0.67$ CO, $r = 0.80$	MI incidence SO <sub>2</sub> : HR 1.97 (0.07, 60)  Covariates: age, race, smoking second-hand smoke, BMI, lifetime physical activity, nutritional factors, alcohol, marital status, menopausal status, hormone replacement therapy, hypertension medication and aspirin, and family history of MI/stroke  Copollutant adjustment: none
<a href="#">†Atkinson et al. (2013)</a>	National GP Patient Cohort England 2003	IQR: 0.83 mean (SD): 1.47	Annual average SO <sub>2</sub> concentration for 2002 at a 1 by 1-km resolution derived from dispersion models and linked to residential post codes  Correlation of SO <sub>2</sub> with: NO <sub>2</sub> , $r = 0.86$	MI incidence HR: 1.34 (1.13, 1.50)  Covariates: age, sex, smoking BMI, diabetes, hypertension, and index of multiple deprivation  Copollutant adjustment: none

**Table 5-32 (Continued): Epidemiologic studies of the association of long term exposure to sulfur dioxide with cardiovascular disease.**

Study	Cohort, Location, and Study Period	Mean ppb	Exposure Assessment	Effect Estimates (95% CI) <sup>a</sup>
<a href="#">†Rosenlund et al. (2006)</a>	SHEEP cohort n = 1,397 cases and 1,870 controls Stockholm, Sweden 1992–1994	Cases med: 9.6 5th–95th: 2.6–18.2  Controls med: 9.3 5th–95th: 7.7–17.5	Dispersion models to estimate SO <sub>2</sub> from heating at residential address. Residential history available for 30 yr exposure estimate.  Correlation of 30 yr SO <sub>2</sub> with: 30 yr NO <sub>2</sub> , <i>r</i> = 0.73 30 yr CO, <i>r</i> = 0.49	First MI OR: 0.99 (0.9, 1.1) per 5 ppb  Covariate adjustment: age, sex, hospital catchment area, smoking diabetes, physical inactivity, and SES  Copollutant adjustment: none
<a href="#">†Ancona et al. (2015)</a>	Rome, Italy (SO <sub>x</sub> : 2001–2010; follow-up: 2001–2010)	2.5 µg/m <sup>3</sup> SO <sub>x</sub> SD: 0.9	Lagrangian particle dispersion model (SPRAY Ver. 5) used SO <sub>x</sub> as exposure marker for petrochemical refinery emissions  PM <sub>10</sub> : 0.81 H <sub>2</sub> S: 0.78	IHD <sup>b</sup> HR men: 0.87 (0.74, 1.02) HR women: 0.83 (0.64, 1.07) CVD <sup>b</sup> HR men: 1.01 (0.93, 1.0) HR women: 1.02 (0.92, 1.12)
<a href="#">Miller et al. (2007)</a>	WHI Cohort U.S. 1994–1998	NR	Annual avg (2000): nearest monitor to residence ZIP code centroid	Cardiovascular events (MI, revascularization, angina, CHF, CHD death) HR: 1.07 (0.95, 1.20)  Covariates: age, ethnicity, education, household income, smoking, diabetes, hypertension, systolic blood pressure, BMI, and hypercholesterolemia  HR: 1.13 (0.98, 1.30) after simultaneous adjustment for PM <sub>2.5</sub> , PM <sub>10–2.5</sub> , CO, NO <sub>2</sub> , and O <sub>3</sub>

**Table 5-32 (Continued): Epidemiologic studies of the association of long term exposure to sulfur dioxide with cardiovascular disease.**

Study	Cohort, Location, and Study Period	Mean ppb	Exposure Assessment	Effect Estimates (95% CI) <sup>a</sup>
<a href="#">†Qin et al. (2015)</a>	N = 24,845 Random selection (18–74 yr) from households in 33 communities in 11 districts of northeastern China	Mean: 20.3 IQR: 7.5	3-yr avg (2006–2008) SO <sub>2</sub> concentration for each district NO <sub>2</sub> , <i>r</i> = 0.38 O <sub>3</sub> , <i>r</i> = 0.87 PM <sub>10</sub> , <i>r</i> = 0.70	CVD BMI<25 kg/m <sup>2</sup> 1.11 (0.97, 1.27) BMI<25 kg/m <sup>2</sup> 1.12 (0.99, 1.25)  Note: sex-stratified analyses also presented  Covariate adjustment: age, race education, income, smoking drinking, exercise, diet, sugar, family history of CVD or stroke, district  Copollutant adjustment: none
<a href="#">†Dong et al. (2013a)</a>	N = 24,845 Random selection (18–74 yr) from households in 33 communities in 11 districts of northeastern China	Mean: 20 med: 18 IQR: 7.5	3-yr avg (2006–2008) SO <sub>2</sub> concentration for each district  NO <sub>2</sub> , <i>r</i> = 0.38 O <sub>3</sub> , <i>r</i> = 0.87 PM <sub>10</sub> , <i>r</i> = 0.70	CHD, MI, or CHF OR: 1.08 (0.93, 1.26)  Note: associations stronger among males  Covariate adjustment: age, sex, educational level, occupation, family income, BMI, hypertension, family history of stroke, family history of CVD, smoking status, drinking, diet, and exercise  Copollutant adjustment: none

BMI = body mass index; CHF = congestive heart failure; CHD = coronary heart disease; CI = confidence interval; CO = carbon monoxide; CVD = cardiovascular disease; GP = general practice; HR = heart rate; HS = hemorrhagic stroke; IDW = inverse distance weighting; IQR = interquartile range; MI = myocardial infarction; n = sample size; N = population number; NO<sub>2</sub> = nitrogen dioxide; NR = not reported; OR = odds ratio; O<sub>3</sub> = ozone; PM<sub>2.5</sub> = particulate matter with a nominal aerodynamic diameter less than or equal to 2.5 μm; PM<sub>10</sub> = particulate matter with a nominal aerodynamic diameter less than or equal to 10 μm; PM<sub>10-2.5</sub> = particulate matter with a nominal aerodynamic diameter less than or equal to 10 μm and greater than a nominal 2.5 μm; *r* = correlation coefficient; RR = relative risk; SD = standard deviation; SES = socioeconomic status; SHEEP = Stockholm Heart Epidemiology Programme; SO<sub>2</sub> = sulfur dioxide; SO<sub>x</sub> = sulfur oxides; WHI = Women’s Health Initiative.

<sup>a</sup>Effect estimates are standardized per 5-ppb increase in SO<sub>2</sub> concentrations.

<sup>b</sup>Effect estimate per 2.88 μg/m<sup>3</sup> increase in SO<sub>x</sub> concentration (as reported by author in original publication).

†Studies published since the 2008 ISA for Sulfur Oxides.

- 1 [Lipsett et al. \(2011\)](#) analyzed the association of incident MI with long-term exposure to
- 2 SO<sub>2</sub>, other gases (NO<sub>2</sub>, CO, O<sub>3</sub>), and PM. These authors studied a cohort of California
- 3 public school teachers aged 20–80 years old (n = 124,614). Each participant’s geocoded
- 4 residential address was linked to pollutant surfaces that were determined by IDW

1 interpolation of pollutant concentrations measured at fixed site monitors during the  
2 period 1996–2005. The average of monthly SO<sub>2</sub> concentrations was modeled as a  
3 time-dependent function for subjects with at least 12 months of exposure. Those living  
4 outside the radial range for which the monitor was intended to provide representative data  
5 were excluded from the analysis. This “representative range” was 3 km for neighborhood  
6 SO<sub>2</sub> monitors and 5 km for the urban/regional SO<sub>2</sub>. The association between SO<sub>2</sub> and  
7 incident MI was imprecise and standardization to an increase in SO<sub>2</sub> concentration of  
8 5 ppb (as opposed to the IQR of 0.43) affected the stability of the estimate. An increased  
9 risk of 1.20 (1.02, 1.41) was observed per 10 µg/m<sup>3</sup> per PM<sub>2.5</sub>. Fewer observations were  
10 available for the SO<sub>2</sub> compared to PM analyses because the requirements for the  
11 participants’ proximity to the monitor were more stringent for SO<sub>2</sub> (residing within 5 km  
12 as opposed to 20 km for PM).

13 [Atkinson et al. \(2013\)](#) examined the association of incident cardiovascular disease with  
14 SO<sub>2</sub>. These authors studied patients (aged 40–89 years) registered with 205 general  
15 practices across England. The authors report that approximately 98% of the population is  
16 registered with a general practitioner minimizing the potential for selective participation.  
17 Predicted annual average SO<sub>2</sub> concentrations within 1 × 1-km grids, estimated using  
18 dispersion models, were assigned to participants based on their residential postal code.  
19 Cardiovascular disease outcomes included in the analysis were MI, stroke, arrhythmias,  
20 and heart failure. Authors reported an association of SO<sub>2</sub> with MI in a fully adjusted  
21 model [HR: 1.34 (95% CI: 1.13, 1.50) per 5 ppb]. The performance of the dispersion  
22 model used to estimate SO<sub>2</sub> concentration was characterized as moderate to poor  
23 depending on the study year. Failure of the model to capture the spatial variability of SO<sub>2</sub>  
24 could lead to bias toward or away from the null ([Section 3.4.4.2](#)). Associations of other  
25 pollutants (i.e., PM<sub>10</sub>, NO<sub>2</sub>, ozone) with MI were also observed in this study.

26 [Rosenlund et al. \(2006\)](#) conducted a population case-control study to examine the  
27 association of first MI with long-term exposure to air pollution in Stockholm, Sweden. In  
28 this study residential histories were used to estimate 30-yr avg SO<sub>2</sub> concentration from  
29 residential heating sources using dispersion models. Although a positive association of  
30 SO<sub>2</sub> and other pollutants (NO<sub>2</sub>, CO, PM<sub>10</sub>) with fatal MI was observed in this study, no  
31 association between nonfatal MI and long-term SO<sub>2</sub> exposure was reported. [Panasevich et](#)  
32 [al. \(2013\)](#) reported higher tumor necrosis factor alpha (TNF-α) levels among those with a  
33 genetic polymorphism of a TNF-α gene (*TNF308G/A*) as well as an increased risk of MI  
34 in the same population ([Section 5.3.2.5](#)).

35 Weak or inverse associations of both cardiovascular and ischemic heart disease were  
36 reported in a study relying on a Lagrangian particle dispersion model (see  
37 [Section 3.3.2.4](#)) to estimate SO<sub>x</sub> emissions (gaseous and particulate component) from a

1 refinery ([Ancona et al., 2015](#)). Exposure model performance statistics were not reported.  
2 Null associations of cardiovascular hospitalizations with PM<sub>10</sub>, which was highly  
3 correlated with SO<sub>x</sub> ( $r = 0.81$ ) in this study, were observed. Because SO<sub>x</sub> was used as a  
4 marker for refinery emissions, which contains multiple toxics including VOCs, the study  
5 was not designed to evaluate the independent effect of SO<sub>2</sub>. In addition to the study by  
6 [Miller et al. \(2007\)](#), which was included in the previous review, two analyses examined  
7 the association of long-term SO<sub>2</sub> exposure with relatively broadly defined outcome that  
8 included several cardiovascular diseases ([Qin et al., 2015](#); [Dong et al., 2013a](#)). These  
9 studies, which were conducted among Chinese adults, reported imprecise increases in the  
10 risk of cardiovascular disease and results suggest the potential for age and body weight to  
11 modify the association with long-term SO<sub>2</sub> exposure. Neither of these analyses adjusted  
12 for copollutant confounding, and the district-level SO<sub>2</sub> concentrations used to indicate  
13 exposure may not have adequately captured the spatial variability of long-term SO<sub>2</sub>  
14 exposure.

15 Overall, these epidemiologic data do not provide support for an association of long-term  
16 SO<sub>2</sub> exposure with IHD or more broadly defined categories of cardiovascular disease.  
17 There is uncertainty related the independent effect of SO<sub>2</sub> on the cardiovascular system.  
18 Comparable associations between concentrations of other pollutants (i.e. PM<sub>2.5</sub> and PM<sub>10</sub>)  
19 and long-term SO<sub>2</sub> exposures were reported in most studies, which were generally not  
20 designed to evaluate copollutant confounding. Further, the exposure assessment  
21 techniques applied in the studies were subject to varying degrees of error depending on  
22 the method. The uncertainties stemming from exposure measurement error were  
23 potentially substantial ([Section 3.4.2](#)).

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### 5.3.2.3 Cerebrovascular Diseases and Stroke

24 [Lipsett et al. \(2011\)](#) evaluated the association of incident stroke with long-term exposure  
25 to SO<sub>2</sub>, other gases (NO<sub>2</sub>, NO<sub>x</sub>, CO, ozone), and PM ([Table 5-33](#)). The authors observed  
26 an imprecise, although positive association between SO<sub>2</sub> and incident stroke. Point  
27 estimates for the association of other pollutants (PM<sub>10</sub>, PM<sub>2.5</sub>, NO<sub>2</sub>, NO<sub>x</sub>, and ozone) with  
28 incident stroke were also increased. A positive association of SO<sub>2</sub> with incident stroke of  
29 1.13 (95% CI: 1.00, 1.34) per 5 ppb was reported by [Atkinson et al. \(2013\)](#) in patients  
30 across England (study methods in [Section 5.3.2.2](#)). Null associations with other pollutants  
31 (PM<sub>10</sub>, NO<sub>2</sub>, and ozone) were observed.

32 Two analyses of a random selection of adults ( $n = 24,845$ ) ranging from 18 to 74 years  
33 old from households in 33 Chinese communities were examined the association between  
34 long-term SO<sub>2</sub> exposure and stroke. Monitor concentrations within each district were

1 used to derive 3-yr avg concentrations that were assigned to participants. The mean  
2 concentration among study participants was 20 ppb. [Dong et al. \(2013a\)](#) reported an  
3 increased risk of stroke [OR: 1.09 (1.01, 1.18) per 5 ppb] with the strongest associations  
4 in males. [Qin et al. \(2015\)](#) further evaluated effect modification by obesity and reported  
5 an increased risk of stroke among participants with BMI greater or equal to 25 kg/m<sup>2</sup>  
6 [OR: 1.18 (1.05, 1.32) per 5 ppb]. Neither of these studies considered copollutants  
7 confounding and both reported associations with at least one of the other pollutants that  
8 were evaluated (PM<sub>10</sub>, NO<sub>2</sub>, or ozone). The district level SO<sub>2</sub> concentrations may not  
9 have adequately captured the spatial variability of SO<sub>2</sub>.

**Table 5-33 Epidemiologic studies of the association of long-term exposure to sulfur dioxide with stroke.**

Study	Cohort, Location, and Study Period	Mean ppb	Exposure Assessment	Effect Estimates (95% CI)
<a href="#">†Lipsett et al. (2011)</a>	California Teachers Study Cohort N = 124,614 California Jun 1996– Dec 2005	SO <sub>2</sub> IQR: 0.43 mean: 1.72	Geocoded residential address linked to pollutant surface developed using IDW (fixed site monitors concentrations from 1995–2005 used to model exposure as a time-dependent function)  Correlation of SO <sub>2</sub> with: ozone, $r = -0.17$ PM <sub>2.5</sub> , $r = 0.02$ PM <sub>10</sub> , $r = 0.54$ NO <sub>2</sub> , $r = 0.67$ CO, $r = 0.80$	Stroke incidence SO <sub>2</sub> : HR 6.21 (0.4, 88)  Covariates: age, race, smoking, second-hand smoke, BMI, lifetime physical activity, nutritional factors, alcohol, marital status, menopausal status, hormone replacement therapy, hypertension medication and aspirin, and family history of MI/stroke  Copollutant adjustment: none
<a href="#">†Atkinson et al. (2013)</a>	National GP Patient Cohort England 2003	IQR: 0.83 mean (SD): 1.47	Annual average SO <sub>2</sub> concentration for 2002 at a 1 by 1 km resolution derived from dispersion models and linked to residential post codes  Correlation of SO <sub>2</sub> with: NO <sub>2</sub> , $r = 0.86$	Stroke incidence HR: 1.13 (1.00, 1.34)  Covariates: age, sex, smoking, BMI, diabetes, hypertension, and index of multiple deprivation  Copollutant adjustment: none

**Table 5-33 (Continued): Epidemiologic studies of the association of long term exposure to sulfur dioxide with stroke.**

Study	Cohort, Location, and Study Period	Mean ppb	Exposure Assessment	Effect Estimates (95% CI)
<a href="#">†Dong et al. (2013a)</a>	N = 24,845 Random selection (18–74 yr) from households in 33 communities in 11 districts of northeastern China	Mean: 20 med: 18 IQR: 7.5	3-yr avg (2006–2008) SO <sub>2</sub> concentration for each district NO <sub>2</sub> , <i>r</i> = 0.38 O <sub>3</sub> , <i>r</i> = 0.87 PM <sub>10</sub> , <i>r</i> = 0.70	Prevalent stroke OR: 1.09 (1.01, 1.18)  Note: associations stronger among males Covariate adjustment: age, sex, educational level, occupation, family income, BMI, hypertension, family history of stroke, family history of CVD, smoking status, drinking, diet, and exercise
<a href="#">†Qin et al. (2015)</a>	N = 24,845 Random selection (18–74 yr) from households in 33 communities in 11 districts of northeastern China	Mean: 20.3 IQR: 7.5	3-yr avg (2006–2008) SO <sub>2</sub> concentration for each district NO <sub>2</sub> , <i>r</i> = 0.38 O <sub>3</sub> , <i>r</i> = 0.87 PM <sub>10</sub> , <i>r</i> = 0.70	Stroke BMI <25 kg/m <sup>2</sup> : OR: 1.03 (0.92, 1.14) BMI 25 kg/m <sup>2</sup> : OR: 1.18 (1.05, 1.32)  Sex-stratified analyses also presented  Covariate adjustment: age, race, education, income, smoking, drinking, exercise, diet, sugar, family history of CVD or stroke, district

**Table 5-33 (Continued): Epidemiologic studies of the association of long term exposure to sulfur dioxide with stroke.**

Study	Cohort, Location, and Study Period	Mean ppb	Exposure Assessment	Effect Estimates (95% CI)
<a href="#">†Johnson et al. (2010)</a>	Edmonton, Alberta Canada Jan 2003– Dec 2007	SO <sub>2</sub> mean: 1.3	IDW average monitor SO <sub>2</sub> concentration assigned at postal code centroid level  Correlation of 5-yr avg SO <sub>2</sub> with: NO <sub>2</sub> , <i>r</i> = 0.40 O <sub>3</sub> , <i>r</i> = 0.41 CO, <i>r</i> = -0.19	Ecological analysis of stroke incidence rates: Stroke ED visits Q1 RR: 1.0 (reference) Q2 RR: 0.91 (0.83, 1.00) Q3 RR: 0.89 (0.81, 0.98) Q4 RR: 0.84 (0.73, 0.96) Q5 RR: 0.93 (0.89, 0.98)  <sup>a</sup> Results for HS, non-HS, and TIA also presented  Covariate adjustment: age, sex, and household income  Copollutant adjustment: none

BMI = body mass index; CI = confidence interval; CO = carbon monoxide; CVD = cardiovascular disease; ED = emergency department; GP = general practice; HR = heart rate; HS = hemorrhagic stroke; IDW = inverse distance weighting; IQR = interquartile range; MI = myocardial infarction; N = population number; NO<sub>2</sub> = nitrogen dioxide; non-HS = nonhemorrhagic stroke; Q1 = 1st quartile; Q2 = 2nd quartile; Q3 = 3rd quartile; Q4 = 4th quartile; Q5 = 5th quartile; OR = odds ratio; O<sub>3</sub> = ozone; PM<sub>2.5</sub> = particulate matter with a nominal aerodynamic diameter less than or equal to 2.5 μm; PM<sub>10</sub> = particulate matter with a nominal aerodynamic diameter less than or equal to 10 μm; *r* = correlation coefficient; RR = relative risk; SD = standard deviation; SO<sub>2</sub> = sulfur dioxide; TIA = transient ischemic attack.

<sup>a</sup>Effect estimates are standardized per 5-ppb increase in SO<sub>2</sub> concentrations.

†Studies published since the 2008 ISA for Sulfur Oxides.

1 An inverse association between SO<sub>2</sub> concentration and stroke incidence was observed in  
2 an ecological analysis of long-term exposure to ambient pollution conducted in  
3 Edmonton ([Johnson et al., 2010](#)) while an association of SO<sub>2</sub> with stroke prevalence was  
4 observed in a study of 33 Chinese communities [OR: 1.21 (95% CI 1.01, 1.46)] ([Dong et](#)  
5 [al., 2013a](#)).

6 In summary, the epidemiologic studies do not provide evidence in strong support of an  
7 effect of long-term SO<sub>2</sub> exposure on stroke morbidity. Findings are not generally  
8 consistent across studies and there are uncertainties related to the potential for exposure  
9 measurement error and confounding by copollutants.

### 5.3.2.4 Blood Pressure and Hypertension

10 Several analyses conducted in China where the mean long-term SO<sub>2</sub> concentration is  
11 18.7 ppb report positive associations with hypertension and increased blood pressure.  
12 [Dong et al. \(2013d\)](#) found increased risk of hypertension [OR: 1.17 (95% CI: 1.06, 1.28)  
13 per 5-ppb increase in SO<sub>2</sub> concentration] among adults greater than 55 years of age in  
14 33 Chinese communities. The absolute change in diastolic and systolic blood pressure in

1 the study population overall was 0.46 mmHg (95% CI: 0.15, 0.75) and 1.18 mmHg (95%  
 2 CI: 0.68, 1.69) per 5-ppb increase in SO<sub>2</sub> concentration, respectively. [Zhao et al. \(2013\)](#)  
 3 reported a greater effect of SO<sub>2</sub> on blood pressure among the overweight and obese in  
 4 this population. A similar trend was also observed with other pollutants (i.e., ozone and  
 5 NO<sub>2</sub>). In a study of children 5–17 years old from elementary schools in seven Chinese  
 6 cities, [Dong et al. \(2014\)](#) reported associations with arterial blood pressure hypertension  
 7 in males [OR: 1.17 (95% CI 1.08, 1.27)] and females [OR 1.19 (95% CI 1.10, 1.28)] per  
 8 5-ppb increase in 4-yr avg SO<sub>2</sub> concentration. In an extended analysis of this cohort,  
 9 [Dong et al. \(2015\)](#) reported large risks associated with SO<sub>2</sub> concentration in overweight  
 10 and obese children. Although an array of risk factors were considered in the analysis as  
 11 potential confounders ([Table 5-34](#)), no adjustment for copollutants was presented nor  
 12 were copollutant correlations reported. Associations of hypertension with the other  
 13 pollutants examined (i.e., PM<sub>10</sub>, ozone, CO, NO<sub>2</sub>) were also reported in these studies.

**Table 5-34 Epidemiologic studies of the association of long-term exposure to sulfur dioxide with hypertension.**

Study	Cohort, Location, and Study Period	Mean ppb	Exposure Assessment	Effect Estimates (95% CI)
<a href="#">†Dong et al. (2013d)</a>	N = 24,845 Random selection (18–74 yr) from households in 33 communities in 11 districts of northeastern China	Mean: 20.3 IQR: 7.5	3-yr avg (2006–2008) SO <sub>2</sub> concentration for each district  NO <sub>2</sub> , <i>r</i> = 0.38 O <sub>3</sub> , <i>r</i> = 0.87 PM <sub>10</sub> , <i>r</i> = 0.70	OR: 1.07 (1.03, 1.12)  SBP: 0.21 mm Hg (0.07, 0.34) DBP: 0.53 mm Hg (0.31, 0.76)  Covariate adjustment: age, race, education, income, smoking, drinking, exercise, diet, sugar, family history of hypertension, district
<a href="#">†Zhao et al. (2013)</a>	N = 24,845 Random selection (18–74 yr) from households in 33 communities in 11 districts of northeastern China	Mean: 20.3 IQR: 7.5	3-yr avg (2006–2008) SO <sub>2</sub> concentration for each district  NO <sub>2</sub> , <i>r</i> = 0.38 O <sub>3</sub> , <i>r</i> = 0.87 PM <sub>10</sub> , <i>r</i> = 0.70	OR normal: 1.03 (0.99–1.08) OR overweight: 1.10 (1.05–1.15) OR obese: 1.10 (0.99–1.23)  Covariate adjustment: race, education, income, smoking, drinking, exercise, diet, sugar, family history of hypertension, district

**Table 5-34 (Continued): Epidemiologic studies of the association of long term exposure to sulfur dioxide with hypertension.**

Study	Cohort, Location, and Study Period	Mean ppb	Exposure Assessment	Effect Estimates (95% CI)
<a href="#">†Dong et al. (2014)</a>	n = 9,354 Children (5–17 yr) Seven cities northeastern China 2012–2013	Mean: 18.7. IQR: 8.8	4-yr avg concentration for one central site monitor within 1 km of participant's home Correlations NR	Hypertension in males: OR 1.17(1.08, 1.27) Hypertension in females: OR 1.19 (1.10, 1.28) per 5 ppb DPB (all children) 0.43 (0.26, 0.61) SBP (all children) 0.71 (0.50, 0.91) per 5 ppb Covariate adjustment: age, sex, BMI, parental education, LBW, premature birth, income, passive smoking exposure, home coal use, exercise time, area residence per person, family history of hypertension, and district
<a href="#">†Dong et al. (2015)</a>	n = 9,354 Children (5–17 yr) Seven cities northeastern China 2012–2013	Mean: 18.7 IQR: 8.8	4-yr avg concentration for one central site monitor within 1 km of participant's home Correlations NR	Hypertension Normal weight: 0.89 (0.83, 0.96) Overweight: 1.36 (1.18, 1.56) Obese: 1.66 (1.46, 1.89) per 5 ppb Covariate adjustment: age, sex, parental education, LBW, premature birth, breastfeeding, income, passive smoking, home coal use, exercise time, area residence per person, family history of hypertension, distance from air pollution monitor, temperature, and district

BMI = body mass index; CI = confidence interval; DPB = diastolic blood pressure; IQR = interquartile range; LBW = low birth rate; n = sample size; N = population number; NO<sub>2</sub> = nitrogen dioxide; NR = not reported; O<sub>3</sub> = ozone; OR = odds ratio; PM<sub>10</sub> = particulate matter with a nominal aerodynamic diameter less than or equal to 10 µm; r = correlation coefficient; SBP = systolic blood pressure; SO<sub>2</sub> = sulfur dioxide.

†Studies published since the 2008 ISA for Sulfur Oxides.

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### 5.3.2.5 Other Cardiovascular Effects

1 Few studies have evaluated other cardiovascular effects associated with long-term SO<sub>2</sub>  
2 concentrations. [Atkinson et al. \(2013\)](#) examined the association of arrhythmias and heart  
3 failure with long-term SO<sub>2</sub> exposure. Study methods are described in [Section 5.3.2.2](#).  
4 Authors reported a positive association of SO<sub>2</sub> with heart failure in a fully adjusted model  
5 [HR: 1.27 (95% CI: 1.06–1.59) per 5 ppb] and with arrhythmia [HR: 1.13 (95% CI 1.00,  
6 1.27)]. A similar pattern of findings was observed for the associations of NO<sub>2</sub> and PM<sub>10</sub>  
7 with which moderate correlations with SO<sub>2</sub> were reported. No association of annual SO<sub>2</sub>  
8 concentration with hospital admissions for heart failure was reported in a study of  
9 county-level air pollution indicator concentrations ([Bennett et al., 2014](#)).

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### 5.3.2.6 Cardiovascular Mortality

10 The recent evidence for associations between long-term SO<sub>2</sub> exposure and total mortality  
11 ([Section 5.5.2](#)) is generally consistent with the evidence in the 2008 ISA for Sulfur  
12 Oxides. Several studies report associations between long-term SO<sub>2</sub> exposure and  
13 cardiovascular mortality ([Figure 5-27](#)); however, there is no consistent trend toward  
14 positive associations for cardiopulmonary or cardiovascular causes of death overall.  
15 Additionally, confounding by copollutants is not ruled out ([Section 3.4.3](#)) and  
16 uncertainties remain regarding the influence of exposure measurement error  
17 ([Section 3.4.2](#)). Together, these uncertainties limit the interpretation of the causal nature  
18 of the associations observed in the available epidemiologic studies of long-term  
19 mortality.

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### 5.3.2.7 Subclinical Effects Underlying Cardiovascular Diseases

20 Carotid intima-media thickness (cIMT) is a measurement of thickness of the inner layers  
21 of the wall of the artery and can be used to indicate the presence of subclinical  
22 atherosclerosis. Other markers of preclinical atherosclerosis include pulse wave velocity  
23 and augmentation index, both of which indicate arterial stiffening. In an analysis of the  
24 Atherosclerosis Risk in Young Adults study, which is a prospective cohort study ([Lenters  
25 et al., 2010](#)), no association of SO<sub>2</sub> concentration with carotid intima-media thickness  
26 (cIMT) was observed; however, there was a weak imprecise increase in aortic pulse wave  
27 velocity reported. The other pollutants examined (NO<sub>2</sub>, PM<sub>2.5</sub>, black smoke) were also  
28 not associated cIMT although associations between NO<sub>2</sub> concentration and both pulse  
29 wave velocity and augmentation index were observed. SO<sub>2</sub> concentration at the home

1 address for the year 2000 was assigned to participants of this study. The correlations of  
2 SO<sub>2</sub> with NO<sub>2</sub>, black smoke, and PM<sub>2.5</sub> reported in this study were low, ranging from  
3  $r = 0.09$  to  $0.12$ . The correlation of SO<sub>2</sub> with metrics of traffic intensity were also low  
4 ( $r = -0.06$  to  $0.06$ ). In another study, [Weng et al. \(2015\)](#) reported that annual average SO<sub>2</sub>  
5 concentration was correlated with brachial-ankle pulse wave velocity in univariate  
6 analyses but not after adjustment for PM<sub>10</sub> and other potential confounders. This study  
7 was based on data from 127 heart disease patients undergoing hemodialysis in Taoyuan,  
8 Taiwan.

9 Inflammation and oxidative stress have been shown to play a role in the progression of  
10 chronic cardiovascular disease. [Forbes et al. \(2009b\)](#) examined the association of  
11 predicted annual average SO<sub>2</sub> concentration with CRP and fibrinogen among the English  
12 population. Multilevel linear regression models were used to determine pooled estimates  
13 across three cross-sectional surveys conducted during different years. Each participant's  
14 postal code of residence was linked to predicted annual average SO<sub>2</sub> concentration  
15 derived from dispersion models. SO<sub>2</sub>, PM<sub>10</sub>, O<sub>3</sub>, and NO<sub>2</sub> were not associated with  
16 increased CRP or fibrinogen in these data. A study conducted among men and women  
17 (45–70 years) in Stockholm reported an association of 30-yr avg source-specific  
18 heating-related SO<sub>2</sub> concentration estimated using dispersion models with increases in  
19 IL-6; however, SO<sub>2</sub> was not associated with CRP, TNF- $\alpha$ , fibrinogen, or plasminogen  
20 activator inhibitor-1 in this study ([Panasevich et al., 2009](#)). Associations between  
21 long-term NO<sub>2</sub> concentration, which were moderately correlated with SO<sub>2</sub> ( $r = 0.53$ ), and  
22 increased plasma IL-6 were also observed in this study. A study conducted among older  
23 adults in Taiwan reported no changes in blood pressure, total cholesterol, fasting glucose,  
24 hemoglobin A1c, IL-6 and neutrophils in association with increasing SO<sub>2</sub> concentration  
25 while associations between these endpoints and other pollutants were observed ([Chuang  
26 et al., 2011](#)).

27 Overall, the body of evidence is limited and there is no consistent positive trend in the  
28 associations observed between SO<sub>2</sub> and subclinical atherosclerosis or circulating markers  
29 of inflammation. These findings are consistent with the general lack of mechanistic  
30 evidence for key events in the proposed mode of action leading to extrapulmonary  
31 effects.

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### 5.3.2.8 Summary and Causal Determination

32 Overall, the evidence is inadequate to infer the presence or absence of a causal  
33 relationship between long-term exposure to SO<sub>2</sub> and cardiovascular health effects.

1 Although a number of epidemiologic studies report positive associations between  
2 long-term exposure to SO<sub>2</sub> concentrations and cardiovascular disease and stroke  
3 ([Section 5.3.2.3](#)), the evidence for any one outcome is limited and inconsistent. As  
4 discussed in [Section 3.4.2.2](#), centrally located monitors may not capture the spatial  
5 variability in SO<sub>2</sub> concentration. Dispersion models generally capture SO<sub>2</sub> variability on  
6 near-source spatial scales (up to tens of km) but exposure estimates from such models are  
7 subject to other uncertainties ([Section 3.3.2.4](#)). Bias stemming from exposure  
8 measurement error can be either direction (i.e. toward or away from the null) and no  
9 studies corrected for such error, complicating the interpretation of findings from studies  
10 of long-term exposure of SO<sub>2</sub> ([Section 3.4.4.2](#)). There is also uncertainty regarding the  
11 potential for copollutant confounding ([Section 3.4.3](#)). Primary pollutants such as NO<sub>2</sub> and  
12 CO typically show moderate to high correlations with SO<sub>2</sub> ([Table 5-32](#), [Table 5-33](#), and  
13 [Table 5-34](#)) and there is a lack of experimental evidence to provide coherence or  
14 biological plausibility for an independent effect of SO<sub>2</sub> on cardiovascular health. Several  
15 epidemiologic studies evaluated the association between SO<sub>2</sub> concentration and  
16 subclinical atherosclerosis or circulating markers of inflammation; however, there is no  
17 consistent positive trend in the associations observed between SO<sub>2</sub> and these potential  
18 key events in a mode of action.

19 The available evidence examining the relationship between long-term exposure to SO<sub>2</sub>  
20 and cardiovascular effects was evaluated using the framework described in Table I and  
21 Table II of the [Preamble](#) to the ISAs ([U.S. EPA, 2015b](#)). The key evidence, supporting or  
22 contradicting, as it relates to the causal framework is summarized in [Table 5-35](#). In  
23 conclusion, the evidence lacks coherence and is of insufficient consistency, and thus, is  
24 inadequate to infer the presence or absence of a causal relationship between long-term  
25 exposure to SO<sub>2</sub> and cardiovascular health effects.

**Table 5-35 Summary of evidence, which is inadequate to infer a causal relationship between long-term sulfur dioxide exposure and cardiovascular effects.**

Rationale for Causal Determination <sup>a</sup>	Key Evidence <sup>b</sup>	Key References <sup>b</sup>	SO <sub>2</sub> Concentrations Associated with Effects <sup>c</sup>
Some epidemiologic studies report positive associations but results are not generally consistent.	Positive associations of SO <sub>2</sub> with MI, CVD events, or stroke events	<a href="#">Lipsett et al. (2011)</a>	1.72 ppb (mean)
		<a href="#">Atkinson et al. (2013)</a>	1.47 ppb (mean)
		<a href="#">Miller et al. (2007)</a>	NR
		<a href="#">Rosenlund et al. (2006)</a>	9.6 ppb (med)
	Null/inverse associations observed with MI and stroke	<a href="#">Johnson et al. (2010)</a>	1.3 ppb (mean)
Limited coherence with evidence for cardiovascular mortality	No consistent positive trend observed in long term studies of cardiovascular mortality.	<a href="#">Section 5.3.2.4</a>	
Uncertainty due to confounding by correlated pollutants	Correlations of SO <sub>2</sub> with CO and NO <sub>2</sub> vary by location but are generally moderate to high.	<a href="#">Table 5-32</a> <a href="#">Table 5-33</a> <a href="#">Table 5-34</a>	
Uncertainty due to exposure measurement error	Centrally located monitors may not capture spatial variability of SO <sub>2</sub> concentrations.	<a href="#">Miller et al. (2007)</a> <a href="#">Section 3.4.2</a>	
	SO <sub>2</sub> estimates from dispersion model show poor to moderate agreement with measured concentrations.	<a href="#">Atkinson et al. (2013)</a> <a href="#">Forbes et al. (2009a)</a>	
	Exposure measurement error can introduce bias away from the null in studies of long-term exposure	<a href="#">Section 3.4.4.2</a>	
Uncertainty due to lack of coherence with other lines of evidence	Lack of experimental human or animal studies evaluating cardiovascular effects of long-term SO <sub>2</sub> exposure		

**Table 5-35 (Continued): Summary of evidence, which is inadequate to infer a causal relationship between long term sulfur dioxide exposure and cardiovascular effects.**

Rationale for Causal Determination <sup>a</sup>	Key Evidence <sup>b</sup>	Key References <sup>b</sup>	SO <sub>2</sub> Concentrations Associated with Effects <sup>c</sup>
Weak evidence to identify key events in the mode of action	Lack of mechanistic evidence for key events leading to extrapulmonary effects  Limited and inconsistent evidence of increased subclinical atherosclerosis and systemic inflammation (e.g., IL-6, CRP) in epidemiologic studies	<a href="#">Section 4.3</a> <a href="#">Section 5.3.2.7</a>	

CO = carbon monoxide; CRP = C-reactive protein; CVD = cardiovascular disease; IL-6 = interleukin-6; MI = myocardial infarction; NO<sub>2</sub> = nitrogen dioxide; NR = not reported; SO<sub>2</sub> = sulfur dioxide.

<sup>a</sup>Based on aspects considered in judgments of causality and weight of evidence in causal framework in Table I and Table II of the [Preamble](#) to the ISAs ([U.S. EPA, 2015b](#)).

<sup>b</sup>Describes the key evidence and references, supporting or contradicting, that contribute most heavily to causal determination. References to earlier sections indicate where full body of evidence is described.

<sup>c</sup>Describes the SO<sub>2</sub> concentrations with which the evidence is substantiated.

## 5.4 Reproductive and Developmental Effects

### 5.4.1 Introduction

1 This section covers studies of health endpoints with exposures to SO<sub>2</sub> occurring during or  
2 around pregnancy and/or the first years of life. This includes not only pregnancy and  
3 birth outcomes (including infant mortality) occurring close in time to the exposure, but  
4 also developmental outcomes potentially occurring years later. Exposures occurring in  
5 pregnancy and early life may alter development, and have effects not immediately  
6 identifiable but evident at later points. These studies are characterized in this section as  
7 they contribute to the weight of evidence for effects of SO<sub>2</sub> on reproductive health and  
8 development. Evidence regarding fertility, reproduction, and pregnancy are discussed in  
9 [Section 5.4.2](#), with a series of birth outcomes [fetal growth ([Section 5.4.3.1](#)), preterm  
10 birth ([Section 5.4.3.2](#)), birth weight ([Section 5.4.3.3](#)), birth defects ([Section 5.4.3.4](#)), fetal  
11 mortality ([Section 5.4.3.5](#)), and infant mortality ([Section 5.4.3.6](#))] discussed in  
12 [Section 5.4.3](#). Studies of developmental outcomes are discussed in [Section 5.4.4](#), with a  
13 focus on respiratory developmental outcomes in [Section 5.4.4.1](#).

14 Epidemiologic studies included in the 2008 SO<sub>x</sub> ISA ([U.S. EPA, 2008d](#)) examined  
15 impacts on reproductive outcomes including preterm birth, birth weight, intra-uterine

1 growth retardation, birth defects, infant mortality, and neonatal respiratory  
2 hospitalizations. While positive associations were observed in the previous SO<sub>x</sub> ISA  
3 ([U.S. EPA, 2008d](#)), there was little biologic plausibility for these associations provided  
4 by supporting toxicological literature. Interpretation of those results was also limited by  
5 the lack of control for potential confounding by copollutants, the small number of studies,  
6 and uncertainty regarding exposure. The 2008 SO<sub>x</sub> ISA ([U.S. EPA, 2008d](#)) concluded the  
7 evidence was inadequate to infer the presence or absence of a causal relationship with  
8 reproductive and developmental effects.

9 The body of literature characterizing the reproductive health effects of exposure to SO<sub>2</sub>  
10 has grown considerably since the 2008 SO<sub>x</sub> ISA ([U.S. EPA, 2008d](#)), with over 50 recent  
11 epidemiologic studies. However, the number of studies for any particular outcome  
12 remains relatively limited. Among the recent epidemiologic studies, birth outcomes  
13 (e.g., small for gestational age, preterm birth, and birth weight) predominate. Several new  
14 studies of congenital anomalies are now available in addition to the single study included  
15 in the 2008 SO<sub>x</sub> ISA. Recent studies of other outcomes, such as fetal mortality, infant  
16 mortality, fertility, and conditions related to pregnancy have also been published. Key  
17 epidemiologic studies are summarized in [Table 5-36](#). In toxicological research, a single  
18 study published at relevant exposure levels (1,500 ppb or lower) investigated  
19 reproductive and developmental changes in exposed female rats and their offspring,  
20 finding altered estrus cyclicity with fewer cycles over time, altered birth outcomes of  
21 increased litter size, and decreased postnatal body weight in offspring whose dams were  
22 exposed to SO<sub>2</sub>. This study is summarized in [Table 5-37](#). The majority of the remaining  
23 animal toxicological evidence for reproductive and development effects is for exposure at  
24 5,000 ppb or greater, doses which are beyond the scope of this document.

25 Several recent articles have reviewed methodological issues relating to the study of  
26 outdoor air pollution and adverse birth outcomes ([Chen et al., 2010a](#); [Woodruff et al.,  
27 2009](#); [Ritz and Wilhelm, 2008](#); [Slama et al., 2008](#)). Some of the key challenges to  
28 interpretation of birth outcome study results include: (1) the difficulty in assessing  
29 exposure as most studies use existing monitoring networks to estimate individual  
30 exposure to ambient air pollution; (2) the need for detailed exposure data and potential  
31 residential movement of mothers during pregnancy; (3) the inability to control for  
32 potential confounders such as other risk factors that affect birth outcomes (e.g., smoking),  
33 evaluating the exposure window (e.g., trimester) of importance; and (4) the limited  
34 evidence on the physiological modes of action for these effects ([Ritz and Wilhelm, 2008](#);  
35 [Slama et al., 2008](#)). An additional limitation is the failure for many studies of  
36 reproductive and developmental outcomes to adjust for co-occurring air pollutants. As  
37 ozone, PM<sub>2.5</sub>, and NO<sub>x</sub> have all been associated with reproductive and developmental  
38 health outcomes, the lack of adjustment makes interpretation of isolated SO<sub>2</sub> effects more

difficult. Recently, an international collaboration was formed to better understand the relationships between air pollution and adverse birth outcomes and to examine some of these methodological issues through standardized parallel analyses in data sets from different countries ([Woodruff et al., 2010](#)). At present, no results for analysis of SO<sub>2</sub> have been reported from this collaboration.

Overall, the number of studies examining associations between exposure to ambient SO<sub>2</sub> and reproductive and developmental outcomes has increased substantially since publication of the 2008 ISA for Sulfur Oxides, yet evidence for an association with individual outcomes remains relatively limited and key uncertainties have not been reduced.

**Table 5-36 Key reproductive and developmental epidemiologic studies for sulfur dioxide.**

Study	Location Sample Size	Mean SO <sub>2</sub> ppb	Exposure Assessment	Selected Effect Estimates <sup>a</sup> 95% CI
<b>Fetal growth</b>				
<a href="#">Liu et al. (2003)</a>	Vancouver (n = 229,085)	4.9	Monitors at census subdivision level	IUGR (those with birth weight fall below the 10th percentile, by sex and gestational week, of all singleton live births in Canada between 1986 and 1998, term) M1: 1.07 (1.01, 1.13) Last mo: 1.00 (0.94, 1.06) T1: 1.07 (1.00, 1.14) T2: 0.98 (0.91, 1.04) T3: 1.03 (0.96, 1.10)
<a href="#">Brauer et al. (2008)</a>	Vancouver (n = 70,249)	2.2	Inverse distance weighting of three closest monitors within 50 km, 14 SO <sub>2</sub> monitors	SGA (those with birth weights below the 10th percentile of the cohort, stratified by sex, for each week of gestation) EP: 1.02 (1.00, 1.03)
<a href="#">Rich et al. (2009)</a>	New Jersey (n = 178)	T1: 5.7 T2: 5.6 T3: 5.5	Nearest monitor (within 10 km)	VSGA (growth ratio <0.75) T1: 1.00 (0.92, 1.08) T2: 1.04 (0.96, 1.13) T3: 1.05 (0.97, 1.14)

**Table 5-36 (Continued): Key reproductive and developmental epidemiologic studies for sulfur dioxide.**

Study	Location Sample Size	Mean SO <sub>2</sub> ppb	Exposure Assessment	Selected Effect Estimates <sup>a</sup> 95% CI
<a href="#">†Le et al. (2012)</a>	Detroit, MI (n = 112,609)	5.8	Nearest monitor (ZIP code within 4 km of one of three monitors)	SGA (infants whose birth weights fell below the 10th percentile by sex and gestational week, based on study population's distribution, term) T1, adjusted for CO, NO <sub>2</sub> , and PM <sub>10</sub> Q1: ref Q2: 1.18 (0.92, 1.51) Q3: 1.01 (0.83, 1.23) Q4: 1.05 (0.87, 1.28) T2, adjusted for CO, NO <sub>2</sub> , and PM <sub>10</sub> Q1: ref Q2: 1.30 (1.01, 1.69) Q3: 1.12 (0.91, 1.37) Q4: 1.11 (0.90, 1.36) T3, adjusted for CO, NO <sub>2</sub> , and PM <sub>10</sub> Q1: ref Q2: 1.17 (0.94, 1.45) Q3: 1.24 (1.02, 1.50) Q4: 1.31 (1.06, 1.60)
<b>Preterm birth</b>				
<a href="#">Liu et al. (2003)</a>	Vancouver, BC (n = 229,085)	4.9	Monitors at census subdivision level	M1: 0.95 (0.88, 1.03) Last mo: 1.09 (1.01, 1.19)
<a href="#">Sagiv et al. (2005)</a>	Pennsylvania (n = 187,997)	7.9	Monitors at county level	Last 6 wk: 1.05 (1.00, 1.10) 3 d lag: 1.02 (0.99, 1.05)
<a href="#">†Zhao et al. (2011)</a>	Guangzhou, China (n = 7,836 preterm births)	20	City average from monitors	Same day: 1.04 (1.02, 1.06) 1 d lag: 1.01 (0.99, 1.04) 2 d lag: 1.02 (0.99, 1.04) 3 d lag: 1.02 (0.99, 1.04)
<a href="#">†Mendola et al. (2016a)</a>	U.S. (n = 223,502)	3.99	Modeled, CMAQ Delivery hospital referral region	Week 34 Asthma: 1.32 (1.05, 1.70) No asthma: 1.02 (0.90, 1.14) Week 35 Asthma: 1.17 (1.02, 1.34) No asthma: 0.98 (0.92, 1.05) Last 6 wk of pregnancy Asthma: 0.90 (0.81, 1.00) No asthma: 0.81 (0.77, 0.92) EP Asthma: 0.93 (0.83, 1.03) No asthma: 0.92 (0.87, 0.97)

**Table 5-36 (Continued): Key reproductive and developmental epidemiologic studies for sulfur dioxide.**

Study	Location Sample Size	Mean SO <sub>2</sub> ppb	Exposure Assessment	Selected Effect Estimates <sup>a</sup> 95% CI
<b>Low birth weight</b>				
<a href="#">Ha et al. (2001)</a>	Seoul, South Korea (n = 276,763)	T1: 13 T3: 12	Monitors averaged to city	T1: 1.05 (1.02, 1.08) T1, adjusted for T3: 1.06 (0.98, 1.13) T3: 0.96 (0.92, 0.99) T3, adjusted for T1: 1.02 (0.94, 1.10)
<a href="#">Lee et al. (2003)</a>	Seoul, South Korea (n = 388,105)	12.1	Monitors averaged to city	EP: 1.02 (0.99, 1.05) T1: 1.05 (1.02, 1.09) T2: 0.97 (0.92, 1.00) T3: 1.12 (1.03, 1.20)
<a href="#">Liu et al. (2003)</a>	Vancouver, BC (n = 229,085)	4.9	Monitors at census subdivision level	M1: 1.11 (1.01, 1.22) Last mo: 0.98 (0.89, 1.08)
<a href="#">Dugandzic et al. (2006)</a>	Nova Scotia (n = 74,284)	10	Nearest monitor (postcode within 25 km)	T1: 1.20 (1.05, 1.38) T2: 0.99 (0.91, 1.09) T3: 0.95 (0.86, 1.04)
<a href="#">†Morello-Frosch et al. (2010)</a>	California (n = 3,545,177)	2.1	Nearest monitor (census block centroid within 3, 5, or 10 km)	EP 3 km: 1.10 (0.95, 1.34) 5 km: 1.05 (0.95, 1.16) 10 km: 1.05 (1.00, 1.10)
<a href="#">†Ebisu and Bell (2012)</a>	Northeastern and mid-Atlantic U.S. (n = 1,207,800)	6.1	County average from monitors	EP: 1.05 (1.01, 1.09)
<a href="#">†Kumar (2012)</a>	Chicago, IL (n = 398,120)	4.7 4.6	Nearest monitor (census tract within 3 miles)  County average from monitors	EP: 1.19 (0.90, 1.57) EP: 1.05 (0.91, 1.20)
<b>Birth Weight</b>				
<a href="#">†Darrow et al. (2011)</a> Distributed lag, 1-h max SO <sub>2</sub>	Atlanta, GA (n = 400,556)	M1: 10.7 T3: 9.5	Population weighted spatial model based on monitors, five-county area, 1-h max	M1: 0.625 (-2.625, 3.875) T3: -6.500 (-12.500, -0.667) Non-Hispanic white T3: -8.667 (-15.333, -2.000) Non-Hispanic black T3: -3.167 (-9.833, 3.667) Hispanic T3: -9.5 (-19.000, -0.167)
<a href="#">†Geer et al. (2012)</a>	Texas (n = 1,548,904)	2.3	County average from monitors	EP: -15.594 (-25.344, -5.844)

**Table 5-36 (Continued): Key reproductive and developmental epidemiologic studies for sulfur dioxide.**

Study	Location Sample Size	Mean SO <sub>2</sub> ppb	Exposure Assessment	Selected Effect Estimates <sup>a</sup> 95% CI
<b>Fetal and infant mortality</b>				
<a href="#">†Hwang et al. (2011)</a>	Taiwan (n = 9,325 cases)	5.7	Inverse distance weighting of monitors to township or district, 72 monitors	Among preterm deliveries EP: 1.16 (1.00, 1.34) M1: 1.22 (1.00, 1.34) M2: 1.22 (1.00, 1.34) M3: 1.16 (1.00, 1.34)  Among term deliveries EP: 0.95 (0.82, 1.10) M1: 1.00 (0.90, 1.16) M2: 1.00 (0.90, 1.16) M3: 0.95 (0.86, 1.16)
<a href="#">†Faiz et al. (2012)</a>	New Jersey (n = 994)	5.9	Nearest monitor (within 10 km, 1 of 16 monitors)	EP: 1.32 (0.95, 1.84) T1: 1.23 (1.02, 1.51) T2: 1.21 (0.89, 1.53) T3: 1.47 (1.05, 1.69)
<a href="#">†Faiz et al. (2013)</a>	New Jersey (n = 1,277)	5.8	Nearest monitor (within 10 km, 1 of 16 monitors)	2-d lag 1.12 (1.02, 1.24) Adjusted PM <sub>2.5</sub> : 1.18 (1.00, 1.40) Adjusted NO <sub>2</sub> : 1.15 (1.00, 1.32) Adjusted CO: 1.05 (0.93, 1.20)
<a href="#">Woodruff et al. (2008)</a>	U.S. (n = 6,639 cases)	3 (median)	Monitors, averaged to county  Exposures for 2 mo after birth	All causes 0.93 (0.84, 1.04)  Respiratory 1.09 (0.89, 1.36)  Adjusted PM <sub>10</sub> , CO, O <sub>3</sub> : 1.13 (0.79, 1.60)  Adjusted PM <sub>2.5</sub> , CO, O <sub>3</sub> : 1.21 (0.79, 1.84)

**Table 5-36 (Continued): Key reproductive and developmental epidemiologic studies for sulfur dioxide.**

Study	Location Sample Size	Mean SO <sub>2</sub> ppb	Exposure Assessment	Selected Effect Estimates <sup>a</sup> 95% CI
<b>Developmental</b>				
<a href="#">Dales et al. (2006)</a>	Atlanta, GA (n = 8,586 cases)	4.3	Monitors, averaged to city	Neonatal hospitalization for respiratory disease 2-d lag 2.59 (1.05, 4.39) Adjusted for O <sub>3</sub> , NO <sub>2</sub> , CO 1.95 (0.54, 3.68) Adjusted for O <sub>3</sub> , NO <sub>2</sub> , CO, PM <sub>10</sub> 1.57 (0.25, 3.29)
† <a href="#">Clark et al. (2010)</a>	British Columbia (n = 3,482 cases)	2	Inverse distance weighting 3 nearest monitors (of 14) within 50 km	Asthma EP: 1.45 (1.28, 1.84) 1st year of life: 1.45 (1.28, 1.84)

CI = confidence interval; CMAQ = Community Multiscale Air Quality; CO = carbon monoxide; EP = entire pregnancy; IUGR = intra-uterine growth restriction; M1 = Month 1; M2 = Month 2; M3 = Month 3; n = sample size; NO<sub>2</sub> = nitrogen dioxide; O<sub>3</sub> = ozone; PM<sub>2.5</sub> = particulate matter with a nominal aerodynamic diameter less than or equal to 2.5 µm; PM<sub>10</sub> = particulate matter with a nominal aerodynamic diameter less than or equal to 10 µm and greater than a nominal 2.5 µm; PM<sub>10-2.5</sub> = particulate matter with a nominal aerodynamic diameter less than or equal to 10 µm and greater than a nominal 2.5 µm; Q1 = 1st quartile; Q2 = 2nd quartile; Q3 = 3rd quartile; Q4 = 4th quartile; SGA = small for gestational age; SO<sub>2</sub> = sulfur dioxide; T1 = 1st trimester; T2 = 2nd trimester; T3 = 3rd trimester; VSGA = very small for gestational age.

<sup>a</sup>Relative risk per 5-ppb change in SO<sub>2</sub>, unless otherwise noted.

†Studies published since the 2008 ISA for Sulfur Oxides.

**Table 5-37 Study specific details from animal toxicological studies of the reproductive and developmental effects of sulfur dioxide.**

Study and Species	Concentration SO <sub>2</sub> Exposure	Measured Outcome(s)
<a href="#">Mamatsashvili (1970b)</a> Rat	0.057 or 1.5 ppm for 72 d	Estrus cyclicity duration (F0 and F1), litter size, offspring growth (body weight)

## 5.4.2 Fertility, Reproduction, and Pregnancy

- 1 Infertility affects approximately 11% of all women ages 15–44 in the U.S. ([Chandra et](#)
- 2 [al., 2013](#)), and can have negative psychological impacts and affect quality of life;

1 infertility and subfertility may also potentially signal poorer physiological health. Those  
2 with fertility problems are at higher risk for adverse pregnancy and birth outcomes if they  
3 do become pregnant ([Hansen et al., 2005](#); [Helmerhorst et al., 2004](#); [Jackson et al., 2004](#)).  
4 Outcomes studied in this area include fecundity (the ability to conceive frequently,  
5 quantified as length of time to pregnancy) and fertility (the ability to have a live birth).  
6 Studies in this area frequently use populations undergoing assisted reproductive  
7 treatment, as these populations have a large amount of data collected on them during  
8 treatment and defined menstrual cycles and start points. In cohorts recruited from the  
9 general population, exact timing can be difficult to determine due to reliance on  
10 participant recall, particularly if they are surveyed well after initiation of pregnancy  
11 attempts. Many pregnancies are unplanned, which also adds a level of complication to  
12 quantifying fertility. Researchers may also investigate potential mechanistic links  
13 between pregnancy conditions and biomarkers and later birth outcomes; such as  
14 pregnancy-related hypertension, which is a leading cause of perinatal and maternal  
15 mortality and morbidity ([Lee et al., 2012](#)).

16 Four recent studies have examined the effects of SO<sub>2</sub> on measures of fertility; all use  
17 different populations and outcomes and observed mainly null effects for SO<sub>2</sub> exposures.  
18 Recent studies examined semen quality parameters in cohorts of men from Chongqing,  
19 China ([Zhou et al., 2014](#)) and Poland ([Radwan et al., 2015](#)) and observed decreases in  
20 normal morphology with increases in SO<sub>2</sub> exposure; however, all other quality metrics  
21 showed null associations. [Slama et al. \(2013\)](#) examined fecundity rate ratios (FRs) with  
22 SO<sub>2</sub> exposures before and after the initiation of unprotected intercourse in a Czech  
23 Republic population. Exposures prior to intercourse initiation (long-term, ~30 or 60 days)  
24 had slightly reduced FRs; however, SO<sub>2</sub> was highly correlated with PM<sub>2.5</sub> and NO<sub>2</sub> in this  
25 population and stronger reductions in fertility were observed with those pollutants. [Legro  
26 et al. \(2010\)](#) examined odds of live birth in a population undergoing in vitro fertilization  
27 and observed null associations for SO<sub>2</sub> with all exposure windows from medication start  
28 to birth (short-term windows during in vitro fertilization, long term from transfer to  
29 pregnancy).

30 Mixed effect estimates are observed with SO<sub>2</sub> exposure across other pregnancy-related  
31 outcomes. Recent studies examined increased blood pressure during pregnancy or  
32 pregnancy-related hypertensive disorders, including pre-eclampsia. Several studies  
33 observed no associations between SO<sub>2</sub> exposure during the first trimester and changes in  
34 late pregnancy blood pressure ([Lee et al., 2012](#)) or hypertensive disorders ([Michikawa et  
35 al., 2015](#)); however, a study in Florida observed increased hypertension with higher SO<sub>2</sub>  
36 exposure during the first trimester ([Xu et al., 2014](#)). [Mendola et al. \(2016b\)](#) observed a  
37 positive association between pre-eclampsia and SO<sub>2</sub> exposure among people with asthma,  
38 but not among people without asthmas; the interaction between exposure to SO<sub>2</sub> and

1 asthma was statistically significant for the first trimester exposure window. A small  
2 Iranian study found no association between pre-eclampsia and SO<sub>2</sub> above versus below  
3 median concentrations ([Nahidi et al., 2014](#)). [Assibey-Mensah et al. \(2015\)](#) observed no  
4 effect of SO<sub>2</sub> on hypertensive disorders in Beijing comparing 2008 Olympic period with  
5 same calendar days in 2009. In fact, there was an inverse relationship between SO<sub>2</sub>  
6 exposure in the third trimester and hypertensive disorders.

7 In other pregnancy-related outcomes, no associations were observed in the Allegheny  
8 County, PA population for short-term near-birth exposures and C-reactive protein, an  
9 inflammatory biomarker linked to increased risk of preterm birth ([Lee et al., 2011b](#)).  
10 [Michikawa et al. \(2016\)](#) observed positive associations with SO<sub>2</sub> exposure and placenta  
11 previa in a Japanese population, although the associations were smaller and less  
12 consistent than those observed for ozone or suspended particulate matter. Increases in  
13 SO<sub>2</sub> exposure during the preconception period and the first trimester were associated with  
14 increased odds of gestational diabetes mellitus ([Robledo et al., 2015](#)). [Assibey-Mensah et](#)  
15 [al. \(2015\)](#) examined other fetal-placental conditions, and observed no associations with  
16 SO<sub>2</sub> exposure in the first or second trimester, but reported a positive association with  
17 fetal-placental conditions and third trimester SO<sub>2</sub> exposures in Beijing comparing 2008  
18 Olympic period with same calendar days in 2009. [Wallace et al. \(2016\)](#) observed positive  
19 associations between premature rupture of membranes and SO<sub>2</sub> exposure averaged over  
20 the whole pregnancy, but not for shorter exposure windows (i.e., days or hours before  
21 rupture).

22 No recent animal studies evaluating fertility and pregnancy were identified. An older  
23 study in laboratory animals exposed to SO<sub>2</sub> demonstrated reproductive toxicity in adult  
24 female rodents and their offspring. Adult female albino rats were exposed to either  
25 0.057 ppm or 1.5 ppm SO<sub>2</sub> by inhalation for 72 days ([Mamatsashvili, 1970b](#)). During the  
26 first month of treatment at 1.5 ppm, substantial alterations in stages of the estrus cycle  
27 were seen including significant decreases in duration of diestrus and metaestrus. During  
28 the 2nd and 3rd month of exposure, prolongation of estrus cyclicity was found with  
29 exposure to 1.5 ppm SO<sub>2</sub>, leading to fewer estrus cycles during the study period. This  
30 change was not permanent as by 7 months after exposure ceased, estrus cyclicity returned  
31 to normal. Exposure of adult female rodents to SO<sub>2</sub> caused disruption of estrus cyclicity  
32 that was not permanent as it returned to normal after cessation of SO<sub>2</sub> exposure.

33 While studies of fertility, reproduction, and pregnancy are limited in number, generally,  
34 SO<sub>2</sub> exposures appear to have no association with these outcomes. A group of studies  
35 examining hypertensive disorders during pregnancy report inconsistent results, with the  
36 majority observing no association with SO<sub>2</sub> exposure. Similarly, studies examining  
37 endpoints related to fertility and other pregnancy conditions are generally inconsistent,

1 with the majority observing no association, and few studies examining any one specific  
2 outcome. Additionally, these studies do not provide evidence to help reduce uncertainty  
3 related to exposure measurement error, copollutant confounding, or biological  
4 mechanism by which SO<sub>2</sub> could cause these effects. These studies are summarized in  
5 Supplemental Table 5S-20 ([U.S. EPA, 2015i](#)).

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### 5.4.3 Birth Outcomes

6 This section discusses several categories of birth outcomes, including fetal growth  
7 ([Section 5.4.3.1](#)), preterm birth ([Section 5.4.3.2](#)), birth weight ([Section 5.4.3.3](#)), birth  
8 defects ([Section 5.4.3.4](#)), fetal mortality ([Section 5.4.3.5](#)), and infant mortality  
9 ([Section 5.4.3.6](#)).

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#### 5.4.3.1 Fetal Growth

10 Fetal growth can be difficult to quantify; typically, small for gestational age (SGA) or  
11 intra-uterine growth restriction (IUGR) are used. These designations, often used  
12 interchangeably, are defined as infants with a birth weight below the 10th percentile for  
13 gestational age, usually with consideration for sex and race as well. There are a number  
14 of limitations in using SGA/IUGR as a metric of poor fetal growth. One is that a  
15 percentile-based measure will always quantify a certain percentage of the infant  
16 population as growth restricted whether or not this is truly the case ([Wollmann, 1998](#)).  
17 For example, in term infants, it is unlikely that 10% are actually growth restricted.  
18 Whereas in preterm infants, it is likely that more than 10% are growth restricted;  
19 therefore, SGA cases would be overestimated in term infants and underestimated in  
20 preterm infants. In addition, exact definitions shift between studies and some studies use  
21 alternate definitions of SGA/IUGR. For example, some studies use the birth weight  
22 distribution of their study population for defining SGA, which will naturally not be  
23 identical for every study population, and others use country standards, likely to be more  
24 stable over time ([Le et al., 2012](#); [Brauer et al., 2008](#); [Liu et al., 2003](#)). An alternate  
25 approach to categorizing growth restriction is to use ultrasound images during gestation  
26 ([Woodruff et al., 2009](#)). This approach has the benefit of examining all fetuses with  
27 ultrasounds, being less subjective to population definition, and distinguishing true growth  
28 restriction from merely small-sized infants. However, not all women receive prenatal care  
29 and ultrasounds, leading to the possibility of selection bias.

30 Several studies report positive associations between fetal growth and SO<sub>2</sub>, although  
31 timing of exposure is inconsistent. A recent study conducted in Australia examined

1 ultrasound measures in midgestation in association with SO<sub>2</sub> exposures during early  
2 pregnancy ([Hansen et al., 2008](#)). [Hansen et al. \(2008\)](#) observed decreases in biparietal  
3 diameter and abdominal circumference with increases in SO<sub>2</sub> during the first 4 months of  
4 pregnancy [5-ppb SO<sub>2</sub> increase in 1st month: -4.25 mm (-6.81, -1.69) biparietal  
5 diameter; -9.31 mm (-19.31, 0.69) abdominal circumference]. Recent studies using the  
6 traditional definition of SGA/IUGR had mixed results. In Vancouver, increases in ORs  
7 for SGA were observed with entire pregnancy exposures ([Brauer et al., 2008](#)) and with  
8 1st month and 1st trimester exposures ([Liu et al., 2003](#)). [Rich et al. \(2009\)](#) used an  
9 alternate definition of SGA—having a growth ratio (infant birth weight divided by  
10 median study cohort birth weight) below 0.75 for very SGA (VSGA), and between  
11 0.75–0.85 for SGA—and observed elevated ORs with 1st trimester exposures for SGA,  
12 and 2nd and 3rd trimester exposures for VSGA. Other studies did not observe positive  
13 associations between fetal growth and SO<sub>2</sub>. In a study conducted in Italy, ([Capobussi et  
14 al., 2016](#)) observe a null association for SGA when SO<sub>2</sub> exposure was estimated for the  
15 entire pregnancy, but modest positive associations when exposure was averaged across  
16 the first or second trimester. Whereas a study conducted in Calgary, Edmonton, and  
17 Montreal, [Liu et al. \(2007\)](#) found lowered ORs for IUGR with exposures in months 1 to 5  
18 of pregnancy and no associations in months 6 to 9. Of the two recent studies in the U.S.,  
19 [Le et al. \(2012\)](#) observed generally null associations for SGA and 1st and last month  
20 exposures; ORs with trimester exposure windows were null, although ORs became  
21 elevated for the 2nd and 3rd trimesters after adjustment for CO, NO<sub>2</sub>, and PM<sub>10</sub>.

22 No recent animal studies evaluating fetal growth were identified.

23 In summary, there is inconsistent evidence for increased odds of fetal growth restriction  
24 with exposure to SO<sub>2</sub> during pregnancy, and the evidence lacks consistency in fetal  
25 growth definition/metric and in exposure timing. Mean SO<sub>2</sub> exposures for these studies  
26 are generally low, although all studies examine average daily SO<sub>2</sub> concentrations.  
27 Additionally, these studies do not provide evidence to help reduce uncertainty related to  
28 exposure measurement error, copollutant confounding, or the biological mechanism by  
29 which SO<sub>2</sub> could cause these effects. Studies examining the association between SO<sub>2</sub> and  
30 fetal growth can be found in Supplemental Table 5S-21 ([U.S. EPA, 2015j](#)).

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#### 5.4.3.2 Preterm Birth

31 Preterm birth (PTB), delivery that occurs before 37 weeks of completed gestation, is a  
32 marker for fetal underdevelopment and a risk factor for further adverse health outcomes  
33 (e.g., infant mortality, neurodevelopmental problems, growth issues) ([Mathews and  
34 MacDorman, 2010](#); [Saigal and Doyle, 2008](#); [IOM, 2007](#); [Gilbert et al., 2003](#)). PTB is

1 characterized by multiple etiologies (spontaneous, premature rupture of membranes, or  
2 medically induced), and identifying exact causes of PTB is difficult. It is likely that some  
3 mechanistic pathways are shared between the three groups; however, isolated causes are  
4 also likely to exist. Few, if any, studies distinguish between these three groups in  
5 examining associations between air pollution and PTB.

6 Given the uncertainty surrounding modes of action leading to PTB, many of the studies  
7 reviewed here consider both short- and long-term exposure periods. For example,  
8 exposure across all of gestation or during a particular trimester for long-term exposure  
9 windows, or weeks or days leading up to birth for short-term exposure windows. With  
10 near-birth exposure periods development will be at different points for term and preterm  
11 infants (e.g., exposure 2 weeks before birth is at 34 weeks for a 36-week PTB, and  
12 38 weeks for a 40-week term birth), which suggests the possibility of different modes of  
13 action for increases in risk observed with near-birth exposures compared to exposures in  
14 specific periods of fetal development.

15 There is evidence supporting a relationship between SO<sub>2</sub> and preterm birth, primarily  
16 with exposure near-birth and including both older and newer studies. Among a U.S. birth  
17 cohort, [Mendola et al. \(2016a\)](#) examined PTB and exposure to SO<sub>2</sub> during different  
18 periods before and during pregnancy, observing generally null results among both women  
19 with and without asthma, except for when exposure was limited to weeks near birth  
20 (specifically weeks 34 and 36) for which positive associations were observed among  
21 women with asthma, but not for women without asthma. Studies in Europe and Asia  
22 report increased ORs/RRs of PTB with exposures across pregnancy, although not  
23 consistently between studies ([Dibben and Clemens, 2015](#); [Zhao et al., 2011](#); [Leem et al.,  
24 2006](#); [Bobak, 2000](#); [Xu et al., 1995](#)). In a recent time-series analysis, [Zhao et al. \(2011\)](#)  
25 found increased RRs with SO<sub>2</sub> exposure days 0–3 lagged from birth, but SO<sub>2</sub> was also  
26 highly correlated with PM<sub>10</sub> (Pearson correlation coefficient = 0.75) and NO<sub>2</sub> (Pearson  
27 correlation coefficient = 0.84) in the study area. [Dibben and Clemens \(2015\)](#) used a  
28 pollution-climate model to assign SO<sub>2</sub> concentrations with high spatial resolution as well  
29 as incorporating daily activity data into the exposure and observed null associations with  
30 PTB and modest, positive associations with VPTB among births in Scotland. [Qian et al.  
31 \(2015\)](#) observed weak negative or null associations between SO<sub>2</sub> exposures and PTB  
32 across a range of different exposure windows among a birth cohort in Wuhan, China.

33 In the U.S. and Canada, studies of SO<sub>2</sub> and PTB in Pennsylvania ([Sagiv et al., 2005](#)) and  
34 Vancouver ([Liu et al., 2003](#)) found increased ORs with near-birth exposures [[Sagiv et al.  
35 \(2005\)](#): 6 week prebirth RR = 1.05 (1.00, 1.10); [Liu et al. \(2003\)](#): last month OR = 1.09  
36 (1.01, 1.19) per 5-ppb increase]. More recently, in a Detroit, MI cohort, [Le et al. \(2012\)](#)  
37 found similar associations for exposures in the last month of pregnancy [OR 4th to 1st

1 quartile: 1.07 (1.01, 1.14)]. Another Vancouver cohort, examining entire pregnancy  
2 exposure, only observed increases [OR = 1.03 (0.93, 1.15) per 5-ppb SO<sub>2</sub> increase] with  
3 PTB <30 weeks ([Brauer et al., 2008](#)). Recent time-series and case-crossover studies in  
4 Atlanta, GA and Brisbane, Australia observed null associations for both 1st month and  
5 near-birth exposures using 1-h max SO<sub>2</sub> [exposure during last week of pregnancy RR per  
6 5-ppb increase = 0.99 (0.98, 1.01)] ([Darrow et al., 2009](#)) and SO<sub>2</sub> concentrations  
7 24–48 hours preceding the onset of labor ([Li et al., 2016](#)). Finally, a cross-sectional study  
8 of PTB across the U.S. reported that SO<sub>2</sub> showed “nonsignificant” effects with PTB for  
9 exposures during the month of birth ([Trasande et al., 2013](#)). In contrast, a recent study  
10 conducted in Italy observed negative associations between SO<sub>2</sub> exposure averaged across  
11 the entire pregnancy as well as each trimester and PTB, suggesting the SO<sub>2</sub> exposure was  
12 associated with longer gestation ([Capobussi et al., 2016](#)).

13 No recent animal studies evaluating preterm birth were identified.

14 In summary, there is some evidence for an association between exposure to SO<sub>2</sub> and  
15 preterm birth particularly with near-birth exposure windows. Studies examining PTB  
16 primarily used average daily SO<sub>2</sub>. The one study that examined 1-h max SO<sub>2</sub> found no  
17 associations for PTB. Recent studies do not provide evidence to help reduce uncertainty  
18 related to exposure measurement error, copollutant confounding, or the biological  
19 mechanism by which SO<sub>2</sub> could cause preterm birth. Studies are characterized in  
20 Supplemental Table 5S-22 ([U.S. EPA, 2015k](#)).

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### 5.4.3.3 Birth Weight

21 Birth weight is a measure of fetal growth and an important indicator of future infant and  
22 child health. Birth weight is determined by gestational age and intra-uterine growth, as  
23 well as maternal, placental, fetal, and environmental factors. Vulnerability to  
24 environmental insults affecting birth weight may occur throughout pregnancy.

25 Implantation or formation of the placenta may be disrupted in the earliest weeks of  
26 pregnancy, leading to decreased fetal nutrition throughout pregnancy; or inflammation  
27 might result in constriction of the umbilical cord during the later trimesters resulting in  
28 poor fetal nutrition. As the largest gains in birth weight occur during the last weeks of  
29 gestation, this may be a particularly vulnerable period for birth weight outcomes.

30 Information on birth weight is routinely collected for vital statistics; given that measures  
31 of birth weight do not suffer the same uncertainties as gestational age or growth  
32 restriction, it is one of the most studied outcomes within air pollution and reproductive  
33 health. Birth weight may be examined as a continuous outcome or dichotomous outcome  
34 as low birth weight (LBW) (less than 2,500 g or 5 lbs, 8 oz).

1 Studies examining LBW have found elevated ORs with exposures in the first trimester or  
2 first month ([Dugandzic et al., 2006](#); [Lee et al., 2003](#); [Liu et al., 2003](#); [Ha et al., 2001](#)) and  
3 with entire pregnancy exposures ([Capobussi et al., 2016](#); [Dibben and Clemens, 2015](#);  
4 [Yorifuji et al., 2015a](#); [Ebisu and Bell, 2012](#); [Kumar, 2012](#); [Morello-Frosch et al., 2010](#)).  
5 In the two studies that examined distance to monitor, using concentrations from closer  
6 monitors lead to stronger effect estimates ([Kumar, 2012](#); [Morello-Frosch et al., 2010](#)).  
7 Some studies examining entire pregnancy exposure have also observed null associations  
8 between SO<sub>2</sub> and LBW ([Brauer et al., 2008](#); [Bell et al., 2007](#)).

9 Studies examining continuous birth weight ( $\Delta$ g) have inconsistent results. In a northeast  
10 U.S. population, [Bell et al. \(2007\)](#) observed no association with change in birth weight  
11 for entire pregnancy exposure [-2.711 g (-13.253, 7.831) per 5 ppb SO<sub>2</sub>], including in a  
12 stratified analysis of white and black mothers. [Kumar \(2012\)](#) reported results that shifted  
13 around the null based on distance from monitor in Chicago; some effects were positive,  
14 and some negative but all had wide confidence intervals. And, in a cross-sectional study  
15 across the county, [Trasande et al. \(2013\)](#) reported only “nonsignificant” effects for SO<sub>2</sub>.  
16 One recent California cohort study reported increases in birth weight with increases in  
17 SO<sub>2</sub> exposure in entire pregnancy and first trimester, although effects were reduced with  
18 use of closer monitors ([Morello-Frosch et al., 2010](#)). A recent Texas study observed  
19 decreases in birth weight with county average SO<sub>2</sub> exposure for the entire pregnancy  
20 [-15.594 g (-25.344, -5.844)] ([Geer et al., 2012](#)). A study in Beijing during the summer  
21 Olympics of 2008 found increased SO<sub>2</sub> in the 8th month of pregnancy associated with  
22 decrements in birth weight; however, SO<sub>2</sub> was highly correlated with PM<sub>2.5</sub> and CO,  
23 which showed similar patterns of effect ([Rich et al., 2015](#)). Finally, a recent study in  
24 Atlanta found decreases in birth weight with increases in 3rd trimester 1-h max SO<sub>2</sub>  
25 ([Darrow et al., 2011](#)). This effect was stronger in non-Hispanic white and Hispanic  
26 mothers than non-Hispanic black mothers ([Darrow et al., 2011](#)).

27 No recent animal studies evaluating birth weight-related outcomes were identified. In  
28 laboratory animals from an older study, exposure to SO<sub>2</sub> affected birth outcomes in adult  
29 female rodents and their offspring. Adult female albino rats were exposed to either  
30 0.057 ppm or 1.5 ppm SO<sub>2</sub> by inhalation for 72 days ([Mamatsashvili, 1970b](#)). At birth,  
31 litter sizes were significantly increased in number from dams that were exposed to SO<sub>2</sub>  
32 versus control dams ([Table 5-37](#)).

33 In summary, there is some evidence that LBW may be associated with SO<sub>2</sub>, while  
34 evidence for an association with change in birth weight is inconsistent. Overall, the  
35 results of studies of LBW and birth weight remain inconsistent and these do not provide  
36 evidence to help reduce uncertainty related to exposure measurement error, copollutant  
37 confounding, or the biological mechanism by which SO<sub>2</sub> could cause these effects.

1 Studies for both LBW and change in birth weight can be found in Supplemental  
2 Table 5S-23 ([U.S. EPA, 2015l](#)).

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#### 5.4.3.4 Birth Defects

3 Birth defects are structural and functional abnormalities that can cause physical disability,  
4 intellectual disability, and other health problems. They are a leading cause of infant  
5 mortality and developmental disability in the U.S. ([Mai et al., 2016](#)). Since 2008, there  
6 have been several studies examining birth defects and SO<sub>2</sub> during pregnancy, particularly  
7 during weeks 3–8 of gestation, which is thought to be highly vulnerable to insults  
8 resulting in birth defects. Because birth defects as a whole are rare and specific birth  
9 defects are rarer, these studies often have effect estimates with very wide confidence  
10 intervals. Individual studies often look at different types of birth defects, meaning the  
11 body of work examining any one birth defect may still be limited. Cardiac birth defects  
12 and oral cleft defects are the most commonly studied anomalies. However, results (even  
13 for these defects) are inconsistent across studies. For example, odds of ventricular septal  
14 defects have been found to be increased ([Gianicolo et al., 2014](#); [Stingone et al., 2014](#);  
15 [Agay-Shay et al., 2013](#); [Gilboa et al., 2005](#)), decreased ([Hwang et al., 2015b](#); [Dadvand et](#)  
16 [al., 2011a, b](#); [Rankin et al., 2009](#)), and null ([Strickland et al., 2009](#)) with increases in SO<sub>2</sub>  
17 exposure. Odds of cleft lip with or without cleft palate have been found to be increased  
18 ([Zhu et al., 2015](#)), decreased ([Hwang and Jaakkola, 2008](#); [Gilboa et al., 2005](#)), or null  
19 ([Dolk et al., 2010](#); [Rankin et al., 2009](#)) with increases in SO<sub>2</sub> exposure. A single study of  
20 limb deformities found increased odds with exposure to SO<sub>2</sub> during weeks 9–12 of  
21 pregnancy ([Lin et al., 2014](#)). Two studies examining repeating chromosomal defects  
22 found no association or correlation between trisomy 21 or any sperm disomy and SO<sub>2</sub>  
23 ([Chung et al., 2014](#); [Jurewicz et al., 2014](#)). Studies of any congenital anomaly in Israel  
24 and China have reported inverse associations with increasing SO<sub>2</sub> ([Farhi et al., 2014](#);  
25 [Liang et al., 2014](#)).

26 No recent animal studies evaluating birth defects were identified.

27 In summary, results for birth defects are either inconsistent across studies or limited in  
28 number of studies. Studies of birth defects and SO<sub>2</sub> are characterized in Supplemental  
29 Table 5S-24 ([U.S. EPA, 2015m](#)).

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#### 5.4.3.5 Fetal Mortality

30 Fetal mortality or stillbirth is the intra-uterine death of a fetus. In most areas fetal deaths  
31 are only reported after 20 weeks of completed gestation; this leads to potential bias, as the

1 population at risk of fetal death is any conception but the actual measured population is  
2 only those fetuses reaching at least 20 weeks gestational age. A single recent case-control  
3 study of spontaneous abortion occurring before 14 weeks of gestation found no  
4 associations with SO<sub>2</sub> exposures determined by time-weighted concentrations for  
5 residence and workplace ([Moridi et al., 2014](#)). A recent large California cohort found no  
6 associations between stillbirth and increasing SO<sub>2</sub> exposure ([Green et al., 2015](#)). In recent  
7 studies of a New Jersey population examining both long-term and short-term exposure  
8 windows, ORs for fetal death were elevated with a 2-day lag [OR per 5-ppb increase in  
9 SO<sub>2</sub>: 1.12 (1.02, 1.24)] and with exposures across pregnancy and in each trimester,  
10 particularly the 3rd trimester [OR per 5-ppb increase in SO<sub>2</sub>: 1.47 (1.05, 1.69)] ([Faiz et](#)  
11 [al., 2013](#); [Faiz et al., 2012](#)). [Hwang et al. \(2011\)](#) examined fetal mortality among term  
12 and preterm deliveries in Taiwan, finding elevated associations for exposures during the  
13 1st trimester only among preterm deliveries. Other studies have also found increased  
14 associations between SO<sub>2</sub> and fetal mortality, although mean SO<sub>2</sub> concentrations were  
15 higher in these studies ([Hou et al., 2014](#); [Pereira et al., 1998](#)). [Pereira et al. \(1998\)](#)  
16 observed elevated RRs in a São Paulo, Brazil time series with short-term exposure.  
17 A recent study by [Enkhmaa et al. \(2014\)](#) found very strong correlations between seasonal  
18 SO<sub>2</sub> and fetal death, and [Hou et al. \(2014\)](#) found elevated ORs with long-term exposures  
19 around the time of conception. Although [Hou et al. \(2014\)](#)'s models were unadjusted for  
20 confounding factors and confidence intervals were very wide. In the study by [Enkhmaa et](#)  
21 [al. \(2014\)](#), other pollutants also showed very strong correlations and were highly  
22 correlated with one another.

23 No recent animal studies evaluating fetal mortality were identified.

24 In summary, although few in number, studies of fetal mortality and SO<sub>2</sub> show elevated  
25 associations for both short- and long-term exposures. However, these studies are limited  
26 by the uncertainties associated reproductive and developmental outcomes identified in the  
27 2008 SO<sub>x</sub> ISA. Studies are characterized in Supplemental Table 5S-25 ([U.S. EPA,](#)  
28 [2015n](#)).

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#### 5.4.3.6 Infant Mortality

29 Studies of infant mortality and SO<sub>2</sub> are limited in number. In a U.S. study, [Woodruff et](#)  
30 [al. \(2008\)](#) observed increased ORs for respiratory-related post-neonatal infant mortality  
31 with long-term (2 months) exposure increases in county-level SO<sub>2</sub> concentrations  
32 [OR = 1.09 (0.89, 1.36) per 5-ppb increase]. This association remained after adjusting for  
33 other pollutants. A time-series study in Seoul, South Korea observed increased RRs for  
34 all cause post-neonatal infant mortality with short-term SO<sub>2</sub> exposure, although exact

1 timing of exposure was unclear ([Son et al., 2008](#)). No recent animal studies evaluating  
2 postnatal mortality were identified. Studies are characterized in Supplemental  
3 Table 5S-25 ([U.S. EPA, 2015n](#)).

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## 5.4.4 Developmental Outcomes

### 5.4.4.1 Respiratory Outcomes

4 Recent studies examined asthma onset in association with early life exposure to SO<sub>2</sub>.  
5 [Clark et al. \(2010\)](#), [Liu et al. \(2016\)](#), [Deng et al. \(2015b\)](#), and [Deng et al. \(2015a\)](#)  
6 observed elevated ORs for asthma with SO<sub>2</sub> exposure during pregnancy and the first year  
7 of life. [Nishimura et al. \(2013\)](#) observed elevated ORs for asthma with SO<sub>2</sub> exposure in  
8 the first 3 years of life, but not the first year of life alone. Asthma onset is covered in  
9 further detail in [Section 5.2.1.2](#).

10 In a time-series study, [Dales et al. \(2006\)](#) investigated neonatal hospitalizations due to  
11 respiratory causes in Atlanta, GA; they observed elevated ORs with 2-day lagged SO<sub>2</sub>  
12 exposure. After adjustment for gaseous copollutants, confidence intervals for associations  
13 with gaseous pollutants and PM<sub>10</sub> were very large, but effect estimates remained elevated.  
14 Hospitalizations due to respiratory causes are covered in [Section 5.2.1.6](#).

15 In summary, there is some evidence for an association between gestational and early-life  
16 exposure to SO<sub>2</sub> and respiratory health effects later in life, although evidence is limited  
17 and exposure windows are uncertain. Key studies are summarized in [Table 5-36](#).

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### 5.4.4.2 Other Developmental Effects

18 Studies examining other developmental exposures are limited in number. A recent study  
19 examined SO<sub>2</sub> exposure with apnea and bradycardia in a subpopulation of infants in  
20 Atlanta, and observed no association for either health outcome ([Peel et al., 2011](#)). [Huang  
21 et al. \(2015a\)](#) observed no associations between prenatal and early life SO<sub>2</sub> exposures and  
22 atopic dermatitis among infants in Taiwan. [Poursafa et al. \(2016\)](#) examined the  
23 association between SO<sub>2</sub> exposure during pregnancy and markers of endothelial  
24 disfunction (i.e., ICAM-1, V-CAM-1, endothelin-1) in cord blood. They observed a  
25 positive association with endothelin-1, but not for other markers of endothelial  
26 disfunction. Among a Japanese cohort, prenatal exposure to SO<sub>2</sub> was associated with  
27 verbal and fine motor delays assessed at ages 2.5 and 5.5 years ([Yorifuji et al., 2015b](#)). In  
28 an older study from the animal toxicology literature, adult female albino rats were

1 exposed to either 0.057 ppm or 1.5 ppm SO<sub>2</sub> by inhalation, 12 hours/day for 72 days  
2 ([Mamatsashvili, 1970b](#)). Changes in offspring postnatal growth or body weight over time  
3 were reported with 1.5-ppm exposure.

4 Sulfur dioxide-dependent synaptic injury was measured in adolescent male rats exposed  
5 to 1.24 ppm SO<sub>2</sub> for 6 hours/day for 90 days ([Yun et al., 2013](#)). Nonsignificant  
6 morphological changes were seen in the hippocampal synaptic junctions using  
7 transmission electron microscopy. In the hippocampus, the synaptic vesicle membrane  
8 protein synaptophysin (SYP) was significantly downregulated as was ERK1/2  
9 phosphorylation. Phosphorylation is an important contributor to synaptic plasticity. Thus,  
10 SO<sub>2</sub> exposure in the adolescent rat contributes to downregulation of synaptic vesicle  
11 protein SYP and decreased ERK1/2 phosphorylation, indicative of disruption at the  
12 hippocampal synapse.

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#### 5.4.5 Summary and Causal Determination

13 Overall the evidence is inadequate to infer a causal relationship between exposure to SO<sub>2</sub>  
14 and reproductive and developmental outcomes. This is consistent with the 2008 ISA for  
15 Sulfur Oxides, which also concluded the evidence was inadequate to infer the presence or  
16 absence of a causal relationship with reproductive and developmental effects. All  
17 available evidence, including more than 50 recent studies, examining the relationship  
18 between exposure to SO<sub>2</sub> and reproductive and developmental effects was evaluated  
19 using the framework described in the [Preamble](#) to the ISAs ([U.S. EPA, 2015b](#)). The key  
20 evidence as it relates to the causal framework is summarized in [Table 5-38](#).

21 There are several well-designed, well-conducted epidemiologic studies, many described  
22 in papers published since the previous ISA, that indicate an association between SO<sub>2</sub> and  
23 reproductive and developmental health outcomes; the bulk of the evidence exists for  
24 adverse birth outcomes. For example, several high quality studies reported positive  
25 associations between SO<sub>2</sub> exposures during pregnancy and fetal growth metrics ([Le et al.,  
26 2012](#); [Rich et al., 2009](#); [Brauer et al., 2008](#); [Liu et al., 2003](#)), preterm birth ([Mendola et  
27 al., 2016a](#); [Le et al., 2012](#); [Zhao et al., 2011](#); [Sagiv et al., 2005](#); [Liu et al., 2003](#)), birth  
28 weight ([Ebisu and Bell, 2012](#); [Darrow et al., 2011](#); [Morello-Frosch et al., 2010](#); [Liu et al.,  
29 2003](#)), and fetal and infant mortality ([Faiz et al., 2012](#); [Hwang et al., 2011](#); [Woodruff et  
30 al., 2008](#)). However, the evidence is not entirely consistent, and has not substantially  
31 reduced any of the uncertainties connected with the associations observed between  
32 exposure to SO<sub>2</sub> and birth outcomes that were identified in the previous ISA.

**Table 5-38 Summary of evidence inadequate to infer a causal relationship between sulfur dioxide exposure and reproductive and developmental effects.**

Rationale for Causal Determination <sup>a</sup>	Key Evidence <sup>b</sup>	Key References <sup>b</sup>	SO <sub>2</sub> Concentrations Associated with Effects <sup>c</sup>
<b>Overall reproductive and developmental effects—inadequate to infer a causal relationship</b>			
Evidence from multiple epidemiologic studies of preterm birth is generally supportive but key uncertainties remain.	Consistent positive associations observed with near-birth exposures to SO <sub>2</sub> and preterm birth after adjustment for common potential confounders. Associations not evaluated in copollutant models.	<a href="#">Liu et al. (2003)</a>	Mean: 4.9 ppb
		<a href="#">Sagiv et al. (2005)</a>	Mean: 7.9 ppb
		† <a href="#">Le et al. (2012)</a>	Mean: 5.8 ppb
		† <a href="#">Mendola et al. (2016a)</a>	Mean: 4.0 ppb
<a href="#">Section 5.4.3.2</a>			
Limited and inconsistent epidemiologic evidence for other birth outcomes	Several studies show positive associations with fetal growth metrics, although definitions vary across studies, and timing of exposure is inconsistent. Associations not evaluated in copollutant models	<a href="#">Section 5.4.3.1</a>	Means: 4.9–5.8 ppb
		<a href="#">Section 5.4.3.3</a>	Means: 2.1–13.2 ppb
	Limited and inconsistent epidemiologic evidence for associations with various birth defects	<a href="#">Section 5.4.3.4</a>	Reported means: 1.9–6
	Limited number of studies of SO <sub>2</sub> and fetal death, positive associations observed across studies, although timing of exposure and outcome definitions are inconsistent  Limited evidence for an association with SO <sub>2</sub> in respiratory related infant mortality	<a href="#">Section 5.4.3.6</a>	Mean: 5.7 ppb Mean: 5.8 ppb Mean: 5.9 ppb Mean: 3 ppb

**Table 5-38 (Continued): Summary of evidence inadequate to infer a causal relationship between sulfur dioxide exposure and reproductive and developmental effects.**

Rationale for Causal Determination <sup>a</sup>	Key Evidence <sup>b</sup>	Key References <sup>b</sup>	SO <sub>2</sub> Concentrations Associated with Effects <sup>c</sup>
	Limited evidence for positive associations between prenatal/early life exposures and childhood respiratory outcomes	<a href="#">Section 5.4.4.1</a>	Means: 2–4.3 ppb
Limited evidence for key events in proposed mode of action	Altered menstrual function, fetal growth, and birth weight outcomes with impaired postnatal growth in in utero exposed pups	<a href="#">Mamatsashvili (1970a)</a>	57 or 1,427 ppb
Lack of evidence from epidemiologic studies to support an association of SO <sub>2</sub> exposure with detrimental effects on fertility or pregnancy	A limited number of studies on fertility and pregnancy outcomes show no associations with SO <sub>2</sub> .	<a href="#">Section 5.4.4.1</a>	Mean 8.4–59 ppb
Uncertainty regarding potential confounding by copollutants	Limited adjustment for copollutants, with no clear directionality or trends for effect estimate shifts after adjustment	†( <a href="#">Faiz et al. (2013)</a> ; <a href="#">Slama et al. (2013)</a> ; <a href="#">Le et al. (2012)</a> )	
Uncertainty regarding exposure measurement error	Central site monitors subject to some degree of exposure error. Spatial and temporal heterogeneity may introduce exposure error in long-term effects and bias could be toward or away from the null.	<a href="#">Chapter 3</a> <a href="#">Section 3.4.4.2</a>	
Uncertainty regarding exposure timing for specific outcomes.	Associations of exposure to SO <sub>2</sub> at particular windows during pregnancy are inconsistent between studies and across outcomes.		

SO<sub>2</sub> = sulfur dioxide.

<sup>a</sup>Based on aspects considered in judgments of causality and weight of evidence in causal framework in the [Preamble](#) to the ISAs ([U.S. EPA, 2015b](#)).

<sup>b</sup>Describes the key evidence and references contributing most heavily to causal determination and where applicable to uncertainties and inconsistencies. References to earlier sections indicate where full body of evidence is described.

<sup>c</sup>Describes the SO<sub>2</sub> concentrations with which the evidence is substantiated (for experimental studies, below 2,000 ppb).

†Studies published since the 2008 ISA for Sulfur Oxides.

1 One uncertainty is timing of exposure, wherein associations remain inconsistent among  
2 studies and across outcomes. For example, some studies observe the strongest  
3 associations when exposure is averaged over the entire pregnancy, while others observe  
4 the strongest association when exposure is averaged over either the first, second, or third  
5 trimester. As an exception to this, studies of PTB generally observed positive associations  
6 between near-birth exposures (e.g., last month of gestation, same, or 3-day lag from birth)  
7 ([Mendola et al., 2016a](#); [Le et al., 2012](#); [Zhao et al., 2011](#); [Sagiv et al., 2005](#); [Liu et al.,](#)  
8 [2003](#)).

9 Another uncertainty centers on spatial and temporal variability in SO<sub>2</sub> exposures. SO<sub>2</sub> is a  
10 temporally and spatially heterogeneous pollutant; it is difficult to accurately estimate for  
11 “long-term” exposures, and there is the potential for exposure measurement error in  
12 long-term SO<sub>2</sub> exposures to bias estimates toward or away from the null ([Section 3.5](#)).  
13 None of the epidemiologic studies made corrections or adjustments for exposure  
14 measurement error or accounted for the potential for bias away from the null, the  
15 potential for which has been demonstrated in simulation studies (see [Section 3.4.4.2](#)).  
16 Current epidemiologic methods are not able to disentangle whether associations are due  
17 to extended exposure to moderate concentrations of SO<sub>2</sub> or repeated short-term exposure  
18 to peaks in SO<sub>2</sub> concentration.

19 Potential confounding by copollutants may explain some of the observed associations and  
20 cannot be ruled out. SO<sub>2</sub> is part of a mix of ambient air pollution; SO<sub>2</sub> shares sources with  
21 particulate matter and is chemically linked to sulfate. Few studies evaluate or provide  
22 information that would inform the independent effect of SO<sub>2</sub> in the context of the greater  
23 air pollution mixture, and of those that do, no clear trends for the effects of copollutant  
24 adjustment are apparent ([Faiz et al., 2013](#); [Slama et al., 2013](#); [Le et al., 2012](#)).

25 There is insufficient information on potential modes of action of SO<sub>2</sub> on reproductive  
26 outcomes at relevant exposure levels for this ISA ([Chapter 4](#)). In a single older study  
27 from [Mamatsashvili \(1970a\)](#), SO<sub>2</sub> inhalation exposure in laboratory rodents demonstrated  
28 reproductive changes in exposed females and their offspring, altered birth outcomes, and  
29 developmental effects. The specific outcomes affected after SO<sub>2</sub> exposure included  
30 altered estrus cycle length of F0 and F1 generations, decrements in offspring body weight  
31 gain or growth after in utero exposure, and changes in litter size. The majority of the  
32 remaining animal toxicological evidence for reproductive and developmental effects is  
33 for exposure at 5,000 ppb or greater, doses which are beyond the scope of this document.

34 Since the 2008 ISA for Sulfur Oxides, researchers have begun evaluating more health  
35 outcomes, including fertility, effects on pregnancy (e.g., pre-eclampsia, gestational  
36 diabetes), and developmental effects. For each of these individual outcomes the literature  
37 base is small, but new studies are quickly accumulating. However, at present there is little

1 coherence or consistency among epidemiologic and toxicological studies for these  
2 outcomes. In general, it is challenging to synthesize study findings on the wide variety of  
3 health outcomes collected under the reproductive and developmental effects heading.  
4 Given the wide variety of potential mechanisms or adverse outcome pathways that could  
5 affect this breadth of outcomes, coherence is unlikely to be reached given the limited  
6 literature base.

7 The state of California, under the auspices of Proposition 65, the California Safe  
8 Drinking Water and Toxic Enforcement Act of 1986, has listed sulfur dioxide as a  
9 chemical known to cause developmental toxicity based on evidence from laboratory  
10 animal studies and epidemiologic studies, with the strongest evidence from IUGR. SO<sub>2</sub> is  
11 not listed as a reproductive toxicant under Proposition 65; much of this evidence is from  
12 toxicological studies with exposure to SO<sub>2</sub> at 5,000 ppb or greater (beyond the scope of  
13 this ISA). Effects seen at the higher doses include male reproductive effects on sperm and  
14 fecundity, as well as oxidative damage to the male reproductive organs, changes in birth  
15 weight or litter size, delayed reflexes in early life, and aberrant behavior of pups after in  
16 utero exposure. Epidemiologic evidence used for this listing is also evaluated under  
17 differing criteria than are employed for the ISA.

18 Overall, many uncertainties remain when evaluating the evidence for these health  
19 endpoints; therefore, the evidence is inadequate to infer a causal relationship between  
20 exposure to SO<sub>2</sub> and reproductive and developmental outcomes.

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## 5.5 Mortality

### 5.5.1 Short-Term Exposure

#### 5.5.1.1 Introduction

21 Earlier studies that examined the association between short-term SO<sub>x</sub> exposure, mainly  
22 SO<sub>2</sub>, and total mortality were limited to historical data on high air pollution episodes  
23 ([U.S. EPA, 1982a](#)). These studies were unable to decipher whether the associations  
24 observed were due to particle pollution or SO<sub>2</sub>. Additional studies evaluated in the 1986  
25 Second Addendum to the 1982 AQCD ([U.S. EPA, 1986b](#)) further confirm the findings of  
26 these initial studies, but were still unable to address uncertainties and limitations related  
27 to examining the effect of SO<sub>2</sub> exposure on mortality, especially at lower concentrations.

1 In the 2008 SO<sub>x</sub> ISA ([U.S. EPA, 2008d](#)), a larger body of literature was available to  
2 assess the relationship between short-term SO<sub>2</sub> exposures and mortality; however, these  
3 studies were still limited in that they primarily focused on PM, with SO<sub>2</sub> only being  
4 examined in single-pollutant models. These studies found that excess risk estimates for  
5 total mortality due to short-term SO<sub>2</sub> exposure from multicity studies and meta-analyses  
6 generally ranged from 0.4 to 2.0% for a 10-ppb increase in 24-h avg SO<sub>2</sub> concentrations.  
7 These associations were primarily observed at mean 24-h avg SO<sub>2</sub> concentrations  
8 <15 ppb. Studies that examined cause-specific mortality found evidence of risk estimates  
9 larger in magnitude for respiratory and cardiovascular mortality compared to total  
10 mortality with the largest associations for respiratory mortality. The larger  
11 SO<sub>2</sub>-respiratory mortality associations observed in the epidemiologic literature were  
12 coherent with the scientific evidence providing stronger support for SO<sub>2</sub> effects on  
13 respiratory morbidity compared to cardiovascular morbidity ([U.S. EPA, 2008d](#)).

14 An examination of potential copollutant confounding of the SO<sub>2</sub>-mortality relationship  
15 was sparse. Studies evaluated in the 2008 SO<sub>x</sub> ISA found that SO<sub>2</sub>-mortality risk  
16 estimates from copollutant models were robust, but imprecise. An additional study that  
17 examined the potential interaction between copollutants [i.e., SO<sub>2</sub> and black smoke (BS)]  
18 did not find evidence of interaction when stratifying days by high and low concentrations  
19 of BS ([Katsouyanni et al., 1997](#)). Of the studies evaluated only the Air Pollution and  
20 Health: A European Approach (APHEA) study examined seasonality and potential effect  
21 modifiers of the SO<sub>2</sub>-mortality relationship, and provided initial evidence of mortality  
22 effects being larger during the warm season and that geographic location may influence  
23 city-specific SO<sub>2</sub>-mortality risk estimates, respectively ([Katsouyanni et al., 1997](#)).  
24 The consistent, positive SO<sub>2</sub>-mortality associations observed across studies were  
25 supported by an intervention study conducted in Hong Kong that examined the health  
26 impact of converting to fuel oil with low sulfur content and found evidence suggesting  
27 that a reduction in SO<sub>2</sub> concentrations leads to a reduction in mortality ([Hedley et al.,  
28 2002](#)). Overall, the relatively sparse number of studies that examined the relationship  
29 between short-term SO<sub>2</sub> exposure and mortality along with the limited data with regard to  
30 potential copollutant confounding resulted in the 2008 SO<sub>x</sub> ISA concluding that the  
31 collective evidence is “suggestive” of a causal relationship between short-term SO<sub>2</sub>  
32 exposure and mortality.

33 Since the completion of the 2008 SO<sub>x</sub> ISA ([U.S. EPA, 2008d](#)), there continues to be a  
34 growing body of epidemiologic literature that has examined the association between  
35 short-term SO<sub>2</sub> exposure and mortality. However, similar to the collection of studies  
36 evaluated in the 2008 SO<sub>x</sub> ISA ([U.S. EPA, 2008d](#)), most of the recent studies do not  
37 focus specifically on the SO<sub>2</sub>-mortality relationship, but instead on PM or O<sub>3</sub>. Of the  
38 studies identified, a limited number have been conducted in the U.S., Canada, and

1 Europe, with the majority being conducted in Asia due to the increased focus on  
2 examining the effect of air pollution on health in developing countries. Although these  
3 studies are informative when evaluating the collective evidence, the interpretation of  
4 these studies in the context of results from studies conducted in the U.S., Canada, and  
5 Western Europe requires caution. This is because studies conducted in Asia encompass  
6 cities with meteorological, outdoor air pollution (e.g., concentrations, mixtures, and  
7 transport of pollutants), and sociodemographic (e.g., disease patterns, age structure, and  
8 socioeconomic variables) ([Chen et al., 2012b](#); [Kan et al., 2010a](#); [Wong et al., 2008b](#))  
9 characteristics that differ from cities in North America and Europe, potentially limiting  
10 the generalizability of results from studies of Asian cities to other cities.

11 As detailed in previous ISAs [e.g., [U.S. EPA \(2013c\)](#)], this section focuses primarily on  
12 multicity studies because they examine the association between short-term SO<sub>2</sub> exposure  
13 and mortality over a large geographic area using a consistent statistical methodology,  
14 which avoids the potential publication bias often associated with single-city studies ([U.S.  
15 EPA, 2008d](#)). However, where applicable single-city studies are evaluated that  
16 encompass a long study-duration, provide additional evidence indicating that a specific  
17 population or lifestage is at increased risk of SO<sub>2</sub>-related mortality, or address a limitation  
18 or uncertainty in the SO<sub>2</sub>-mortality relationship not represented in multicity studies.  
19 The remaining studies identified are not evaluated in this section due to issues associated  
20 with study design or insufficient sample size, and are detailed in Supplemental  
21 Table 5S-26 ([U.S. EPA, 2015o](#)).

22 The organization of the material on short-term SO<sub>2</sub> exposure and mortality is as follows.  
23 [Section 5.5.1.2](#) evaluates studies that examined the association between short-term SO<sub>2</sub>  
24 exposure and mortality, with the remaining sections addressing key limitations and  
25 uncertainties in the SO<sub>2</sub>-mortality relationship that were evident at the completion of the  
26 2008 SO<sub>x</sub> ISA ([U.S. EPA, 2008d](#)). Subsequent sections evaluate whether there is  
27 evidence of: confounding (i.e., copollutants and seasonal/temporal) ([Section 5.5.1.3](#)),  
28 effect modification (i.e., sources of heterogeneity in risk estimates across cities or within  
29 a population) ([Section 5.5.1.4](#)), modification of the SO<sub>2</sub>-mortality association including  
30 seasonal heterogeneity ([Section 5.5.1.5](#)), and the SO<sub>2</sub>-mortality C-R relationship and  
31 related issues, such as the lag structure of associations ([Section 5.5.1.5](#)).

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### 5.5.1.2 Associations between Short-Term Sulfur Dioxide Exposure and Mortality in All-Year Analyses

32 Multicity studies and meta-analyses evaluated in the 2008 SO<sub>x</sub> ISA reported consistent,  
33 positive associations between short-term SO<sub>2</sub> exposure and total mortality in all-year  
34 analyses ([U.S. EPA, 2008d](#)). Although only a small number of multicity studies have

1 been conducted since the completion of the 2008 SO<sub>x</sub> ISA, these studies, as well as a  
 2 meta-analysis of studies conducted in Asia ([Atkinson et al., 2012](#)), build upon and  
 3 provide additional evidence for an association between short-term SO<sub>2</sub> exposure and total  
 4 mortality ([Figure 5-17](#)). Air quality characteristics and study specific details for the  
 5 studies evaluated in this section are provided in [Table 5-39](#).

**Table 5-39 Air quality characteristics of multicity studies and meta-analyses evaluated in the 2008 SO<sub>x</sub> ISA and recently published multicity studies and meta-analyses.**

Study	Location	Years	Mortality Outcome(s)	Averaging Time	Mean Concentration ppb	Upper Percentile Concentrations ppb
<b>North America</b>						
<a href="#">Dominici et al. (2003)</a>	72 U.S. cities (NMMAPS) <sup>a</sup>	1987–1994	Total	24-h avg	0.4–14.2	---
<a href="#">Burnett et al. (2004)</a>	12 Canadian cities	1981–1999	Total cardiovascular respiratory	24-h avg	0.9–9.6	---
† <a href="#">Moolgavkar et al. (2013)</a>	85 U.S. cities (NMMAPS) <sup>e</sup>	1987–2000	Total	24-h avg	---	---
<b>Europe</b>						
<a href="#">Katsouyanni et al. (1997)</a>	12 European cities (APHEA-1)	1980–1992	Total	24-h avg	5.0–28.2 <sup>b</sup>	90th: 17.2–111.8
<a href="#">Biggeri et al. (2005)</a>	Eight Italian cities (MISA-1)	1990–1999	Total cardiovascular respiratory	24-h avg	2.5–15.6	95th: 6.0–50.1 Max: 7.1–111.0
<a href="#">Hoek (2003)</a>	Netherlands	1986–1994	Total cardiovascular respiratory	24-h avg	3.5–5.6	---
† <a href="#">Berglind et al. (2009)</a>	Five European cities <sup>f</sup>	1992–2002	Total	24-h avg	1.0–1.6 <sup>g</sup>	---
† <a href="#">Bellini et al. (2007)</a>	15 Italian cities (MISA-2)	1996–2002	Total cardiovascular respiratory	24-h avg	---	---

**Table 5-39 (Continued: Air quality characteristics of multicity studies and meta analyses evaluated in the 2008 SO<sub>x</sub> ISA and recently published multicity studies and meta analyses.**

Study	Location	Years	Mortality Outcome(s)	Averaging Time	Mean Concentration ppb	Upper Percentile Concentrations ppb
<b>Asia</b>						
<a href="#">†Kan et al. (2010b); Wong et al. (2008b); Wong et al. (2010)</a>	Four Asian cities (PAPA)	1996–2004 <sup>h</sup>	Total cardiovascular respiratory	24-h avg	5.0–17.1	75th: 6.0–21.5 Max: 23.4–71.7
<a href="#">†Chen et al. (2012b)</a>	17 Chinese cities (CAPES)	1996–2010 <sup>i</sup>	Total cardiovascular respiratory	24-h avg	6.1–38.2	75th: 6.5–56.1 Max: 25.2–298.5
<a href="#">†Chen et al. (2013)</a>	Eight Chinese cities	1996–2008 <sup>i</sup>	Stroke	24-h avg	6.1–32.1	---
<a href="#">†Meng et al. (2013)</a>	Four Chinese cities	1996–2008 <sup>k</sup>	COPD	24-h avg	6.8–19.1	---
<b>Meta-analyses</b>						
<a href="#">Stieb et al. (2003)</a>	Meta-analysis	1958–1999 <sup>e</sup>	Total	24-h avg	0.7–75.2	---
<a href="#">HEI (2004)</a>	Meta-analysis (South Korea, China, Taiwan, India, Singapore, Thailand, Japan)	1980–2003 <sup>d</sup>	Total	24-h avg	~10->200	---
<a href="#">†Atkinson et al. (2012)</a>	Meta-analysis (Asia)	1980–2007 <sup>i</sup>	Total cardiovascular respiratory COPD	24-h avg	---	---
<a href="#">†Shah et al. (2015)</a>	Meta-analysis	1948–Jan 2014	Stroke	NR	6.2 <sup>c</sup>	Max: 30.2

**Table 5-39 (Continued: Air quality characteristics of multicity studies and meta analyses evaluated in the 2008 SO<sub>x</sub> ISA and recently published multicity studies and meta analyses.**

Study	Location	Years	Mortality Outcome(s)	Averaging Time	Mean Concentration ppb	Upper Percentile Concentrations ppb
† <a href="#">Yang et al. (2014b)</a>	Meta-analysis (Asia, Europe, and North America)	1996–2013	Stroke	24-h avg	Asia: 11.4 <sup>b</sup> Europe: 5.2 <sup>b</sup> North America: 4.2 <sup>b</sup>	75th: Asia: 18.6 Europe: 2.3 North America: 7.6

APHEA = Air Pollution and Health: A European Approach study; CAPES = China Air Pollution and Health Effects Study; COPD = chronic obstructive pulmonary disease; ISA = Integrated Science Assessment; MISA = Meta-analysis of the Italian studies on short-term effects of air pollution; NMMAPS = The National Morbidity Mortality Air Pollution Study; NR = not reported; PAPA = Public Health and Air Pollution in Asia; SO<sub>x</sub> = sulfur oxides.

<sup>a</sup>Of the 90 cities included in the NMMAPS analysis only 72 had SO<sub>2</sub> data.

<sup>b</sup>Median concentration.

<sup>c</sup>The mortality time series of studies included in the meta-analysis spanned these years.

<sup>d</sup>Studies included within this meta-analysis were published during this time period.

<sup>e</sup>Of the 108 cities included in the analyses using NMMAPS data, only 85 had SO<sub>2</sub> data.

<sup>f</sup>SO<sub>2</sub> data was not available for Barcelona; therefore, the SO<sub>2</sub> results only encompass four cities.

<sup>g</sup>Median concentrations.

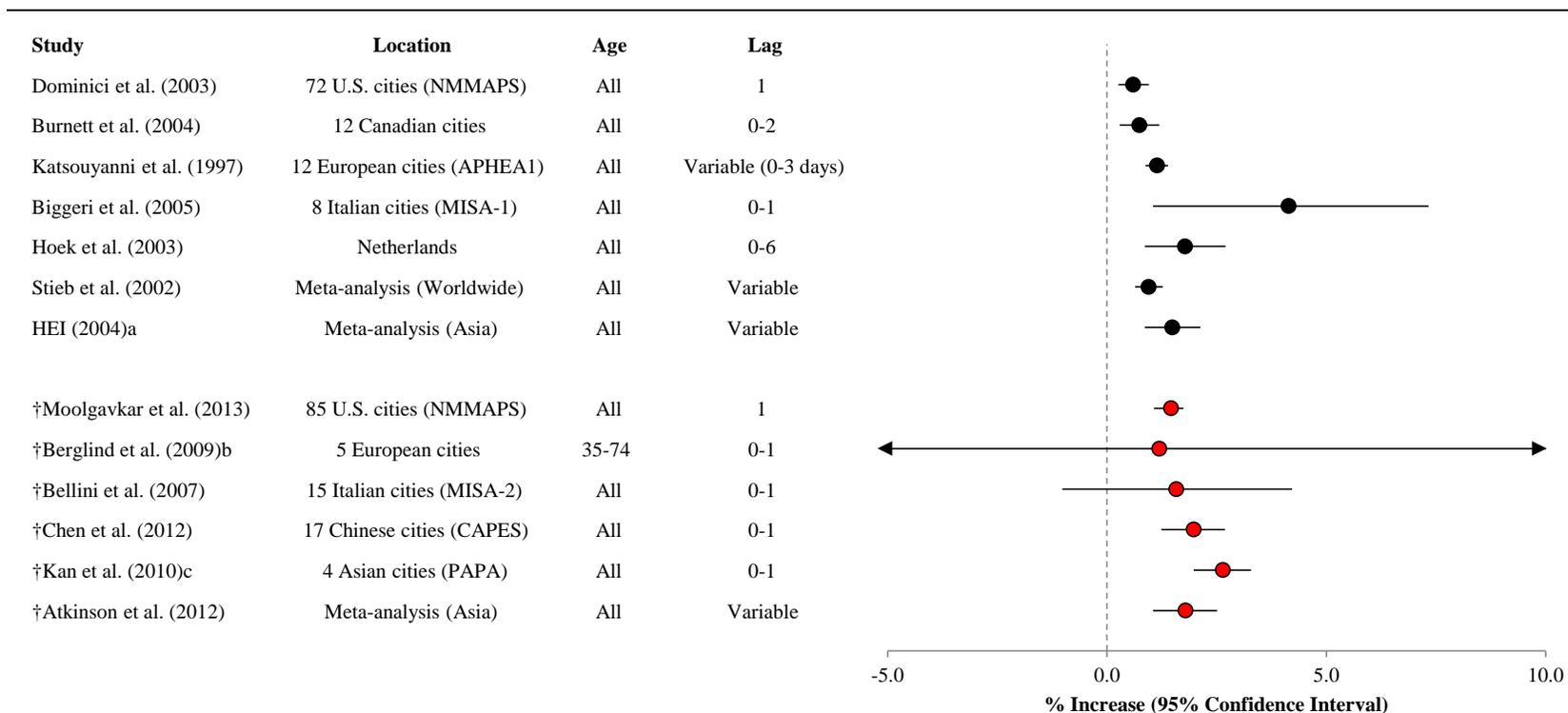
<sup>h</sup>The study period varied for each city, Bangkok: 1999–2003, Hong Kong: 1996–2002, and Shanghai and Wuhan: 2001–2004.

<sup>i</sup>Study period varied for each city and encompassed 2 to 7 yr. Hong Kong was the only city that had air quality data prior to 2000.

<sup>j</sup>Year defined represent the year in which studies were published that were included in the meta-analysis.

<sup>k</sup>Study period varied from 2 to 7 yr. Hong Kong was the only city that had air quality data prior to 2001.

† = Studies published since the 2008 SO<sub>x</sub> ISA.



APHEA = Air Pollution and Health: A European Approach study; CAPES = China Air Pollution and Health Effects Study; MISA = Meta-analysis of the Italian studies on short-term effects of air pollution; NMMAPS = The National Morbidity Mortality Air Pollution Study; PAPA = Public Health and Air Pollution in Asia.

Note: † = studies published since the 2008 ISA for Sulfur Oxides;

a = Meta-analysis of Asian cities: South Korea, China, Hong Kong, Taipei, India, Singapore, Thailand, Japan ([HEI, 2004](#));

b = Study was of myocardial infarction survivors therefore only included individuals 35+ ([Berglind et al., 2009](#));

c = [Kan et al. \(2010b\)](#) reported results that were also found in ([Wong et al., 2010](#); [Wong et al. \(2008b\)](#)).

Corresponding quantitative results are reported in Supplemental Table 5S-27 ([U.S. EPA, 2016](#))bb.

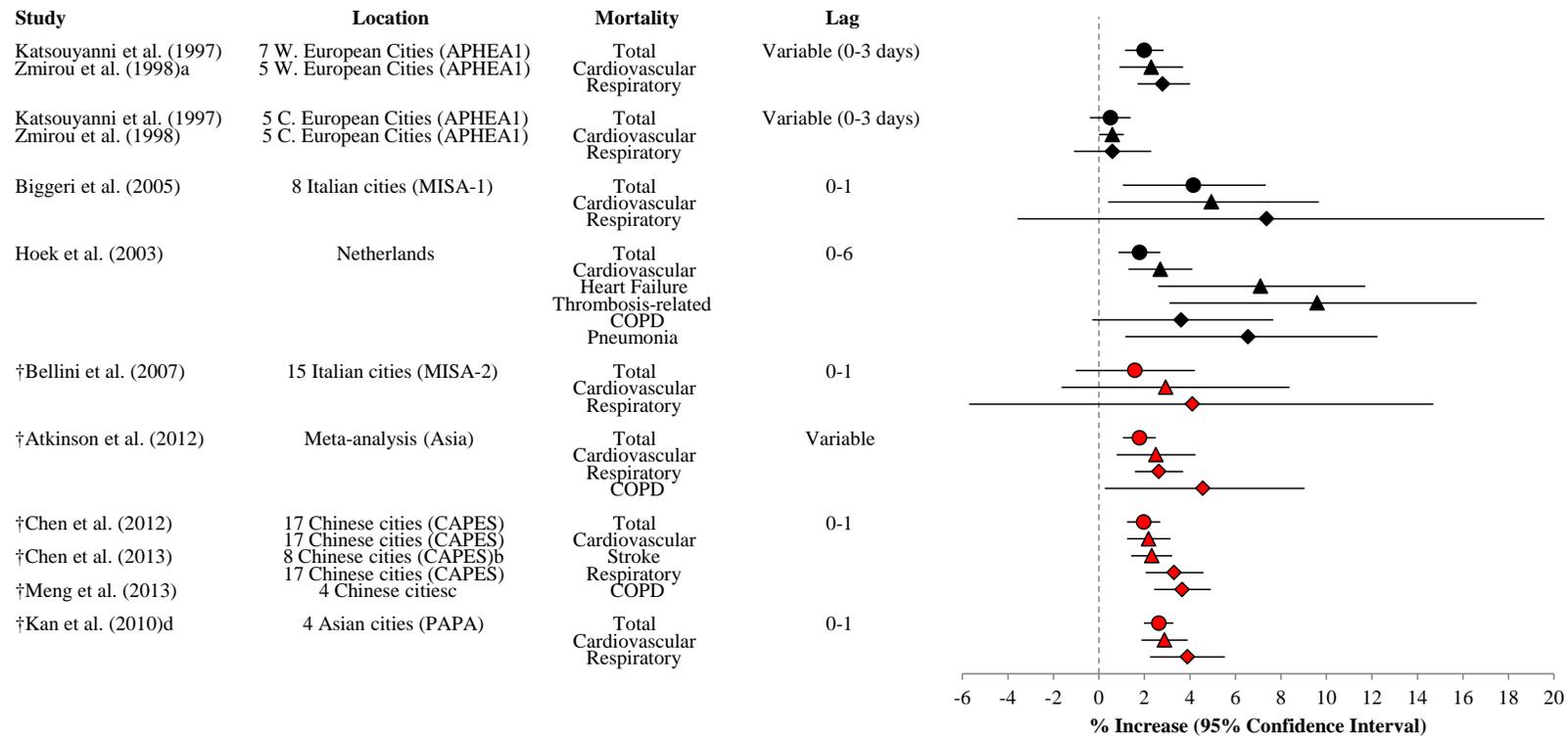
**Figure 5-17 Percent increase in total mortality from multicity studies and meta-analyses evaluated in the 2008 ISA for Sulfur Oxides (black circles) and recently published multicity studies (red circles) for a 10-ppb increase in 24-h avg sulfur dioxide concentrations.**

1 When focusing on specific causes of mortality, some studies evaluated in the 2008 SO<sub>x</sub>  
2 ISA reported similar risk estimates across mortality outcomes [e.g., ([Zmirou et al. \(1998\)](#));  
3 [Katsouyanni et al. \(1997\)](#))], while others indicated larger risk estimates for respiratory  
4 mortality ([Figure 5-18](#)). However, a study conducted in the Netherlands by [Hoek \(2003\)](#)  
5 suggested that specific cardiovascular mortality outcomes have larger risk estimates  
6 compared to all cardiovascular, total, and respiratory-related mortality outcomes. Recent  
7 multicity mortality studies provide additional support indicating larger risk estimates for  
8 respiratory mortality compared to total and cardiovascular mortality. Additionally, the  
9 results from the studies depicted in [Figure 5-18](#) lend additional support to the body of  
10 evidence indicating SO<sub>2</sub>-induced respiratory effects presented in the 2008 SO<sub>x</sub> ISA, as  
11 well as [Section 5.2](#) of this ISA. Unlike the results reported in [Hoek \(2003\)](#), recent studies  
12 do not provide evidence indicating associations larger in magnitude for SO<sub>2</sub>-related  
13 cardiovascular mortality compared to other mortality outcomes.

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### 5.5.1.3 Potential Confounding of the Sulfur Dioxide-Mortality Relationship

14 A limitation of the studies evaluated in the 2008 SO<sub>x</sub> ISA, was the relatively sparse  
15 analyses of the potential confounding effects of copollutants on the SO<sub>2</sub>-mortality  
16 relationship ([U.S. EPA, 2008d](#)). The 2008 SO<sub>x</sub> ISA specifically stated that the “potential  
17 confounding and lack of understanding regarding the interaction of SO<sub>2</sub> with  
18 copollutants” was one of the major limitations of the scientific literature that contributed  
19 to the conclusion that the evidence is “suggestive of a causal relationship” between  
20 short-term SO<sub>2</sub> exposures and mortality. Copollutant analyses conducted in recent studies  
21 further attempt to identify whether SO<sub>2</sub> has an independent effect on mortality. In  
22 addition to examining potential copollutant confounding, some studies have also  
23 examined whether the covariates included in statistical models employed to examine  
24 short-term SO<sub>2</sub> exposures and mortality adequately control for the potential confounding  
25 effects of season/temporal trends and weather.



APHEA = Air Pollution and Health: A European Approach study; CAPES = China Air Pollution and Health Effects Study; COPD = chronic obstructive pulmonary disease; MISA = Meta-analysis of the Italian studies on short-term effects of air pollution; PAPA = Public Health and Air Pollution in Asia.

Note: † = studies published since the 2008 ISA for Sulfur Oxides; total mortality = circle; cardiovascular-related mortality = triangle; and respiratory-related mortality = diamond.  
a = [Zmirou et al. \(1998\)](#) reported on only five of the seven cities included in [Katsouyanni et al. \(1997\)](#), which had cause-specific mortality data and were included in the analysis;  
b = [Chen et al. \(2012b\)](#) examined stroke only in the China Air Pollution and Health Effects Study cities that had stroke data;  
c = [Meng et al. \(2013\)](#) was not part of CAPES, but the four cities included had data for the same years as the CAPES study;  
d = [Kan et al. \(2010b\)](#) reported results which were also presented in [Wong et al. \(2008b\)](#) and [Wong et al. \(2010\)](#).  
Corresponding quantitative results are reported in Supplemental Table 5S-28 ([U.S. EPA, 2016w](#)).

**Figure 5-18 Percent increase in total, cardiovascular, and respiratory mortality from multicity studies evaluated in the 2008 ISA for Sulfur Oxides (black) and recently published multicity studies (red) for a 10-ppb increase in 24-h avg sulfur dioxide concentrations.**

## Examination of Potential Copollutant Confounding

1 In the 2008 SO<sub>x</sub> ISA ([U.S. EPA, 2008d](#)), the analysis of potential copollutant  
2 confounding was limited to studies conducted by [Dominici et al. \(2003\)](#) within the U.S.  
3 as part of the National Morbidity Mortality Air Pollution Study (NMMAPS),  
4 [Katsouyanni et al. \(1997\)](#) in Europe as part of the Air Pollution and Health: A European  
5 Approach (APHEA-1) study, [Hoek \(2003\)](#) in the Netherlands, and [Burnett et al. \(2004\)](#) in  
6 12 Canadian cities. Copollutant models in these studies focused on the effect of PM<sub>10</sub>, BS  
7 or NO<sub>2</sub> on the SO<sub>2</sub>-mortality relationship. The SO<sub>2</sub>-mortality risk estimate was found to  
8 either increase ([Hoek, 2003](#)) or slightly attenuate ([Dominici et al., 2003](#); [Katsouyanni et](#)  
9 [al., 1997](#)) in models with BS or PM<sub>10</sub>; while risk estimates were reduced, but still  
10 remained positive in models with NO<sub>2</sub> ([Burnett et al., 2004](#)). Additionally, there was  
11 limited evidence from [Burnett et al. \(2000\)](#) of attenuation of the SO<sub>2</sub> association when  
12 PM<sub>2.5</sub> was included in the model. Recent multicity studies conducted in the U.S. and Asia  
13 have also examined whether there is evidence of copollutant confounding; however,  
14 similar to the literature base considered in the 2008 SO<sub>x</sub> ISA ([U.S. EPA, 2008d](#)), the  
15 evaluation of copollutant confounding on the SO<sub>2</sub>-mortality relationship has remained  
16 limited.

17 In a study of 108 U.S. cities using data from the NMMAPS for 1987–2000 (of which 85  
18 had SO<sub>2</sub> data), [Moolgavkar et al. \(2013\)](#) used a subsampling approach where a random  
19 sample of 4 cities were removed from the 108 cities over 5,000 bootstrap cycles to  
20 examine associations between short-term air pollution concentrations and total mortality.  
21 This approach was used instead of the two-stage Bayesian hierarchical approach  
22 employed in the original NMMAPS analysis, which assumes that city-specific risk  
23 estimates are normally distributed around a national mean ([Dominici et al., 2003](#)). In a  
24 single-pollutant model using 100 df (~7 df/year, which is consistent with NMMAPS) to  
25 control for temporal trends, [Moolgavkar et al. \(2013\)](#) found a 1.5% (95% CI: 1.1, 1.7)  
26 increase in total (nonaccidental) mortality at lag 1 for a 10-ppb increase in 24-h avg SO<sub>2</sub>  
27 concentrations. In a copollutant analysis, the SO<sub>2</sub>-mortality risk estimate remained robust  
28 and was similar in magnitude to the single pollutant result upon the inclusion of PM<sub>10</sub>  
29 [1.3% (95% CI: 0.4, 2.0)]. An analysis of the influence of NO<sub>2</sub> on SO<sub>2</sub>-mortality risk  
30 estimates was not conducted. The results of [Moolgavkar et al. \(2013\)](#) provide additional  
31 support for an SO<sub>2</sub>-mortality association, as observed in [Dominici et al. \(2003\)](#), through  
32 an analysis that included more cities and used a different statistical approach than  
33 previously employed in multicity studies.

34 Additional multicity studies in Asia, conducted more extensive analyses of potential  
35 copollutant confounding by examining the effect of gaseous pollutants, in addition to

1 PM<sub>10</sub>, on the SO<sub>2</sub>-mortality relationship. In a study of 17 Chinese cities as part of the  
 2 CAPES, ([Chen et al., 2012b](#)) examined associations between short-term SO<sub>2</sub> exposures  
 3 and multiple mortality outcomes. The potential confounding effects of other pollutants on  
 4 the SO<sub>2</sub>-mortality relationship was assessed in copollutant models with PM<sub>10</sub> and NO<sub>2</sub>.  
 5 Within the cities examined, SO<sub>2</sub> was found to be moderately correlated with PM<sub>10</sub>  
 6 ( $r = 0.49$ ) and NO<sub>2</sub> ( $r = 0.65$ ), respectively. The results from copollutant models  
 7 ([Table 5-40](#)) indicate that although SO<sub>2</sub> risk estimates remained positive, they were  
 8 attenuated by approximately 39–54% in models with PM<sub>10</sub> and 65–79% in models with  
 9 NO<sub>2</sub>. These results are consistent with those observed in [Chen et al. \(2013\)](#), which  
 10 focused on stroke mortality in a subset of the CAPES cities (i.e., eight cities) and also  
 11 reported a similar reduction in SO<sub>2</sub> risk estimates in models with PM<sub>10</sub> and NO<sub>2</sub>.

**Table 5-40 Percent increase in total, cardiovascular, and respiratory mortality for a 10-ppb increase in 24-h avg sulfur dioxide concentrations at lag 0–1 in single and copollutant models.**

	Copollutant	Total Mortality % Increase (95% CI)	Cardiovascular Mortality % Increase (95% CI)	Respiratory Mortality % Increase (95% CI)
SO <sub>2</sub>	---	1.98 (1.24, 2.69)	2.19 (1.24, 3.15)	3.31 (2.05, 4.59)
	+PM <sub>10</sub>	1.10 (0.45, 1.76)	1.00 (0.08, 1.92)	2.03 (0.89, 3.17)
	+NO <sub>2</sub>	0.42 (-1.56, 1.00)	0.47 (-0.47, 1.42)	1.16 (-0.03, 2.37)

CI = confidence interval; NO<sub>2</sub> = nitrogen dioxide; PM<sub>10</sub> = particulate matter with a nominal aerodynamic diameter less than or equal to 10 μm.

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

12 [Kan et al. \(2010b\)](#) examined the association between short-term SO<sub>2</sub> exposures and  
 13 mortality within four Asian cities as part of the PAPA study. Although the authors did not  
 14 examine copollutant models in a combined four-city analysis, they did on a city-to-city  
 15 basis. Similar to [Chen et al. \(2012b\)](#), in single pollutant models across cities and  
 16 mortality outcomes, there was evidence of a consistent positive association ([Figure 5-19](#)).  
 17 Of note is the highly imprecise estimate for Bangkok, but it is speculated that the  
 18 variability in risk estimates for Bangkok could be attributed to the lack of variability in  
 19 SO<sub>2</sub> concentrations in this city compared to the Chinese cities (standard deviation in SO<sub>2</sub>  
 20 concentrations of 1.8 ppb; Chinese cities: 4.6–9.7 ppb) ([Kan et al., 2010b](#)). Across  
 21 mortality outcomes and cities, SO<sub>2</sub>-mortality risk estimates were attenuated, and in many  
 22 cases null in copollutant models with NO<sub>2</sub>. However, only in Shanghai and Wuhan were  
 23 SO<sub>2</sub> correlations with NO<sub>2</sub> greater than 0.60 ( $r = 0.64$  and  $0.76$ , respectively). Similarly,

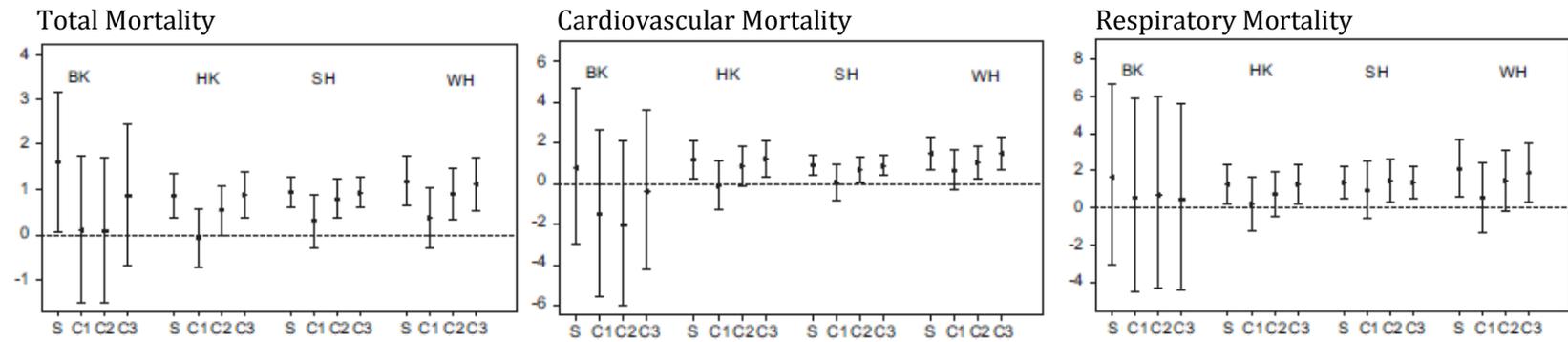
1 SO<sub>2</sub> was also found to be moderately correlated with PM<sub>10</sub> in Shanghai ( $r = 0.67$ ) and  
2 Wuhan ( $r = 0.65$ ), but SO<sub>2</sub> mortality risk estimates, although attenuated, remained  
3 positive across cities. In copollutant models with O<sub>3</sub>, SO<sub>2</sub> mortality risk estimates were  
4 almost unchanged compared to single-pollutant results.

5 Recent multicity studies add to the limited number of studies that have examined the  
6 potential confounding effects of copollutants on the SO<sub>2</sub>-mortality relationship. Within  
7 the only recent U.S. study, [Moolgavkar et al. \(2013\)](#) reported that SO<sub>2</sub>-mortality risk  
8 estimates remained robust in copollutant models with PM<sub>10</sub>, which is consistent with  
9 [Dominici et al. \(2003\)](#), but these studies did not evaluate potential confounding by  
10 gaseous pollutants. Studies that examined gaseous pollutants, including [Chen et al.](#)  
11 [\(2012b\)](#) and [Kan et al. \(2010b\)](#) along with [Burnett et al. \(2004\)](#), found that in models  
12 with NO<sub>2</sub>, SO<sub>2</sub> risk estimates were reduced to a large extent, but remained positive.  
13 However, the overall assessment of copollutant confounding remains limited, and it is  
14 unclear how the results observed in Asia translate to other locations, specifically due to  
15 the unique air pollution mixture and higher concentrations observed in Asian cities.

### **Modeling Approaches to Control for Weather and Temporal Confounding**

16 Mortality risk estimates may be sensitive to model specification, which includes the  
17 selection of weather covariates to include in statistical models to account for the potential  
18 confounding effects of weather in short-term exposure studies. As such, some recent  
19 studies have conducted sensitivity analyses to examine the influence of alternative  
20 approaches to control for the potential confounding effects of weather on mortality risk  
21 estimates.

22 As part of the CAPES study, [Chen et al. \(2012b\)](#) examined the influence of alternative  
23 lag structures for controlling the potential confounding effects of temperature on the  
24 SO<sub>2</sub>-mortality relationship by varying the lag structure of the temperature variable  
25 (i.e., lag 0, lag 0–3, or lag 0–7). The authors found that although the SO<sub>2</sub>-mortality  
26 associations remained positive and statistically significant across alternative lag  
27 structures, risk estimates were attenuated as the number of lag days specified increased.  
28 The attenuation observed when using a temperature variable lagged from 0–3 to 0–7 days  
29 could be due to [Chen et al. \(2012b\)](#) only including one temperature term in the statistical  
30 model. This approach differs from that used in some of the seminal multicity studies  
31 (e.g., NMMAPS, APHEA) that include a temperature term averaged over multiple days  
32 (e.g., average of lag 1–3 days). A second temperature term is often included in models, in  
33 addition to a same-day temperature term, to account for (1) the potential delayed effects  
34 of temperature on mortality and (2) potential residual confounding due to temperature.



BK = Bangkok; HK = Hong Kong; SH = Shanghai; WH = Wuhan.

Note: S = single-pollutant model; C1 = sulfur dioxide + nitrogen dioxide; C2 = sulfur dioxide + PM<sub>10</sub>; C3 = sulfur dioxide + ozone.

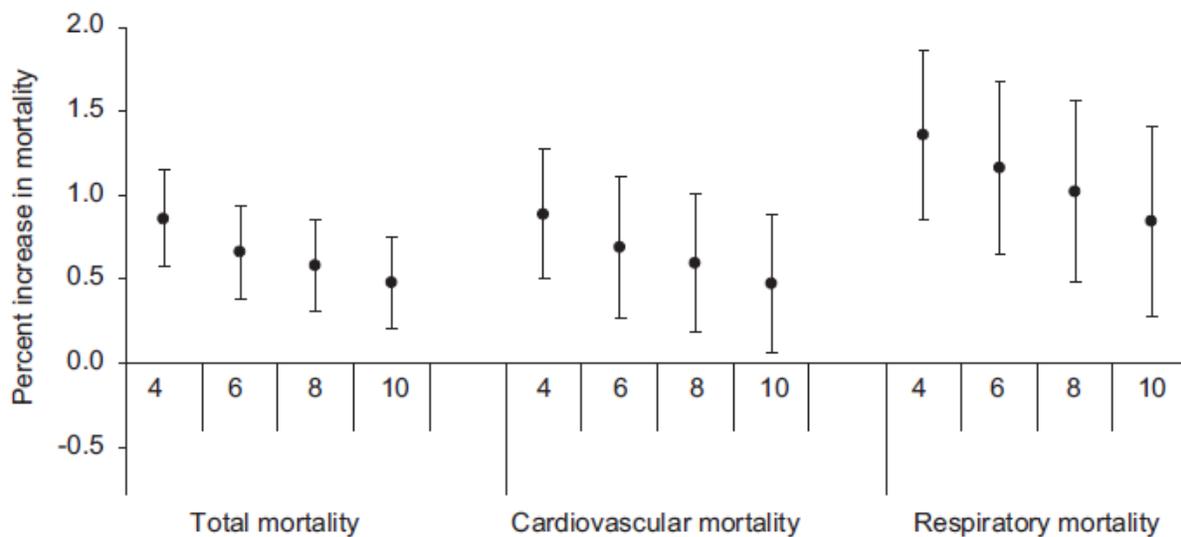
Source: Figure adapted from [Kan et al. \(2010b\)](#).

**Figure 5-19** Percent increase in total, cardiovascular, and respiratory mortality associated with a 10 µg/m<sup>3</sup> (3.62 ppb) increase in 24-h avg sulfur dioxide concentrations, lag 0–1, in single and copollutants models in Public Health and Air Pollution in Asia cities.

### Temporal

In addition to examining the influence of model specification on mortality risk estimates through the use of alternative weather covariates, recent studies have also examined whether air pollution-mortality risk estimates are sensitive to the df per year employed to control for temporal trends.

Within the CAPES study, [Chen et al. \(2012b\)](#) examined the influence of increasing the number of degrees of freedom per year (i.e., 4, 6, 8, and 10 df per year) to control for temporal confounding on SO<sub>2</sub>-mortality risk estimates. The authors found that as the number of df per year increased the percent increase in both total and cause-specific mortality attributed to SO<sub>2</sub> was slightly attenuated, but remained positive across the range of df examined ([Figure 5-20.](#))

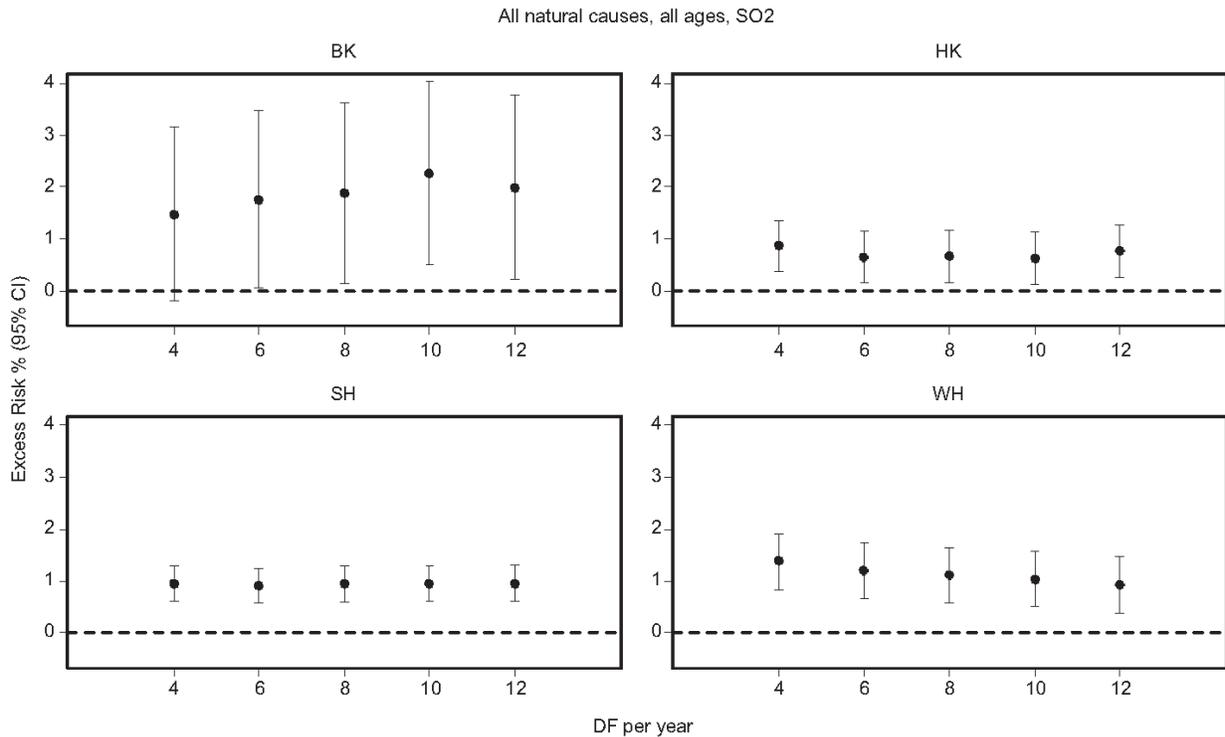


Source: [Chen et al., 2012b](#).

**Figure 5-20** Percent increase in daily mortality associated with a 10 µg/m<sup>3</sup> (3.62 ppb) increase in 24-h avg sulfur dioxide concentrations at lag 0–1 days using various degrees of freedom per year for time trend, China Air Pollution and Health Effects Study cities, 1996–2008.

The results of [Chen et al. \(2012b\)](#) are consistent with those reported by [Kan et al. \(2010b\)](#) in an analysis of each individual city within the PAPA study. In models using 4, 6, 8, 10, or 12 df per year, the authors reported relatively similar SO<sub>2</sub>-mortality risk estimates

1 across cities. However, as depicted in [Figure 5-20](#), and in some cities in [Figure 5-21](#),  
 2 using 4 df per year likely leads to inadequate control for temporal trends based on the  
 3 higher risk estimate observed compared to increasing the degrees of freedom.



BK = Bangkok; CI = confidence interval; df = degrees of freedom; HK = Hong Kong; SH = Shanghai; WH = Wuhan.  
 Source: ([Kan et al., 2010b](#)).

**Figure 5-21 Percent increase in total mortality associated with a 10 µg/m<sup>3</sup> (3.62 ppb) increase in 24-h avg sulfur dioxide concentrations at lag 0–1 in Public Health and Air Pollution in Asia cities, using different degrees of freedom per year for time trend.**

4 Unlike [Chen et al. \(2012b\)](#) and [Kan et al. \(2010b\)](#), which conducted a systematic analysis  
 5 of the influence of increasing the df per year to control for temporal trends on the  
 6 SO<sub>2</sub>-mortality relationship, [Moolgavkar et al. \(2013\)](#) only compared models that used  
 7 50 df (~3.5 df per year) or 100 df (~7 df per year). Similar to both [Chen et al. \(2012b\)](#) and  
 8 [Kan et al. \(2010b\)](#), the authors reported relatively similar SO<sub>2</sub>-mortality risk estimates in  
 9 both models [1.6% (95% CI: 0.9, 1.9) for a 10-ppb increase in 24-h avg SO<sub>2</sub>  
 10 concentrations at lag 1 in the 50-df model and 1.5% (95% CI: 1.1, 1.7) in the 100 df  
 11 model].

1 Overall, the studies that examined the effect of alternative approaches to control for the  
2 potentially confounding effects of weather and temporal trends report relatively  
3 consistent SO<sub>2</sub>-mortality risk estimates across models. The results of these studies are  
4 further supported by an analysis conducted by [Sacks et al. \(2012\)](#), which examined  
5 whether the different modeling approaches (to control for both weather and temporal  
6 trends) used in a number of multicity studies (e.g., NMMAPS, APHEA) resulted in  
7 similar risk estimates when using the same data set. In all-year analyses focusing on  
8 cardiovascular mortality, SO<sub>2</sub>-mortality risk estimates remained relatively stable across  
9 models using different weather covariates and a varying number of df per year (ranging  
10 from 4 to 8 df per year across models) to control for temporal trends. Although the results  
11 of [Sacks et al. \(2012\)](#) are consistent with [Chen et al. \(2012b\)](#), [Kan et al. \(2010b\)](#), and  
12 [Moolgavkar et al. \(2013\)](#) in all-year analyses, seasonal analyses indicate that differences  
13 in model specification may be more important when examining effects by season for  
14 some pollutants, such as SO<sub>2</sub>.

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#### 5.5.1.4 Modification of the Sulfur Dioxide-Mortality Relationship

##### Individual- and Population-Level Factors

15 To date, a limited number of studies have examined potential factors that may increase  
16 the risk of SO<sub>2</sub>-related mortality. In the 2008 SO<sub>x</sub> ISA ([U.S. EPA, 2008d](#)), only  
17 [Katsouyanni et al. \(1997\)](#) examined potential effect measure modifiers and within the  
18 APHEA-2 study reported that geographic location may influence city-specific  
19 SO<sub>2</sub>-mortality risk estimates. Similar to the 2008 SO<sub>x</sub> ISA, only few recent multicity  
20 studies [i.e., ([Chen et al. \(2012b\)](#); [Berglind et al. \(2009\)](#); [Wong et al. \(2008b\)](#))] conducted  
21 extensive analyses of potential effect measure modifiers of the SO<sub>2</sub>-mortality relationship  
22 as detailed in [Chapter 6](#). These studies along with some single-city studies focusing on  
23 SO<sub>2</sub> and mortality provide limited evidence for potential differences in the risk of  
24 SO<sub>2</sub>-related mortality by lifestage, sex, and socioeconomic status (SES).

##### Season and Weather

25 A limited number of studies have examined whether there is evidence of seasonal  
26 differences or that certain weather patterns modify in the SO<sub>2</sub>-mortality relationship. In  
27 the 2008 SO<sub>x</sub> ISA, only [Zmirou et al. \(1998\)](#) examined whether there are seasonal  
28 differences in SO<sub>2</sub>-mortality risk associations in a subset of the APHEA-1 cities.  
29 The authors found some indication of larger associations in the summer months  
30 compared to the winter months.

1 Since the completion of the 2008 SO<sub>x</sub> ISA, only a few recent studies have examined  
2 whether there are seasonal differences in SO<sub>2</sub>-mortality associations, and these studies  
3 reported results consistent with [Zmirou et al. \(1998\)](#). In a study of 15 Italian cities  
4 (MISA-2), [Bellini et al. \(2007\)](#) is the only multicity study that examined whether there  
5 were seasonal differences in SO<sub>2</sub>-mortality risk estimates. The authors found a similar  
6 pattern of associations across mortality outcomes with SO<sub>2</sub>-mortality risk estimates being  
7 larger in the summer compared to the winter (total mortality: summer 3.2% vs. winter  
8 1.4%; respiratory mortality: summer 12.0% vs. winter 4.1%; cardiovascular mortality:  
9 summer 9.4% vs. winter 1.6%). These results are consistent, with the only U.S.-based  
10 study that examined seasonal patterns in SO<sub>2</sub>-mortality associations. In a study conducted  
11 in New York City focusing on cardiovascular mortality, [Ito et al. \(2011\)](#) reported larger  
12 risk estimates in the warm season [2.9% (95% CI: -1.2, 7.1)] compared to the cold  
13 season [0.0% (95% CI: -1.7, 1.8)] for a 10-ppb increase in 24-h avg SO<sub>2</sub> concentrations.

14 Instead of examining whether only specific seasons modify the SO<sub>2</sub>-mortality  
15 association, [Vanos et al. \(2013\)](#) focused on weather patterns, referred to as synoptic  
16 weather types, in a study of 10 Canadian cities. Distinct weather types were identified by  
17 combining a number of variables including temperature, dew point temperature, sea level  
18 pressure, cloud cover, and wind velocity. Across the nine different synoptic weather  
19 types examined, for SO<sub>2</sub> [Vanos et al. \(2013\)](#) reported that mortality risk estimates in all  
20 age analyses tended to be larger in magnitude for dry versus moist weather types,  
21 particularly in warmer seasons.

22 Overall, the limited number of studies that conducted seasonal analyses reported initial  
23 evidence indicating larger SO<sub>2</sub>-mortality associations during the summer season.  
24 Additionally, there is preliminary evidence that specific weather patterns in combination  
25 with certain seasons may modify the SO<sub>2</sub>-mortality association.

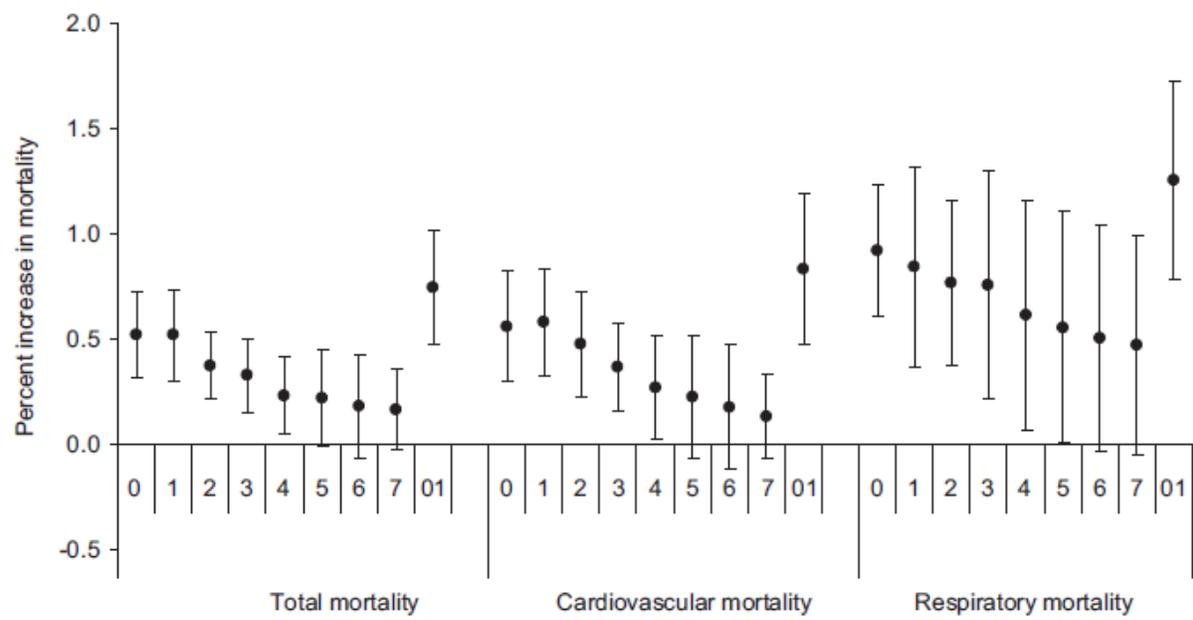
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### 5.5.1.5 Sulfur Dioxide-Mortality Concentration-Response Relationship and Related Issues

#### Lag Structure of Associations

26 Of the studies evaluated in the 2008 SO<sub>x</sub> ISA, the majority selected lag days a priori and  
27 did not extensively examine the lag structure of associations for short-term SO<sub>2</sub>  
28 exposures and mortality. These studies primarily focused on single- or multiday lags  
29 within the range of 0–3 days. However, in a study in the Netherlands, [Hoek \(2003\)](#)  
30 conducted more extensive analyses to examine whether there was evidence of immediate  
31 or delayed SO<sub>2</sub>-mortality effects. The authors provided preliminary evidence of larger

1 SO<sub>2</sub>-mortality risk estimates at a multiday lag of 0–6 days compared to a single-day lag  
 2 (i.e., lag 1 day). Recent multicity studies have conducted additional analyses further  
 3 examining the lag structure of associations for short-term SO<sub>2</sub> exposures and mortality.  
 4 [Chen et al. \(2012b\)](#), within the CAPES study, examined individual lag days (lag day 0 to  
 5 7) and a multiday lag of 0–1 days. As depicted in [Figure 5-22](#), the authors found evidence  
 6 of immediate SO<sub>2</sub> effects on mortality that slowly declined over time with the multiday  
 7 lag of 0–1 days exhibiting the largest risk estimate across mortality outcomes.

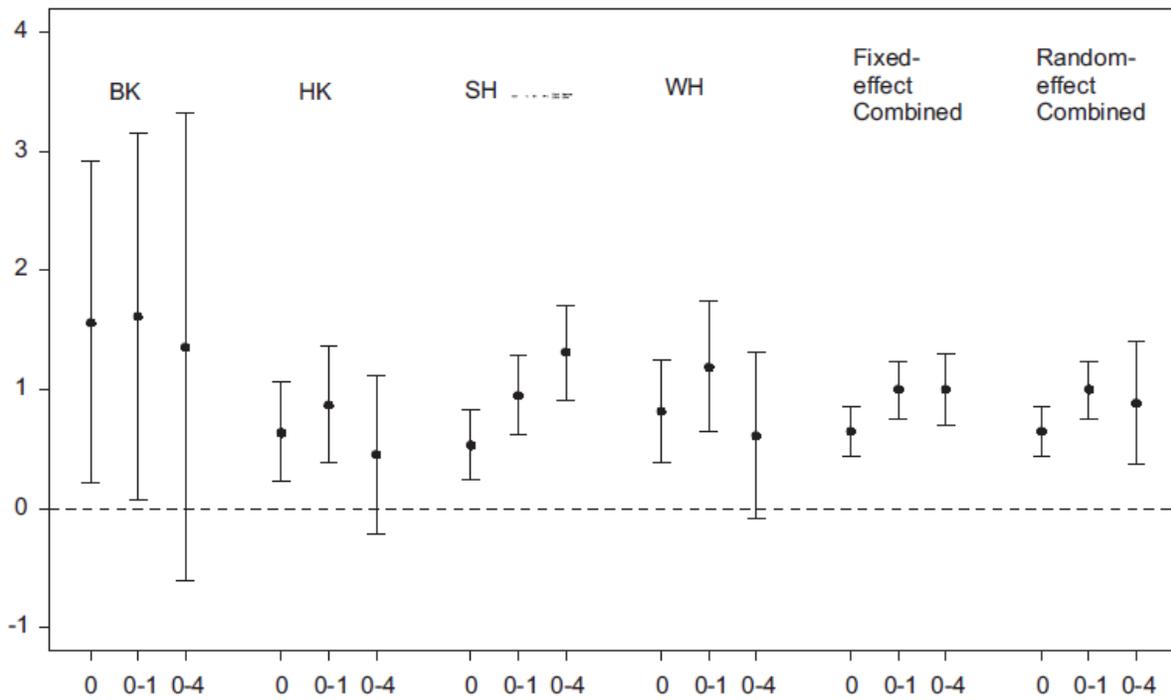


Source: [Chen et al., 2012b](#).

**Figure 5-22** Percent increase in daily mortality associated with a 10 µg/m<sup>3</sup> (3.62 ppb) increase in 24-h avg sulfur dioxide concentrations, using various lag structures for sulfur dioxide in the China Air Pollution and Health Effects Study cities, 1996–2008.

8 [Kan et al. \(2010b\)](#) also examined the lag structure of associations for the SO<sub>2</sub>-mortality  
 9 relationship within the PAPA study, but did not examine an extensive number of  
 10 alternative lags, instead focusing on lag 0 and moving averages of 0–1 and 0–4 days  
 11 ([Figure 5-23](#)). Unlike [Chen et al. \(2012b\)](#), which focused on the combined risk estimate  
 12 across all cities, [Kan et al. \(2010b\)](#) examined the lag structure of associations both within  
 13 individual cities and in a combined analyses across all PAPA cities. The results of both

1 the individual city and combined analyses are consistent with those observed by [Chen et](#)  
 2 [al. \(2012b\)](#) in the CAPES study (i.e., the effect largest in magnitude across the lag days  
 3 examined occurred primarily at lag 0–1 days) ([Figure 5-22](#)).



BK = Bangkok; HK = Hong Kong; SH = Shanghai; WH = Wuhan.  
 Source: [Kan et al. \(2010b\)](#).

**Figure 5-23** Percent increase in total mortality associated with a 10 µg/m<sup>3</sup> (3.62 ppb) increase in 24-h avg sulfur dioxide concentrations for different lag structures in individual Public Health and Air Pollution in Asia cities and in combined four city analyses.

4 [Bellini et al. \(2007\)](#) took a slightly different approach to examining the lag structure of  
 5 associations in a study of 15 Italian cities (MISA-2) by focusing on whether there was  
 6 evidence of mortality displacement. The authors reported larger SO<sub>2</sub>-mortality effects at  
 7 lag 0–15 days (3.8% for a 10-ppb increase in 24-h avg SO<sub>2</sub> concentrations) compared to a  
 8 lag of 0–1 days (1.6%), which supports no evidence of mortality displacement.  
 9 Additional information on the lag structure can be observed by examining the percent  
 10 increase in mortality associated with short-term SO<sub>2</sub> exposures at each individual lag day  
 11 of the lag 0–15-day model. The individual lag day results remained positive up to

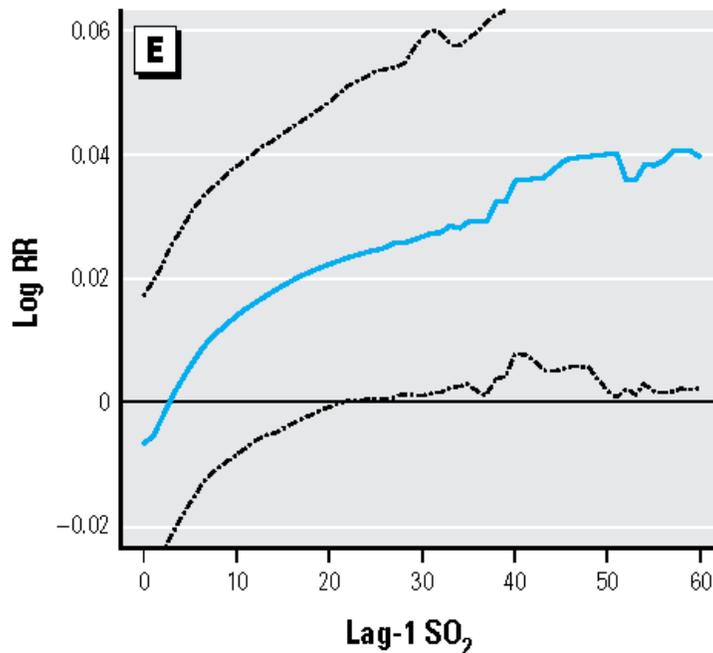
1 approximately lag day 10, which is consistent with the results from [Chen et al. \(2012b\)](#)  
2 ([Figure 5-22](#)). However, examining associations at single-day lags over a week, such as  
3 10 days, may be uninformative due to potential inadequate control for weather variables  
4 at these longer durations. Additionally, these longer lags may not be biologically  
5 plausible due to controlled human exposure and animal toxicological studies  
6 demonstrating that effects attributed to SO<sub>2</sub> exposure are rather immediate  
7 ([Section 5.2.1.2](#)).

8 Overall, the limited analyses that have examined the lag structure of associations for  
9 short-term SO<sub>2</sub> exposures and mortality suggest that the greatest effects occur within the  
10 first few days after exposure (lag 0–1). However, the studies evaluated indicate that  
11 positive associations may persist longer although the magnitude of those effects  
12 diminishes over time.

### **Concentration-Response Relationship**

13 The studies evaluated in the 2008 SO<sub>x</sub> ISA ([U.S. EPA, 2008d](#)), as well as prior  
14 assessments, have not conducted formal analyses of the SO<sub>2</sub>-mortality C-R relationship.  
15 Although limited in number, a few recent studies published since the completion of the  
16 2008 SO<sub>x</sub> ISA have conducted analyses to examine the shape of the SO<sub>2</sub>-mortality C-R  
17 relationship and whether a threshold exists in the combined C-R relationship across  
18 multiple cities, or in an evaluation of single-city C-R relationships in the context of a  
19 multicity study. However, these studies have not conducted extensive analyses examining  
20 alternatives to linearity in the shape of the SO<sub>2</sub>-mortality C-R relationship.

21 Using a subsampling approach, [Moolgavkar et al. \(2013\)](#) examined the shape of the C-R  
22 relationship between short-term air pollution exposures and mortality in the NMMAPS  
23 data set by applying a nonlinear function (i.e., natural splines with 6 df) to each pollutant.  
24 As demonstrated in [Figure 5-24](#), the analysis conducted by [Moolgavkar et al. \(2013\)](#)  
25 provides support for a linear, no threshold relationship between short-term SO<sub>2</sub> exposures  
26 and total mortality.



SO<sub>2</sub> = sulfur dioxide; RR = relative risk.

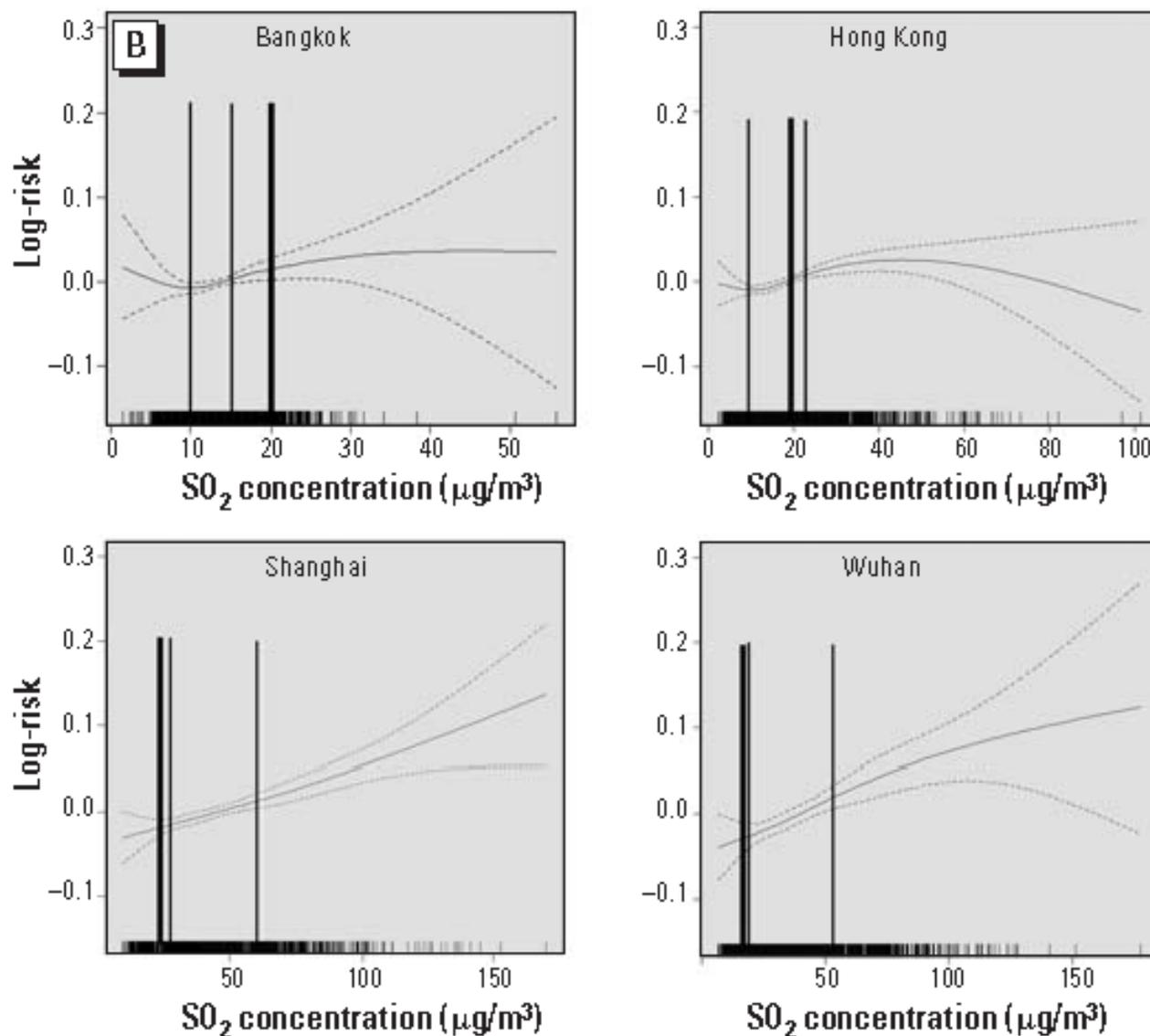
Note: Pointwise means and 95% confidence intervals adjusted for size of the bootstrap sample (d = 4).

Source: Reprinted from Environmental Health Perspectives; [Moolgavkar et al. \(2013\)](#).

**Figure 5-24 Flexible ambient concentration-response relationship between short-term sulfur dioxide (ppb) exposure (24-h avg concentrations) and total mortality at lag 1.**

1 In the four-city PAPA study, [Kan et al. \(2010b\)](#) also examined the SO<sub>2</sub>-mortality C-R  
 2 relationship, but only focused on the shape of the C-R curve in each individual city.  
 3 The C-R curve for the SO<sub>2</sub>-mortality relationship was assessed by applying a natural  
 4 spline smoother with 3 df to SO<sub>2</sub> concentrations. To examine whether the SO<sub>2</sub>-mortality  
 5 relationship deviates from linearity, the deviance between the smoothed (nonlinear)  
 6 pollutant model and the unsmoothed (linear) pollutant model was examined. When  
 7 examining the deviance, the authors only reported evidence for potential nonlinearity in  
 8 Hong Kong. However, across the cities, there is evidence of a linear, no threshold,  
 9 relationship within the range of SO<sub>2</sub> concentrations where the data density is the highest,  
 10 specifically within the IQR ([Figure 5-25](#)). The linear relationship is most pronounced in  
 11 Shanghai and Wuhan, with evidence of an inverted U-shape for Bangkok and Hong  
 12 Kong. It should be noted, there is an overall lack of confidence in the shape of the C-R  
 13 curve at the high end of the distribution of SO<sub>2</sub> concentrations in Bangkok and Shanghai  
 14 due to the lower data density within this range of concentrations observed in both cities.  
 15 A difficulty apparent in comparing the results across cities within [Kan et al. \(2010b\)](#) is

- 1 the drastically different range of SO<sub>2</sub> concentrations in Bangkok and Hong Kong
- 2 compared Shanghai and Wuhan. However, the cities with similar distributions of SO<sub>2</sub>
- 3 concentrations also have similar shapes to their respective SO<sub>2</sub>-mortality C-R curves.



SO<sub>2</sub> = sulfur dioxide.

Note: x-axis is the average of lag 0–1 24-h avg SO<sub>2</sub> concentrations (µg/m<sup>3</sup>). Solid lines indicate the estimated mean percent change in daily mortality, and the dotted lines represent twice the standard error. Thin vertical lines represent the interquartile range of SO<sub>2</sub> concentrations within each city, while the thin vertical bar represents the World Health Organization guideline of 20 µg/m<sup>3</sup> for a 24-h avg time of SO<sub>2</sub>.

Source: Reprinted from Environmental Health Perspectives; ([Wong et al., 2008b](#)).

**Figure 5-25 Concentration-response curves for total mortality (degrees of freedom = 3) for sulfur dioxide in each of the four Public Health and Air Pollution in Asia cities.**

1 Both [Moolgavkar et al. \(2013\)](#) and [Kan et al. \(2010b\)](#) examined the shape of the  
2 SO<sub>2</sub>-mortality C-R relationship by focusing on all-cause (total) mortality. Additional  
3 information on the shape of the C-R curve can be assessed in studies that focused on  
4 cause-specific mortality as discussed in [Section 5.2.1.8](#) (respiratory mortality) and  
5 [Section 5.3.1.9](#) (cardiovascular mortality). In studies of multiple Chinese cities, [Meng et](#)  
6 [al. \(2013\)](#) and [Chen et al. \(2013\)](#) examined the shape of the C-R relationship for mortality  
7 and short-term air pollution exposures on COPD and stroke mortality, respectively. In  
8 both studies the authors conducted similar analyses of linearity by examining the  
9 deviance between linear and spline models. [Meng et al. \(2013\)](#) and [Chen et al. \(2013\)](#)  
10 both found no evidence of a deviation in linearity in the SO<sub>2</sub>-COPD mortality and  
11 SO<sub>2</sub>-stroke mortality relationship, respectively ([Figure 5-11](#) and [Figure 5-16](#)).

12 To date studies have conducted a rather limited exploration of potential alternatives to  
13 linearity when examining the shape of the C-R relationship, which in combination with  
14 the spatial and temporal variability in SO<sub>2</sub> concentrations, complicates the interpretation  
15 of the SO<sub>2</sub>-mortality C-R relationship ([Section 3.4.2.2](#), and [Section 3.4.2.3](#)). With these  
16 limitations in mind, studies that examined the C-R relationship provide evidence that  
17 indicates a linear, no threshold relationship between short-term SO<sub>2</sub> concentrations and  
18 mortality, specifically within the range of SO<sub>2</sub> concentrations where the data density is  
19 highest. Some differences in the shape of the curve were observed on a city-to-city basis,  
20 which is consistent with the mortality C-R results that have been reported for other  
21 criteria air pollutants.

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### 5.5.1.6 Summary and Causal Determination

22 Recent multicity studies evaluated since the completion of the 2008 SO<sub>x</sub> ISA continue to  
23 provide consistent evidence of positive associations between short-term SO<sub>2</sub> exposures  
24 and total mortality. Although the body of evidence is larger, key uncertainties and data  
25 gaps still remain, which contribute to the conclusion that the evidence for short-term SO<sub>2</sub>  
26 exposures and total mortality is suggestive of, but not sufficient to infer, a causal  
27 relationship. This conclusion is consistent with that reached in the 2008 SO<sub>x</sub> ISA ([U.S.](#)  
28 [EPA, 2008d](#)). Recent multicity studies evaluated have further informed key uncertainties  
29 and data gaps in the SO<sub>2</sub>-mortality relationship identified in the 2008 SO<sub>x</sub> ISA including  
30 confounding, modification of the SO<sub>2</sub>-mortality relationship, potential seasonal  
31 differences in SO<sub>2</sub>-mortality associations, and the shape of the SO<sub>2</sub>-mortality C-R  
32 relationship. However, questions remain regarding whether SO<sub>2</sub> has an independent  
33 effect on mortality, which can be attributed to: (1) the limited number of studies that  
34 examined potential copollutant confounding, (2) the relative lack of copollutant analyses  
35 with PM<sub>2.5</sub>, (3) and the evidence indicating attenuation of SO<sub>2</sub>-mortality associations in

1 copollutant models with NO<sub>2</sub> and PM<sub>10</sub>. Additionally, all of the studies evaluated  
 2 averaged SO<sub>2</sub> concentrations over multiple monitors and used a 24-h avg exposure metric  
 3 when assigning exposure, which may not adequately capture the spatial and temporal  
 4 variability in SO<sub>2</sub> concentrations ([Section 3.4.2.2](#). and [Section 3.4.2.3](#)). While  
 5 correlations between 24-h avg and 1-h max SO<sub>2</sub> concentrations are high ( $r > 0.75$ ) at  
 6 most monitors, lower correlations may occur at some monitors and in individual studies  
 7 which can add uncertainty to the ability of 24-h avg metrics to capture peak SO<sub>2</sub>  
 8 concentrations. This section describes the evaluation of evidence for total mortality, with  
 9 respect to the causal determination for short-term exposures to SO<sub>2</sub> using the framework  
 10 described in Table II of the [Preamble](#) to the ISAs ([U.S. EPA, 2015b](#)). The key evidence,  
 11 as it relates to the causal framework, is summarized in [Table 5-41](#).

**Table 5-41 Summary of evidence, which is suggestive of, but not sufficient to infer, a causal relationship between short-term sulfur dioxide exposure and total mortality.**

Rationale for Causal Determination <sup>a</sup>	Key Evidence <sup>b</sup>	Key References <sup>b</sup>	SO <sub>2</sub> Concentrations Associated with Effects <sup>c</sup>
Consistent epidemiologic evidence from multiple, high quality studies at relevant SO <sub>2</sub> concentrations	Increases in mortality in multicity studies conducted in the U.S., Canada, Europe, and Asia	<a href="#">Section 5.5.1.2</a> <a href="#">Figure 5-15</a>	Mean 24-h avg: U.S., Canada, South America, Europe: 0.4–28.2 <sup>e</sup> ppb Asia: 0.7–>200 ppb <a href="#">Table 5-39</a>
Uncertainty regarding potential confounding by copollutants	The magnitude of SO <sub>2</sub> associations remained positive, but were reduced in copollutant models with PM <sub>10</sub> and NO <sub>2</sub> . No studies examined copollutant models with PM <sub>2.5</sub> . SO <sub>2</sub> generally exhibits low to moderate correlations with other NAAQS pollutants at collocated monitors, and attenuation of SO <sub>2</sub> –mortality association may be a reflection of spatial variability among the pollutants.	<a href="#">Section 5.5.1.3</a> <a href="#">Section 3.4.3</a>	
Uncertainty regarding exposure measurement error	U.S. studies that examine the association between short-term SO <sub>2</sub> exposures and mortality rely on single or the average of multiple monitors in an area and SO <sub>2</sub> generally has low to moderate spatial correlations across urban geographical scales.	<a href="#">Section 3.4.2.2</a>	

**Table 5-41 (Continued): Summary of evidence, which is suggestive of, but not sufficient to infer, a causal relationship between short term sulfur dioxide exposure and total mortality.**

Rationale for Causal Determination <sup>a</sup>	Key Evidence <sup>b</sup>	Key References <sup>b</sup>	SO <sub>2</sub> Concentrations Associated with Effects <sup>c</sup>
Uncertainty due to limited coherence and biological plausibility with cardiovascular and respiratory morbidity evidence	Generally supportive, but not entirely consistent epidemiologic evidence for ischemic events such as triggering a myocardial infarction. Inconclusive epidemiologic and experimental evidence for other cardiovascular endpoints. Uncertainties with respect to the independent effect of SO <sub>2</sub> on cardiovascular effects contributing to limited coherence and biological plausibility for SO <sub>2</sub> -related cardiovascular mortality, which comprises ~35% of total mortality. <sup>d</sup>	<a href="#">Section 5.3.1.11</a> <a href="#">Table 5-31</a>	
	Consistent evidence of asthma exacerbations from controlled human exposure studies demonstrating respiratory effects (i.e., respiratory symptoms and decreased lung function) in response to typically 5–10-min exposures, with generally supportive evidence from short-term SO <sub>2</sub> exposure epidemiologic studies demonstrating asthma-related morbidity, specifically hospital admissions and ED visits. Uncertainty as to the biological mechanism that explains the continuum of effects leading to SO <sub>2</sub> -related respiratory mortality, which comprises ~8% of total mortality. <sup>d</sup>	<a href="#">Section 5.2.1.8</a> <a href="#">Table 5-21</a>	

ED = emergency department; NAAQS = National Ambient Air Quality Standards; NO<sub>2</sub> = nitrogen dioxide; PM<sub>10</sub> = particulate matter with a nominal aerodynamic diameter less than or equal to 10 µm; SO<sub>2</sub> = sulfur dioxide.

<sup>a</sup>Based on aspects considered in judgments of causality and weight of evidence in causal framework in Table I and Table II of the [Preamble](#) to the ISAs ([U.S. EPA, 2015b](#)).

<sup>b</sup>Describes the key evidence and references, supporting or contradicting, contributing most heavily to causal determination and, where applicable, to uncertainties or inconsistencies. References to earlier sections indicate where full body of evidence is described.

<sup>c</sup>Describes the SO<sub>2</sub> concentrations with which the evidence is substantiated.

<sup>d</sup>Statistics taken from [American Heart Association \(2011\)](#).

<sup>e</sup>The value of 28.2 represents the median concentration from [Katsouyanni et al. \(1997\)](#).

1 Collectively, the evidence from recent multicity studies of short-term SO<sub>2</sub> exposures and  
2 mortality consistently demonstrate positive SO<sub>2</sub>-mortality associations in single-pollutant  
3 models. In the limited number studies that conducted copollutant analysis, correlations  
4 between SO<sub>2</sub> and other pollutants were low ( $r < 0.4$ ) to moderate ( $r = 0.4-0.7$ ). Although  
5 SO<sub>2</sub>-mortality associations remain positive in copollutant models with PM<sub>10</sub> and NO<sub>2</sub> they  
6 were often attenuated to a large degree, questioning the independent effect of SO<sub>2</sub> on  
7 mortality. However, SO<sub>2</sub> is more spatially variable than other pollutants as reflected in  
8 the generally low to moderate spatial correlations across urban geographical scales

1 ([Section 3.4.2.2](#)); therefore, the attenuation in SO<sub>2</sub> associations in copollutant models  
2 may be a reflection of the different degree of exposure error across pollutants  
3 ([Section 3.4.3](#)). It is important to note, the majority of recent studies that examined  
4 potential copollutant confounding have been conducted in Asian countries where  
5 correlations between pollutants may be higher, possibly limiting the generalizability of  
6 results to other study areas where SO<sub>2</sub> concentrations along with the concentrations of  
7 other air pollutants are much lower. This is reflected in the results of [Moolgavkar et al.](#)  
8 ([2013](#)) in a U.S. multicity study where there was very little evidence of attenuation of the  
9 SO<sub>2</sub>-mortality association in copollutant models with PM<sub>10</sub>; whereas, the multicity studies  
10 conducted in Asian cities showed a rather pronounced reduction in SO<sub>2</sub> associations. In  
11 addition to copollutant analyses, recent studies examined the influence of the extent of  
12 temporal adjustment and the lag structure for weather covariates on the SO<sub>2</sub>-mortality  
13 association. When examining, the extent of temporal adjustment, multiple studies  
14 reported similar SO<sub>2</sub>-mortality associations across a range of degrees of freedom per year.  
15 Only [Chen et al. \(2012b\)](#) examined the lag structure for weather covariates, specifically  
16 temperature, and found evidence of a difference in SO<sub>2</sub>-mortality associations as the  
17 number of lag days increased, but this could be attributed to the analysis being based on  
18 only one covariate for temperature.

19 An examination of factors that may contribute to increased risk of SO<sub>2</sub>-related mortality,  
20 as discussed in [Chapter 6](#), found evidence indicating that older adults (≥65 years of age)  
21 may be at increased risk with very limited evidence of potential differences by sex and  
22 socioeconomic status. In the 2008 SO<sub>x</sub> ISA, initial evidence suggested potential seasonal  
23 differences in SO<sub>2</sub>-mortality associations, particularly in the summer months. A recent  
24 multicity study conducted in Italy along with single-city studies conducted in the U.S.  
25 add to this initial body of evidence suggesting larger associations during the summer or  
26 warm months. Preliminary evidence indicates that not only season, but season in  
27 combination with specific weather patterns may modify the SO<sub>2</sub>-mortality association.  
28 Additionally, an examination of different modeling approaches provides evidence that the  
29 magnitude of the seasonal association may depend on the modeling approach employed  
30 to control for the potential confounding effects of weather ([Sacks et al., 2012](#)).

31 Those studies that examined the lag structure of associations for the SO<sub>2</sub>-mortality  
32 relationship generally observed that there is evidence of an immediate effect (i.e., lag 0 to  
33 1 days) of short-term SO<sub>2</sub> exposures on mortality. Multicity studies conducted in the U.S.  
34 and Asia have examined the shape of the C-R relationship and whether a threshold exists  
35 in both a multi- and single-city setting. These studies have used different statistical  
36 approaches and consistently demonstrated a linear relationship with no evidence of a  
37 threshold within the range of SO<sub>2</sub> concentrations where the data density is highest.  
38 The evidence of linearity in the SO<sub>2</sub>-mortality C-R relationship is further supported by

1 studies of cause-specific mortality as detailed in [Section 5.2.1.8](#) (respiratory mortality)  
2 and [Section 5.3.1.9](#) (cardiovascular). However, to date, studies have not conducted  
3 extensive analyses exploring alternatives to linearity when examining the shape of the  
4 SO<sub>2</sub>-mortality C-R relationship.

5 Overall, recent epidemiologic studies build upon and support the conclusions of the 2008  
6 SO<sub>x</sub> ISA for total mortality. However, the biological mechanism that could lead to  
7 mortality as a result of short-term SO<sub>2</sub> exposures has not been clearly characterized. This  
8 is evident when evaluating the underlying health effects (i.e., cardiovascular effects in  
9 [Section 5.3](#) and respiratory effects in [Section 5.2](#)) that could lead to cardiovascular  
10 (~35% of total mortality) and respiratory (~9% of total mortality) mortality, the  
11 components of total mortality most thoroughly evaluated ([Hoyert and Xu, 2012](#)). For  
12 cardiovascular effects the evidence is “inadequate to infer a causal relationship” with  
13 exposure to short-term SO<sub>2</sub> concentrations. An evaluation of epidemiologic studies that  
14 examined the relationship between short-term SO<sub>2</sub> exposure and cardiovascular effects  
15 found a number positive associations but the evidence was not entirely consistent. Within  
16 the collective body of evidence for cardiovascular effects, important uncertainties remain  
17 especially regarding disentangling whether there is an independent effect of SO<sub>2</sub> on  
18 cardiovascular effects, which is the same uncertainty in total mortality studies. Overall,  
19 this evidence complicates the interpretation of the relationship between SO<sub>2</sub> and  
20 cardiovascular mortality.” For respiratory effects the evidence indicates a causal  
21 relationship for short-term SO<sub>2</sub> exposures. The strongest evidence for respiratory effects  
22 is from studies examining SO<sub>2</sub>-related asthma exacerbations, specifically controlled  
23 human exposure studies demonstrating respiratory effects (i.e., respiratory symptoms and  
24 decreased lung function) ([Section 5.2.1.2](#)) in people with asthma in response to short  
25 term, generally 5–10-minutes, SO<sub>2</sub> exposures. The results from controlled human  
26 exposure studies are generally supported by epidemiologic studies reporting  
27 respiratory-related morbidity including hospital admissions and ED visits, specifically for  
28 asthma. However, the biological mechanism that explains the continuum of effects that  
29 could lead to respiratory-related mortality remains unclear. Additionally, it is important  
30 to note epidemiologic studies that examine the association between short-term SO<sub>2</sub>  
31 exposures and mortality rely on single or the average of multiple monitors over an area to  
32 assign exposure. Therefore, the exposure assessment approach used in the mortality  
33 studies may contribute to exposure measurement error and underestimate associations  
34 observed due to the spatially heterogeneous distribution of SO<sub>2</sub> concentrations over a  
35 wide area ([Section 3.4.2.2](#)). In conclusion, the consistent positive associations observed  
36 across various multicity studies is limited by the uncertainty due to whether SO<sub>2</sub> is  
37 independently associated with total mortality, the representativeness of monitors and the  
38 24-h avg SO<sub>2</sub> exposure metric in capturing the spatial and temporal variability in  
39 exposure to SO<sub>2</sub> ([Section 3.4.2.2](#) and [Section 3.4.2.3](#)), and the uncertainty in the

1 biological mechanism that could lead to SO<sub>2</sub>-induced mortality ([Section 4.3](#)).  
2 Collectively, this body of evidence is suggestive, but not sufficient to conclude there is a  
3 causal relationship between short-term SO<sub>2</sub> exposure and total mortality.

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## 5.5.2 Long-Term Exposure

4 In past reviews, a limited number of epidemiologic studies have assessed the relationship  
5 between long-term exposure to SO<sub>2</sub> and mortality in adults. The 2008 SO<sub>x</sub> ISA  
6 concluded that the scarce amount of evidence was “inadequate to infer a causal  
7 relationship” ([U.S. EPA, 2008d](#)). The 2008 SO<sub>x</sub> ISA identified concerns as to whether  
8 the observed associations were due to SO<sub>2</sub> alone, or if sulfate or other particulate SO<sub>x</sub>,  
9 such as H<sub>2</sub>SO<sub>4</sub>, or PM indices could have contributed to these associations.  
10 The possibility that the observed effects may not be due to SO<sub>2</sub>, but other constituents  
11 that come from the same source as SO<sub>2</sub>, or that PM may be more toxic in the presence of  
12 SO<sub>2</sub> or other components associated with SO<sub>2</sub>, could not be ruled out. Overall, a lack of  
13 consistency across studies, inability to distinguish potential confounding by copollutants,  
14 and uncertainties regarding the geographic scale of analysis limited the interpretation of  
15 the causal relationship between long-term exposure to SO<sub>2</sub> and mortality.

16 This section includes a review of the evidence for an association between long-term  
17 exposure to SO<sub>2</sub> and mortality, integrating evidence presented in previous NAAQS  
18 reviews with evidence that is newly available to this review. The evidence in this section  
19 will focus on epidemiologic studies because experimental studies of long-term exposure  
20 and mortality are generally not conducted. However, this section will draw from the  
21 morbidity evidence presented for different health endpoints across the scientific  
22 disciplines (i.e., animal toxicological, controlled human exposure studies, and  
23 epidemiology) to support the association observed for cause-specific mortality. Studies  
24 are discussed by geographic region, with U.S. studies discussed in [Section 5.5.2.1](#),  
25 European studies in [Section 5.5.2.2](#), and Asian studies in [Section 5.5.2.3](#). [Section 5.5.2.4](#)  
26 describes studies that evaluated the SO<sub>2</sub>-mortality relationship over small geographic  
27 scales. A brief summary of the studies included in these sections can be found in  
28 [Table 5-42](#).

**Table 5-42 Summary of studies of long-term exposure and mortality.**

Study	Location Years	Mean SO <sub>2</sub> ppb	Exposure Assessment	Correlation with Other Pollutants	Selected Effect Estimates (95% CI) <sup>a</sup>
<a href="#">†Hart et al. (2011)</a>	U.S. (SO <sub>2</sub> : 1985–2000; follow-up: 1985–2000)	4.8	Annual average exposures based on residential address from model using spatial smoothing and GIS-based covariates; current calendar year and long-term average from 1985–2000		All cause: 1.09 (1.03, 1.15) Respiratory: 1.10 (0.89, 1.35) COPD: 0.93 (0.71, 1.22) Lung cancer: 1.11 (0.98, 1.27)
<a href="#">Krewski et al. (2000)</a>	U.S. HSC: (SO <sub>2</sub> : 1977–1985; follow-up: 1974–1991) ACS: (SO <sub>2</sub> : 1980; follow-up: 1982–1989)	HSC: 1.6–24.0 ACS: 9.3	HSC: mean levels from central site monitors ACS: City-specific annual mean	HSC: PM <sub>2.5</sub> : 0.85 SO <sub>4</sub> : 0.85 NO <sub>2</sub> : 0.84	All cause: HSC: 1.05 (1.02, 1.09) ACS: 1.06 (1.05, 1.07) Lung cancer: HSC: 1.03 (0.91, 1.16)
<a href="#">Pope et al. (2002)</a>	U.S. (SO <sub>2</sub> : 1982–1998; follow-up: 1982–1998)	6.7–9.7	Average across monitoring stations in each metropolitan area for each study year using daily average (i.e., 24-h avg) concentrations, averaged over 1 yr (1980) and the entire study period (1982–1998)		All cause: 1.03 (1.02, 1.05)
<a href="#">†Lipfert et al. (2009)</a>	U.S. (SO <sub>2</sub> : 1999; follow-up: 1976–2001)	4.3	County-level estimates from AER plume-in-grid air quality model; based on 1999 emissions inventory from point and area sources for 36 × 36-km grid squares	Subject-weighted: EC: 0.68 NO <sub>x</sub> : 0.65 SO <sub>4</sub> <sup>2-</sup> : 0.79	All cause: 1.02 (1.01, 1.03)
<a href="#">†Krewski et al. (2009)</a>	U.S. (SO <sub>2</sub> : 1980; follow-up: 1982–2000)	9.6	City-specific annual mean		All cause: 1.02 (1.02, 1.03) Lung cancer: 1.00 (0.98, 1.02)

**Table 5-42 (Continued): Summary of studies of long term exposure and mortality.**

Study	Location Years	Mean SO <sub>2</sub> ppb	Exposure Assessment	Correlation with Other Pollutants	Selected Effect Estimates (95% CI) <sup>a</sup>
<a href="#">Lipfert et al. (2006a)</a>	U.S. (SO <sub>2</sub> : 1999–2001; follow-up: 1997–2001)	16.3	County-level “peak” concentrations	Subject-weighted: PM <sub>2.5</sub> : 0.71 NO <sub>2</sub> : 0.41 Peak O <sub>3</sub> : 0.21 Peak CO: 0.41 SO <sub>4</sub> <sup>2-</sup> : 0.77 OC: 0.34 EC: -0.13	All cause: 0.99 (0.97, 1.01)
<a href="#">Abbey et al. (1999)</a>	U.S. (SO <sub>2</sub> : 1966–1992; follow-up: 1977–1992)	5.6 IQR: 3.7	ZIP code-level mo averages cumulated and averaged over time	Mean concentration: PM <sub>10</sub> : 0.31 O <sub>3</sub> : 0.09 SO <sub>4</sub> : 0.68 When exceeding 100 ppb (O <sub>3</sub> ) or 100 µg/m <sup>3</sup> (PM <sub>10</sub> ) PM <sub>10</sub> : -0.05 O <sub>3</sub> : 0.13	All cause: Men: 1.07 (0.92, 1.25) Women: 1.00 (0.88, 1.14) Lung cancer: Men: 2.52 (1.34, 4.77) Women: 4.40 (2.34, 8.33)
<a href="#">Beelen et al. (2008b)</a>	Netherlands (SO <sub>2</sub> : 1976–1985, 1987–1996; follow-up: 1987–1996)	5.2 SD: 1.9	IDW to regional background monitors at baseline residential address		All cause: 0.94 (0.80, 1.10) Respiratory: 0.92 (0.64, 1.31) Lung cancer: 0.99 (0.73, 1.35)
<a href="#">Nafstad et al. (2004)</a>	Norway (SO <sub>2</sub> : 1974–1995; follow-up: 1972–1998)	3.6	Model results (per square kilometer) for some year/urban locations, supplemented with background monitoring data		All cause: 0.97 (0.95, 1.01) Respiratory: 1.04 (0.91, 1.19) Lung cancer: 1.00 (0.91, 1.11)
<a href="#">Filleul et al. (2005)</a>	France (SO <sub>2</sub> : 1974–1976; follow-up: 1974–2000)	3.0–8.2	3-yr mean concentrations for 24 areas in seven different cities	BS: 0.29 TSP: 0.17 NO -0.01 NO <sub>2</sub> -0.10	All cause: 1.01 (0.99, 1.04) Lung cancer: 0.99 (0.90, 1.09)
<a href="#">†Bentayeb et al. (2015)</a>	France (SO <sub>2</sub> : 1989–2008; follow-up: 1989–2013)	2.3	Annual concentrations from CHIMERE chemical-transport model	O <sub>3</sub> : -0.13 PM <sub>2.5</sub> : 0.58 PM <sub>10</sub> : 0.57 PM <sub>10-2.5</sub> : 0.30 NO <sub>2</sub> : 0.56	All cause: 1.23 (0.98, 1.52) Respiratory: 0.76 (0.43, 1.33) CVD: 0.85 (0.44, 1.67)

**Table 5-42 (Continued): Summary of studies of long term exposure and mortality.**

Study	Location Years	Mean SO <sub>2</sub> ppb	Exposure Assessment	Correlation with Other Pollutants	Selected Effect Estimates (95% CI) <sup>a</sup>
† <a href="#">Hansell et al. (2016)</a>	England (SO <sub>2</sub> : 1971, 1981, 1991; follow-up: 1971–2009)	1971: 32.4 1981: 16.4 1991: 11.2	LUR models for annual concentrations in 1971, 1981 and 1991		1991 All cause: 1.09 (1.05, 1.15) Resp: 1.20 (1.09, 1.33) COPD: 1.43 (1.23, 1.66) Lung cancer: 1.29 (1.12, 1.47) CVD: 1.05 (0.99, 1.13)
† <a href="#">Carey et al. (2013)</a>	England (SO <sub>2</sub> : 2002; follow-up: 2003–2007)	1.5 SD: 0.8 IQR: 0.8	Annual mean for 1-km grid cells from air dispersion models (poor validation results for SO <sub>2</sub> )	PM <sub>10</sub> : 0.45 NO <sub>2</sub> : 0.37 O <sub>3</sub> : -0.41	All cause: 1.26 (1.19, 1.34) Respiratory: 1.67 (1.42, 1.97) Lung cancer: 1.34 (1.06, 1.58)
† <a href="#">Ancona et al. (2015)</a>	Rome, Italy (SO <sub>x</sub> : 2001–2010; follow-up: 2001–2010)	2.5 µg/m <sup>3</sup> SO <sub>x</sub> SD: 0.9	Lagrangian particle dispersion model (SPRAY Ver. 5) used SO <sub>x</sub> as exposure marker for petrochemical refinery emissions	PM <sub>10</sub> : 0.81 H <sub>2</sub> S: 0.78	All cause: Men: 1.04 (0.92, 1.18) Women: 0.93 (0.81, 1.07) CVD: Men: 1.08 (0.89, 1.31) Women: 1.00 (0.81, 1.25) IHD: Men: 1.05 (0.79, 1.41) Women: 1.25 (0.89, 1.75) Respiratory: Men: 1.31 (0.88, 1.95) Women: 0.64 (0.32, 1.28)
† <a href="#">Cao et al. (2011)</a>	China (SO <sub>2</sub> : 1991–2000; follow-up: 1991–2000)	27.7	Annual average by linking fixed site monitoring data with residential ZIP code		All cause: 1.02 (1.02, 1.03) CVD: 1.02 (1.00, 1.03) Respiratory: 1.04 (1.02, 1.06) Lung cancer: 1.06 (1.03, 1.08)

**Table 5-42 (Continued): Summary of studies of long term exposure and mortality.**

Study	Location Years	Mean SO <sub>2</sub> ppb	Exposure Assessment	Correlation with Other Pollutants	Selected Effect Estimates (95% CI) <sup>a</sup>
<a href="#">†Chen et al. (2016)</a>	China (SO <sub>2</sub> : 1998- 2009; follow- up: 1998- 2009)	25.5	1-yr avg and time-varying exposure from monitoring stations calculated from 24-h avg		Lung cancer: 1.02 (1.01, 1.03)
<a href="#">†Dong et al. (2012)</a>	China (SO <sub>2</sub> : 1998–2009; follow-up: 1998–2009)	23.9 SD: 5.7	1-yr avg from five monitors		Respiratory: 1.05 (0.96, 1.16)
<a href="#">†Zhang et al. (2011)</a>	Shenyang, China (SO <sub>2</sub> : 1998–2009; follow-up: 1998–2009)	23.9	1-yr avg and yearly deviations in each of five monitoring stations calculated from 24-h avg		All cause: 0.93 (0.90, 0.99)
<a href="#">†Katanoda et al. (2011)</a>	Japan (SO <sub>2</sub> : 1974–1983; follow-up: 1983–1995)	2.4–19.0	Annual mean concentrations from monitoring station near each of eight study areas	Pearson: SPM: 0.47	Respiratory: 1.20 (1.15, 1.24) COPD: 1.15 (0.94, 1.41) Pneumonia: 1.20 (1.16, 1.25) Lung cancer: 1.12 (1.03, 1.22)
<a href="#">Elliott et al. (2007)</a>	Great Britain (SO <sub>2</sub> : 1966–1970, 1990–1994; follow-up: 1982–1986, 1994–1998)	12.2–41.4	4-yr exposure windows from annual average concentrations from monitoring sites located in residential areas		All cause: 1.02 (1.02, 1.02) Respiratory: 1.06 (1.06, 1.07) Lung cancer: 1.00 (0.99, 1.01)
<a href="#">†Bennett et al. (2014)</a>	Warwickshire, U.K. (SO <sub>2</sub> : 2010; mortality data: 2007–2012)	NR	Single recorded level for each ward from 2010		Heart failure: 1.11 (0.988, 1.22)

**Table 5-42 (Continued): Summary of studies of long term exposure and mortality.**

Study	Location Years	Mean SO <sub>2</sub> ppb	Exposure Assessment	Correlation with Other Pollutants	Selected Effect Estimates (95% CI) <sup>a</sup>
† <a href="#">Wang et al. (2009)</a>	Brisbane, Australia  (SO <sub>2</sub> : 1996–2004; follow-up: 1996–2004)	5.4	1-h max from 13 monitoring stations aggregated to annual means used with IDW		Cardiopulmonary: 1.26 (1.03, 1.54)
† <a href="#">Wang et al. (2014a)</a>	China  (SO <sub>2</sub> : 2004–2010; life table: 2010)	46.31	Annual average across monitoring stations in 85 city regions		Life expectancy: 10-µg/m <sup>3</sup> increase in SO <sub>2</sub> correlated with 0.28–0.47 yr decrease in life expectancy

ACS = American Cancer Society; AER = Atmospheric and Environmental Research; BS = black smoke; CHIMERE = regional chemistry transport model; CI = confidence interval; CO = carbon monoxide; COPD = chronic obstructive pulmonary disease; CVD = cardiovascular disease; EC = elemental carbon; GIS = geographic information systems; H<sub>2</sub>S = hydrogen sulfide; HSC = Harvard Six Cities; IDW = inverse distance weighting; IHD = ischemic heart disease; IQR = interquartile range; LUR = land use regression; NO = nitric oxide; NO<sub>2</sub> = nitrogen dioxide; NO<sub>x</sub> = the sum of NO and NO<sub>2</sub>; NR = not reported; O<sub>3</sub> = ozone; OC = organic carbon; PM<sub>2.5</sub> = particulate matter with a nominal aerodynamic diameter less than or equal to 2.5 µm; PM<sub>10</sub> = particulate matter with a nominal aerodynamic diameter less than or equal to 10 µm; PM<sub>10-2.5</sub> = particulate matter with a nominal aerodynamic diameter less than or equal to 10 µm and greater than a nominal 2.5 µm; SD = standard deviation; SO<sub>2</sub> = sulfur dioxide; SO<sub>4</sub> = sulfate; SO<sub>4</sub><sup>2-</sup> = sulfate; SO<sub>x</sub> = oxides of sulfur; SPM = suspended particulate matter; TSP = total suspended solids.

<sup>a</sup>Effect estimates are standardized per 5-ppb increase in SO<sub>2</sub> concentrations.

†Studies published since the 2008 ISA for Sulfur Oxides.

### 5.5.2.1 U.S. Cohort Studies

1 A number of longitudinal cohort studies have been conducted in the U.S. and have found  
2 small, statistically significant positive associations between long-term exposure to SO<sub>2</sub>  
3 and total mortality ([Hart et al., 2011](#); [Lipfert et al., 2009](#); [Pope et al., 2002](#); [Krewski et](#)  
4 [al., 2000](#)). The body of evidence is smaller and less consistent when these studies  
5 examine cause-specific mortality, although [Hart et al. \(2011\)](#) observed positive, yet  
6 imprecise associations with respiratory, lung cancer, and cardiovascular mortality. In the  
7 Trucking Industry Particle Study, [Hart et al. \(2011\)](#) used the work records for over  
8 50,000 men employed in four U.S. trucking companies to identify all-cause and  
9 cause-specific mortality. Occupational exposures were assigned based on job title, while  
10 exposure to ambient air pollution (i.e., PM<sub>10</sub>, SO<sub>2</sub>, and NO<sub>2</sub> averaged over the study  
11 period) were determined using spatial smoothing and geographic information system  
12 (GIS)-based covariates based on residential address. All three pollutants were  
13 independently associated with all-cause mortality, with central estimates the highest for  
14 the association with NO<sub>2</sub> and lowest for the association with PM<sub>10</sub>. Both NO<sub>2</sub> and SO<sub>2</sub>

1 were positively associated with lung cancer, cardiovascular disease, and respiratory  
2 disease mortality, and negatively associated with COPD mortality. Correlation  
3 coefficients between SO<sub>2</sub> and other measured air pollutants were not reported, making it  
4 difficult to evaluate for the potential of copollutants confounding on the associations  
5 attributed to SO<sub>2</sub>. There was no evidence of confounding by occupational exposures  
6 (based on job-title).

7 The Harvard Six Cities study is a prospective cohort study of the effects of air pollution  
8 with the main focus on PM components in six U.S. cities and provides limited evidence  
9 for an association between mortality and exposure to SO<sub>2</sub>. Cox proportional hazards  
10 regression was conducted with data from a 14- to 16-year follow-up study of 8,111 adults  
11 in the six cities. [Dockery et al. \(1993\)](#) reported that lung cancer and cardiopulmonary  
12 mortality were more strongly associated with the concentrations of inhalable and fine PM  
13 and sulfate particles than with the levels of TSP, SO<sub>2</sub>, NO<sub>2</sub>, or acidity of the aerosol.  
14 [Krewski et al. \(2000\)](#) conducted a sensitivity analysis of the Harvard Six Cities study and  
15 examined associations between gaseous pollutants (i.e., O<sub>3</sub>, NO<sub>2</sub>, SO<sub>2</sub>, and CO) and  
16 mortality, observing positive associations between SO<sub>2</sub> and total mortality and  
17 cardiopulmonary deaths. In this data set SO<sub>2</sub> was highly correlated with PM<sub>2.5</sub> ( $r = 0.85$ ),  
18 sulfate ( $r = 0.85$ ), and NO<sub>2</sub> ( $r = 0.84$ ), making it difficult to attribute the observed  
19 associations to an independent effect of SO<sub>2</sub>.

20 [Pope et al. \(1995\)](#) investigated associations between long-term exposure to PM and the  
21 mortality outcomes in the ACS cohort and provides limited evidence for an association  
22 between exposure to SO<sub>2</sub> and mortality. Ambient air pollution data from 151 U.S.  
23 metropolitan areas in 1981 were linked with individual risk factors in 552,138 adults who  
24 resided in these areas when enrolled in the prospective study in 1982. Death outcomes  
25 were ascertained through 1989. Gaseous pollutants were not analyzed in the original  
26 analysis. Extensive reanalysis of the ACS data, augmented with additional gaseous  
27 pollutants data, showed positive associations between mortality and SO<sub>2</sub>, but not for the  
28 other gaseous pollutants ([Jerrett et al., 2003](#); [Krewski et al., 2000](#)). [Pope et al. \(2002\)](#)  
29 extended analysis of the ACS cohort with double the follow-up time (to 1998) and triple  
30 the number of deaths compared to the original study ([Pope et al., 1995](#)). Both PM<sub>2.5</sub> and  
31 SO<sub>2</sub> were associated with all the mortality outcomes, although only SO<sub>2</sub> was associated  
32 with the deaths attributable to “all other causes.” The association of SO<sub>2</sub> with mortality  
33 for “all other causes” makes it difficult to interpret the effect estimates due to a lack of  
34 biological plausibility for this association. More recently, [Krewski et al. \(2009\)](#)  
35 conducted an extended reanalysis of the study conducted by [Pope et al. \(2002\)](#), including  
36 examination of ecologic covariates (e.g., education attainment, housing characteristics,  
37 income) and evaluation of exposure windows. The inclusion of ecologic covariates  
38 generally resulted in increased risk estimates, with the greatest effect on mortality from

1 IHD. The authors also evaluated individual time-dependent exposure profiles to examine  
2 whether there is a critical exposure time window most strongly associated with mortality  
3 from ambient air pollution. The time window immediately preceding death (1–5 years)  
4 produced the strongest effects for mortality associated with exposure to SO<sub>2</sub>, while later  
5 time windows (6–10 years and 11–15 years) generally showed null associations between  
6 SO<sub>2</sub> and mortality.

7 [Lipfert et al. \(2000a\)](#) conducted an analysis of a national cohort of ~70,000 male U.S.  
8 military veterans who were diagnosed as hypertensive in the mid-1970s and were  
9 followed up for about 21 years (up to 1996) and provides scant evidence for an  
10 association between exposure to SO<sub>2</sub> and mortality. This cohort was 35% black and 57%  
11 of the cohort were current smokers (81% of the cohort had been smokers at one time).  
12 PM<sub>2.5</sub>, PM<sub>10</sub>, PM<sub>10-2.5</sub>, TSP, sulfate, CO, O<sub>3</sub>, NO<sub>2</sub>, SO<sub>2</sub>, and lead (Pb) were examined in  
13 these analyses. The county of residence at the time of entry to the study was used to  
14 estimate exposures. Four exposure periods (from 1960 to 1996) were defined, and deaths  
15 during each of the three most recent exposure periods were considered. The results for  
16 SO<sub>2</sub> as part of their preliminary screening were generally null. [Lipfert et al. \(2000a\)](#) noted  
17 that Pb and SO<sub>2</sub> were not found to be associated with mortality, thus, were not considered  
18 further. They also noted that the pollution effect estimates were sensitive to the regression  
19 model specification, exposure periods, and the inclusion of ecological and individual  
20 variables. The authors reported that indications of concurrent mortality risks were found  
21 for NO<sub>2</sub> and peak O<sub>3</sub>. In a subsequent analysis, [Lipfert et al. \(2006b\)](#) examined  
22 associations between traffic density and mortality in the same cohort, extending the  
23 follow-up period to 2001. As in their previous study ([Lipfert et al., 2000a](#)), four exposure  
24 periods were considered but included more recent years, and reported that traffic density  
25 was a better predictor of mortality than ambient air pollution variables with the possible  
26 exception of O<sub>3</sub>. The log-transformed traffic density variable was only weakly correlated  
27 with SO<sub>2</sub> ( $r = 0.32$ ) and PM<sub>2.5</sub> ( $r = 0.50$ ) in this data set. [Lipfert et al. \(2006a\)](#) further  
28 extended analysis of the veterans' cohort data to include the U.S. EPA's Speciation  
29 Trends Network (STN) data, which collected chemical components of PM<sub>2.5</sub>. They  
30 analyzed the STN data for 2002, again using county-level averages. PM<sub>2.5</sub> and gaseous  
31 pollutants data for 1999 through 2001 were also analyzed. As in the previous study  
32 ([Lipfert et al., 2006b](#)), traffic density was the most important predictor of mortality, but  
33 associations were also observed for elemental carbon, vanadium, nickel, and nitrate.  
34 Ozone, NO<sub>2</sub>, and PM<sub>10</sub> also showed positive but weaker associations. Once again, no  
35 associations were observed between long-term exposure to SO<sub>2</sub> and mortality. [Lipfert et](#)  
36 [al. \(2009\)](#) re-examined these associations, this time averaging the exposure variables over  
37 the entire follow-up period (1976–2001). For this exposure period, they observed positive  
38 associations between SO<sub>2</sub> and mortality. When the data set was stratified by county-level  
39 traffic density, the SO<sub>2</sub> association with mortality was stronger in the counties with high

1 density traffic, and attenuated to near null in the counties with lower traffic density.  
2 The fact that the association between long-term exposure to SO<sub>2</sub> and mortality is only  
3 observed in areas where traffic density has been characterized as high, along with the  
4 moderate to strong correlations between SO<sub>2</sub> and other traffic-related pollutants  
5 (e.g., PM<sub>2.5</sub>, NO<sub>2</sub>, NO<sub>x</sub>, EC) in these analyses, makes it difficult to discern whether these  
6 associations are truly attributable to SO<sub>2</sub>, or could be due to some other traffic-related  
7 pollutant or mixture of pollutants.

8 [Abbey et al. \(1999\)](#) investigated associations between long-term ambient concentrations  
9 of PM<sub>10</sub>, sulfate, SO<sub>2</sub>, O<sub>3</sub>, and NO<sub>2</sub> and mortality in a cohort of 6,338 nonsmoking  
10 California Seventh-Day Adventists. Monthly indices of ambient air pollutant  
11 concentrations at 348 monitoring stations throughout California were interpolated to ZIP  
12 codes according to home or work location of study participants, cumulated, and then  
13 averaged over time. They reported associations between PM<sub>10</sub> and total mortality for  
14 males and nonmalignant respiratory mortality for both sexes. SO<sub>2</sub> was positively  
15 associated with total mortality for males but not for females. Generally, null associations  
16 were observed for cardiopulmonary deaths and respiratory mortality for both males and  
17 females.

18 Overall, the majority of the limited evidence informing the association between long-term  
19 exposure to SO<sub>2</sub> and mortality from U.S. cohort studies was included in the 2008 SO<sub>x</sub>  
20 ISA. A recent cohort study of male truck drivers ([Hart et al., 2011](#)) provided some  
21 additional evidence for an association between long-term exposure to SO<sub>2</sub> and both  
22 respiratory mortality and total mortality, while updates to the ACS ([Krewski et al., 2009](#))  
23 and Veterans ([Lipfert et al., 2009](#)) cohort studies provides some limited evidence for an  
24 association with total mortality, although none of these recent studies help to resolve the  
25 uncertainties identified in the 2008 SO<sub>x</sub> ISA related to copollutant confounding or the  
26 geographic scale of the analysis.

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### 5.5.2.2 European Cohort Studies

27 A number of European cohort studies examined the association between both total  
28 mortality and cause-specific mortality and SO<sub>2</sub> concentrations, and found generally  
29 inconsistent results. [Beelen et al. \(2008b\)](#) analyzed data from the Netherlands Cohort  
30 Study on Diet and Cancer with 120,852 subjects. Traffic-related pollutants (BS, NO<sub>2</sub>,  
31 SO<sub>2</sub>, PM<sub>2.5</sub>), and four types of traffic-exposure estimates were analyzed. While the local  
32 traffic component was estimated for BS, NO<sub>2</sub>, and PM<sub>2.5</sub>, no such attempt was made for  
33 SO<sub>2</sub> because there was “virtually no traffic contributions to this pollutant.” Thus, only  
34 “background” SO<sub>2</sub> levels were reflected in the exposure estimates. Traffic intensity on the

1 nearest road was associated with all-cause mortality and a larger RR was observed for  
2 respiratory mortality. Results were similar for BS, NO<sub>2</sub> and PM<sub>2.5</sub>, but no associations  
3 were observed for SO<sub>2</sub>.

4 Several studies noting declining SO<sub>2</sub> concentrations during the follow-up period (from  
5 the mid-1970s through the mid-1990s) did not observe positive associations with  
6 mortality. [Nafstad et al. \(2004\)](#) linked data from 16,209 males (aged 0 to 49 years) living  
7 in Oslo, Norway with data from the Norwegian Death Register and with estimates of the  
8 average annual air pollution levels at the participants' home addresses. PM was not  
9 considered in this study because measurement methods changed during the study period.  
10 Exposure estimates for NO<sub>x</sub> and SO<sub>2</sub> were constructed using models based on subject  
11 addresses, emission data for industry, heating, and traffic, and measured concentrations.  
12 While NO<sub>x</sub> was associated with total, respiratory, lung cancer, and ischemic heart disease  
13 deaths, SO<sub>2</sub> did not show any associations with mortality. In this study, SO<sub>2</sub> levels were  
14 reduced by a factor of 7 during the study period (from 5.6 ppb in 1974 to 0.8 ppb in  
15 1995), whereas NO<sub>x</sub> did not show any clear downward trend. [Filleul et al. \(2005\)](#) linked  
16 daily measurements of SO<sub>2</sub>, TSP, BS, NO<sub>2</sub>, and NO with data on mortality for  
17 14,284 adults who resided in 24 areas from seven French cities enrolled in the Air  
18 Pollution and Chronic Respiratory Diseases survey in 1974. Models were run before and  
19 after exclusion of six area monitors influenced by local traffic as determined by a  
20 NO:NO<sub>2</sub> ratio of >3. Before exclusion of the six areas, none of the air pollutants was  
21 associated with mortality outcomes. After exclusion of these areas, analyses showed  
22 associations between total mortality and TSP, BS, NO<sub>2</sub>, and NO but not SO<sub>2</sub> or  
23 acidimetric measurements. In this study, SO<sub>2</sub> levels declined by a factor of two to three  
24 (depending on the city) between the 1974 through 1976 period and the 1990 through  
25 1997 period. The changes in air pollution levels over the study period complicate  
26 interpretation of reported effect estimates.

27 [Carey et al. \(2013\)](#) examined the associations between long-term exposure to ambient air  
28 pollutants and total and cause-specific mortality in a national English cohort  
29 (n = 835,607). The authors used air dispersion models to estimate annual mean air  
30 pollution concentrations for 1-km grid cells for a single year prior to the follow-up  
31 period. Model validation using national air quality monitors and networks demonstrated  
32 good agreement for NO<sub>2</sub> and O<sub>3</sub>, moderate agreement for PM<sub>10</sub> and PM<sub>2.5</sub>, but relatively  
33 poor agreement for SO<sub>2</sub> ( $R^2 = 0-0.39$ ). The authors observed positive associations with  
34 total mortality for all of the air pollutants, and these associations were stronger for PM<sub>2.5</sub>,  
35 NO<sub>2</sub>, and SO<sub>2</sub> and respiratory and lung cancer mortality. Associations were generally not  
36 observed with cardiovascular mortality and any of the pollutants. Although the authors  
37 observed positive associations between SO<sub>2</sub> and mortality (especially respiratory  
38 mortality), these associations are difficult to interpret due to the poor validation of the

1 dispersion model for SO<sub>2</sub>. [Ancona et al. \(2015\)](#) used a Lagrangian particle dispersion  
2 model (see [Section 3.3.2.4](#) for details) to estimate annual means of SO<sub>x</sub> (as an exposure  
3 marker for emissions from a petrochemical refinery) in Rome, Italy and associations with  
4 all-cause and cause-specific mortality among men and women. The authors did not  
5 present any validation results for their dispersion model. Predicted concentrations of SO<sub>x</sub>  
6 were highly correlated with predicted concentrations of PM<sub>10</sub> ( $r = 0.81$ ), and because SO<sub>x</sub>  
7 was used as an exposure marker for petrochemical refinery emissions, it would likely be  
8 correlated with other stack or fugitive refinery emissions, including PM<sub>2.5</sub> and VOCs.  
9 The authors observed associations for all-cause mortality and CVD mortality that were  
10 near the null value for both men and women. When restricted to IHD mortality, the  
11 association remained near the null value for men, but was elevated among women.  
12 Conversely, slightly increased risks were observed for respiratory mortality and mortality  
13 due to digestive diseases among men, while the risks for these were attenuated among  
14 women. Due to the unknown validity of the dispersion model and the high correlations  
15 with additional copollutants, it is difficult to interpret these associations.

16 Overall, the results of the European cohort studies provide very little evidence for an  
17 association between long-term exposure to SO<sub>2</sub> and mortality. The majority of these  
18 studies were included in the 2008 SO<sub>x</sub> ISA ([Beelen et al., 2008b](#); [Filleul et al., 2005](#);  
19 [Nafstad et al., 2004](#)). Only the study by [Carey et al. \(2013\)](#) provided new evidence for  
20 this review. None of the studies used copollutant models or accounted for potential  
21 confounding or effect measure modification by other ambient air pollutants, including  
22 sulfate. The study by [Carey et al. \(2013\)](#) had the potential to inform uncertainties related  
23 to the geographic scale of the exposure assessment; however, the poor validation results  
24 of the dispersion model used to estimate the SO<sub>2</sub> concentrations for 1-km grid cells  
25 makes it difficult to interpret these results.

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### 5.5.2.3 Asian Cohort Studies

26 Four recent cohort studies have been conducted in China to examine the association  
27 between long-term exposure to SO<sub>2</sub> and mortality ([Chen et al., 2016](#); [Dong et al., 2012](#);  
28 [Cao et al., 2011](#); [Zhang et al., 2011](#)) and observed inconsistent results. Each of these  
29 studies used annual area-wide average concentrations from fixed site monitoring stations  
30 to assign exposure. Notably, the mean SO<sub>2</sub> concentrations in these study areas was much  
31 higher than concentrations observed in other locations (see [Table 5-42](#)). [Cao et al. \(2011\)](#)  
32 observed generally modest positive associations with all-cause, respiratory and lung  
33 cancer mortality. [Chen et al. \(2016\)](#) observed a positive association with lung cancer  
34 mortality, though the correlation between SO<sub>2</sub> and PM<sub>10</sub> was high ( $r > 0.94$ ), and it is  
35 possible that copollutant confounding could at least partially explain this relationship.

1 [Dong et al. \(2012\)](#) observed a modest, positive association with respiratory mortality,  
2 while [Zhang et al. \(2011\)](#) observed modest negative associations with all-cause mortality.

3 [Katanoda et al. \(2011\)](#) conducted a cohort study in Japan investigating the association  
4 between long-term exposure to PM<sub>2.5</sub>, NO<sub>2</sub>, and SO<sub>2</sub> and lung cancer and respiratory  
5 mortality. The authors used annual mean concentrations from fixed site monitoring  
6 stations near each of eight study areas. The authors observed positive associations  
7 between long-term exposure to PM<sub>2.5</sub>, NO<sub>2</sub>, and SO<sub>2</sub> and lung cancer and respiratory  
8 mortality, with the strongest effect observed for the SO<sub>2</sub> associations.

9 Overall, these recent Asian cohort studies provide some new evidence of an association  
10 between long-term exposure to SO<sub>2</sub> and mortality; however, they generally report similar  
11 associations for other ambient air pollutants, and do not evaluate for potential bias due to  
12 copollutant confounding (using copollutants models, reporting correlation coefficients  
13 between SO<sub>2</sub> and other measured pollutants, or other methods). Generally, these recent  
14 studies do not help to resolve the uncertainties identified in the 2008 SO<sub>x</sub> ISA related to  
15 copollutant confounding or the geographic scale of the analysis.

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#### 5.5.2.4 Cross-Sectional Analysis Using Small Geographic Scale

16 [Elliott et al. \(2007\)](#) examined associations of BS and SO<sub>2</sub> with mortality in Great Britain  
17 using a cross-sectional analysis. However, unlike the earlier ecological cross-sectional  
18 mortality analyses in the U.S. in which mortality rates and air pollution levels were  
19 compared using large geographic boundaries (i.e., MSAs or counties), [Elliott et al. \(2007\)](#)  
20 compared the mortality rates and air pollution concentrations using a much smaller  
21 geographic unit, the electoral ward, with a mean area of 7.4 km<sup>2</sup> and a mean population  
22 of 5,301 per electoral ward. Of note, SO<sub>2</sub> levels declined from 41.4 ppb in the 1966 to  
23 1970 period to 12.2 ppb in 1990 to 1994. This type of analysis does not allow  
24 adjustments for individual risk factors, but the study did adjust for socioeconomic status  
25 data available for each ward from the 1991 census. Social deprivation and air pollution  
26 were more highly correlated in the earlier exposure windows. They observed positive  
27 associations for both BS and SO<sub>2</sub> and mortality outcomes. The estimated effects were  
28 stronger for respiratory illness than other causes of mortality for the most recent exposure  
29 period and most recent mortality period (when pollution levels were lower).  
30 The adjustment for social deprivation reduced the effect estimates for both pollutants.  
31 Simultaneous inclusion of BS and SO<sub>2</sub> reduced effect estimates for BS but not SO<sub>2</sub>.  
32 [Elliott et al. \(2007\)](#) noted that the results were consistent with those reported in the  
33 [Krewski et al. \(2000\)](#) reanalysis of the ACS study. Similarly, [Bennett et al. \(2014\)](#)  
34 observed a positive association between ward-level SO<sub>2</sub> concentrations measured in 2010

1 and ward-level data on heart failure mortality from 2007–2012 in Warwickshire, U.K.  
2 Stronger associations were observed for estimated benzene exposure in this population,  
3 while estimated PM exposure was inversely associated with heart failure mortality. These  
4 analyses are ecological, but the exposure estimates in the smaller area compared to that in  
5 the U.S. cohort studies may have resulted in less exposure misclassification error, and the  
6 large underlying population appears to be reflected in the narrow confidence bands of  
7 effect estimates.

8 In a recent cross-sectional analysis, [Wang et al. \(2009\)](#) examined the long-term exposure  
9 to gaseous air pollutants (i.e., NO<sub>2</sub>, O<sub>3</sub>, and SO<sub>2</sub>) and cardio-respiratory mortality in  
10 Brisbane, Australia. Pollutant concentrations were estimated for small geographic units,  
11 statistical local areas, using IDW. The authors observed a positive association between  
12 cardio-respiratory mortality and SO<sub>2</sub>, but generally null associations for NO<sub>2</sub> and O<sub>3</sub>.

13 The results of these cross-sectional studies are inconsistent, with much higher mortality  
14 effects attributed to SO<sub>2</sub> in Brisbane, Australia ([Wang et al., 2009](#)) and Warwickshire,  
15 U.K. ([Bennett et al., 2014](#)) than in Great Britain ([Elliott et al., 2007](#)). While each of these  
16 studies took a geospatial approach to their analyses, the cross-sectional nature of the  
17 study designs and the lack of control for potential bias due to copollutant confounding  
18 limit the interpretation of their results.

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### 5.5.2.5 Summary and Causal Determination

19 [Figure 5-26](#) presents total mortality effect estimates associated with long-term exposure  
20 to SO<sub>2</sub>. The overall range of effects spans 0.93 to 1.26 per 5-ppb increase in the annual  
21 (or longer period) average SO<sub>2</sub> concentration. The analyses of the Harvard Six Cities and  
22 the ACS cohort data, which likely provide effect estimates that are most useful for  
23 evaluating possible health effects in the U.S., observed effect estimates of 1.02 to 1.06,  
24 while the effect estimate from the recent cohort study of truck drivers was 1.09. Note that  
25 each of the U.S. cohort studies has its own advantages and limitations. The Harvard Six  
26 Cities data have a small number of exposure estimates, but the study cities were carefully  
27 chosen to represent a range of air pollutant exposures. The ACS cohort had far more  
28 subjects, but the population was more highly educated than the representative U.S.  
29 population. Because educational status appeared to be an important effect modifier of air  
30 pollution effects in both studies, the overall effect estimate for the ACS cohort may  
31 underestimate the more general population. The evidence from the cohort studies  
32 conducted in Europe and Asia is generally similar to that observed from the U.S. cohort  
33 studies. That is, the magnitude of the effect estimates is generally similar, although there  
34 is greater inconsistency in the direction of the association. Also, the effect estimate

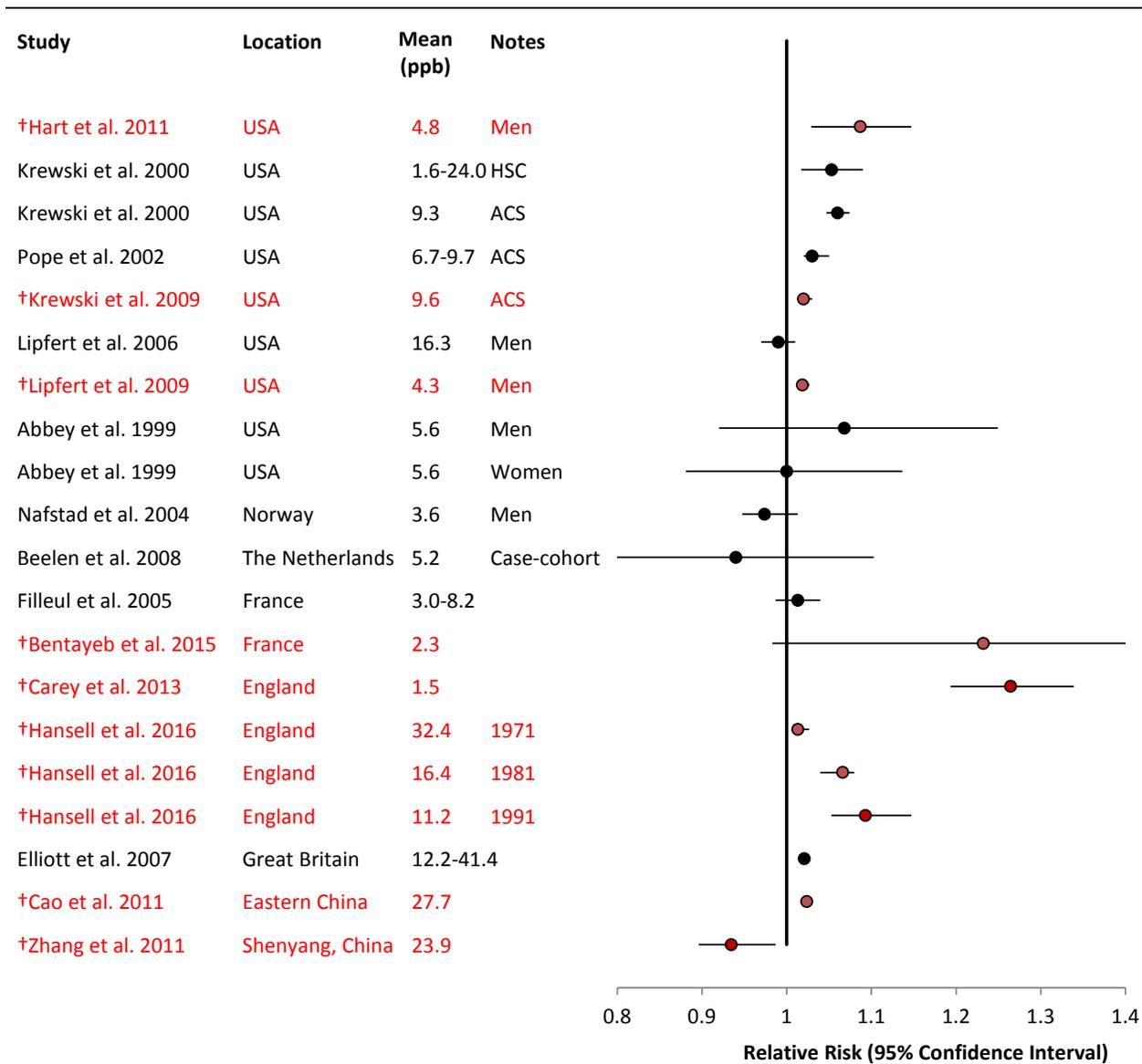
1 observed by [Carey et al. \(2013\)](#) is much higher than that observed in any of the other  
2 studies. Generally, these results are consistent with a recent study ([Wang et al., 2014a](#))  
3 that evaluated the correlation between life expectancy and SO<sub>2</sub> concentrations in 85  
4 major city regions in China. After accounting for a surrogate for socioeconomic status,  
5 they observed that city regions with higher SO<sub>2</sub> concentrations were correlated with  
6 lower life expectancies.

7 [Figure 5-27](#) presents the cause-specific mortality effect estimates associated with  
8 long-term exposure to SO<sub>2</sub>. The overall range of effects spans 0.93 to 4.40 per 5-ppb  
9 increase in the annual (or longer period) average SO<sub>2</sub> concentration. Generally, there was  
10 a trend toward more positive associations for respiratory and lung cancer mortality  
11 compared to cardiopulmonary, cardiovascular, and other causes of death. Specifically,  
12 recent studies examining respiratory mortality provide some evidence that this cause of  
13 death may be more consistently associated with long-term exposure to SO<sub>2</sub> than other  
14 causes of death. This is consistent with both the short- and long-term exposure to SO<sub>2</sub>  
15 that are associated with respiratory effects.

16 Overall, the majority of the limited evidence informing the association between long-term  
17 exposure to SO<sub>2</sub> and mortality was included in the 2008 SO<sub>x</sub> ISA. The 2008 SO<sub>x</sub> ISA  
18 identified concerns regarding the consistency of the observed associations, whether the  
19 observed associations were due to SO<sub>2</sub> alone, or if sulfate or other particulate SO<sub>x</sub> or PM  
20 indices could have contributed to these associations, and the geographic scale of the  
21 exposure assessment. Specifically, the 2008 SO<sub>x</sub> ISA noted the possibility that the  
22 observed effects may not be due to SO<sub>2</sub>, but other co-occurring pollutants that come from  
23 the same source as SO<sub>2</sub>, or that PM may be more toxic in the presence of SO<sub>2</sub> or other  
24 components associated with SO<sub>2</sub>, could not be ruled out. None of the epidemiologic  
25 studies made corrections or adjustments for exposure measure measurement error, or  
26 accounted for the potential for bias away from the null, the potential for which has been  
27 demonstrated in simulation studies (see [Section 3.4.4.2](#)). Overall, a lack of consistency  
28 across studies, inability to distinguish potential confounding by copollutants, and  
29 uncertainties regarding the geographic scale of analysis limited the interpretation of the  
30 causal relationship between long-term exposure to SO<sub>2</sub> and mortality.

31 The recent evidence is generally consistent with the evidence in the 2008 SO<sub>x</sub> ISA.  
32 The biggest notable difference is in the improved consistency in the association between  
33 long-term exposure to SO<sub>2</sub> and both respiratory and total mortality that comes from the  
34 inclusion of recent cohort studies. However, none of these recent studies help to resolve  
35 the uncertainties identified in the 2008 SO<sub>x</sub> ISA related to copollutant confounding or the  
36 geographic scale of the analysis. All available evidence for mortality due to long-term  
37 exposure to SO<sub>2</sub> was evaluated using the framework described in Table II of the

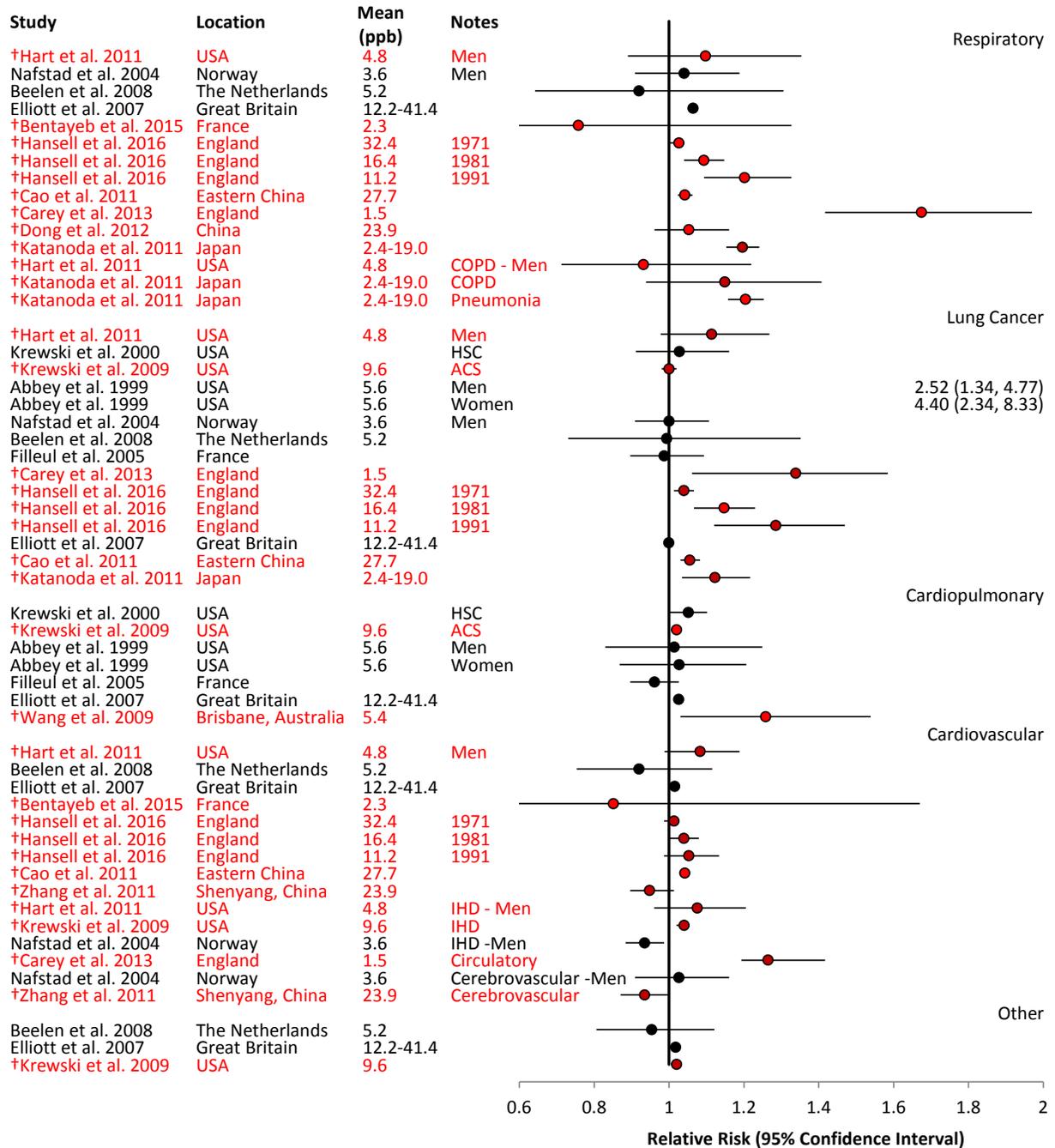
1 [Preamble](#) to the ISAs ([U.S. EPA, 2015b](#)). The key evidence as it relates to the causal  
 2 framework is summarized in [Table 5-43](#). The overall evidence is inadequate to infer a  
 3 causal relationship between long-term exposure to SO<sub>2</sub> and total mortality among adults.



ACS = American Cancer Society Study; HSC = Harvard Six Cities Study.

Note: studies in red are recent studies. Studies in black were included in the 2008 ISA for Sulfur Oxides. Relative risks are standardized to a 5-ppb increase in sulfur dioxide concentrations. Corresponding quantitative results are reported in Supplemental Table 5S-29 ([U.S. EPA, 2016x](#)).

**Figure 5-26** Relative risks (95% confidence interval) of sulfur dioxide-associated total mortality.



ACS = American Cancer Society Study; COPD = chronic obstructive pulmonary disease; HSC = Harvard Six Cities Study; IHD = ischemic heart disease.

Note: Studies in red are recent studies. Studies in black were included in the 2008 ISA for Sulfur Oxides. Relative risks are standardized to a 5-ppb increase in sulfur dioxide concentrations. Corresponding quantitative results are reported in Supplemental Table 5S-30 ([U.S. EPA, 2016v](#)).

**Figure 5-27** Relative risks (95% confidence interval) of sulfur dioxide-associated cause-specific mortality.

**Table 5-43 Summary of evidence, which is inadequate to infer a causal relationship between long-term sulfur dioxide exposure and total mortality.**

Rationale for Causal Determination <sup>a</sup>	Key Evidence <sup>b</sup>	Key References <sup>b</sup>	SO <sub>2</sub> Concentrations Associated with Effects <sup>c</sup>
Some epidemiologic studies report positive associations but results are not entirely consistent.	Small, positive associations between long-term exposure to SO <sub>2</sub> and mortality in the HSC cohort, the ACS cohort, and the Veterans cohort, even after adjustment for common potential confounders	<a href="#">Krewski et al. (2000)</a> <a href="#">Krewski et al. (2009)</a> <a href="#">Jerrett et al. (2003)</a> <a href="#">Krewski et al. (2000)</a>	Mean: 1.6–24.0 ppb City-specific annual mean: 9.3–9.6 ppb
	Recent cohort studies in the U.S. observe increases in total mortality and mortality due to lung cancer and cardiovascular and respiratory disease, but exposure assessment and statistical methods were not adequate for study of SO <sub>2</sub> .	<a href="#">Lipfert et al. (2009)</a> <a href="#">Hart et al. (2011)</a>	County-level mean from air quality model: 4.3 ppb Annual average at residential address from model: 4.8 ppb
Some epidemiologic studies report no associations.	No association observed in European cohort studies for total, respiratory, or cardiovascular mortality	<a href="#">Beelen et al. (2008b)</a>	IDW to regional monitors: 5.2 ppb
		<a href="#">Nafstad et al. (2004)</a>	Model/monitor hybrid: 3.6 ppb
		<a href="#">Filleul et al. (2005)</a>	3-yr mean: 3.0–8.2 ppb
Uncertainty due to potential confounding from correlated pollutants	When reported, correlations with copollutants were generally moderate (0.4–0.7) to high (>0.7). Confounding of observed associations by other pollutants or pollutant mixtures cannot be ruled out.	<a href="#">Table 5-42</a>	
Uncertainty regarding how exposure measurement error may influence the results	SO <sub>2</sub> has low (<0.4) to moderate (0.4–0.7) spatial correlations across urban geographical scales. The geographical scale for estimating exposure used in these studies may be too large for a highly spatially heterogeneous pollutant such as SO <sub>2</sub> .	<a href="#">Section 3.4.2</a>	
	Exposure measurement error in long-term SO <sub>2</sub> exposure can lead to bias toward or away from the null.	<a href="#">Section 3.4.4.2</a>	
	No evidence for long-term exposure and respiratory health effects in adults to support the observed associations with respiratory mortality	<a href="#">Section 5.2.2.4</a>	

**Table 5-43 (Continued): Summary of evidence, which is inadequate to infer a causal relationship between long term sulfur dioxide exposure and total mortality.**

Rationale for Causal Determination <sup>a</sup>	Key Evidence <sup>b</sup>	Key References <sup>b</sup>	SO <sub>2</sub> Concentrations Associated with Effects <sup>c</sup>
No coherence with evidence for respiratory and cardiovascular morbidity	No evidence for long-term exposure and cardiovascular health effects in adults to support the observed associations with cardiovascular mortality	<a href="#">Section 5.3.2.4</a>	

ACS = American Cancer Society; HSC = Harvard Six Cities; IDW = inverse distance weighting; SO<sub>2</sub> = sulfur dioxide.

<sup>a</sup>Based on aspects considered in judgments of causality and weight of evidence in causal framework in Table I and Table II of the [Preamble](#) to the ISAs ([U.S. EPA, 2015b](#)).

<sup>b</sup>Describes the key evidence and references contributing most heavily to causal determination and, where applicable, to uncertainties or inconsistencies. References to earlier sections indicate where full body of evidence is described.

<sup>c</sup>Describes the SO<sub>2</sub> concentrations with which the evidence is substantiated (for experimental studies, below 5,000 ppb).

†Studies published since the 2008 ISA for Sulfur Oxides.

## 5.6 Cancer

### 5.6.1 Introduction

1 The body of literature characterizing the carcinogenic, genotoxic, and mutagenic effects  
2 of exposure to SO<sub>2</sub> has grown since the 2008 SO<sub>x</sub> ISA ([U.S. EPA, 2008d](#)). The cancer  
3 section of the ISA characterizes epidemiologic associations between SO<sub>2</sub> exposure and  
4 cancer incidence or cancer mortality, as well as the animal toxicology carcinogenicity  
5 studies ([Section 5.6.2](#)). Subsections discuss the evidence relating to lung cancer  
6 ([Section 5.6.2.1](#)), bladder cancer ([Section 5.6.2.2](#)), and other cancers ([Section 5.6.2.3](#)).  
7 Laboratory studies of mutagenicity or genotoxicity are discussed in [Section 5.6.3](#).  
8 The 2008 SO<sub>x</sub> ISA summarized the literature on SO<sub>2</sub> concentrations and lung cancer as  
9 “inconclusive” ([U.S. EPA, 2008d](#)). Multiple studies across the U.S. and Europe  
10 investigated the relationship between SO<sub>2</sub> concentrations and lung cancer incidence and  
11 mortality. Many studies reported generally null associations, but some studies  
12 demonstrated positive associations. However, some studies were limited by a small  
13 number of cancer cases. The following summaries add to the previous knowledge on SO<sub>2</sub>  
14 concentrations and cancer incidence and mortality. The sections below describe studies  
15 investigating lung cancer, bladder cancer, and other cancers. Supplemental Tables  
16 provide detailed summaries of the respective new epidemiologic [Table 5S-31([U.S. EPA,](#)  
17 [2016z](#))] and genotoxic/mutagenic [Table 5S-32 ([U.S. EPA, 2016](#){[aa](#)}] literature.  
18 The animal toxicology literature of SO<sub>2</sub> exposure is dominated by studies of SO<sub>2</sub> acting

1 as a cocarcinogen or tumor promoter, with one study of SO<sub>2</sub> inhalation associated with an  
2 increased rate of lung tumor formation in lung tumor-susceptible female rodents.  
3 Genotoxicity and mutagenicity studies show mixed results with null studies in a  
4 *Drosophila* model and positive micronuclei findings in a mouse inhalation model of SO<sub>2</sub>  
5 exposure.

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## 5.6.2 Cancer Incidence and Mortality

### 5.6.2.1 Lung Cancer Incidence and Mortality

6 International studies exploring the associations between SO<sub>2</sub> concentrations and lung  
7 cancer incidence have provided inconsistent results. No recent studies on SO<sub>2</sub>  
8 concentration and lung cancer incidence in the U.S. have been published. Large studies  
9 conducted using the Netherlands Cohort Study on Diet and Cancer examined the  
10 association between SO<sub>2</sub> concentration and lung cancer incidence ([Brunekreef et al.,  
11 2009](#); [Beelen et al., 2008a](#)). Null associations were reported in both analyses of the full  
12 cohort and a case-cohort design. None of the analyses adjusted for copollutants. An  
13 ecological study in Israel examining lung cancer incidence among men also reported null  
14 results for the association with SO<sub>2</sub> concentrations ([Eitan et al., 2010](#)). Results were  
15 relatively unchanged when adjusting for PM<sub>10</sub>. No association was observed between SO<sub>2</sub>  
16 concentrations and lung cancer hospitalizations among men or women in southern France  
17 in an ecological study that did not control for copollutants ([Pascal et al., 2013](#)). However,  
18 an ecological analysis performed among women in Taiwan demonstrated a positive  
19 association between SO<sub>2</sub> concentration and lung cancer incidence ([Tseng et al., 2012](#)).  
20 This positive association remained in a regression model adjusted for other pollutants  
21 (CO, NO<sub>2</sub>, NO, O<sub>3</sub>, and PM<sub>10</sub>; none of these air pollutants exhibited an association with  
22 lung cancer incidence). The association was present in analyses for both types of lung  
23 cancer examined, adenocarcinomas and squamous cell carcinomas. Thus, overall,  
24 multiple ecologic studies have been performed examining SO<sub>2</sub> concentrations and lung  
25 cancer incidence with inconsistent findings, and analyses using a large cohort study  
26 reported no association between SO<sub>2</sub> concentrations and lung cancer incidence but had no  
27 control of copollutant confounders. Each of these studies used SO<sub>2</sub> concentrations  
28 measured at central site monitors to assign exposure. [Beelen et al. \(2008a\)](#) and  
29 [Brunekreef et al. \(2009\)](#) used inverse distance weighting between the central site monitor  
30 location and residential address, and combined this with the output of land use regression  
31 (LUR) models for urban contributions. [Eitan et al. \(2010\)](#) generated spatially interpolated  
32 surfaces for a 7-year period, while the other ecological studies relied on annual averages

1 from the central site monitors. None of the studies corrected for exposure measurement  
2 error.

3 Studies in the U.S. have reported inconsistent findings for the association between SO<sub>2</sub>  
4 concentrations and lung cancer mortality (see [Section 5.5.2](#) and [Figure 5-27](#)). No  
5 association between SO<sub>2</sub> concentrations and lung cancer mortality was present in a report  
6 by Health Effect Institute ([Krewski et al., 2009](#)). Estimates stratified by high school  
7 education (less than high school education, high school education, or greater) were also  
8 examined and no association was present in either subgroup. In addition to the entire time  
9 period of the study, the researchers also examined 5-year increments, none of which  
10 demonstrated an association. However, a recent study of men in the trucking industry  
11 found a slight positive association between SO<sub>2</sub> concentrations and lung cancer mortality  
12 ([Hart et al., 2011](#)). With the inclusion of PM<sub>10</sub> and NO<sub>2</sub> in the model, the 95% CI  
13 included the null but the point estimate was in the positive direction and only slightly  
14 attenuated.

15 Recent studies have also been performed in Asia and Europe examining the relationship  
16 between SO<sub>2</sub> and lung cancer mortality. In China, a positive association was observed  
17 between SO<sub>2</sub> and lung cancer mortality ([Chen et al., 2016](#); [Cao et al., 2011](#)). In the study  
18 by [Cao et al. \(2011\)](#), this association was relatively unchanged with adjustment of either  
19 TSP or NO<sub>x</sub>. A study in Japan also reported a positive association between SO<sub>2</sub> and lung  
20 cancer mortality ([Katanoda et al., 2011](#)). However, the estimate was reduced when  
21 additional potential confounders (smoking of parents during subjects' childhood,  
22 consumption of nonyellow or nongreen vegetables, occupation, and health insurance)  
23 were controlled for and no copollutant assessment was performed. Positive associations  
24 were also observed for suspended PM, PM<sub>2.5</sub>, and NO<sub>2</sub> concentrations. When examining  
25 subgroups, the association was highest among male smokers. The point estimate was  
26 similar to the overall estimate for male former smokers but the 95% confidence interval  
27 was wide due to the small size of the study population. The estimate was lowest among  
28 female never smokers. The number of male never smokers and female smokers were too  
29 small to assess individually. A study in the U.K. also demonstrated a positive association  
30 between SO<sub>2</sub> concentration and lung cancer mortality ([Carey et al., 2013](#)).

31 The association was slightly attenuated when education was included in the model  
32 instead of income. However, a large study using the Netherlands Cohort Study on Diet  
33 and Cancer reported no association between SO<sub>2</sub> concentration and lung cancer mortality  
34 ([Brunekreef et al., 2009](#)). This study was mentioned above and also did not demonstrate  
35 an association between SO<sub>2</sub> concentration and lung cancer incidence. No copollutant  
36 models were examined. In summary, consistent with studies conducted in the U.S.  
37 examining SO<sub>2</sub> concentrations and cancer mortality, recent studies performed in Asia and  
38 Europe also had inconsistent findings. Many of these studies used SO<sub>2</sub> concentrations

1 measured at central site monitors to assign exposure, and none of the studies corrected for  
2 exposure measurement error. [Brunekreef et al. \(2009\)](#) used inverse distance weighting  
3 between the central site monitor location and residential address, and combined this with  
4 the output of land use regression (LUR) models for urban contributions. [Hart et al. \(2011\)](#)  
5 used spatial smoothing, and [Carey et al. \(2013\)](#) used a dispersion model constructed with  
6 emissions data to assign exposure.

7 A study in Italy used a Lagrangian dispersion model to estimate SO<sub>x</sub> concentrations as a  
8 marker for refinery plant emissions [exposure assessment technique summarized in  
9 [Section 3.3.2.4 \(Ancona et al., 2015\)](#)]. The relationship between these estimates and  
10 cancer mortality and hospitalizations were investigated. No association was observed for  
11 lung cancer among men or women; however, these results are difficult to interpret.  
12 The estimated SO<sub>x</sub> concentrations were highly correlated with estimates of PM<sub>10</sub>, which  
13 is expected as SO<sub>x</sub> was being treated as a marker for petrochemical refinery emissions.  
14 This makes interpretation difficult as copollutant models were not shown for lung cancer  
15 and additionally the validity of the model is unknown.

16 A recent meta-analysis ([Chen et al., 2015a](#)) combined the results of five studies of SO<sub>2</sub>  
17 and lung cancer and found an overall OR of 1.03 (95% CI: 1.02, 1.05), although one of  
18 the five studies [[\(Cao et al., 2011\)](#); characterized above] accounted for nearly 80% of the  
19 weight contributing to the overall OR and was the only study of the five to observe a  
20 positive and statistically significant association between SO<sub>2</sub> exposure and lung cancer.  
21 Three of the remaining studies included in the meta-analysis observed null associations  
22 between SO<sub>2</sub> and lung cancer.

### **Sulfur Dioxide Lung Carcinogenesis, Cocarcinogenic Potential, and Tumor Promotion in Laboratory Animal Models**

23 The toxicological evidence for effects of sulfur dioxide in carcinogenicity, mutagenicity,  
24 or genotoxicity is characterized below. Other regulatory agencies have characterized the  
25 carcinogenic potential of sulfur dioxide and its metabolites. The International Agency for  
26 Research on Cancer (IARC) has determined sulfur dioxide, sulfites, bisulfites, and  
27 metabisulfites are not classifiable as to their carcinogenicity to humans (Group 3) and the  
28 American Conference of Governmental Industrial Hygienists has rated sulfur dioxide as  
29 not classifiable as a human carcinogen (A4).

30 Direct evidence of carcinogenicity was studied evaluating incidence of lung tumors in a  
31 lung adenoma-susceptible mouse strain, (the LX mouse), with chronic exposure to sulfur  
32 dioxide at 500 ppm, 5 minutes/day, 5 days/week for 2 years ([Peacock and Spence, 1967](#)).  
33 SO<sub>2</sub>-exposed female mice had an increase in the number of lung tumors subgrouped as  
34 (1) adenomas and (2) primary carcinomas versus controls. Males had a smaller increase

1 in adenomas versus controls and similar levels of primary carcinomas compared to  
2 controls.

3 Evidence exists for SO<sub>2</sub> to be a cocarcinogen ([Pauluhn et al., 1985](#)); SO<sub>2</sub> and  
4 benzo[a]pyrene, B[a]P, coexposure increased the incidence of lung tumor formation in  
5 rodents versus B[a]P exposure alone. Chronic coexposure to SO<sub>2</sub> and B[a]P resulted in  
6 increased incidence of upper respiratory tract neoplasia in rats ([Laskin et al., 1976](#)) and  
7 hamsters ([Pauluhn et al., 1985](#)) over B[a]P exposure alone. SO<sub>2</sub> exposure shortened the  
8 induction period for spontaneous squamous cell lung tumor formation after B[a]P  
9 exposure ([Laskin et al., 1976](#)); rats were exposed 5 days a week, 6 hours/day for their  
10 lifetime to 10 ppm SO<sub>2</sub> alone via inhalation or 4 ppm SO<sub>2</sub> + 10 mg/m<sup>3</sup> B[a]P (1 hour  
11 B[a]P/day). SO<sub>2</sub> exposure also shortened the induction time for  
12 methylcholanthrene-induced carcinogenesis.

13 Multiple studies explored SO<sub>2</sub> as a cocarcinogen or promoter after particulate-induced  
14 tumorigenesis. In a study of suspended particulate matter- (SPM-) induced tumorigenesis  
15 (proliferative lesions of pulmonary endocrine cells) in the rat, SO<sub>2</sub> did not exacerbate  
16 SPM-dependent hyperplasia when rats were exposed to the mixture of SPM and SO<sub>2</sub> ([Ito  
17 et al., 1997](#)). Adult male rats were exposed to SO<sub>2</sub> for 11 months, 16 hours/day ± SPM  
18 for 4 weeks, once/week by intratracheal injection. SO<sub>2</sub> did not act as a tumor promoter or  
19 cocarcinogen in this model. In a separate study of diesel exhaust particle- (DEP-)  
20 dependent lung tumorigenesis, SO<sub>2</sub> was able to promote DEP-dependent tumorigenesis  
21 ([Ohyama et al., 1999](#)). Adult male rats were intratracheally instilled with diesel exhaust  
22 particle extract-coated carbon black particles (DEcCBP) and exposed to 4 ppm SO<sub>2</sub> for  
23 10 months. Eighteen months after starting the experiment, the animals were examined for  
24 respiratory tract tumors and DNA adducts were measured in lung tissue. Lung tumors and  
25 DNA adducts were seen in animals with coexposure to SO<sub>2</sub> and DEcCBP but not in  
26 animals only exposed to DEcCBP. SO<sub>2</sub> acted as a tumor promoter in animals exposed to  
27 DEcCBP. In a separate investigation, hamsters were exposed to diesel engine exhaust  
28 (separately with and without particles) and a mixture of SO<sub>2</sub> and NO<sub>2</sub> with or without  
29 exposure to the carcinogen diethyl-nitrosamine to investigate the potential cocarcinogenic  
30 effect of exposure to the dioxides mixture and diesel engine exhaust in the respiratory  
31 tract ([Heinrich et al., 1989](#)). These adult male hamster were exposed for 19 hours/day,  
32 5 days/week for 6, 10.5, 15, or 18 months to diesel exhaust, filtered diesel exhaust  
33 (without particles), a dioxide mixture of NO<sub>2</sub> (5 ppm) and SO<sub>2</sub> (10 ppm), or clean air.  
34 Two exposure groups from each of the aforementioned test groups were also given a  
35 single subcutaneous injection of diethylnitrosamine (DEN) (3 mg or 6 mg/kg body  
36 weight). Exposure to the dioxide mixture by itself did not elevate tumor rate (tumor  
37 induction), nor did it exacerbate DEN-dependent effects (tumor promotion) in the  
38 hamster. In summary, a comparison of multiple studies of SO<sub>2</sub> coexposure with particles

1 reported mixed results in various models of carcinogenicity, cocarcinogenic potential, or  
2 tumor promotion.

3 Oncogene and tumor suppressor genes also appear to be affected by SO<sub>2</sub> exposure,  
4 especially with coexposure to benzo[a]pyrene, B[a]P. Synergistic expression of c-fos and  
5 c-jun with SO<sub>2</sub> and B[a]P coexposure was observed in rodent lungs ([Qin and Meng,  
6 2006](#)). SO<sub>2</sub> and B[a]P coexposure in male Wistar rats (26.5 ppm SO<sub>2</sub> inhalation,  
7 6 hours/day for 7 days; 3 mg B[a]P instilled) statistically significantly downregulated  
8 expression of tumor suppressor genes *p16* and *myc*, and increased expression of  
9 oncogenes *c-myc*, *H-ras*, and *p53*. Others have reported that SO<sub>2</sub> exposure alone could  
10 induce *p53* expression in rats ([Bai and Meng, 2005](#)).

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### 5.6.2.2 Bladder Cancer Incidence and Mortality

11 Several studies on the relationship between SO<sub>2</sub> concentrations and bladder cancer  
12 incidence and mortality have been published since the 2008 SO<sub>x</sub> ISA ([U.S. EPA, 2008d](#)).  
13 Positive associations were observed in studies of bladder cancer mortality but not bladder  
14 cancer incidence. An ecological study in southern France reported on the relationship  
15 between SO<sub>2</sub> concentrations and hospitalizations for bladder cancer without examination  
16 of copollutant models ([Pascal et al., 2013](#)). Null associations were observed for men and  
17 women. Another ecological study in Israel examining bladder cancer incidence also  
18 reported sex-stratified results ([Eitan et al., 2010](#)). Neither sex demonstrated an association  
19 between SO<sub>2</sub> concentrations and bladder cancer in models with and without adjustment  
20 for PM<sub>10</sub>. However, an association was observed in a study examining the relationship  
21 between SO<sub>2</sub> and bladder cancer mortality ([Liu et al., 2009a](#)). [Liu et al. \(2009a\)](#)  
22 investigated the association between SO<sub>2</sub> and bladder cancer mortality using controls with  
23 mortality due to causes unrelated to neoplasm or genitourinary-related disease and  
24 matched by sex, year of birth, and year of death. A positive association was observed  
25 between SO<sub>2</sub> concentration in the second and third tertiles of exposure and bladder cancer  
26 mortality. For further investigations, the authors created a three-level exposure variable  
27 combining NO<sub>2</sub> and SO<sub>2</sub> concentrations: the lowest tertile of SO<sub>2</sub> and NO<sub>2</sub> concentrations  
28 ( $\leq 4.32$  ppb and  $\leq 20.99$  ppb, respectively), the highest tertile of SO<sub>2</sub> and NO<sub>2</sub>  
29 concentrations ( $> 6.49$  ppb and  $> 27.33$  ppb, respectively), and other  
30 categorizations/combinations. The ORs were 1.98 (95% CI 1.36, 2.88) for the highest  
31 level of NO<sub>2</sub> and SO<sub>2</sub> and 1.37 (95% CI 1.03, 1.82) for the middle level categorizations.  
32 Although the point estimates are higher than those observed for SO<sub>2</sub> alone (see  
33 Supplemental Table 5S-31, [U.S. EPA, 2016z](#)), the 95% confidence intervals overlap,  
34 and therefore, conclusions that NO<sub>2</sub> and SO<sub>2</sub> combined contribute to higher odds of  
35 mortality than either alone cannot be drawn. Finally, a study using SO<sub>x</sub> concentration

1 estimated using a Lagrangian dispersion model reported no association between SO<sub>x</sub>  
2 concentration and bladder cancer mortality or hospitalizations among men or women  
3 ([Ancona et al., 2015](#)). However, results of this study are difficult to interpret because of  
4 unknown validity of the model (see [Section 3.3.2.4](#)) and high correlation with PM<sub>10</sub> and  
5 H<sub>2</sub>S.

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### 5.6.2.3 Incidence of Other Cancers

6 Recent studies of SO<sub>2</sub> concentrations and other cancer types have been published since  
7 the 2008 ISA for Sulfur Oxides ([U.S. EPA, 2008d](#)), but provide limited information on  
8 associations with SO<sub>2</sub>. An ecological study in southern France investigated the  
9 relationships between SO<sub>2</sub> and hospitalizations for breast cancer, acute leukemia,  
10 myeloma, and non-Hodgkin lymphoma ([Pascal et al., 2013](#)). Null associations were  
11 observed in sex-stratified analyses among men and women, with the exception of a  
12 positive association between SO<sub>2</sub> and acute leukemia among men. However, the authors  
13 urge caution when interpreting the results due to a small number of male acute leukemia  
14 cases. This study did not examine copollutant confounding. Another ecologic study used  
15 Surveillance, Epidemiology, and End Results data to examine the correlation between  
16 SO<sub>2</sub> concentrations and breast cancer incidence ([Wei et al., 2012](#)). A positive relationship  
17 was detected, but there was no control for potential confounders of other air pollutants  
18 (of which CO, NO<sub>x</sub>, and VOCs, but not PM<sub>10</sub>, also demonstrated a positive correlation  
19 with breast cancer incidence). Both of these studies are limited by their ecologic nature  
20 and the lack of individual-level data. A cross-sectional study was conducted in South  
21 Korea that looked at the association between symptom scores for prostate cancer and  
22 emissions data for SO<sub>x</sub> (measured in kg/year/person) and a number of other air pollutants  
23 ([Shim et al., 2015](#)). In logistic regression models adjusted for age, the authors observed  
24 positive associations between men living in areas with greater emissions of SO<sub>x</sub> and  
25 symptom scores for prostate cancer. Similar results were observed for NO<sub>x</sub>, CO, PM<sub>10</sub>,  
26 VOCs and NH<sub>3</sub>. The lack of control for potential confounding by other air pollutants or  
27 risk factors (e.g., smoking, SES) limit the interpretation of these results.

28 A cohort study examined the relationship between SO<sub>x</sub> concentrations, estimated using a  
29 Lagrangian dispersion model, and hospitalizations and mortality for various cancer types  
30 ([Ancona et al., 2015](#)). No associations were found between SO<sub>x</sub> concentrations and either  
31 hospitalizations or mortality due to cancers of the stomach, colon/rectum, liver, kidney,  
32 brain, or breast. Positive associations were observed for SO<sub>x</sub> concentration and mortality  
33 due to pancreatic and larynx cancers among women but not men. The 95% confidence  
34 interval showed a large degree of imprecision in the estimates for cancer of the larynx.  
35 The association with pancreatic cancer was not robust to adjustment with H<sub>2</sub>S or PM<sub>10</sub>.

1 When examining the association between estimated SO<sub>x</sub> concentration and  
2 hospitalizations, a positive, but imprecise, association was observed for cancer of the  
3 larynx among women and an inverse association was noted for cancers of lymphatic and  
4 hematopoietic tissue.

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#### 5.6.2.4 Summary of Cancer Incidence and Mortality

5 Similar to studies of SO<sub>2</sub> concentrations and lung cancer in the previous ISA ([U.S. EPA,](#)  
6 [2008d](#)), recent studies of SO<sub>2</sub> concentrations and lung cancer have provided inconsistent  
7 results ([Carey et al., 2013](#); [Pascal et al., 2013](#); [Tseng et al., 2012](#); [Cao et al., 2011](#); [Hart et](#)  
8 [al., 2011](#); [Katanoda et al., 2011](#); [Eitan et al., 2010](#); [Brunekreef et al., 2009](#); [Krewski et al.,](#)  
9 [2009](#); [Beelen et al., 2008a](#)). Studies of bladder cancer appear to find no association  
10 between SO<sub>2</sub> concentrations and bladder cancer incidence ([Pascal et al., 2013](#); [Eitan et](#)  
11 [al., 2010](#)), but a study of SO<sub>2</sub> concentration and bladder cancer mortality reported a  
12 positive association ([Liu et al., 2009a](#)). Limited information is available regarding other  
13 cancers. Animal toxicology models of SO<sub>2</sub> inhalation exposure show SO<sub>2</sub> acting as a  
14 promoter or cocarcinogen, with one study showing increased lung tumor formation in a  
15 lung tumor-prone animal model.

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#### 5.6.3 Genotoxicity and Mutagenicity

16 Multiple studies of genotoxicity or mutagenesis with SO<sub>2</sub> in vivo or SO<sub>2</sub> in vitro exposure  
17 have been reported in the literature and are detailed below in Supplemental Table 5S-32  
18 ([U.S. EPA, 2016f](#))<sup>aa</sup>.

19 After inhalation exposure to SO<sub>2</sub>, mouse bone marrow micronuclei formation (MN) was  
20 significantly elevated in both males and females after exposure to SO<sub>2</sub> (5.4, 10.7, 21.4, or  
21 32.1 ppm SO<sub>2</sub>, 4 hours/day for 7 days) ([Meng et al., 2002](#)). The polychromatophilic  
22 erythroblasts of the bone marrow (MNPCE) were formed in significantly increased  
23 numbers with SO<sub>2</sub> exposure. Another study recapitulated these findings; subacute  
24 exposure to SO<sub>2</sub> (10.7 ppm SO<sub>2</sub> for 5 day, 6 hours/days) induced a significant increase in  
25 MNPCE with this effect attenuated by exogenous antioxidant SSO pretreatment ([Ruan et](#)  
26 [al., 2003](#)).

27 The rate of DNA single strand breaks induced by B[a]P exposure in fetal hamster lung  
28 cells (50 ppm for 2 weeks) ([Pool et al., 1988b](#)) and rat liver cells (2.5, 5, 9.9, or 19.9 ppm,  
29 4 hours/day for 7 days) ([Pool et al., 1988a](#)) was significantly attenuated by concomitant  
30 exposure to SO<sub>2</sub> (50 ppm for 2 weeks).

1 Genotoxicity testing of *Drosophila* sperm for sex-linked recessive lethals after feeding  
2 larvae 0.04 M or 0.08 M sodium sulfite in a 1% glucose solution was performed and no  
3 increase was found above background. One caveat is that sulfite can interact with  
4 glucose, making the exposure assessment more complicated.

5 Multiple studies of genotoxicity or mutagenesis with SO<sub>2</sub> in vivo or in vitro exposure  
6 have been reported in the literature and are summarized in Supplemental Table 5S-32  
7 ([U.S. EPA, 2016f](#))<sup>aa</sup>. Mixed results of genotoxicity or mutagenicity have been reported  
8 after SO<sub>2</sub> exposure including positive associations with SO<sub>2</sub> inhalation exposure in the  
9 mouse MN assay.

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#### 5.6.4 Summary and Causal Determination

10 The overall evidence for long-term SO<sub>2</sub> exposure and cancer is inadequate to infer a  
11 causal relationship. This conclusion is based on the inconsistent evidence from  
12 epidemiologic studies, as well as mixed evidence within the animal toxicology and mode  
13 of action framework for mutagenesis and genotoxicity. In past reviews, a limited number  
14 of epidemiologic studies had assessed the relationship between long-term SO<sub>2</sub>  
15 concentrations and cancer incidence and mortality. The 2008 ISA for Sulfur Oxides  
16 concluded that the evidence was “inconclusive” ([U.S. EPA, 2008d](#)). Recent studies  
17 include evidence on lung cancer as well as new types of cancer, evaluating both  
18 incidence and mortality. However the additional recent evidence has not informed any of  
19 the uncertainties identified in the previous review, including uncertainties due to  
20 exposure measurement error, potential copollutant confounding, and limited mechanistic  
21 evidence or biological plausibility. All available evidence for cancer due to long-term  
22 SO<sub>2</sub> concentrations was evaluated using the framework described in Table II of the  
23 [Preamble](#) to the ISAs ([U.S. EPA, 2015b](#)). The key evidence as it relates to the causal  
24 framework is summarized in [Table 5-44](#).

25 American Conference of Governmental Industrial Hygienists has rated sulfur dioxide as  
26 A4, not classifiable as a human carcinogen. The IARC has classified SO<sub>2</sub> as a Group 3  
27 substance, not classifiable as to its carcinogenicity to humans. The Registry of Toxic  
28 Effects of Chemical Substances of National Institute for Occupational Safety and Health  
29 lists SO<sub>2</sub> as tumorigenic and cocarcinogenic by inhalation in rats and mice. The National  
30 Toxicology Program of the National Institutes of Health and the U.S. Environmental  
31 Protection Agency have not classified SO<sub>2</sub> for its potential carcinogenicity. Overall, there  
32 is inconsistent evidence for an association between long-term SO<sub>2</sub> exposure and cancer  
33 from epidemiologic and toxicological studies. Some of the epidemiologic studies  
34 observed positive associations while others did not. Some of these studies with positive

1 associations were relatively unchanged with the inclusion of various cofounders and  
 2 copollutants, although many did not evaluate the potential for copollutant confounding.  
 3 Cohort studies have reported null associations between SO<sub>2</sub> concentrations and lung  
 4 cancer incidence. Similarly, some ecological studies also reported no associations;  
 5 although, an ecological study in Taiwan among women did report an association between  
 6 SO<sub>2</sub> concentrations and lung cancer incidence that was relatively unchanged when  
 7 including other pollutants. Positive associations were also observed in a study of SO<sub>2</sub>  
 8 concentrations and bladder cancer mortality but not in ecological studies of bladder  
 9 cancer incidence. The study of bladder cancer mortality examined the relationship  
 10 between bladder cancer mortality and joint exposure to high levels of NO<sub>2</sub> and SO<sub>2</sub>, but  
 11 no copollutant assessment was performed controlling for NO<sub>2</sub> or other air pollutants.  
 12 None of the epidemiologic studies made corrections or adjustments for exposure measure  
 13 measurement error, or accounted for the potential for bias away from the null, the  
 14 potential for which has been demonstrated in simulation studies (see [Section 3.4.4.2](#)).

15 Animal toxicological studies employing SO<sub>2</sub> exposure with other known carcinogens  
 16 provide some evidence, showing that inhaled SO<sub>2</sub> can increase tumor load in laboratory  
 17 rodents. Toxicological data provided by a study in LX mice, lung adenoma susceptible  
 18 animals, showed evidence of the direct carcinogenic potential of SO<sub>2</sub>. Other studies in  
 19 animal models show SO<sub>2</sub> as a cocarcinogen with B[a]P or as a tumor promoter with  
 20 particulate-induced tumorigenesis. Nonetheless, toxicological data provide no clear  
 21 evidence of SO<sub>2</sub> acting as a complete carcinogen and not all epidemiologic studies report  
 22 positive associations.

23 Collectively, the inconsistent evidence from several toxicological and epidemiologic  
 24 studies is inadequate to infer a causal relationship between long-term exposure to SO<sub>2</sub> and  
 25 cancer incidence and mortality.

**Table 5-44 Summary of evidence, which is inadequate to infer a causal relationship between long-term sulfur dioxide exposure and cancer.**

Rationale for Causal Determination <sup>a</sup>	Key Evidence <sup>b</sup>	Key References <sup>b</sup>	SO <sub>2</sub> Concentrations Associated with Effects <sup>c</sup>
Among a small body of evidence, evidence from epidemiologic studies is inconsistent.	Generally null associations from studies of cancer incidence, with some observed increases in lung cancer and bladder cancer mortality in studies conducted in the U.S., Europe, and Asia	<a href="#">Section 5.6.2</a>	Means varied across studies including areas estimating mean concentrations of SO <sub>2</sub> as low as 1.49 ppb to as high as 27.87 ppb. Associations observed with bladder cancer mortality at levels as low as 4.39–6.09 ppb.

**Table 5-44 (Continued): Summary of evidence, which is inadequate to infer a causal relationship between long term sulfur dioxide exposure and cancer.**

Rationale for Causal Determination <sup>a</sup>	Key Evidence <sup>b</sup>	Key References <sup>b</sup>	SO <sub>2</sub> Concentrations Associated with Effects <sup>c</sup>
Uncertainty due to exposure measurement error	Central site monitors used in cancer studies may not capture spatial variability of SO <sub>2</sub> concentrations.	<a href="#">Section 3.4.2.2</a>	
	Exposure measure measurement error in long-term SO <sub>2</sub> exposure assessment can bias toward or away from the null.	<a href="#">Section 3.4.4.2</a>	
Uncertainty due to confounding by correlated copollutants	Correlations of SO <sub>2</sub> with other pollutants vary by study or are not examined. Some pollutants are moderately to highly correlated with SO <sub>2</sub> but are not always taken into account as potential confounders.	<a href="#">Section 3.4.3</a>	
Uncertainty due to limited coherence with toxicological evidence	Studies in a tumor-susceptible mouse model, females had increased numbers of lung adenomas and carcinomas. Studies of facilitation of metastasis and coexposures with known carcinogens show mixed SO <sub>2</sub> related effects.	<a href="#">Peacock and Spence (1967)</a>	500,000 ppb
		<a href="#">Laskin et al. (1976)</a>	10,000 ppb
		<a href="#">Pauluhn et al. (1985)</a>	172,000 ppb
		<a href="#">Ohyama et al. (1999)</a>	4,000 ppb
		<a href="#">Heinrich et al. (1989)</a>	5,000 or 10,000 ppb
		<a href="#">Ito et al. (1997)</a>	4,000 ppb
		<a href="#">Section 5.6.2.1</a>	
Some evidence identifies key events within the MOA from mutagenesis and genotoxicity.	Mixed evidence of mutagenicity and genotoxicity formation in animal cells exposed to SO <sub>2</sub>	<a href="#">Meng et al. (2002)</a> , <a href="#">Ruan et al. (2003)</a> , <a href="#">Pool et al. (1988b)</a> <a href="#">Section 5.6.3</a>	5,000, 10,700, 21,400, 32,100 ppb

MOA = mode of action; SO<sub>2</sub> = sulfur dioxide.

<sup>a</sup>Based on aspects considered in judgments of causality and weight of evidence in causal framework in Table I and Table II of the [Preamble](#) to the ISAs ([U.S. EPA, 2015b](#)).

<sup>b</sup>Describes the key evidence and references contributing most heavily to causal determination and, where applicable, to uncertainties or inconsistencies. References to earlier sections indicate where full body of evidence is described.

<sup>c</sup>Describes the NO<sub>2</sub> concentrations with which the evidence is substantiated (for experimental studies, below 5,000 ppb).

## Annex for Chapter 5: Evaluation of Studies on Health Effects of Sulfur Oxides

**Table A-1 Scientific considerations for evaluating the strength of inference from studies on the health effects of sulfur oxides.**

<b>Evaluation Factors</b>
<b>Study Design</b>
<b>Controlled Human Exposure:</b>
Studies should clearly describe the primary and any secondary objectives of the study, or specific hypotheses being tested. Study subjects should be randomly exposed without knowledge of the exposure condition. Preference is given to balanced crossover (repeated measures) or parallel design studies that include control exposures (e.g., to clean filtered air). In crossover studies, a sufficient and specified time between exposure days should be employed to avoid carry over effects from prior exposure days. In parallel design studies, all arms should be matched for individual characteristics such as age, sex, race, anthropometric properties, and health status. In studies evaluating effects of disease, appropriately matched healthy controls are desired for interpretative purposes.
<b>Animal Toxicology:</b>
Studies should clearly describe the primary and any secondary objectives of the study, or specific hypotheses being tested. Studies should include appropriately matched control exposures (e.g., to clean filtered air, time matched). Studies should use methods to limit differences in baseline characteristics of control and exposure groups. Studies should randomize assignment to exposure groups and where possible conceal allocation from research personnel. Groups should be subjected to identical experimental procedures and conditions; animal care including housing, husbandry, etc. should be identical between groups. Blinding of research personnel to study group may not be possible due to animal welfare and experimental considerations; however, differences in the monitoring or handling of animals in all groups by research personnel should be minimized.
<b>Epidemiology:</b>
Inference is stronger for studies that clearly describe the primary and any secondary aims of the study, or specific hypotheses being tested. For short-term exposure, time-series, case crossover, and panel studies are emphasized over cross-sectional studies because they examine temporal correlations and are less prone to confounding by factors that differ between individuals (e.g., SES, age). Studies with large sample sizes and conducted over multiple years are considered to produce more reliable results. If other quality parameters are equal, multicity studies carry more weight than single-city studies because they tend to have larger sample sizes and lower potential for publication bias. For long-term exposure, inference is considered to be stronger for prospective cohort studies and case-control studies nested within a cohort (e.g., for rare diseases) than cross-sectional, other case-control, or ecologic studies. Cohort studies can better inform the temporality of exposure and effect. Other designs can have uncertainty related to the appropriateness of the control group or validity of inference about individuals from group-level data. Study design limitations can bias health effect associations in either direction.

**Table A-1 (Continued): Scientific considerations for evaluating the strength of inference from studies on the health effects of sulfur oxides.**

<b>Evaluation Factors</b>
<b>Study Population/Test Model</b>
<b>Controlled Human Exposure:</b>
In general, the subjects recruited into study groups should be similarly matched for age, sex, race, anthropometric properties, and health status. In studies evaluating effects of specific subject characteristics (e.g., disease, genetic polymorphism, etc.), appropriately matched healthy controls are preferred. Relevant characteristics and health status should be reported for each experimental group. Criteria for including and excluding subjects should be clearly indicated. For the examination of populations with an underlying health condition (e.g., asthma), independent, clinical assessment of the health condition is ideal, but self reporting of physician diagnosis generally is considered to be reliable for respiratory and cardiovascular disease outcomes. <sup>a</sup> The loss or withdrawal of recruited subjects during the course of a study should be reported. Specific rationale for excluding subject(s) from any portion of a protocol should be explained.
<b>Animal Toxicology:</b>
Ideally, studies should report species, strain, substrain, genetic background, age, sex, and weight. Unless data indicate otherwise, all animal species and strains are considered appropriate for evaluating effects of SO <sub>2</sub> exposure. It is preferred that the authors test for effects in both sexes and multiple lifestages, and report the result for each group separately. All animals used in a study should be accounted for, and rationale for exclusion of animals or data should be specified.
<b>Epidemiology:</b>
Confidence in results is greater in studies that recruit the study population from the target population and examine a study population that is representative of the target population. Studies with high participation and low drop-out over time that is not dependent on exposure or health status are considered to have low potential for selection bias. Clear indication of criteria for including and excluding subjects can facilitate assessment of selection bias. For populations with an underlying health condition, independent, clinical assessment of the health condition is valuable, but self report of physician diagnosis generally is considered to be reliable for respiratory and cardiovascular outcomes. Comparisons of groups with and without an underlying health condition are more informative if groups are from the same source population. Selection bias can influence results in either direction or may not affect the validity of results but rather reduce the generalizability of findings to the target population.
<b>Pollutant</b>
<b>Controlled Human Exposure:</b>
The focus is on studies testing SO <sub>2</sub> exposure.
<b>Animal Toxicology:</b>
The focus is on studies testing SO <sub>2</sub> exposure.
<b>Epidemiology:</b>
The focus is on studies testing SO <sub>2</sub> exposure.

**Table A-1 (Continued): Scientific considerations for evaluating the strength of inference from studies on the health effects of sulfur oxides.**

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**Evaluation Factors**

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**Exposure Assessment or Assignment**

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**Controlled Human Exposure:**

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For this assessment, the focus will be on studies that use SO<sub>2</sub> concentrations less than or equal to 2 ppm (Section 1.2). Studies that use higher exposure concentrations may provide information relevant to mode of action, dosimetry, inter-species variation, or at-risk human populations. Controlled human exposure studies considering short-term, (e.g. generally exposures from 5–10 min, to 0.2–0.6 ppm SO<sub>2</sub>, were emphasized) (Section 1.2).

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**Animal Toxicology:**

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For this assessment, the focus will be on studies that use SO<sub>2</sub> concentrations less than or equal to 2,000 ppb (Section 1.2). Studies that use higher exposure concentrations may provide information relevant to mode of action, dosimetry, inter-species variation, or at-risk human populations. Studies should characterize pollutant concentration, temperature, and relative humidity and/or have measures in place to adequately control the exposure conditions. The focus is on inhalation exposure. Noninhalation exposure experiments may provide information relevant to mode of action. In vitro studies may be included if they provide mechanistic insight or examine similar effects as in vivo, but are generally not included. All studies should include exposure control groups (e.g., clean filtered air).

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**Epidemiology:**

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Of primary relevance are relationships of health effects with the ambient component of exposure to SO<sub>2</sub>. However, information about ambient exposure rarely is available for individual subjects; most often, inference is based on ambient concentrations. Studies that compare exposure assessment methods are considered to be particularly informative. Inference is stronger when the duration or lag of the exposure metric corresponds with the time course for physiological changes in the outcome (e.g., up to a few days for symptoms) or latency of disease (e.g., several years for cancer).

Given the spatial heterogeneity in ambient SO<sub>2</sub> and potentially variable relationships between personal exposures and ambient concentrations (Section 3.4.2.2 and Section 3.4.1), validated methods that capture the extent of variability for the particular study design (temporal vs. spatial contrasts) and location carry greater weight. Central site measurements, whether averaged across multiple monitors or assigned from the nearest or single available monitor, have well-recognized limitations in capturing spatial variation in air pollutants. Monitors impacted by large SO<sub>2</sub> sources are particularly subject to concentration fluctuations due to changes in emission rates and meteorological conditions and may not fully represent population exposure. Results based on central site measurements can be informative if correlated with personal exposures, closely located to study subjects, highly correlated across monitors within a location, used in locations with well-distributed sources, or combined with time-activity information.

In studies of short-term exposure, temporal variability of the exposure metric is of primary interest. Metrics that may capture variation in ambient sulfur oxides and strengthen inference include concentrations in subjects' microenvironments and individual-level outdoor concentrations combined with time-activity data. Atmospheric models may be used for exposure assessment in place of or to supplement SO<sub>2</sub> measurements in epidemiologic analyses. Dispersion models (e.g., AERMOD) can provide valuable information on fine-scale temporal and spatial variations (within tens of km) of SO<sub>2</sub> concentrations, which is particularly important for assessing exposure near large stationary sources. Alternatively, grid-scale models (e.g., CMAQ) that represent SO<sub>2</sub> exposure over relatively large spatial scales (e.g., typically greater than 4 × 4-km grid size) often do not provide enough spatial resolution to capture acute SO<sub>2</sub> peaks that influence short-term health outcomes. Uncertainty in exposure predictions from these models is largely influenced by model formulations and the quality of model input data pertaining to emissions or meteorology, which tends to vary on a study-by-study basis.

For long-term exposures, models that capture within-community spatial variation in individual exposure may be given more weight for spatially variable ambient SO<sub>2</sub>.

Exposure measurement error often attenuates health effect estimates or decreases the precision of the association (i.e., wider 95% CIs), particularly associations based on temporal variation in short-term exposure (Section 3.4.2.3). However, exposure measurement error can bias estimates away from the null, particularly for long-term exposures.

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**Table A-1 (Continued): Scientific considerations for evaluating the strength of inference from studies on the health effects of sulfur oxides.**

<b>Evaluation Factors</b>
<b>Outcome Assessment/Evaluation</b>
<b>Controlled Human Exposure:</b>
Endpoints should be assessed in the same manner for control and exposure groups (e.g., time after exposure, methods, endpoint evaluator) using valid, reliable methods. Blinding of endpoint evaluators is ideal, especially for qualitative endpoints (e.g., histopathology). For each experiment and each experimental group, including controls, precise details of all procedures carried out should be provided including how, when, and where. Time of the endpoint evaluations is a key consideration that will vary depending on the endpoint evaluated. Endpoints should be assessed at time points that are appropriate for the research questions.
<b>Animal Toxicology:</b>
Endpoints should be assessed in the same manner for control and exposure groups (e.g., time after exposure, methods, endpoint evaluator) using valid, reliable methods. Blinding of endpoint evaluators is ideal, especially for qualitative endpoints (e.g., histopathology). For each experiment and each experimental group, including controls, precise details of all procedures carried out should be provided including how, when, and where. Time of the endpoint evaluations is a key consideration that will vary depending on the endpoint evaluated. Endpoints should be assessed at time points that are appropriate for the research questions.
<b>Epidemiology:</b>
Inference is stronger when outcomes are assessed or reported without knowledge of exposure status. Knowledge of exposure status could produce artifactual associations. Confidence is greater when outcomes assessed by interview, self reporting, clinical examination, or analysis of biological indicators are defined by consistent criteria and collected by validated, reliable methods. Independent, clinical assessment is valuable for outcomes such as lung function or incidence of disease, but report of physician diagnosis has shown good reliability. <sup>a</sup> Outcomes assessed at time intervals that correspond with the time course for physiological changes (e.g., up to a few days for symptoms) are emphasized. When health effects of long-term exposure are assessed by acute events such as symptoms or hospital admissions, inference is strengthened when results are adjusted for short-term exposure. Validated questionnaires for subjective outcomes such as symptoms are regarded to be reliable, <sup>b</sup> particularly when collected frequently and not subject to long recall. For biological samples, the stability of the compound of interest and the sensitivity and precision of the analytical method is considered. If not based on knowledge of exposure status, errors in outcome assessment tend to bias results toward the null.
<b>Potential Copollutant Confounding</b>
<b>Controlled Human Exposure:</b>
Exposure should be well characterized to evaluate independent effects of SO <sub>2</sub> .
<b>Animal Toxicology:</b>
Exposure should be well characterized to evaluate independent effects of SO <sub>2</sub> .

**Table A-1 (Continued): Scientific considerations for evaluating the strength of inference from studies on the health effects of sulfur oxides.**

<b>Evaluation Factors</b>
<b>Epidemiology:</b>
<p>Not accounting for copollutant confounding can produce artifactual associations; thus, studies that examine copollutant confounding carry greater weight. The predominant method is copollutant modeling, which is especially informative when measurement error is comparable for copollutants and correlations are not high. Interaction and joint effect models are examined to a lesser extent. Evaluating correlations between SO<sub>2</sub> and copollutants and comparing health associations between SO<sub>2</sub> and copollutants in single-pollutant models can add to the analysis of potential copollutant confounding, particularly when exposure measurement error is comparable among pollutants. Studies that examine SO<sub>2</sub> only in single-pollutant models provide minimal information on the potential for copollutant confounding. Copollutant confounding is evaluated based on the extent of observed correlations and relationships with health effects. Highly variable correlations have been observed between SO<sub>2</sub> and other criteria pollutants at collocated monitors (<a href="#">Section 3.4.3</a>), ranging from negative to strong correlations, making evaluation of copollutant confounding necessary on a study-specific, rather than a general, basis.</p>
<b>Other Potential Confounding Factors</b>
<b>Controlled Human Exposure:</b>
<p>Preference is given to studies using experimental and control groups that are matched for individual level characteristics (e.g., body weight, smoking history, age) and time-varying factors (e.g., seasonal and diurnal patterns).</p>
<b>Animal Toxicology:</b>
<p>Preference is given to studies using experimental and control groups that are matched for individual level characteristics (e.g., body weight, litter size, food and water consumption) and time-varying factors (e.g., seasonal and diurnal patterns).</p>
<b>Epidemiology:</b>
<p>Factors are considered to be potential confounders if demonstrated in the scientific literature to be related to health effects and correlated with SO<sub>2</sub>. Not accounting for confounders can produce artifactual associations; thus, studies that statistically adjust for multiple factors or control for them in the study design are emphasized. Less weight is placed on studies that adjust for factors that mediate the relationship between SO<sub>2</sub> and health effects, which can bias results toward the null. In the absence of information linking health risk factors to SO<sub>2</sub>, a factor may be evaluated as a potential effect measure modifier, but uncertainty is noted as to its role as a confounder. Confounders vary according to study design, exposure duration, and health effect and may include, but are not limited to, the following:</p> <p>For time-series and panel studies of short-term exposure:</p> <ul style="list-style-type: none"> <li>• Respiratory effects—meteorology, day of week, season, medication use, allergen exposure (potential effect modifier)</li> <li>• Cardiovascular effects—meteorology, day of week, season, medication use</li> <li>• Total mortality—meteorology, day of week, season, long-term temporal trends</li> </ul> <p>For studies of long-term exposure:</p> <ul style="list-style-type: none"> <li>• Respiratory effects—socioeconomic status, race, age, medication use, smoking, stress</li> <li>• Cardiovascular, reproductive, and development effects—socioeconomic status, race, age, medication use, smoking, stress, noise</li> <li>• Total mortality—socioeconomic status, race, age, medication use, smoking, comorbid health conditions</li> <li>• Cancer—socioeconomic status, race, age, occupational exposure</li> </ul>

**Table A-1 (Continued): Scientific considerations for evaluating the strength of inference from studies on the health effects of sulfur oxides.**

Evaluation Factors
<p><b>Statistical Methodology</b></p>
<p><b>Controlled Human Exposure:</b></p>
<p>Statistical methods should be clearly described and appropriate for the study design and research question (e.g., correction for multiple comparisons). Generally, statistical significance is used to evaluate the findings of controlled human exposure studies. Detection of statistical significance is influenced by a variety of factors including, but not limited to, the size of the study, exposure and outcome measurement error, and statistical model specifications. Sample size is not a criterion for exclusion; ideally, the sample size should provide adequate power to detect hypothesized effects (e.g., sample sizes less than three are considered less informative). Because statistical tests have limitations, consideration is given to both trends in data and reproducibility of results.</p>
<p><b>Animal Toxicology:</b></p>
<p>Statistical methods should be clearly described and appropriate for the study design and research question (e.g., correction for multiple comparisons). Generally, statistical significance is used to evaluate the findings of animal toxicology studies. Detection of statistical significance is influenced by a variety of factors including, but not limited to, the size of the study, exposure and outcome measurement error, and statistical model specifications. Sample size is not a criterion for exclusion; ideally, the sample size should provide adequate power to detect hypothesized effects (e.g., sample sizes less than three are considered less informative). Because statistical tests have limitations, consideration is given to both trends in data and reproducibility of results.</p>
<p><b>Epidemiology:</b></p>
<p>Multivariable regression models that include potential confounding factors are emphasized. However, multipollutant models (more than two pollutants) are considered to produce too much uncertainty due to copollutant collinearity to be informative. Models with interaction terms aid in the evaluation of potential confounding as well as effect modification. Sensitivity analyses with alternate specifications for potential confounding inform the stability of findings and aid in judgments of the strength of inference of results. In the case of multiple comparisons, consistency in the pattern of association can increase confidence that associations were not found by chance alone. Statistical methods that are appropriate for the power of the study carry greater weight. For example, categorical analyses with small sample sizes can be prone to bias results toward or away from the null. Statistical tests such as <i>t</i>-tests and Chi-squared tests are not considered sensitive enough for adequate inferences regarding pollutant-health effect associations. For all methods, the effect estimate and precision of the estimate (i.e., width of 95% CI) are important considerations rather than statistical significance.</p>
<p>AERMOD = American Meteorological Society/U.S. EPA Regulatory Model; CI = confidence interval; CMAQ = Community Multiscale Air Quality; SES = socioeconomic status; SO<sub>2</sub> = sulfur dioxide.</p> <p><sup>a</sup><a href="#">Toren et al. (1993)</a>; <a href="#">Murgia et al. (2014)</a>; <a href="#">Weakley et al. (2013)</a>; <a href="#">Yang et al. (2011)</a>; <a href="#">Heckbert et al. (2004)</a>; <a href="#">Barr et al. (2002)</a>; <a href="#">Muhajarine et al. (1997)</a>.</p> <p><sup>b</sup><a href="#">Burney et al. (1989)</a>.</p> <p><sup>c</sup>Many factors evaluated as potential confounders can be effect measure modifiers (e.g., season, comorbid health condition) or mediators of health effects related to SO<sub>2</sub> (comorbid health condition).</p>

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# Chapter 6 Populations and Lifestages Potentially at Increased Risk for Health Effects Related to Sulfur Dioxide Exposure

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## 6.1 Introduction

1 Interindividual variation in human responses to air pollution exposure can result in some  
2 groups or lifestages being at increased risk for health effects in response to ambient  
3 exposure to an air pollutant. The NAAQS are intended to protect public health with an  
4 adequate margin of safety. Protection is provided for both the population as a whole and  
5 those potentially at increased risk for health effects in response to exposure to a criteria  
6 air pollutant (e.g., SO<sub>2</sub>) [see [Preamble](#) to the ISAs ([U.S. EPA, 2015b](#))]. The scientific  
7 literature has used a variety of terms to identify factors and subsequently populations or  
8 lifestages that may be at increased risk of an air pollutant-related health effect, including  
9 *susceptible*, *vulnerable*, *sensitive*, and *at risk*, with recent literature introducing the term  
10 *response-modifying factor* ([Vinikoor-Imler et al., 2014](#)) [see [Preamble](#) to the ISAs ([U.S.](#)  
11 [EPA, 2015b](#))]. Due to the inconsistency in definitions for these terms across the scientific  
12 literature and the lack of a consensus on terminology in the scientific community, as  
13 detailed in the [Preamble](#) to the ISAs ([U.S. EPA, 2015b](#)), this chapter focuses on  
14 identifying those populations or lifestages potentially “at risk” of an SO<sub>2</sub>-related health  
15 effect. This leads to a focus on the identification, evaluation, and characterization of  
16 factors to address the main question of what populations and lifestages are at increased  
17 risk of an SO<sub>2</sub>-related health effect. Some factors may lead to a reduction in risk, and  
18 these are recognized during the evaluation process, but for the purposes of identifying  
19 those populations or lifestages at greatest risk to inform decisions on the NAAQS, the  
20 focus of this chapter is on characterizing those factors that may increase risk.

21 Individuals, and ultimately populations, can be at increased risk of an air pollutant-related  
22 health effect in a number of ways. As discussed in the [Preamble](#) to the ISAs ([U.S. EPA,](#)  
23 [2015b](#)), risk may be modified by intrinsic or extrinsic factors that act synergistically with  
24 SO<sub>2</sub> on a health endpoint (e.g., sociodemographic or behavioral factors), differences in  
25 internal dose (e.g., due to variability in ventilation rates or exercise behaviors), or  
26 differences in exposure to air pollutant concentrations (e.g., more time spent in areas with  
27 higher ambient concentrations). The objective of this chapter is to identify, evaluate, and  
28 characterize the evidence for factors that potentially increase the risk of health effects  
29 related to exposure to SO<sub>2</sub>. Note also that although individual factors that may increase  
30 the risk of an SO<sub>2</sub>-related health effect are discussed in this chapter, it is likely in many  
31 cases that portions of the population are at increased risk of an SO<sub>2</sub>-related health effect

1 due to a combination of factors [e.g., residential location and socioeconomic status  
2 (SES)], but information on the interaction among factors remains limited. Thus, the  
3 following sections identify, evaluate, and characterize the overall confidence that  
4 individual factors potentially result in increased risk for SO<sub>2</sub>-related health effects [see  
5 [Preamble](#) to the ISAs ([U.S. EPA, 2015b](#))].

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## 6.2 Approach to Evaluating and Characterizing the Evidence for At Risk Factors

6 The systematic approach used to evaluate factors that may increase the risk of a  
7 population or specific lifestage to an air pollutant-related health effect is described in  
8 more detail in the [Preamble](#) to the ISAs ([U.S. EPA, 2015b](#)). The evidence evaluated  
9 includes relevant studies discussed in [Chapter 5](#) of this ISA and builds on the evidence  
10 presented in the 2008 ISA for Sulfur Oxides ([U.S. EPA, 2008d](#)). Based on the approach  
11 developed in previous ISAs ([U.S. EPA, 2016e](#), [2013b](#), [c](#)) evidence is integrated across  
12 scientific disciplines, across health effects, and where available, with information on  
13 exposure and dosimetry ([Chapter 3](#) and [Chapter 4](#)). Greater emphasis is placed on those  
14 health outcomes for which a “causal” relationship was concluded in [Chapter 5](#) of this  
15 ISA, while information from studies of health outcomes for which the causal  
16 determination is “suggestive” is only used as supporting evidence where warranted.  
17 Studies examining health outcomes for which an “inadequate” relationship was  
18 concluded are not included in this chapter due to the uncertainty in the independent  
19 association between exposure to SO<sub>2</sub> and the health outcome; as a result, these studies are  
20 unable to provide information on whether certain populations are at increased risk of  
21 SO<sub>2</sub>-related health effects. Conclusions are drawn based on the overall confidence that a  
22 specific factor may result in a population or lifestage being at increased risk of an  
23 SO<sub>2</sub>-related health effect.

24 As discussed in the [Preamble](#) to the ISAs ([U.S. EPA, 2015b](#)), this evaluation includes  
25 evidence from epidemiologic, controlled human exposure, and toxicological studies in  
26 addition to considering relevant exposure-related information. With regard to  
27 epidemiologic studies, the evaluation focuses on those studies that include stratified  
28 analyses to compare populations or lifestages exposed to similar air pollutant  
29 concentrations within the same study design along with consideration of the strengths and  
30 limitations of each study. Other epidemiologic studies that do not stratify results but  
31 instead examine a specific population or lifestage can provide supporting evidence for the  
32 pattern of associations observed in studies that formally examine effect modification.  
33 Similar to the characterization of evidence in [Chapter 5](#), statistical significance is not the  
34 sole criterion by which effect modification is determined; the greatest emphasis is placed

1 on patterns or trends in results across studies. Experimental studies in human subjects or  
 2 animal models that focus on factors, such as genetic background or health status, are  
 3 evaluated because they provide coherence and biological plausibility of effects observed  
 4 in epidemiologic studies. Also evaluated are studies examining whether factors may  
 5 result in differential exposure to SO<sub>2</sub> and subsequent increased risk of SO<sub>2</sub>-related health  
 6 effects.

7 The objective of this chapter is to identify, evaluate, and characterize the overall  
 8 confidence that various factors may increase the risk of an SO<sub>2</sub>-related health effect in a  
 9 population or lifestage, building on the conclusions drawn in the ISA with respect to SO<sub>2</sub>  
 10 exposure and health effects. The broad categories of factors evaluated in this chapter  
 11 include pre-existing disease/condition ([Section 6.3](#)), genetic factors ([Section 6.4](#)), and  
 12 sociodemographic and behavioral factors ([Section 6.5](#)). Formal conclusions are made  
 13 with respect to whether a specific factor increases the risk of an SO<sub>2</sub>-related health effect  
 14 based on the characterization of evidence framework detailed in [Table 6-1](#). A summary of  
 15 the characterization of the evidence for each factor considered in this chapter is presented  
 16 in [Section 6.6](#).

**Table 6-1 Characterization of evidence for factors potentially increasing the risk for sulfur dioxide-related health effects.**

Classification	Health Effects
Adequate evidence	There is substantial, consistent evidence within a discipline to conclude that a factor results in a population or lifestage being at increased risk of air pollutant-related health effect(s) relative to some reference population or lifestage. Where applicable, this evidence includes coherence across disciplines. Evidence includes multiple high-quality studies.
Suggestive evidence	The collective evidence suggests that a factor results in a population or lifestage being at increased risk of air pollutant-related health effect(s) relative to some reference population or lifestage, but the evidence is limited due to some inconsistency within a discipline or, where applicable, a lack of coherence across disciplines.
Inadequate evidence	The collective evidence is inadequate to determine whether a factor results in a population or lifestage being at increased risk of air pollutant-related health effect(s) relative to some reference population or lifestage. The available studies are of insufficient quantity, quality, consistency, and/or statistical power to permit a conclusion to be drawn.
Evidence of no effect	There is substantial, consistent evidence within a discipline to conclude that a factor does not result in a population or lifestage being at increased risk of air pollutant-related health effect(s) relative to some reference population or lifestage. Where applicable, the evidence includes coherence across disciplines. Evidence includes multiple high-quality studies.

## 6.3 Pre-existing Disease/Condition

1 Individuals with pre-existing disease may be considered at greater risk for some air  
 2 pollution-related health effects because they are likely in a compromised biological state  
 3 depending on the disease and severity. The 2008 ISA for Sulfur Oxides ([U.S. EPA,](#)  
 4 [2008d](#)) concluded that those with pre-existing pulmonary conditions were likely to be at  
 5 greater risk for SO<sub>2</sub>-related health effects, especially individuals with asthma. Of the  
 6 recent epidemiologic studies evaluating effect modification of respiratory effects by  
 7 pre-existing disease, most focused on asthma ([Section 6.3.1](#)). [Table 6-2](#) presents the  
 8 prevalence of asthma and other respiratory diseases according to the Centers for Disease  
 9 Control and Prevention’s (CDC’s) National Center for Health Statistics ([Schiller et al.,](#)  
 10 [2012](#)), including the proportion of adults with a current diagnosis categorized by age and  
 11 geographic region. The large proportions of the U.S. population affected by many chronic  
 12 diseases indicates the potential public health impact, and thus, the importance of  
 13 characterizing the risk of SO<sub>2</sub>-related health effects for affected populations.

**Table 6-2 Prevalence of respiratory diseases among adults by age and region in the U.S. in 2012.**

Chronic Disease/Condition	Adults (18+)	Age (%) <sup>a</sup>					Region (%) <sup>b</sup>			
	N (in Thousands)	<18 <sup>c</sup>	18–44	45–64	65–74	75+	North-east	Midwest	South	West
All (N, in thousands)	234,921	6,292	111,034	82,038	23,760	18,089	42,760	53,378	85,578	53,205
<b>Selected respiratory diseases</b>										
Asthma <sup>d</sup>	24,009	8.6	8.1	8.4	7.8	6.0	9.2	8.1	7.3	7.8
COPD—chronic bronchitis	8,658	--	2.5	4.7	4.9	5.2	3.2	4.4	3.9	2.4
COPD—emphysema	4,108	--	0.3	2.3	4.7	4.7	1.3	2.0	1.9	1.0

COPD = chronic obstructive pulmonary disease; N = population number.

<sup>a</sup>Percentage of individual adults and children within each age group with disease, based on N (at the top of each age column).

<sup>b</sup>Percentage of individual adults (18+) within each geographic region with disease, based on N (at the top of each region column).

<sup>c</sup>Statistics for <18 category from [http://www.cdc.gov/asthma/most\\_recent\\_data.htm](http://www.cdc.gov/asthma/most_recent_data.htm), last updated March 2016; accessed on July 28, 2016.

<sup>d</sup>Asthma prevalence is reported for “still has asthma.”

Source: [Blackwell et al. \(2014\)](#); National Center for Health Statistics: Data from Tables 1–4, 7, 8, 28, and 29 of the Centers for Disease Control and Prevention report.

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### 6.3.1 Asthma

1 Approximately 8.0% of adults and 8.6% of children (age <18 years) in the U.S. currently  
2 have asthma ([Blackwell et al., 2014](#); [Bloom et al., 2013](#)), and it is the leading chronic  
3 illness affecting children ([Bloom et al., 2013](#)). Based on evidence from the 2008 ISA for  
4 Sulfur Oxides ([U.S. EPA, 2008d](#)) and recent studies, [Chapter 5](#) concludes that a causal  
5 relationship exists between short-term SO<sub>2</sub> exposure and respiratory effects, based  
6 primarily on evidence from controlled human exposure studies demonstrating decrements  
7 in lung function in individuals with asthma ([Section 5.2.1.2](#) and [Section 5.2.1.9](#)). This is  
8 nearly the same body of evidence evaluated in the 2008 ISA for Sulfur Oxides ([U.S.  
9 EPA, 2008d](#)), which also concluded that individuals with asthma are more sensitive to  
10 exposures to ambient SO<sub>2</sub>. Children with asthma may be particularly at risk compared to  
11 adults with asthma due to (1) their increased responsiveness to methacholine, a potential  
12 surrogate for SO<sub>2</sub> ([Section 5.2.1.2](#)), relative to adults; (2) children's increased ventilation  
13 rates relative to body mass compared to adults; and (3) the increased proportion of oral  
14 breathing observed among children, particularly boys, relative to adults ([Section 4.1.2](#)).  
15 In addition, children tend to spend more time outdoors (where SO<sub>2</sub> levels are higher,  
16 compared to indoor levels), and have the potential to be exposed to higher levels of SO<sub>2</sub>.  
17 Such oral breathing allows greater SO<sub>2</sub> penetration into the tracheobronchial region of the  
18 lower airways than nasal breathing ([Section 4.2.2](#)). This section briefly describes  
19 evidence from the experimental studies and supporting evidence from epidemiologic  
20 studies ([Table 6-3](#)).

**Table 6-3 Controlled human exposure, epidemiology, and animal toxicology studies evaluating pre-existing asthma and sulfur dioxide exposure.**

Factor Evaluated	Reference Category	Direction of Effect Modification or Effect <sup>a</sup>	Outcome	Study Population <sup>b</sup>	Study Details	Study
<b>Controlled human exposure</b>						
Asthma, adolescents (14–18 yr)	Healthy adults (21–55 yr)	↑	Decrements in $V_{max75}$ and $V_{max50}$	n = 9 adolescents	1 ppm $SO_2$ + 1 mg/m <sup>3</sup> NaCl droplet, 1 mg/m <sup>3</sup> NaCl droplet for 60 min at rest	<a href="#">Koenig et al. (1980)</a>
		-	Decrements in sRaw and FEV <sub>1</sub>			
Asthma (atopic)	Healthy	↑	Lung function (sRaw)	n = 4 normal adults,	0.2, 0.4, 0.6 ppm $SO_2$ for 1 h with exercise; Exposures were repeated eight times	<a href="#">Linn et al. (1987)</a>
Mild asthma		↑		n = 21 atopic adults		
Moderate/severe asthma		↑		n = 16 adults with mild asthma		
Asthma (atopic)		↑	Lung function (FEV <sub>1</sub> )	n = 24 adults with moderate/severe asthma		
Mild asthma	↑					
Moderate/severe asthma	↑					
Asthma (atopic)	Healthy	↑	Respiratory symptoms during exposure			
Mild asthma		↑				
Moderate/severe asthma		↑				
Asthma	Healthy	↑	Lung function (sRaw)	n = 46 adults with bronchial asthma, 12 healthy adults	0.5 ppm $SO_2$ for 10 min tidal breathing, 10 min of isocapnic hyperventilation (30 L/min); Histamine challenge	<a href="#">Magnussen et al. (1990)</a>

**Table 6-3 (Continued): Controlled human exposure, epidemiology, and animal toxicology studies evaluating pre existing asthma and sulfur dioxide exposure.**

Factor Evaluated	Reference Category	Direction of Effect Modification or Effect <sup>a</sup>	Outcome	Study Population <sup>b</sup>	Study Details	Study
Asthma	Healthy	-	Lung function (FEV <sub>1</sub> , FVC, MMEF)	n = 12 adults with asthma, 12 healthy adults	0.2 ppm SO <sub>2</sub> for 1 h at rest	<a href="#">Tunnicliffe et al. (2003)</a>
<b>Epidemiology</b>						
With asthma n = 84	Without asthma n = 422	-	Lung function (PEF)	n = 506 elementary school children ages 8–13 yr	Guadeloupe (French West Indies) December 2008–December 2009	<a href="#">Amadeo et al. (2015)</a>
With asthma n = 8	Without asthma n = 28	-	Oxidative stress (8-oxo-7,8-dihydro-2'-deoxyguanosine and malondi-aldehyde)	n = 36 elementary school children (fourth grade, mean age 10.6 yr)	Beijing, China June 2007–September 2008	<a href="#">Lin et al. (2015)</a>
<b>Toxicology</b>						
Rat asthma model (OVA sensitization)	Normal rats	↑	AHR (methacholine)	Rats (Sprague-Dawley), n = 10 males/group (4 wk)	2 ppm SO <sub>2</sub> for 4 h/d for 4 wk beginning at 15 d	<a href="#">Song et al. (2012)</a>
		↑	IL-4 in BALF			
		-	IFN-γ in BALF			
		↑	Airway smooth muscle cell stiffness (in vitro)			
		↑	Airway smooth muscle cell contractility (in vitro)			

AHR = airway hyperresponsiveness; BALF = bronchoalveolar lavage fluid; FEV<sub>1</sub> = forced expiratory volume in 1 sec; FVC = forced vital capacity; IFN-γ = interferon gamma; IL-4 = interleukin 4; MMEF = maximum mid-expiratory flow; n = sample size; NaCl = sodium chloride; OVA = ovalbumin; PEF = peak expiratory flow; SO<sub>2</sub> = sulfur dioxide; sRAW = specific airway resistance; V<sub>max50</sub> = maximal expiratory flow rate at 50%; V<sub>max75</sub> = maximal expiratory flow rate at 75%.

<sup>a</sup>Up facing arrow (↑) indicates that the effect of SO<sub>2</sub> is greater (e.g., larger lung function decrement, larger increase in airway inflammation) in the group with the factor evaluated than in the reference group. Down facing arrow (↓) indicates that the effect of SO<sub>2</sub> is smaller in the group with the factor evaluated than in the reference group. A dash (-) indicates no substantial difference in SO<sub>2</sub>-related health effect between groups. In some studies, only a population with pre-existing disease was examined; therefore, the arrow or dash represents the direction of the effect in that population after exposure to SO<sub>2</sub> relative to exposure to filtered air.

<sup>b</sup>Unless ages are indicated in the row for each study, the mean age or range was not reported in the study aside from indication of adult subjects.

1 Across experimental evidence, adults with asthma consistently have greater decrements  
2 in lung function with SO<sub>2</sub> exposure than those without asthma. Controlled human  
3 exposure studies have evaluated respiratory outcomes among adults at SO<sub>2</sub>  
4 concentrations ranging from 0.2 to 1 ppm and included exposures with and without  
5 exercise. [Linn et al. \(1987\)](#) conducted an extensive study examining several  
6 concentrations of SO<sub>2</sub> with repeated exposures in healthy individuals, individuals with  
7 mild asthma, individuals with atopic asthma, and individuals with moderate/severe  
8 asthma and reported respiratory effects (airway resistance, FEV<sub>1</sub>, symptoms) with  
9 increasing SO<sub>2</sub> exposures according to clinical status, with individuals having moderate  
10 and severe asthma showing the greatest SO<sub>2</sub>-dependent effects. In addition, subject-level  
11 characteristics other than clinical status did not influence response. [Magnussen et al.](#)  
12 [\(1990\)](#) also reported greater decrements in sRaw in subjects with asthma relative to  
13 healthy controls with SO<sub>2</sub> exposures incorporating exercise; however, consistent  
14 decrements in lung function were not observed in adults and adolescents with asthma  
15 relative to healthy controls when exposed at rest ([Tunnicliffe et al., 2003](#); [Koenig et al.,](#)  
16 [1980](#)). It is important to note that these studies were limited by exposure design and small  
17 sample sizes. In addition to controlled human exposure studies, a long-term exposure  
18 study conducted in ovalbumin (OVA)-sensitized rats as an asthma model demonstrated  
19 that 4 weeks of exposure to 2 ppm SO<sub>2</sub> resulted in increased airway resistance compared  
20 to normal rats ([Song et al., 2012](#)).

21 Of the literature included in this ISA, two epidemiologic studies included stratification by  
22 asthma status and did not find differences for short-term exposure to ambient SO<sub>2</sub> with  
23 respiratory outcomes [[Table 6-3](#); ([Amadeo et al., 2015](#); [Lin et al., 2015](#))]. However,  
24 evidence presented in [Section 5.2.1.2](#) generally demonstrates consistent positive  
25 associations between ambient SO<sub>2</sub> concentrations and asthma-related hospitalizations and  
26 ED visits. In addition, some evidence from recent panel studies and studies reviewed in  
27 the 2008 ISA for Sulfur Oxides ([U.S. EPA, 2008d](#)) indicates that children with asthma  
28 experience respiratory symptoms associated with exposure to ambient SO<sub>2</sub>.

29 In conclusion, evidence from controlled human exposure studies and animal toxicology  
30 studies is consistent in demonstrating decrements in lung function with SO<sub>2</sub> exposures.  
31 There is also clear biological plausibility, including key events contributing to the mode  
32 of action ([Section 4.3](#)), supporting the observed effects from experimental studies.  
33 Furthermore, epidemiologic studies report associations between SO<sub>2</sub> exposure and  
34 emergency department visits and hospital admissions due to asthma, and that individuals  
35 with asthma experience respiratory symptoms associated with exposure to ambient SO<sub>2</sub>.  
36 Overall, there is adequate evidence from multiple, high-quality studies and coherence  
37 across scientific disciplines to conclude that people with pre-existing asthma are at  
38 increased risk of SO<sub>2</sub>-induced respiratory effects.

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## 6.4 Genetic Factors

1 Genetic variation in the human population is known to contribute to numerous diseases  
2 and differential physiologic responses. The 2008 ISA for Sulfur Oxides ([U.S. EPA,  
3 2008d](#)) discussed the biological plausibility of individuals with certain genotypes known  
4 to result in reduced function in genes encoding antioxidant enzymes being at increased  
5 risk for respiratory effects related to ambient air pollution. However, the evidence base  
6 was limited to two studies demonstrating individuals with polymorphisms in *GSTP1* and  
7 tumor necrosis factor to be at increased risk for SO<sub>2</sub>-related asthma and decrements in  
8 lung function. A recently conducted study reviewed in this ISA examined effect measure  
9 modification by genotype ([Reddy et al., 2012](#)) and reported inconsistent results across  
10 *GSTM1* and *GSTP1* genotypes in a relatively small sample of children in South Africa.  
11 The *GSTM1* null genotype and the *GSTP1 Ile105Ile* and *Ile105Val* genotypes are  
12 associated with reduced antioxidant enzyme function; however, effect measure  
13 modification of these genotypes on SO<sub>2</sub>-associated intra-day variability of FEV<sub>1</sub> showed  
14 conflicting results. Despite biological plausibility, the limited and inconsistent evidence  
15 base is inadequate to determine whether genetic background contributes to increased risk  
16 for SO<sub>2</sub>-related health effects.

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## 6.5 Sociodemographic and Behavioral Factors

### 6.5.1 Lifestage

17 The 2008 ISA for Sulfur Oxides ([U.S. EPA, 2008d](#)) discussed some evidence for  
18 increased risk of health effects related to SO<sub>2</sub> exposure among different lifestages  
19 (i.e., children and older adults). Lifestage refers to a distinguishable time frame in an  
20 individual's life characterized by unique and relatively stable behavioral or physiological  
21 characteristics associated with development and growth ([U.S. EPA, 2014b](#)). Differential  
22 health effects of SO<sub>2</sub> across lifestages theoretically could be due to several factors. With  
23 regard to children, the human respiratory system is not fully developed until 18–20 years  
24 of age, and therefore, children could plausibly have intrinsic risk for respiratory effects  
25 due to potential perturbations in normal lung development ([Finkelstein and Johnston,  
26 2004](#)). Older adults (typically considered those 65 years of age or greater) have weakened  
27 immune function, impaired healing, decrements in pulmonary and cardiovascular  
28 function, and greater prevalence of chronic disease [[Rosenthal and Kavic, 2004](#)];  
29 [Table 6-2](#)], which may contribute to or worsen health effects related to SO<sub>2</sub> exposure.  
30 Also, exposure or internal dose of SO<sub>2</sub> may vary across lifestages due to varying  
31 ventilation rates, increased oronasal breathing at rest, and time-activity patterns.

1 The following sections present the evidence comparing lifestages from the recent  
2 literature, which builds on the evidence presented in the 2008 ISA for Sulfur Oxides  
3 ([U.S. EPA, 2008d](#)).

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### 6.5.1.1 Children

4 According to the 2010 census, 24% of the U.S. population is less than 18 years of age,  
5 with 6.5% less than age 6 ([Howden and Meyer, 2011](#)). The large proportion of children  
6 within the U.S. demonstrates the public health importance of characterizing the risk of  
7 SO<sub>2</sub>-related health effects among children. This is especially so because of the causal  
8 relationship between ambient SO<sub>2</sub> exposure and respiratory outcomes, with strong  
9 evidence demonstrating lung function decrements in individuals with asthma, which  
10 affects approximately 11% of children 5 years and older. The 2008 ISA for Sulfur Oxides  
11 ([U.S. EPA, 2008d](#)) presented evidence indicating an increased risk of SO<sub>2</sub>-related  
12 respiratory outcomes in children compared to adults; however, recent evidence is not  
13 entirely consistent with the evidence considered previously ([Table 6-4](#)). Although [Son et](#)  
14 [al. \(2013\)](#) found children (0–14 years) to be at greater risk for SO<sub>2</sub>-related asthma  
15 hospital admissions, neither [Ko et al. \(2007b\)](#) nor [Alhanti et al. \(2016\)](#) observed  
16 differences between children and adults when examining associations of ambient SO<sub>2</sub> and  
17 asthma hospitalizations or emergency department visits. When examining evidence for  
18 different age groups of children, [Jalaludin et al. \(2008\)](#) observed that associations for  
19 respiratory-related ED visits among children ages 1–4 years were greater than for  
20 children ages 10–14 years; however, [Samoli et al. \(2011\)](#) and [Villeneuve et al. \(2007\)](#) did  
21 not find stronger associations for asthma-related hospital admissions or ED visits among  
22 younger children. Similarly, [Dong et al. \(2013c\)](#) did not find age-related differences  
23 among children for SO<sub>2</sub>-associated asthma, and [Sahsuvaroglu et al. \(2009\)](#) found children  
24 ages 6–7 years had smaller SO<sub>2</sub>-associated nonallergic asthma compared to adolescents  
25 at 13–14 years.

26 Overall, the combined evidence from the previous and current ISA examining respiratory  
27 outcomes across lifestages is suggestive of increased risk in children, given the  
28 inconsistencies across epidemiologic studies and limited toxicological evidence to inform  
29 plausibility. There are biological factors (e.g., increased ventilation rates relative to body  
30 mass among children and increased oral breathing that lead to greater SO<sub>2</sub> penetration  
31 and bronchial surface doses) that could support increased risk to children. However,  
32 recent evidence, mainly from epidemiologic studies of respiratory ED visits and hospital  
33 admissions, does not consistently show increased risk among children ([Table 6-4](#)).

**Table 6-4 Epidemiologic studies evaluating childhood lifestage and sulfur dioxide exposure.**

Factor Evaluated	Reference Category	Direction of Effect Modification <sup>a</sup>	Outcome	Study Population	Study Details	Study
<b>Short-term exposure</b>						
Childhood ages 0–14 yr n = 60.1/d	All ages n = 104.9/d	↓	Hospital admissions for acute respiratory distress	14 hospitals	Hong Kong, China 1996–2002	<a href="#">Wong et al. (2009)</a>
Childhood ages 0–14 yr n = 23,596	Adulthood ages 15–65 yr n = 21,204	-	Asthma hospital admissions	15 hospitals n = 69,176 admissions	Hong Kong, China 2000–2005	<a href="#">Ko et al. (2007b)</a>
Childhood ages 0–14 yr n = 8.7/d	Adulthood ages 15–64 yr n = 4.3/d	↑	Asthma hospital admissions	Database accounting for 48% of South Korean population n = 19/d	Eight South Korean cities 2003–2008	<a href="#">Son et al. (2013)</a>
Childhood ages 0–4 yr n = 72%	Childhood ages 5–14 yr n = 28%	-	Asthma hospital admissions	Three main children's hospitals approximately 85% of pediatric beds of metropolitan area of Athens n = 3,601	Athens, Greece 2001–2004	<a href="#">Samoli et al. (2011)</a>
Childhood ages 2–4 yr n = 7,247	Childhood ages 5–14 yr n = 13,145	-	Asthma ED visits	Five hospitals servicing more than 80% of the metropolitan area n = 57,192 visits	Edmonton, Canada 1992–2002	<a href="#">Villeneuve et al. (2007)</a>
Childhood ages 1–4 yr n = 109/d	Childhood ages 10–14 yr n = 25/d	↑	Respiratory-related ED visits	Daily number of ED visits in metropolitan Sydney from the New South Wales Health Department n = 174/d	Sydney, Australia 1997–2001	<a href="#">Jalaludin et al. (2008)</a>

**Table 6-4 (Continued): Epidemiologic studies evaluating childhood lifestage and sulfur dioxide exposure.**

Factor Evaluated	Reference Category	Direction of Effect Modification <sup>a</sup>	Outcome	Study Population	Study Details	Study
Childhood ages 5–18 yr n = 59.6/d	Adulthood ages 19–39 yr n = 41.1/d	-	Asthma ED visits	Daily number of ED visits in metropolitan area n = 62.8/d (Atlanta) n = 76.3/d (Dallas) n = 50.6/d (St. Louis)	Three U.S. cities (Atlanta, GA 1993–2009; Dallas, TX 2006–2009; St. Louis, MO 2001–2007)	<a href="#">Alhanti et al. (2016)</a>
<b>Long-term exposure</b>						
Childhood ages 2–5 yr n = 7,508	Childhood ages 6–14 yr n = 23,541	-	Doctor-diagnosed asthma	n = 31,049 Children ages 2–14 yr	Seven northeastern cities study, Liaoning Province, northeast China 2008–2009	<a href="#">Dong et al. (2013c)</a>
		↑	Respiratory symptoms (cough, phlegm, current wheeze)			
Younger children ages 6–7 yr n = 918	Older children ages 13–14 yr n = 549	↓	Non-allergic asthma	n~ 1,467 Children grades 1 (ages 6–7 yr) and 8 (ages 13–14 yr)	Hamilton, Canada 1994–1995	<a href="#">Sahsuvaroglu et al. (2009)</a>

ED = emergency department; n = sample size.

<sup>a</sup>Up facing arrow indicates that the effect of is greater (e.g., larger increase in hospital admission) in the group with the factor evaluated than in the reference group. Down facing arrow indicates that the effect of sulfur dioxide is smaller in the group with the factor evaluated than in the reference group. A dash indicates no substantial difference in sulfur dioxide-related health effect between groups.

### 6.5.1.2 Older Adults

1 According to the 2008 National Population Projections issued by the U.S. Census  
 2 Bureau, approximately 12.9% of the U.S. population is age 65 years or older, and by  
 3 2030, this fraction is estimated to grow to 20% ([Vincent and Velkoff, 2010](#)). Thus, this  
 4 lifestage represents a substantial proportion of the U.S. population that is potentially at  
 5 increased risk for health effects related to SO<sub>2</sub> exposure.

1 The 2008 ISA for Sulfur Oxides ([U.S. EPA, 2008d](#)) indicated that compared with  
2 younger adults, older adults (typically ages 65 years and older) may be at increased risk  
3 for SO<sub>2</sub>-related respiratory emergency department visits and hospitalizations, but limited  
4 evidence was available to inform risk related to respiratory effects. Recently published  
5 studies evaluating risk in older adults compared to younger adults are characterized in  
6 [Table 6-5](#) and generally support conclusions from the 2008 ISA for Sulfur Oxides ([U.S.](#)  
7 [EPA, 2008d](#)). [Villeneuve et al. \(2007\)](#) and [Son et al. \(2013\)](#) both reported that  
8 asthma-related ED visits and hospital admissions were more strongly associated with  
9 short-term ambient SO<sub>2</sub> exposure in individuals older than 75 years than adults  
10 65–74 years or those younger than 65. However, the handful of recent studies evaluating  
11 asthma and nonasthma respiratory admissions or ED visits in adults greater than 65 years  
12 of age reported inconsistent results compared to the earlier literature ([Alhanti et al., 2016](#);  
13 [Son et al., 2013](#); [Arbex et al., 2009](#); [Wong et al., 2009](#); [Ko et al., 2007b](#)). In addition to  
14 these studies of short-term SO<sub>2</sub> exposure, [Forbes et al. \(2009c\)](#) found older adults (45–74  
15 and older than 75 years) to have larger decrements in lung function compared to adults  
16 aged 16–44. Additionally, [Bravo et al. \(2015\)](#), [Chen et al. \(2012c\)](#), and [Wong et al.](#)  
17 [\(2008b\)](#) found evidence for increased risk of total mortality with short-term SO<sub>2</sub>  
18 exposures in adults older than 75 years compared to other age groups, which is consistent  
19 with age-specific evidence from respiratory studies. Evidence examining short-term SO<sub>2</sub>  
20 exposure and total mortality is suggestive of, but not sufficient to infer, a causal  
21 relationship ([Section 5.5.1](#)).

22 Taken together, the collective evidence builds on conclusions from the previous ISA and  
23 is suggestive that older adults may be at increased risk for SO<sub>2</sub>-related health effects.  
24 The evidence from the current and previous ISA related to respiratory hospitalizations  
25 and ED visits indicates that older adults, particularly those older than 75 years, may be at  
26 increased risk for SO<sub>2</sub>-related health effects, although this evidence is not entirely  
27 consistent. Evidence is much more consistent for total mortality, demonstrating that older  
28 adults (>65 or 75 years) are at greater risk than younger individuals, although there is  
29 uncertainty in the independent association between short-term SO<sub>2</sub> exposure and total  
30 mortality.

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## 6.5.2 Sex

31 A vast number of health conditions and diseases have been shown to differ by sex, and  
32 there is some indication of differences by sex in the relationship between air pollution  
33 and health effects. The 2010 U.S. census indicates an approximately equal distribution of  
34 males and females in the U.S.: 49.2% male and 50.8% female ([Howden and Meyer,](#)  
35 [2011](#)). However, the distribution varies by age, with a greater prevalence of females

1 above 65 years of age compared to males. Thus, the public health implications of  
 2 potential sex-based differences in air pollution-related health effects may vary among age  
 3 groups within the population.

**Table 6-5 Epidemiologic studies evaluating older adult lifestage and sulfur dioxide exposure.**

Factor Evaluated	Reference Category	Direction of Effect Modification <sup>a</sup>	Outcome	Study Population	Study Details	Study
Older adulthood ages >65 yr n = 24,916	Younger adulthood ages 15–65 yr n = 21,204	-	Asthma hospital admissions	15 hospitals n = 69,176 admissions	Hong Kong, China 2000–2005	<a href="#">Ko et al. (2007b)</a>
Older adulthood ages 65–74 yr n = 4,705	Younger adulthood ages 15–64 yr n = 32,815	-	Asthma ED visits	Five hospitals n = 57,912 visits	Edmonton, Canada 1992–2002	<a href="#">Villeneuve et al. (2007)</a>
Older adulthood ages ≥75 yr n = 1,855		↑				
Adulthood ages 65+ yr n = 4.7/d	Adulthood ages 19–39 yr n = 41.1/d	-	Asthma ED visits	Daily number of ED visits in metropolitan area n = 62.8/d (Atlanta) n = 76.3/d (Dallas) n = 50.6/d (St. Louis)	Three U.S. cities (Atlanta, GA 1993–2009; Dallas, TX 2006–2009; St. Louis, MO 2001–2007)	<a href="#">Alhanti et al. (2016)</a>
Older adulthood ages ≥65 yr n = 789	Younger adulthood ages 40–64 yr n = 980	↑	COPD ED visits	São Paulo Hospital, daily records for patients >40 yr n = 1,769	São Paulo, Brazil 2001–2003	<a href="#">Arbex et al. (2009)</a>
Older adulthood ages 65–74 yr n = 5.8/d	Younger adulthood ages 15–64 yr n = 8.8/d	-	Asthma and allergic disease hospital admissions	Hospital admission database accounting for 48% of Korean population n = 37.7/d	Eight South Korean cities 2003–2008	<a href="#">Son et al. (2013)</a>

**Table 6-5 (Continued): Epidemiologic studies evaluating older adult lifestage and sulfur dioxide exposure.**

Factor Evaluated	Reference Category	Direction of Effect Modification <sup>a</sup>	Outcome	Study Population	Study Details	Study
Older adulthood ages ≥75 yr n = 5.8/d	Younger adulthood ages 15–64 yr n = 8.8/d	↑				
Older adulthood ages ≥65 yr n = 59.6	All ages n = 91.5	-	COPD hospital admissions	14 hospitals	Hong Kong, China 1996–2002	<a href="#">Wong et al. (2009)</a>
Older adulthood ages ≥65 yr n = 138.5	All ages n = 270.3	-	Respiratory disease hospital admissions			
Older adulthood ages ≥65 yr <sup>b</sup>	Adulthood, childhood ages 5–64 yr <sup>b</sup>	↑	Total mortality	Data from Municipal Centers for Disease Control and Prevention	17 Chinese cities	<a href="#">Chen et al. (2012c)</a>
Older adulthood ages ≥75 yr	All ages (≥65 yr)	↑	Total mortality	Data from the Ministry of Public Health, Bangkok; the Census and Statistic Department, Hong Kong; the Shanghai Municipal Center of Disease Control and Prevention, Shanghai; and the Wuhan Centre for Disease Prevention and Control	Bangkok, Thailand; Hong Kong, Shanghai, and Wuhan, China 1996–2004	<a href="#">Wong et al. (2008b)</a>
Older adulthood ages 65–74 yr n = 194,202	Ages 35–64 n = 315,435	↑	Mortality	N = 849,127	Sao Paulo, Brazil May 1996–December 2010	<a href="#">Bravo et al. (2015)</a>
Older adulthood ages ≥75 yr n = 339,490	Ages 35–64 n = 315,435	↑				

COPD = chronic obstructive pulmonary disease; ED = emergency department; n = sample size.

<sup>a</sup>Up facing arrow indicates that the effect of sulfur dioxide is greater (e.g., larger risk of hospital admission, larger decrement in heart rate variability) in the group with the factor evaluated than in the reference group. Down facing arrow indicates that the effect of sulfur dioxide is smaller in the group with the factor evaluated than in the reference group. A dash indicates no substantial difference in sulfur dioxide-related health effect between groups.

<sup>b</sup>Sample size not reported.

There are a number of studies evaluating sex-based differences in SO<sub>2</sub>-associated health effects, as detailed in [Table 6-6](#). Studies of short-term SO<sub>2</sub> exposures and respiratory effects in children and adults did not consistently indicate differences by sex. [Ishigami et al. \(2008\)](#) found adult females to have increased respiratory symptoms with ambient SO<sub>2</sub> exposure compared to adult males; however, [Son et al. \(2013\)](#) found larger associations for asthma or allergic disease hospitalizations for males compared to females. No differences were found between men and women for SO<sub>2</sub>-related COPD ED visits ([Arbex et al., 2009](#)). In children, SO<sub>2</sub>-associated decrements in lung function were not different between boys and girls ([Linares et al., 2010](#); [Dales et al., 2009](#)), although [Samoli et al. \(2011\)](#) found boys to have higher associations between ambient SO<sub>2</sub> exposure and asthma hospital admissions. In a long-term SO<sub>2</sub> exposure study, [Deng et al. \(2015a\)](#) observed stronger associations with asthma incidence among boys compared to girls.

The collective body of evidence does not clearly indicate that SO<sub>2</sub>-related health effects differ between males and females. Due to the inconsistent results demonstrated across epidemiologic studies and a lack of experimental studies examining sex-based differences, the evidence is inadequate to determine whether males or females may be at increased risk for SO<sub>2</sub>-related health effects.

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### 6.5.3 Socioeconomic Status

SES is a composite measure that usually consists of economic status measured by income, social status measured by education, and work status measured by occupation. Generally, persons with lower SES have been found to have a higher prevalence of pre-existing diseases, potential inequities in access to resources such as healthcare, and possibly increased nutritional deficiencies, which may increase their risk to SO<sub>2</sub>-related health effects ([Wong et al., 2008a](#); [WHO, 2006](#)). According to U.S. census data, 15.9% (approximately 48.5 million) of Americans lived below the poverty threshold in 2011 as defined by household income, which is one metric used to define SES ([Bishaw, 2012](#)). The wide array of SES factors that can be used to describe or assign SES can complicate any synthesis of findings because definitions of SES vary across countries based on population demographics, bureaucracy, and the local economy. As a result of these complexities, the ability to draw conclusions regarding SES as a factor for increased risk for health effects related to SO<sub>2</sub> exposure can be difficult.

**Table 6-6 Epidemiologic studies evaluating effect modification by sex and sulfur dioxide exposure.**

Factor Evaluated	Reference Category	Direction of Effect Modification <sup>a</sup>	Outcome	Study Population	Study Details	Study
<b>Short-term exposure</b>						
Female 20% person h	Male 80% person h	↑	Respiratory symptoms (cough, scratchy throat, sore throat, breathlessness)	Healthy adult volunteers working on an active volcanic island after the evacuation order was lifted n = 955	Miyakejima Island, Japan 2005	<a href="#">Ishigami et al. (2008)</a>
Female n = 39	Male n = 114	-	Lung function (FEV <sub>1</sub> )	Elementary school children with asthma (no cigarette smoking in home) n = 182 children (ages 9–14 yr)	Windsor, Canada October–December 2005	<a href="#">Dales et al. (2009)</a>
Female n = 235	Male n = 229	-	Lung function (FEV <sub>1</sub> , FVC, PEF, FEV <sub>1</sub> /FVC)	Children recruited from two schools with different roadway proximity n = 464 (6–14 yr)	Salamanca, Mexico 2004–2005	<a href="#">Linares et al. (2010)</a>
Female n = 794	Male n = 875	-	COPD ED visits	São Paulo Hospital, daily records for patients >40 yr n = 1,769	São Paulo, Brazil 2001–2003	<a href="#">Arbex et al. (2009)</a>
Female n = 7.4 admissions/ d	Male n = 8 admissions/ d	↓	Asthma hospital admissions		Eight South Korean cities 2003–2008	<a href="#">Son et al. (2013)</a>

**Table 6-6 (Continued): Epidemiologic studies evaluating effect modification by sex and sulfur dioxide exposure.**

Factor Evaluated	Reference Category	Direction of Effect Modification <sup>a</sup>	Outcome	Study Population	Study Details	Study
Female n = 7.1 admissions/ d	Male n = 8 admissions/ d	↓	Allergic disease hospital admissions	Database accounting for 48% of South Korean population n = 19/d		
Female n = 1,332	Male n = 2,269	↓	Asthma hospital admissions	Three main children's hospitals—approximately 85% of pediatric beds of metropolitan area of Athens n = 3,601	Athens, Greece 2001–2004	<a href="#">Samoli et al. (2011)</a>
<b>Long-term exposure</b>						
Female n = 1,153	Male n = 1,337	↓	Asthma incidence	Children from 36 different kindergartens n = 2,490	Changsha, China	<a href="#">Deng et al. (2015a)</a>

COPD = chronic obstructive pulmonary disease; ED = emergency department; FEV<sub>1</sub> = forced expiratory volume in 1 sec; FVC = forced vital capacity; n = sample size; PEF = peak expiratory flow.

<sup>a</sup>Up facing arrow indicates that the effect of SO<sub>2</sub> is greater (e.g., larger risk of hospital admission) in the group with the factor evaluated than in the reference group. Down facing arrow indicates that the effect of sulfur dioxide is smaller in the group with the factor evaluated than in the reference group. A dash indicates no substantial difference in sulfur dioxide-related health effect between groups.

1 A single study ([Cakmak et al., 2016](#)) evaluated the potential for SES (income or  
2 education) to modify the effect of long-term exposure to SO<sub>2</sub> on respiratory effects,  
3 specifically measures of lung function. The authors observed greater decrements in lung  
4 function for those in the lowest income and education groups when compared to those in  
5 the highest. In addition, a study evaluated effect modification by education on  
6 SO<sub>2</sub>-associated health outcomes. [Chen et al. \(2012c\)](#) found lower education to increase  
7 risk for mortality with short-term SO<sub>2</sub> exposure. Overall, the evidence for effect  
8 modification by SES on SO<sub>2</sub>-related health outcomes is limited to a single study of  
9 respiratory health effects and one of mortality. Evidence examining short-term SO<sub>2</sub>  
10 exposure and total mortality is suggestive of, but not sufficient to infer, a causal  
11 relationship ([Section 5.5.1](#)). This limited evidence is inadequate to determine whether  
12 low SES increases risk for SO<sub>2</sub>-related health effects.

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#### 6.5.4 Smoking

1 Smoking is a common behavior as indicated by the 2010 National Health Interview  
2 Survey, which estimated that approximately 19.2% of the U.S. adult population report  
3 being current smokers and 21.5% report being former smokers ([Schiller et al., 2012](#)).  
4 Smoking is a well-documented risk factor for many diseases, but it is unclear whether  
5 smoking exacerbates health effects associated with air pollutant exposures, including  
6 SO<sub>2</sub>.

7 [Dong et al. \(2012\)](#), [Forbes et al. \(2009c\)](#), and [Smith et al. \(2016\)](#) investigated effect  
8 modification of the relationship between long-term exposure to SO<sub>2</sub> and respiratory  
9 endpoints by smoking status. [Dong et al. \(2012\)](#) found that among the few respiratory  
10 deaths included in their retrospective cohort study, associations with long-term ambient  
11 SO<sub>2</sub> were only present with current smoking. [Smith et al. \(2016\)](#) observed positive  
12 associations between long-term average SO<sub>2</sub> concentration and pulmonary tuberculosis  
13 among ever smokers, but not with never smokers. [Forbes et al. \(2009c\)](#), on the other  
14 hand, did not find current smoking to increase risk for lung function decrements with  
15 long-term SO<sub>2</sub> exposure compared to not smoking; however, former smoking did appear  
16 to increase risk in this study.

17 Overall, the inconsistent evidence is inadequate to determine whether smoking  
18 exacerbates SO<sub>2</sub>-related health effects. A limited number of long-term exposure studies  
19 observed positive associations among current or former smokers, but not for never  
20 smokers for various respiratory health endpoints, including respiratory mortality. No  
21 studies evaluated smoking as an effect modifier of the relationship between short-term  
22 exposure to SO<sub>2</sub> and respiratory outcomes, for which there is the most confidence in the  
23 causal nature of the relationship.

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#### 6.6 Conclusions

24 This chapter characterized factors that may result in populations and lifestyles being at  
25 increased risk for SO<sub>2</sub>-related health effects; a summary of at-risk factors and resulting  
26 evidence classifications is included in [Table 6-7](#). The evaluation of each factor focused  
27 on the consistency, coherence, and biological plausibility of evidence integrated across  
28 scientific disciplines: specifically, epidemiologic, controlled human exposure, and  
29 toxicological studies using the weight-of-evidence approach detailed in [Table 6-1](#). In  
30 evaluating and integrating evidence related to at-risk factors, it is important to consider  
31 additional information including exposure concentrations, dosimetry, modes of action,  
32 and/or the independence of relationships of SO<sub>2</sub> exposure with health effects as detailed

1 in [Chapter 5](#). For many potential at-risk factors summarized in [Table 6-7](#), the evidence  
 2 was limited with respect to ambient exposures to SO<sub>2</sub>.

**Table 6-7 Summary of evidence for potential increased sulfur dioxide exposure and increased risk of sulfur dioxide-related health effects.**

Evidence Classification	Factor Evaluated	At-Risk Group	Rationale for Classification
Adequate evidence	Pre-existing disease	Individuals with Asthma ( <a href="#">Section 6.3.1</a> )	Consistent evidence for increased risk for SO <sub>2</sub> -related lung function decrements in controlled human exposure studies Support provided by epidemiologic studies of hospital admissions and ED visits for respiratory causes
Suggestive evidence	Lifestage	Children ( <a href="#">Section 6.5.1.1</a> )	Evidence for increased risk among children provided in previous ISA; older studies provide biological plausibility; recent epidemiologic studies provide limited support, and are not entirely consistent
		Older adults ( <a href="#">Section 6.5.1.2</a> )	Evidence for increased risk for older adults provided in previous ISA; mixed results in recent epidemiologic studies for respiratory-related outcomes and mortality
Inadequate evidence	Genetic background ( <a href="#">Section 6.4</a> )	None identified	Epidemiologic findings inconsistently show differences in SO <sub>2</sub> -related health effects, show no difference, or are limited in quantity
	Sex ( <a href="#">Section 6.5.2</a> )	None identified	Uncertainty in independent relationships with SO <sub>2</sub> provides limited basis for inferences about differential risk
	Socioeconomic status ( <a href="#">Section 6.5.3</a> )	None identified	
	Smoking ( <a href="#">Section 6.5.4</a> )	None identified	
Evidence of no effect	None		

ED = emergency department; ISA = Integrated Science Assessment; SO<sub>2</sub> = sulfur dioxide.

3 Consistent with observations made in the 2008 ISA for Sulfur Oxides ([U.S. EPA, 2008d](#)),  
 4 the evidence is adequate to conclude that people with asthma are at increased risk for

1 SO<sub>2</sub>-related health effects. Most of the evidence for this conclusion was presented in the  
2 previous ISA, but recent studies consistently indicate increased risk across studies.  
3 Furthermore, the evidence is based on findings for short-term SO<sub>2</sub> exposure and  
4 respiratory effects (specifically lung function decrements), for which a causal relationship  
5 exists ([Section 5.2.1.9](#)). There are a limited number of epidemiologic studies evaluating  
6 SO<sub>2</sub>-related respiratory effects in people with asthma, but there is evidence for  
7 asthma-related hospital admissions and emergency department visits ([Section 5.2.1.2](#)).  
8 Further support for increased risk in individuals with asthma is provided by biological  
9 plausibility drawn from modes of action.

10 There is suggestive evidence of an increased risk of SO<sub>2</sub>-related respiratory effects in  
11 children and older adults. Although the 2008 ISA for Sulfur Oxides ([U.S. EPA, 2008d](#))  
12 discussed several studies indicating stronger associations between SO<sub>2</sub> and respiratory  
13 outcomes for these lifestages, the evidence in the current ISA is less consistent. For  
14 children, studies comparing SO<sub>2</sub>-associated respiratory outcomes reported mixed results,  
15 but known age-related factors such as higher ventilation rates and time-activity patterns  
16 provide plausibility for higher SO<sub>2</sub> exposure and/or dose in children. For adults, recent  
17 research generally finds similar associations for SO<sub>2</sub>-related respiratory outcomes or  
18 mortality across age groups, although individuals over 75 years were more consistently at  
19 increased risk. In addition, there was limited toxicological evidence to support  
20 observations made across epidemiologic studies.

21 For all other at-risk factors considered based on information available in the studies  
22 included in the current ISA, evidence was inadequate to determine whether those factors  
23 result in increased risk for SO<sub>2</sub>-related health effects. Generally, there was a limited  
24 number of studies available evaluating SES, genetic background, race/ethnicity, and  
25 smoking. Many of these factors are interrelated and are known to impact health risks  
26 related to air pollution in general, but the scientific evidence available in the published  
27 literature specific to health effects associated with ambient SO<sub>2</sub> exposure is inadequate to  
28 determine whether these factors confer increased risk.

29 In conclusion, evidence is adequate to conclude that people with asthma are at increased  
30 risk for SO<sub>2</sub>-related health effects. Asthma prevalence in the U.S. is approximately  
31 8–11% across age groups ([Blackwell et al., 2014](#); [Bloom et al., 2013](#)), and thus,  
32 represents a substantial fraction of the population that may be at risk for respiratory  
33 effects related to ambient SO<sub>2</sub> concentrations.

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See Note below<sup>1</sup>

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<sup>1</sup> Note: Hyperlinks to the reference citations throughout this document will take you to the NCEA HERO database (Health and Environmental Research Online) at <https://hero.epa.gov/hero>. HERO is a database of scientific literature used by the 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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