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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

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

Clean Air Scientific Advisory Committee Sulfur Oxides NAAQS Review Panel

Chair of the Sulfur Oxides Review Panel

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

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

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

Acronym/ Abbreviation	Meaning
α	alpha, exposure factor
A4	not classifiable for humans or animals
AA	adenine-adenine genotype
ACS	American Cancer Society
AER	air exchange rate; Atmospheric and Environmental Research
AERMOD	American Meteorological Society/U.S. EPA Regulatory Model
ag	agriculture
AG	adenine-guanine genotype
AGL	above ground level
AHR	airway hyperresponsiveness
AIRS	Aerometric Information Retrieval System; Atmospheric Infrared Sounder
AL	Alabama
ALRI	acute lower respiratory infection
a.m.	ante meridiem (before noon)
APEX	Air Pollution Exposure model
APHEA	Air Pollution and Health: A European Approach study
APIMS	atmospheric pressure ionization mass spectrometry
AQCD	air quality criteria document
AQS	air quality system
ARIES	Aerosol Research Inhalation Epidemiology Study
ARP	Acid Rain Program
ASM	airway smooth muscle
AT	Atascadero
ATD	atmospheric transport and dispersion
ATS	American Thoracic Society
avg	average
AZ	Arizona
β	beta
BAL	bronchoalveolar lavage
BALF	bronchoalveolar lavage fluid
B[a]P	benzo[a]pyrene
bax	B-cell lymphoma 2-like protein 4
BC	black carbon
Bcl-2	B-cell lymphoma 2
BHR	bronchial hyperreactivity
BK	Bangkok
BMA	Bayesian Model Averaging
BMI	body mass index
BP	blood pressure
BrO	bromine oxide
BS	black smoke
C	degrees Celsius; the product of microenvironmental concentration; carbon
C1	sulfur dioxide + nitrogen dioxide
C2	sulfur dioxide + PM_{10}
C3	sulfur dioxide + ozone
CA	California
C_a	central site ambient SO_2 concentration
$C_{a,csm}$	ambient concentration at a central site monitor
CAA	Clean Air Act
CAIR	Clean Air Interstate Rule
CAPES	China Air Pollution and Health Effects Study
CASAC	Clean Air Scientific Advisory Committee
CBSA	core-based statistical area
CCN	cloud condensation nuclei
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
cGMP	cyclic guanosine monophosphate
CH_3SH	methyl mercaptan

Acronym/ Abbreviation	Meaning
CH_3-S-CH_3	dimethyl sulfide
$CH_3-S-S-CH_3$	dimethyl disulfide
$(CH_3)_2SO$	dimethyl sulfoxide
CH_3SO_3H	methanesulfonic acid
CHAD	Consolidated Human Activity Database
CHD	coronary heart disease
CHF	congestive heart failure
CI(s)	confidence interval(s)
cIMT	carotid intima-media thickness
Cj	airborne SO_2 concentration at microenvironment *j*
Cl	chlorine radical
CMAQ	Community Multiscale Air Quality
CO	carbon monoxide; Colorado
CO_2	carbon dioxide
COH	coefficient of haze
Conc	concentration
Cong.	congress
COPD	chronic obstructive pulmonary disease
COX-2	cyclooxygenase-2
C-R	concentration-response (relationship)
CRDS	cavity ring-down spectroscopy
CRP	c-reactive protein
CS_2	carbon disulfide
CT	Connecticut
CTM	chemical transport models
CVD	cardiovascular disease
D.C. Cir	District of Columbia Circuit
d	day
DBP	diastolic blood pressure
DC	District of Columbia
DEcCBP	diesel exhaust particle extract-coated carbon black particles
DEP	diesel exhaust particles
df	degrees of freedom

Acronym/ Abbreviation	Meaning
DFA	detrended fluctuation analysis
DL	distributed lag
DMDS	dimethyl disulfide
DMS	dimethyl sulfide
DNA	deoxyribonucleic acid
DOAS	differential optical absorption spectroscopy
DVT	deep vein thrombosis
e.g.	exempli gratia (for example)
E_a	exposure to SO_2 of ambient origin
EBC	exhaled breath condensate
EC	elemental carbon
ECG	electrocardiographic
ECRHS	European Community Respiratory Health Survey
ED	emergency department
EGF	epidermal growth factor
EGFR	epidermal growth factor receptor
EGU	electric power generating unit
EIB	exercise-induced bronchospasm
EKG	electrocardiogram
ELF	epithelial lining fluid
EMSA	electrophoretic mobility shift assay
E_{na}	exposure to SO_2 of nonambient origin
eNO	exhaled nitric oxide
EP	entire pregnancy
EPA	U.S. Environmental Protection Agency
E_T	total exposure over a time period of interest
EWPM	emission-weighted proximity model
Exp(B)	odds ratio of bivariate associations
F	female
FB	fractional bias
FC	fuel combustion

Acronym/ Abbreviation	Meaning
$FEF_{25-75\%}$	forced expiratory flow at 25−75% of exhaled volume
$FEF_{50\%}$	forced expiratory flow at 50% of forced vital capacity
$FEF_{75\%}$	forced expiratory flow at 75% of forced vital capacity
FEF_{max}	maximum forced expiratory flow
FEM	federal equivalent method
FeNO	fractional exhaled nitric oxide
FEV	forced expiratory volume
FEV_1	forced expiratory volume in 1 second
FL	Florida
FOXp3	forkhead box P3
FPD	flame photometric detection
FR	Federal Register
FRC	functional residual capacity
FRM	federal reference method
func	functional residual capacity
FVC	forced vital capacity
g	gram
GA	Georgia
GALA II	Genes-Environments and Admixture in Latino Americans
GG	guanine-guanine genotype
GIS	geographic information system
GM	geometric mean
GP	general practice
GPS	global positioning system
GSD	geometric standard deviation
GSTM1	glutathione S-transferase Mu 1
GSTP	glutathione S-transferase P
GSTP1	glutathione S-transferase Pi 1
h	hour(s)
H^+	hydrogen ion
H_2O	water
H_2O_2	hydrogen peroxide
H_2S	hydrogen sulfide
H_2SO_3	sulfurous acid
H_2SO_4	sulfuric acid
HERO	Health and Environmental Research Online
HF	high frequency component of HRV
HI	Hawaii
HK	Hong Kong
HO_2	hydroperoxyl radical
HR	hazard ratio(s); heart rate
HRV	heart rate variability
HS	hemorrhagic stroke
HSO_3^-	bisulfite
HSC	Harvard Six Cities
i.p.	intraperitoneal
IARC	International Agency for Research on Cancer
i.e.	id est (that is)
ICAM-1	intercellular adhesion molecule 1
ICC	intraclass correlation coefficient
ICD	International Classification of Diseases; implantable cardioverter defibrillators
IDW	inverse distance weighting
IFN-γ	interferon gamma
IgE	immunoglobulin E
IgG	immunoglobulin G
IHD	ischemic heart disease
IKKβ	inhibitor of nuclear factor kappa-B kinase subunit beta
IL	Illinois
IL-4	interleukin-4
IL-5	interleukin-5
IL-6	interleukin-6
IL-8	interleukin-8
Ile	isoleucine
IQR	interquartile range
IS	ischemic stroke
ISA	Integrated Science Assessment
ISAAC	International Study of Asthma and Allergies in Children

Acronym/ Abbreviation	Meaning
IUGR	intrauterine growth restriction
IκBα	nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha
j	microenvironment
JE	joint model estimate
k	reaction rate; decay constant derived from empirical data; rate of SO_2 loss in the microenvironment
K_{ATP}	adenosine triphosphate (ATP)-sensitive potassium channel
kg	kilogram(s)
km	kilometer(s)
KS	Kansas
L	liter(s)
LBW	low birth weight
LED	light-emitting diode
LF	low-frequency component of HRV
LF/HF	ratio of LF and HF components of HRV
LIF	laser induced fluorescence
ln	natural logarithm
LOD	limit of detection
LOESS	locally weighted scatterplot smoothing
Lp-PLA_2	lipoprotein-associated phospholipase A2
LUR	land use regression
LX	lung adenoma-susceptible mouse strain
µ	mu; micro
µg/m^3	micrograms per cubic meter
m	meter
M	male
MA	Massachusetts
M1	Month 1
M2	Month 2
M3	Month 3
M12	average of M1 and M2
max	maximum
MAX-DOAS	multiaxis differential optical absorption spectroscopy
MCh	methacholine
MD	Maryland
MDL	method detection limit
ME	Maine
med	median
mg	milligram
MI	myocardial infarction ("heart attack"); Michigan
min	minimum; minute
MINAP	Myocardial Ischaemia National Audit Project
MISA	Meta-analysis of the Italian studies on short-term effects of air pollution
mL	milliliter(s)
mm	millimeters
MMEF	maximum midexpiratory flow
MMFR	Maximal midexpiratory flow rate
mmHg	millimeters of mercury
MN	Minnesota
MN	micronuclei formation
MNPCE	polychromatophilic erythroblasts of the bone marrow
mo	month(s)
MO	Missouri
MOA	mode(s) of action
MODIS	Moderate Resolution Imaging Spectroradiometer
mRNA	messenger ribonucleic acid
MS	Mississippi
MSA	methane sulfonic acid
MSE	mean standardized error
MUC5AC	mucin 5AC glycoprotein
n	sample size; total number of microenvironments that the individual has encountered
N	population number

Acronym/ Abbreviation	Meaning
N_2	molecular nitrogen
N/A	not applicable
NA	not available
NAAQS	National Ambient Air Quality Standards
NaCl	sodium chloride
NALF	nasal lavage fluid
NBP	NO_X Budget Program
NC	North Carolina
NCore	National Core network
NEI	National Emissions Inventory
NFκB	nuclear factor kappa-light-chain-enhancer of activated B cells
NH	New Hampshire
NH_3	ammonia
NH_4^+	ammonium ion
NHAPS	National Human Activity Pattern Survey
NHLBI	National Heart, Lung, and Blood Institute
NJ	New Jersey
NLCS	Netherlands Cohort Study on Diet and Cancer
nm	nanometer
NMMAPS	The National Morbidity Mortality Air Pollution Study
NO	nitric oxide
NO_2	nitrogen dioxide
NO_3^-	nitrate
NO_3	nitrate radical
non-HS	non-hemhorragic stroke
NO_X	the sum of NO and NO_2
NR	not reported
NY	New York
O_3	ozone
obs	observations
OC	organic carbon
OCS	carbonyl sulfide
OH	hydroxide; Ohio
OHCA	out-of-hospital cardiac arrests
OMI	Ozone Monitoring Instrument
OR	odds ratio(s)
OVA	ovalbumin
p	probability
P	Pearson correlation
P53	tumor protein 53
PA	Pennsylvania
PAH(s)	polycyclic aromatic hydrocarbon(s)
PAPA	Public Health and Air Pollution in Asia
Pb	lead
PC(SO_2)	provocative concentration of SO_2
PE	pulmonary embolism
PEF	peak expiratory flow
Penh	enhanced pause
PEFR	peak expiratory flow rate
PM	particulate matter
PM_{10}	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.

Acronym/ Abbreviation	Meaning
$PM_{10-2.5}$	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_{10}. 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.
$PM_{2.5}$	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
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^2	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_2O	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_2	sulfur dioxide
SO_3^{2-}	sulfite
SO_3	sulfur trioxide
SO_4	sulfur tetroxide
SO_4^{2-}	sulfate
SO_X	sulfur oxides
SPE	single-pollutant model estimate
SPM	source proximity model; suspended particulate matter
sRaw	specific airway resistance

Acronym/ Abbreviation	Meaning
ST segment	segment of the electrocardiograph between the end of the S wave and beginning of the T wave
STN	Speciation Trends Network
subj	subject
t	fraction of time spent in a microenvironment across an individual's microenvironmental exposures, time
TBARS	thiobarbituric acid reactive substances (species)
T1	first trimester
T2	second trimester
T3	third trimester
T1−T1	correlation between 1st trimester SO_2 and copollutants
TC	total hydrocarbon
Tg	teragram(s)
Th1	T-helper 1
Th2	T-helper 2
TIA	transient ischemic attack
TN	Tennessee
TNF-α	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_{max50}	maximal expiratory flow rate at 50%
V_{max75}	maximal expiratory flow rate at 75%
V_{max25}	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
wk	week
WHI	Women's Health Initiative
WI	Wisconsin
yr	year(s)
Z*	the true concentration

Preface

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

Two sections of the Clean Air Act (CAA) govern the establishment, review, and revision of the National Ambient Air Quality Standards (NAAQS). Section 108 [42 U.S. Code (U.S.C.) 7408] directs the Administrator to identify and list certain air pollutants and then to issue air quality criteria for those pollutants. The Administrator is to list those air pollutants that in her "judgment, cause or contribute to air pollution which may reasonably be anticipated to endanger public health or welfare," "the presence of which in the ambient air results from numerous or diverse mobile or stationary sources," and "for which … [the Administrator] plans to issue air quality criteria …" [42 U.S.C. 7408(a)(1); (CAA, 1990a)]. Air quality criteria are intended to "accurately reflect the latest scientific knowledge useful in indicating the kind and extent of all identifiable effects on public health or welfare, which may be expected from the presence of [a] pollutant in the ambient air …" [42 U.S.C. 7408(b)]. Section 109 [42 U.S.C. 7409; (CAA, 1990b)] directs the Administrator to propose and promulgate "primary" and "secondary" NAAQS for pollutants for which air quality criteria are issued. Section 109(b)(1) defines a primary standard as one "the attainment and maintenance of which in the judgment of the Administrator, based on such criteria and allowing an adequate margin of safety, are requisite to protect the public health."[1] A secondary standard, as defined in Section 109(b)(2), must "specify a level of air quality the attainment and maintenance of which, in the judgment of the Administrator, based on such criteria, is requisite to protect the public welfare from any known or anticipated adverse effects associated with the presence of [the] air pollutant in the ambient air."[2]

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

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

[2] 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).

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

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

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

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

[1] 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).

[2] 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).

[3] See Lead Industries Association v. EPA, 647 F.2d at 1161−62; Mississippi v. EPA, 744 F. 3d at 1353.

[4] See generally, *Whitman v. American Trucking Associations*, 531 U.S. 457, 465−472, 475−476 (2001).

[5] See American Petroleum Institute v. Costle, 665 F. 2d at 1185.

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

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

NAAQS are defined by four basic elements: indicator, averaging time, level, and form. The indicator defines the pollutant to be measured in the ambient air for the purpose of determining compliance with the standard. The averaging time defines the time period over which air quality measurements are to be obtained and averaged or cumulated, considering evidence of effects associated with various time periods of exposure. The level of a standard defines the air quality concentration used (i.e., an ambient concentration of the indicator pollutant) in determining whether the standard is achieved. The form of the standard defines the air quality statistic that is compared to the level of the standard in determining whether an area attains the standard. For example, the form of the current primary 1-hour sulfur dioxide (SO_2) standard is the 3-year average of the 99th percentile of the annual distribution of 1-hour daily maximum SO_2 concentrations. The Administrator considers these four elements collectively in evaluating the protection to public health provided by the primary NAAQS.

The U.S. EPA considers the term sulfur oxides to refer to multiple gaseous oxidized sulfur species such as SO_2 and sulfur trioxide (SO_3). SO_2 was chosen as the indicator for sulfur oxides because as in previous reviews, the presence of other sulfur oxides in the atmosphere has not been demonstrated, and SO_2 has a large body of health effects evidence associated with it. The atmospheric chemistry, exposure, and health effects associated with sulfur compounds present in particulate matter (PM) were most recently considered in the U.S. EPA’s review of the NAAQS for PM. Some of the welfare effects resulting from deposition of sulfur oxides (e.g., effects associated with ecosystem loading) are being considered in a separate assessment as part of the review of the secondary NAAQS for nitrogen dioxide and SO_2 (U.S. EPA, 2013d).

The U.S. EPA completed the initial review of the air quality criteria for sulfur oxides in 1969 [34 Federal Register (FR) 1988; (HEW, 1969)]. Based on this review, the U.S. EPA promulgated NAAQS for sulfur oxides in 1971, establishing the indicator as SO_2 [36 FR

[1] 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.

8186; (U.S. EPA, 1971)]. The 1971 primary standards were set at 365 μg/m^3 [equal to 0.14 parts per million (ppm)] averaged over a 24-hour period, not to be exceeded more than once per year, and at 80 μg/m^3 (equal to 0.03 ppm) annual arithmetic mean.[1] Since then, the Agency has completed multiple reviews of the air quality criteria and standards, 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_2	24 h 1 yr	140 ppb[a] 30 ppb[a]	One allowable exceedance 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_2	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_2 standards revoked.			

FR = Federal Register; SO_2 = sulfur dioxide.

[a]The initial level of the 24-h SO_2 standard was 365 μg/m^3 which is equal to 0.14 parts per million (ppm) or 140 parts per billion (ppb). The initial level of the annual SO_2 standard was 80 μg/m^3 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).

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

[1] 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.

As a result of public comments on the 1988 proposal and other post-proposal developments, the U.S. EPA published a second proposal on November 15, 1994 (59 FR 58958). The 1994 re-proposal was based in part on a supplement to the second addendum of the criteria document, which evaluated new findings on the respiratory effects of short-term SO_2 exposures in individuals with asthma (U.S. EPA, 1994). As in the 1988 proposal, the U.S. EPA proposed to retain the existing 24-hour and annual standards. The U.S. EPA also solicited comment on three regulatory alternatives to further reduce the health risk posed by exposure to high 5-minute peaks of SO_2 if additional protection were judged to be necessary. The three alternatives were: (1) revising the existing primary SO_2 NAAQS by adding a new 5-minute standard of 0.60 ppm SO_2; (2) establishing a new regulatory program under Section 303 of the Act to supplement protection provided by the existing NAAQS, with a trigger level of 0.60 ppm SO_2 with one expected exceedance; and (3) augmenting implementation of existing standards by focusing on those sources or source types likely to produce high 5-minute concentrations of SO_2.

In assessing the regulatory options mentioned above, the Administrator concluded that the likely frequency of 5-minute concentrations of concern should also be a consideration in assessing the overall public health risks. Based upon an exposure analysis conducted by the U.S. EPA, the Administrator concluded that exposure of individuals with asthma to SO_2 at levels that can reliably elicit adverse health effects was likely to be a rare event when viewed in the context of the entire population of individuals with asthma. Thus, the Administrator judged that high 5-minute SO_2 concentrations did not pose a broad public health problem when viewed from a national perspective, and a 5-minute standard was not promulgated. In addition, no other regulatory alternative was finalized, and the 24-hour and annual average primary SO_2 standards were retained in 1996 (61 FR 25566).

The American Lung Association and the Environmental Defense Fund challenged the U.S. EPA's decision not to establish a 5-minute standard. On January 30, 1998, the Court of Appeals for the District of Columbia ("D.C. Circuit") found that the U.S. EPA had failed to adequately explain its determination that no revision to the SO_2 NAAQS was appropriate and remanded the decision back to the U.S. EPA for further explanation.[1] Specifically, the court found that the U.S. EPA had failed to provide adequate rationale to support the Agency judgment that exposures to high 5-minute concentrations of SO_2 do not pose a public health problem from a national perspective even though these peaks will likely cause adverse health impacts in a subset of individuals with asthma. Following the remand, the U.S. EPA requested that states voluntarily submit 5-minute SO_2 monitoring data to be used to conduct air quality analyses in order to gain a better

[1] See *American Lung Ass'n v. EPA*, 134 F. 3d 388 (D.C. Cir. 1998).

understanding of the magnitude and frequency of high, 5-minute peak SO_2 concentrations. The data submitted by states and the analyses based on this data helped inform the last review of the SO_2 NAAQS, which ultimately addressed the issues raised in the 1998 remand.

The last review of the health-related air quality criteria for sulfur oxides and the primary SO_2 standard was initiated in May 2006 (71 FR 28023).[1,2] The Agency's plans for conducting the review were presented in the Integrated Review Plan (IRP) for the Primary National Ambient Air Quality Standards for Sulfur Oxides (U.S. EPA, 2007a), which included consideration of comments received during a CASAC consultation as well as public comment on a draft IRP. The science assessment for the review was described in the 2008 ISA for Sulfur Oxides—Health Criteria (U.S. EPA, 2008d), multiple drafts of which received review by CASAC and the public. The U.S. EPA also conducted quantitative human risk and exposure assessments after having consulted with CASAC and receiving public comment on a draft analysis plan (U.S. EPA, 2007b). These technical analyses were presented in the Risk and Exposure Assessment (REA) to Support the Review of the SO_2 Primary National Ambient Air Quality Standards (U.S. EPA, 2009b), multiple drafts of which were reviewed by CASAC and the public.

On June 22, 2010, the U.S. EPA revised the primary SO_2 NAAQS to provide requisite protection of public health with an adequate margin of safety (75 FR 35520). Specifically, after concluding that the then-existing 24-hour and annual standards were inadequate to protect public health with an adequate margin of safety, the U.S. EPA established a new 1-hour SO_2 standard at a level of 75 parts per billion (ppb), based on the 3-year average of the annual 99th percentile of 1-hour daily maximum concentrations. This standard was promulgated to provide substantial protection against SO_2-related health effects associated with short-term exposures ranging from 5 minute to 24 hours. More specifically, U.S. EPA concluded that a 1-hour SO_2 standard at 75 ppb would substantially limit exposures associated with the adverse respiratory effects (e.g., decrements in lung function and/or respiratory symptoms) reported in exercising asthmatics following 5−10 minute exposures in controlled human exposure studies, as well as the more serious health associations (e.g., respiratory-related emergency department visits and hospitalizations) reported in epidemiologic studies that mostly used daily metrics (1-h daily max and 24-h avg). In the last review, the U.S. EPA also revoked the then-existing 24-hour and annual primary standards based largely on the recognition

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

[2] The U.S. EPA conducted a separate review of the secondary SO_2 NAAQS jointly with a review of the secondary NO_2 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).

that the new 1-hour standard at 75 ppb would generally maintain 24-hour and annual SO_2 concentrations well below the NAAQS, so that retaining the corresponding standards would not provide additional public health protection (75 FR 35550). The decision to set a 1-hour standard at 75 ppb—in part to substantially limit exposure to 5-minute concentrations of SO_2 resulting in adverse respiratory effects in exercising asthmatics—also satisfied the remand by the D.C. Circuit in 1998.

As mentioned above, the U.S. EPA's last review placed considerable weight on substantially limiting health effects associated with high 5-minute SO_2 concentrations. Thus, as part of the final rulemaking, the U.S. EPA for the first time required the states to report either the highest 5-minute concentration for each hour of the day, or all twelve 5-minute concentrations for each hour of the day. The rationale for this requirement was that this additional monitored data could then be used in future reviews to evaluate the extent to which the 1-hour SO_2 NAAQS at 75 ppb provides protection against 5-minute concentrations of concern.

After publication of the final rule, a number of industry groups and states filed petitions for review arguing that the U.S. EPA failed to follow notice-and-comment rulemaking procedures, and that the decision to establish the 1-hour SO_2 NAAQS at 75 ppb was arbitrary and capricious because it was lower than statutorily authorized. The D.C. Circuit rejected these challenges, thereby upholding the standard in its entirety [*National Environmental Development Association's Clean Air Project v. EPA*, 686 F. 3d 803 (D.C. Cir. 2012), cert. denied *Asarco LLC v. EPA*, 133 S. Ct. 983 (Jan. 22, 2013)].

Executive Summary

Purpose and Scope of the Integrated Science Assessment

This Integrated Science Assessment (ISA) is a comprehensive evaluation and synthesis of policy-relevant science aimed at characterizing exposures to ambient sulfur oxides (SO_X) and the health effects associated with these exposures.[1] Thus, this ISA serves as the scientific foundation for the review of the primary (health-based) National Ambient Air Quality Standard (NAAQS) for sulfur dioxide (SO_2). The indicator[2] for the current standard is SO_2 because it is the most prevalent species of SO_X (a group of closely related gaseous compounds including SO_2 and SO_3) in the atmosphere and has health effects for which there is a large body of scientific evidence. The health effects of sulfate and other sulfur aerosols are considered as part of the review of the NAAQS for particulate matter [e.g., in the 2009 Integrated Science Assessment for Particulate Matter (U.S. EPA, 2009a)].[3] Some of the welfare effects resulting from deposition of sulfur oxides (e.g., effects associated with ecosystem loading) are being considered in a separate assessment as part of the review of the secondary (welfare-based) NAAQS for oxides of nitrogen and sulfur (U.S. EPA, 2013d).

In 2010, the U.S. Environmental Protection Agency (U.S. EPA) established a new 1-hour SO_2 primary standard of 75 parts per billion (ppb) based on the 3-year average of the 99th percentile of each year's 1-hour daily maximum concentrations (75 FR 35520).[4] The 1-hour standard was established to protect against a broad range of respiratory effects associated with short-term exposures in potential at-risk populations, such as people with asthma. This standard was based on clear evidence of SO_2-related effects in controlled human exposure studies of exercising individuals with asthma, as well as epidemiologic evidence of associations between ambient SO_2 concentrations and respiratory-related emergency department visits and hospitalizations. The U.S. EPA also revoked the existing 24-hour and annual primary SO_2 standards of 140 and 30 ppb, respectively, based largely on the recognition that the new 1-hour standard would generally maintain 24-hour and annual SO_2 concentrations well below the NAAQS, and thus retaining these standards would not provide additional public health protection (75

[1] 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.

[2] The four components to a NAAQS are: (1) indicator (e.g., SO_2), (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).

[3] In this ISA, the blue electronic links can be used to navigate to cited chapters, sections, tables, figures, and studies.

[4] The legislative requirements and history of the SO_2 NAAQS are described in detail in the Preface to this ISA.

FR 35550). The U.S. EPA also began requiring states to report 5-min avg SO_2 concentrations in light of evidence from controlled human exposure studies of health effects associated with 5-minute SO_2 exposures.

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

As in the 2008 SO_X ISA, this ISA determines the causal nature of relationships with health effects only for SO_2 Chapter 5). Health effects of other SO_X species are not considered, because their presence in the atmosphere has not been demonstrated, (Chapter 2), transformation products of SO_X such as sulfate are considered in the ISA for Particulate Matter (U.S. EPA, 2009a), and the health literature is focused on SO_2. Key to interpreting the health effects evidence is understanding the sources, chemistry, and distribution of SO_2 in the ambient air (Chapter 2) that influence exposure, (Chapter 3), the uptake of inhaled SO_2 in the respiratory tract, and what biological mechanisms may subsequently be affected (Chapter 4). Further, the ISA aims to characterize the independent effect of SO_2 on health (Chapter 5). The ISA also informs policy-relevant issues (Chapter 1 and Chapter 6), such as (1) exposure durations and patterns associated with health effects; (2) concentration-response relationship(s), including evidence of potential thresholds for effects; and (3) populations or lifestages at increased risk for health effects related to SO_2 exposure (Section 1.7.4 and Chapter 6).

Sources and Human Exposure to Sulfur Dioxide

The main objective of the ISA is to characterize health effects related to ambient SO_2 exposure. This requires understanding the factors that affect both the exposure to ambient SO_2 and the uncertainty in estimating exposure. These factors include spatial variability in SO_2 concentrations, exposure to copollutants, and uncharacterized time-activity patterns.

Emissions of SO_2 have decreased by approximately 72% from 1990 to 2011 due to several federal air quality regulatory programs. Coal-fired electricity generation units are the dominant sources, emitting 4.6 million tons of SO_2 in 2011, nearly 10 times more than the next largest source (coal-fired boilers for industrial fuel combustion;

Section 2.2). In addition to emission rate, important factors that affect ambient SO_2 concentrations at downwind locations include local meteorology (e.g., wind, atmospheric stability, humidity, and cloud/fog cover) and chemistry in the plume (Section 2.3).

The national average daily 1-hour max SO_2 concentration reported during 2013−2015 was 5.4 ppb with a 99th percentile concentration of 64 ppb (Section 2.5). However, 1-hour daily max SO_2 concentrations were 75 ppb or higher at some monitors located near point sources, such as power plants or metals processing facilities, or natural sources, such as volcanoes. The national average of 5-minute hourly max concentrations during 2013−2015 was 2.1 ppb, with a 99th percentile concentration of 24 ppb. Hourly 5-minute max concentrations tracked closely with their corresponding 1-h avg concentrations, with 75% of sites having a correlation above 0.9, indicating that fluctuations in 5-minute hourly max concentrations are well represented by changes in 1-h avg concentrations. The ratio of 5-minute hourly max concentrations to their corresponding 1-h avg concentrations was generally in the range of 1−3, although higher ratios were also observed during some hours. Background SO_2 concentrations due to natural sources and man-made sources located outside the U.S. are very low across most of the U.S. (less than 0.03 ppb) except in areas affected by volcanoes, such as Hawaii and the West Coast.

Air quality models are used to estimate SO_2 concentrations in locations without ambient SO_2 monitors (Section 2.6). As part of the implementation program for the 2010 primary SO_2 NAAQS, air quality modeling may be used to characterize air quality for determining compliance with the standard where existing ambient SO_2 monitors may not capture peak 1-hour concentrations (75 FR 35520). The widely used dispersion model American Meteorological Society/U.S. EPA Regulatory Model (AERMOD) is based on Gaussian dispersion models with enhancements to improve modeling of SO_2 plumes. AERMOD is relatively unbiased in estimating upper-percentile 1-hour concentration values over averaging times from 1 hour to 1 year. Lagrangian puff dispersion models, such as CALPUFF, have been developed as an alternative to Gaussian dispersion models. Uncertainties in model predictions are influenced by uncertainties in model inputs, particularly emissions data and meteorological conditions.

Correlations between ambient concentrations of SO_2 and copollutants are generally low (<0.4), although they vary across location, study, and SO_2 averaging time and are greater than 0.7 at some monitoring sites (Section 3.4.3). Median correlations of 1-hour daily maximum and 24-h avg SO_2 concentrations with particulate matter, nitrogen dioxide (NO_2), and carbon monoxide (CO) during 2013−2015 ranged from 0.2−0.4, while for ozone (O_3) the median daily copollutant correlation with SO_2 was less than 0.1 (Figure 3-5).

Estimating exposure to ambient SO_2 for use in epidemiologic studies can be done in multiple ways. Common techniques include using air quality monitoring data, personal SO_2 monitoring, and modeling. Air quality monitoring data from central site monitors (rather than near-source monitors), which are assumed to represent population exposure, are frequently used, but these monitors may not capture the spatial variation in ambient SO_2 concentrations across an urban area, which can be relatively high in areas affected by large point sources. Modeling approaches combining air quality data with geographic information or time-activity patterns, or both, can provide estimates of local ambient concentration or exposure concentration, although more complex approaches need more detailed inputs and have the potential for uncertainty related to missing sources, overly smooth concentration gradients, and other factors.

"Exposure error," which refers to the bias and uncertainty associated with using exposure metrics to represent the actual exposure of an individual or population, can contribute to error in health effect estimates in epidemiologic studies (Section 3.4.4). Several exposure-related factors (including uncharacterized time-activity patterns, spatial and temporal variability of SO_2 concentrations, and distance of individuals and populations from air quality monitors used in the statistical analyses) contribute to error in estimating exposure to ambient SO_2. Variation in activity patterns across individuals and over time results in corresponding variations in exposure concentration. Uncharacterized spatial variability in SO_2 concentrations can contribute to exposure error that tends to add uncertainty and reduce the magnitude of effect estimates in daily time-series epidemiologic studies. For long-term (e.g., annual) studies, the effect estimate may be increased or reduced by using central site monitoring data, depending on the relative locations of sources, monitors, and exposed people. The exposure error associated with using central site monitors is generally expected to widen confidence intervals beyond the nominal coverage of those intervals that would be produced had the true exposure been used for all study types.

Dosimetry and Mode of Action of Inhaled Sulfur Dioxide

Understanding the absorption and fate of SO_2 in the body (dosimetry) and the biological pathways that potentially underlie health effects (mode of action) is crucial to provide biological plausibility for linking SO_2 exposure with observed health effects.

Inhaled SO_2 is readily absorbed in the nasal passages of resting humans and laboratory animals (Section 4.2). As physical activity increases, there is an increase in breathing rate and a shift to breathing through the mouth, resulting in greater SO_2 penetration into the lower airways. Relative to healthy adults, children, and individuals with asthma or allergic rhinitis have an increased amount of oral breathing, and thus, may be expected to

have greater SO_2 penetration into the lungs. Children also generally have a greater intake dose of SO_2 per body mass than adults.

The distribution and clearance of inhaled SO_2 from the respiratory tract involves several chemical transformations, particularly the formation of sulfite and S-sulfonates. Sulfite is metabolized into sulfate, which is rapidly excreted through the urine, while S-sulfonates are cleared more slowly from the circulation over a period of days. Although SO_2-derived products have been found in the blood and urine within minutes of an inhalation exposure, a substantial portion of these products appear to be retained within the upper airways, particularly during nasal breathing, with only slow absorption into the blood.

Although inhaled SO_2 produces sulfite that is distributed through the circulation, overall sulfite levels are heavily influenced by production within the body (endogenous production) and by eating food with sulfur-containing amino acids or sulfite itself (Section 4.2.6). For both adults and children, metabolism of sulfur-containing amino acids produces much more sulfite than is ingested as food additives. Sulfite produced endogenously generates levels two or more orders of magnitude higher than inhalation-derived sulfite levels for both children and adults, even for full-day exposures to 75 ppb SO_2 (i.e., the level of the 1-hour NAAQS). Sulfite ingestion from food additives varies widely, but is generally expected to exceed sulfite intake from inhalation in both adults and children, even for full-day exposures to 75 ppb SO_2. However, an important distinction is that inhalation-derived SO_2 products can accumulate in the respiratory tract, whereas sulfite from ingestion or endogenous production does not.

SO_2 inhalation produces bronchoconstriction in both healthy adults and those with asthma (Section 4.3), but the underlying processes are somewhat different. The response to SO_2 in healthy adults occurs primarily from activation of sensory nerves in the respiratory tract resulting in neural reflex responses through the vagus nerve. In adults with asthma, the response is only partly due to this neural reflex response, with inflammatory mediators also being involved. Inhalation of SO_2 increases allergic inflammation in adults with asthma and in animals with allergic airways disease, which shares many features with asthma. Furthermore, SO_2 inhalation increases allergic sensitization in animals not already allergic, and once allergic, these animals respond to an allergen challenge with greater allergic inflammation and airway obstruction (likely due to bronchoconstriction) compared to animals who were not exposed to SO_2. These findings suggest that allergic inflammation and increased airway responsiveness due to short-term SO_2 exposure (minutes up to 1 month) may be linked to asthma exacerbation seen in epidemiologic studies.

For long-term SO_2 exposure (more than 1 month to years), animal studies provide additional evidence of airway inflammation, airway remodeling, AHR, and allergic

sensitization. In animals that are not allergic, SO_2 inhalation leads to airway inflammation and allergic sensitization. In animals with allergic airway disease, SO_2 exposure increases airway responsiveness and airway remodeling. Thus, inhalation of SO_2 may lead to the development and worsening of allergic airway disease. The development of AHR may link long-term exposure to SO_2 to the epidemiologic outcome of physician-diagnosed asthma (new onset asthma).

While there is some evidence for extrapulmonary effects of inhaled SO_2, the mode of action underlying these responses is uncertain. Controlled human exposure studies provide evidence suggesting activation of sensory nerves in the respiratory tract resulting in a neural reflex response by SO_2 exposure, which could lead to changes in heart rate or heart rate variability. Additionally, the transport of sulfite into the circulation could result in redox stress, but this is likely to only occur at elevated or prolonged exposures due to the body's efficient metabolism of sulfite to sulfate.

Health Effects of Sulfur Dioxide Exposure

This ISA integrates information on SO_2 exposure and health effects from controlled human exposure, epidemiologic, and toxicological studies to form conclusions about the causal nature of relationships between SO_2 exposure and health effects. For most health effect categories, with the exception of reproductive and developmental effects, effects are evaluated separately for short-term exposures and long-term exposures. Health effects are considered in relation to the full range of SO_2 concentrations relevant to ambient conditions. Based on upper-percentile ambient concentrations (Section 2.5) and the ISA's emphasis on ambient-relevant exposures within one to two orders of magnitude of current conditions [Preamble to the ISAs (U.S. EPA, 2015b), Section 5c], SO_2 concentrations up to 2,000 ppb[1] are defined to be ambient-relevant. A consistent and transparent framework [Preamble to the ISAs (U.S. EPA, 2015b), Table II] is applied to classify the health effects evidence according to a five-level hierarchy:

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

[1] The 2,000-ppb upper limit applies mostly to animal toxicological studies and also a few controlled human exposure studies. Experimental studies examining SO_2 exposures greater than 2,000 ppb were included if they provided information on the uptake of SO_2 in the respiratory tract or on potential biological mechanisms.

The causal determinations presented in Table ES-1 are informed by recent findings and whether these recent findings, integrated with information from the 2008 SO_X ISA, support a change in causal conclusions. Important considerations include: (1) determining whether laboratory studies of humans and animals demonstrate an independent health effect of SO_2 exposure and what the potential underlying biological mechanisms are; (2) determining whether there is consistency in epidemiologic evidence across various methods used to estimate SO_2 exposure; (3) examining epidemiologic studies of the potential influence of factors that could bias associations observed with SO_2 exposure; (4) determining the coherence of findings integrated across controlled human exposure, epidemiologic, and toxicological studies; and (5) making judgments regarding error and 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[a] and Exposure Duration	Causal Determination	
	2008 SO_X ISA	**Current Draft ISA**
Respiratory effects—Short-term exposure Section 5.2.1, Table 5-21	Causal relationship	Causal relationship
Respiratory effects—Long-term exposure Section 5.2.2, Table 5-24	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 Section 5.3.1, Table 5-34	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 Section 5.3.2, Table 5-35	Not included	Inadequate to infer the presence or absence of a causal relationship
Reproductive and developmental effects[b] Section 5.4, Table 5-38	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 Section 5.5.1, Table 5-41	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 Section 5.5.2, Table 5-43	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 Section 5.6, Table 5-44	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_X = sulfur oxides.

Previous causal determinations taken from the 2008 SO_X ISA (U.S. EPA, 2008d).

[a]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_2 concentrations with which health effects have been associated.

[b]Reproductive and developmental effects studies consider a wide range of exposure durations.

Sulfur Dioxide Exposure and Respiratory Effects

As in the 2008 SO_X ISA (U.S. EPA, 2008d), the current ISA concludes that there is a causal relationship between short-term SO_2 exposure and respiratory effects, particularly in individuals with asthma (Section 5.2.1). This determination is based on consistent, coherent, and biologically plausible evidence for asthma exacerbation due to SO_2 exposure. The clearest evidence for this conclusion comes from controlled human exposure studies available at the time of the 2008 SO_X ISA showing lung function decrements and respiratory symptoms in adults with asthma exposed to SO_2 for 5−10 minutes at elevated breathing rates. The effects observed in these studies are consistent with the processes leading to asthma exacerbation described in the mode of action section (Section 4.3). Epidemiologic evidence, including recent studies not available at the time of the 2008 SO_X ISA, also supports a causal relationship, primarily due to studies reporting positive associations for asthma hospital admissions and emergency department visits with short-term SO_2 exposures, specifically for children. This is coherent with studies showing that children have increased airway responsiveness to a trigger and have greater oral breathing and body-mass-adjusted intake dose relative to adults, suggesting they will have a greater response to SO_2 exposure than adults. Hospital admissions and emergency department visits studies that examined potential copollutant confounding reported associations were generally unchanged in copollutant models. Additional support comes from studies reporting positive associations between short-term SO_2 exposures and respiratory symptoms in children with asthma, although the evidence from respiratory symptoms studies in adults with asthma is less consistent. Finally, epidemiologic studies that report consistent positive associations between short-term SO_2 concentrations and respiratory mortality indicate a potential continuum of effects.

For long-term SO_2 exposure and respiratory effects the evidence is suggestive of, but not sufficient to infer, a causal relationship (Section 5.2.2). The strongest evidence is provided by coherence among findings of epidemiologic studies showing associations between long-term SO_2 exposure and increases in asthma incidence among children and results of animal toxicological studies that provide a pathophysiologic basis for the development of asthma. Some evidence regarding respiratory symptoms and/or respiratory allergies among children provides limited support for a possible relationship between long-term SO_2 exposure and the development of asthma. This represents a change in the causal determination made in the 2008 SO_X ISA from inadequate to suggestive, based on a limited body of new evidence.

Sulfur Dioxide Exposure and Other Health Effects

There is more uncertainty regarding relationships between SO_2 exposure and health effects outside of the respiratory system. SO_2 itself is unlikely to enter the bloodstream; however, its reaction products, such as sulfite, may do so. The amount of circulating sulfite due to inhalation of ambient-relevant concentrations of SO_2 is far less than the contribution from metabolism of sulfur-containing amino acids.

For short-term SO_2 exposure and total mortality, the current ISA reaches the same conclusion as the 2008 SO_X ISA (U.S. EPA, 2008d); that the evidence is suggestive of, but not sufficient to infer, a causal relationship (Section 5.5.1). This conclusion is based on previous and recent multicity epidemiologic studies providing consistent evidence of positive associations. While recent multicity studies have analyzed some key uncertainties and data gaps identified in the 2008 SO_X ISA, questions remain regarding the potential for SO_2 to have an independent effect on mortality, considering issues such as the limited number of studies that examined copollutant confounding, evidence for a decrease in the size of SO_2-mortality associations in copollutant models with NO_2 and PM_{10}, and the lack of a potential biological mechanism for mortality following short-term exposures to SO_2.

For the remaining health effect categories (short-term and long-term SO_2 exposure and cardiovascular effects, long-term exposure and total mortality, reproductive and developmental effects, and long-term exposure and cancer), the evidence is inadequate to infer the presence or absence of a causal relationship, mainly due to inconsistent evidence across specific outcomes and uncertainties regarding exposure measurement error, copollutant confounding, and potential modes of action. These conclusions are consistent with those made in the 2008 SO_X ISA, as illustrated in Table ES-1.

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

This section describes issues relevant for considering the potential importance of impacts of ambient SO_2 exposure on public health, including exposure durations observed to cause health effects, the shape of the concentration-response relationship, regional differences, and at-risk populations and lifestages.

Evidence from controlled human exposure studies of respiratory effects after exposures of 5−10 minutes indicates a rapid onset of SO_2-related effects and provides support for the 1-h avg time used in the primary SO_2 NAAQS (Section 5.2.1). Epidemiologic studies of asthma hospital admissions and emergency department visits using daily exposure metrics (24-h avg and 1-h daily max) show positive associations that are generally

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

Substantial interindividual variability was observed in controlled human exposure studies of SO_2 and respiratory effects, but there was a clear increase in the magnitude of respiratory effects with increasing exposure concentrations between 200 and 1,000 ppb during 5−10 minute SO_2 exposures (Section 5.2.1.2). Both the number of affected individuals with asthma and the severity of the response increased as SO_2 concentrations increased. Epidemiologic studies evaluating the shape of the concentration-response function have found no evidence for a population-level threshold or nonlinearity, although the evidence is limited.

SO_2 concentrations are highly spatially heterogeneous, with SO_2 concentrations at some monitors possibly not highly correlated with the community average concentration (Section 3.4.2.2). The predominance of point sources results in an uneven distribution of SO_2 concentrations across an urban area. This spatial and temporal variability in SO_2 concentrations can contribute to exposure error in epidemiologic studies, whether the studies rely on central site monitor data or concentration modeling for exposure assessment.

Consistent with the findings of the 2008 SO_X ISA (U.S. EPA, 2008d), this ISA concludes there is adequate evidence that people with asthma, particularly children, are at increased risk for SO_2-related health effects compared with those without asthma (Chapter 6). This conclusion is based on the evidence for short-term SO_2 exposure and respiratory effects (specifically lung function decrements), for which a causal relationship has been determined. The ISA concludes there is suggestive evidence that children are at increased risk for SO_2-related health effects, based on their increased ventilation rates relative to body mass and increased oral breathing, together with some epidemiologic evidence of increased associations between SO_2 and respiratory effects relative to adults, even though recent epidemiologic evidence is less consistent. There is also evidence suggestive of increased risk of SO_2-related health effects for older adults relative to other lifestages.

Chapter 1 Integrative Synthesis of the ISA

1.1 Purpose and Overview of the Integrated Science Assessment

The Integrated Science Assessment (ISA) is a comprehensive evaluation and synthesis of the policy-relevant science "useful in indicating the kind and extent of all identifiable effects on public health or welfare which may be expected from the presence of [a] pollutant in the ambient air," as described in Section 108 of the Clean Air Act (CAA, 1990a).[1] This ISA communicates critical science judgments of the health-related air quality criteria for the broad category of sulfur oxides (SO_X). As such, this ISA serves as the scientific foundation for the review of the current primary (health-based) National Ambient Air Quality Standard (NAAQS) for sulfur dioxide (SO_2). SO_X include several related gaseous compounds such as SO_2 and sulfur trioxide (SO_3) (Section 2.3). SO_2 was chosen as the indicator[2] for the NAAQS because as in previous reviews, the presence of other sulfur oxides in the atmosphere has not been demonstrated (U.S. EPA, 1996b; HEW, 1969),[3] and there is a large body of evidence on health effects following exposure to SO_2. In addition, the 2010 Final Rule concluded that "measures leading to reductions in population exposures to SO_2 can generally be expected to lead to reductions in population exposures to SO_X." (75 FR 35536). Health effects of particulate sulfur-containing species (e.g., sulfate) are being considered in the current review of the NAAQS for particulate matter (PM) and were previously evaluated in the 2009 ISA for PM (U.S. EPA, 2009a). Some of the welfare effects resulting from deposition of SO_X (e.g., effects associated with ecosystem loading) are being evaluated in a separate assessment conducted as part of the review of the secondary (welfare-based) NAAQS for oxides of nitrogen (NO_X) and SO_X (U.S. EPA, 2013d).

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

[1] 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).

[2] The four components to a NAAQS are: (1) indicator (e.g., SO_2); (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).

[3] In this ISA, the blue electronic links can be used to navigate to cited chapters, sections, tables, figures, and studies.

available for the 2008 SO_X ISA, which informed decisions on the primary SO_2 NAAQS in the review completed in 2010. In 2010, the U.S. Environmental Protection Agency (U.S. EPA) established a new 1-hour standard of 75 parts per billion (ppb) SO_2 based on the 3-yr avg of the 99th percentile of each year's 1-hour daily max concentrations.[1] The 1-hour standard was established to protect against a broad range of respiratory effects associated with short-term exposures in potential at-risk populations such as people with asthma. This standard was based on clear evidence of SO_2-related effects in controlled human exposure studies of exercising individuals with asthma, as well as epidemiologic evidence of associations between ambient SO_2 concentrations and respiratory-related emergency department visits and hospitalizations. The U.S. EPA also revoked the existing 24-hour and annual primary SO_2 standards of 140 and 30 ppb, respectively. The 24-hour and annual primary standards were revoked largely based on the recognition that the new 1-hour standard at 75 ppb would generally maintain 24-hour and annual SO_2 concentrations well below the NAAQS, and thus, retaining these standards would not provide additional public health protection (75 FR 35550). In light of considerable weight being placed on health effects associated with 5-minute peak SO_2 concentrations, the U.S. EPA for the first time required state reporting of either the highest 5-minute concentration for each hour of the day, or all twelve 5-minute concentrations for each hour of the day (U.S. EPA, 2010b).

This new review of the primary SO_2 NAAQS is guided by several policy-relevant questions that are identified in The *Integrated Review Plan for the Primary National Ambient Air Quality Standard for Sulfur Dioxide* (U.S. EPA, 2014a). To address these questions and update the scientific judgments in the 2008 ISA for Sulfur Oxides (U.S. EPA, 2008d), this ISA aims to:

- Characterize the evidence for health effects associated with short-term (minutes up to 1 month) and long-term (more than 1 month to years) exposure to SO_X by integrating findings across scientific disciplines and across related health outcomes and by considering important uncertainties identified in the interpretation of the scientific evidence, including the role of SO_2 within the broader ambient mixture of pollutants.
- Inform policy-relevant issues related to quantifying health risks, such as exposure concentrations, durations, and patterns associated with health effects; concentration-response (C-R) relationships and existence of thresholds below which effects do not occur; and populations and lifestages potentially with increased risk of health effects related to exposure to SO_X.

Sulfur dioxide is the most abundant species of SO_X in the atmosphere, while the presence of other SO_X species in the atmosphere has not been demonstrated (Section 2.1). Most studies on the health effects of SO_X focus on SO_2. In evaluating the health evidence, this

[1] The legislative requirements and history of the SO_2 NAAQS are described in detail in the Preface to this ISA.

ISA considers possible influences of other atmospheric pollutants, including interactions of SO_2 with co-occurring pollutants such as PM, NO_X, carbon monoxide (CO), and ozone (O_3).

In addressing policy-relevant questions, this ISA aims to characterize the independent health effects of SO_2. As described in this ISA, recent evidence continues to support a causal relationship between short-term SO_2 exposure and respiratory effects based on the consistency of findings, coherence among evidence from controlled human exposure, epidemiologic, and toxicological studies, and biological plausibility for effects specifically related to asthma exacerbation. The information summarized in this ISA will serve as the scientific foundation for the review of the current primary 1-hour SO_2 NAAQS.

1.2 Process for Developing Integrated Science Assessments

The U.S. EPA uses a structured and transparent process for evaluating scientific information and determining the causal nature of relationships between air pollution exposures and health effects [details provided in the *Preamble to the Integrated Science Assessments* (U.S. EPA, 2015b)]. The ISA development process describes approaches for literature searches, criteria for selecting and evaluating relevant studies, and a framework for evaluating the weight of evidence and forming causal determinations. As part of this process, the ISA is reviewed by the Clean Air Scientific Advisory Committee (CASAC), which is a formal independent panel of scientific experts, and by the public. As this ISA informs the review of the primary SO_2 NAAQS, it integrates and synthesizes information characterizing exposure to SO_2 and potential relationships with health effects. Relevant studies include those examining atmospheric chemistry, spatial and temporal trends, and exposure assessment, as well as U.S. EPA analyses of air quality and emissions data. Relevant health research includes epidemiologic, controlled human exposure, and toxicological studies on health effects, as well as studies on dosimetry and modes of action.

The U.S. EPA initiated the current review of the primary NAAQS for SO_2 in August 2013 with a call for information from the public (U.S. EPA, 2013d). Thereafter, the U.S. EPA routinely conducted literature searches to identify relevant peer-reviewed studies published since the previous ISA (i.e., from January 2008 through August 2016). Multiple search methods were used [Preamble to the ISAs (U.S. EPA, 2015b), Section 2], including searches in the PubMed and Web of Science databases. Subject-area experts and the public were also able to recommend studies and reports during a science/policy issue "kick-off" workshop held at the U.S. EPA in June 2013. The U.S. EPA identified

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

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

The Preamble to the ISAs (U.S. EPA, 2015b) describes the general framework for evaluating scientific information, including criteria for assessing study quality and developing scientific conclusions. Aspects specific to evaluating studies of SO_X are described in the Annex for Chapter 5. For epidemiologic studies, emphasis is placed on studies that (1) characterize quantitative relationships between SO_2 and health effects, (2) examine exposure metrics that well represent the variability in concentrations in the study area, (3) consider the potential influence of other air pollutants and factors correlated with SO_2, (4) examine potential at-risk populations and lifestages, or (5) combine information across multiple cities. With respect to the evaluation of controlled human exposure and toxicological studies, emphasis is placed on studies that examine effects relevant to humans and SO_2 concentrations relevant to ambient exposures. Based on peak ambient concentrations (Section 2.5) and the ISA's emphasis on ambient-relevant exposures within one to two orders of magnitude of current ambient

concentrations, SO_2 concentrations of 2,000 ppb[1] or less are defined to be ambient-relevant. Experimental studies with higher exposure concentrations were included if they contributed to an understanding of dosimetry or potential modes of action. For the evaluation of human exposure to ambient SO_2, emphasis is placed on studies that examine the quality of data sources used to assess exposures, such as central site monitors, personal exposure monitors, and dispersion models. The ISA also emphasizes studies that examine factors that influence exposure such as time-activity patterns and building ventilation characteristics.

Integrating information across scientific disciplines and related health outcomes and synthesizing evidence from previous and recent studies, the ISA draws conclusions about relationships between SO_2 exposure and health effects. Determinations are made about causation, not just association, and are based on judgments of aspects such as the consistency, coherence, and biological plausibility of observed effects (i.e., evidence for effects on key events in the mode of action) as well as related uncertainties. The ISA uses a formal causal framework [Table II of the Preamble to the ISAs (U.S. EPA, 2015b)] to classify the weight of evidence according to the five-level hierarchy summarized below.

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

[1] The 2,000-ppb upper limit applies largely to animal toxicological studies but also a few controlled human exposure studies.

1.3 Organization of the Integrated Science Assessment

This ISA comprises the Preface (legislative requirements of the NAAQS and history of the primary SO_2 NAAQS), Executive Summary, and six chapters. This chapter (Chapter 1) synthesizes the scientific evidence that best informs policy-relevant questions that frame this review of the primary SO_2 NAAQS. Chapter 2 characterizes the sources, atmospheric processes involving SO_X, and trends in ambient concentrations. Chapter 3 describes methods to estimate human exposure to SO_X and the impact of error in estimating exposure on relationships with health effects. Chapter 4 describes the dosimetry and modes of action for SO_2. Chapter 5 evaluates and integrates epidemiologic, controlled human exposure, and toxicological evidence for health effects related to short-term and long-term exposure to SO_X. Chapter 6 evaluates information on potential at-risk populations and lifestages. In addition, the Preamble to the ISAs (U.S. EPA, 2015b) describes the general process for developing an ISA.

The purpose of this chapter is not to summarize each of the aforementioned chapters but to synthesize the key findings for each topic that informed the characterization of SO_2 exposure and relationships with health effects. This chapter also integrates information across the ISA to inform policy-relevant issues such as SO_2 exposure metrics associated with health effects, concentration-response relationships, and the public health impact of SO_2-related health effects (Section 1.7). A key consideration in the health effects assessment is the extent to which evidence indicates that SO_2 exposure independently causes health effects. To that end, this chapter draws upon information about the sources, distribution, and exposure to ambient SO_2 and identifies pollutants and other factors related to the distribution of or exposure to ambient SO_2 that can potentially influence epidemiologic associations observed between health effects and SO_2 exposure (Section 1.4). The chapter also summarizes information on the dosimetry and mode of action of inhaled SO_2 that can provide biological plausibility for observed health effects (Section 1.5). The discussions of the health effects evidence and causal determinations (Section 1.6) describe the extent to which epidemiologic studies accounted for factors that may influence epidemiologic study results and the extent to which findings from controlled human exposure and animal toxicological studies support independent relationships between SO_2 exposure and health effects.

1.4 From Emissions Sources to Exposure to Sulfur Dioxide

Characterizing human exposure is key to understanding the relationships between ambient SO_2 exposure and health effects. The sources of SO_X and the transformations that occur in ambient air influence the spatial and temporal pattern of SO_2 concentrations

in the air. These patterns have implications for variation in exposure in the population, the adequacy of methods used to estimate exposure, and in turn, the strength of inferences that can be drawn about health effects related to SO_2 exposure.

1.4.1 Emission Sources and Distribution of Ambient Concentrations

Emissions of SO_2 have declined by approximately 72% for all sources from 1990 to 2011 as a result of several U.S. air quality regulatory programs. Coal-fired electricity generation units (EGUs) remain the dominant sources by nearly an order of magnitude above the next highest source (industrial fuel combustion), emitting 4.6 million tons of SO_2 annually, according to the 2011 National Emissions Inventory (NEI; Section 2.2).

In addition to emission rate, the two important variables that determine the concentration of SO_2 downwind of the source are the photochemical and other removal processes (e.g., formation of particle-phase reduced sulfur compounds) occurring in the emissions plume and the local meteorology, including wind, atmospheric stability, humidity, and cloud/fog cover (Section 2.3). The primary gas-phase photochemical SO_2 oxidation mechanism requires the hydroxyl radical (OH). Another oxidation mechanism involves a Criegee intermediate biradical that participates in converting SO_2 to SO_3, which rapidly reacts with water vapor to form sulfuric acid (H_2SO_4). The Criegee-based SO_2 oxidation mechanism may amplify the rate of SO_2 removal and formation of organosulfur compounds in areas with high concentrations of Criegee precursors (i.e., low-molecular-weight organic gases, such as biogenic compounds and unsaturated hydrocarbons present downwind of industrial sites and refineries). Aqueous-phase oxidation of SO_2 is also an important removal mechanism. Clouds and fog can reduce local SO_2 concentrations by converting it to H_2SO_4 in the droplet phase.

Changes were undertaken to the existing U.S. EPA monitoring network as a result of the new 1-hour primary NAAQS standard promulgated in 2010 (Section 2.4). First, the automated pulsed ultraviolet fluorescence (UVF) method, the method most commonly used by state and local monitoring agencies for NAAQS compliance, was designated as a federal reference method (FRM). Second, new SO_2 monitoring guidelines require states to report either the highest 5-minute concentration for each hour of the day or all twelve 5-minute concentrations for each hour of the day in light of health effects evidence on respiratory effects among exercising individuals with asthma following a 5−10-minute exposure to SO_2. Analysis of environmental concentrations of SO_2 data reported in Section 2.5 reflect the monitoring network changes, particularly the analysis of the recent 5-minute data.

On a nationwide basis, the average 1-h daily max SO_2 reported during 2013−2015 is 5.4 ppb with a 99th percentile concentration of 64 ppb (Section 2.5). However, peak concentrations (99th percentile) of 1-h daily max SO_2 concentrations can be greater than 75 ppb at some monitoring sites located near large anthropogenic sources (e.g., power plants or metal processing facilities) or natural sources (e.g., volcanoes). The mean 5-minute hourly max concentration across the U.S. in 2013−2015 was 2.1 ppb, with a 99th percentile concentration of 24.0 ppb. Correlations between hourly 5-minute max SO_2 concentrations and their corresponding 1-h avg concentrations are high, with approximately 75% of sites having correlations greater than 0.9. Peak-to-mean ratios (PMRs) between the two metrics are generally less than 3, although higher PMRs are observed during some hours (Section 2.5.4). Background concentrations of SO_2 from natural sources and sources outside the U.S. are very low across most of the country (less than 0.03 ppb), accounting for less than 1% of ambient SO_2 concentrations except in areas where volcanic emissions are important, such as Hawaii and the West Coast (Section 2.5.5).

SO_2 concentrations are highly variable across urban spatial scales, exhibiting moderate to poor correlations between SO_2 measured at different monitoring sites across a metropolitan area. This high degree of urban spatial variability may not be fully captured by central site monitors used in epidemiologic studies, and thus, has implications for the interpretation of human exposure and health effects data (Section 2.5.2.2 and Section 3.4.4).

Air quality models, including dispersion models and chemical transport models, can be used to estimate SO_2 concentrations in locations where monitoring is not practical or sufficient (Section 2.6). Because existing ambient SO_2 monitors may not be sited in locations to capture peak 1-hour concentrations, the implementation program for the 2010 primary SO_2 NAAQS allows for air quality modeling to be used to characterize air quality for informing designation decisions (75 FR 35520). In addition, modeling is critical to the assessment of the impact of future sources or proposed modifications where monitoring cannot inform, and for the design and implementation of mitigation techniques. Dispersion models have also been used to estimate SO_2 exposure concentrations in epidemiologic studies, particularly in long-term studies (Section 3.3.2.4, Chapter 5). The widely used dispersion model American Meteorological Society/U.S. EPA Regulatory Model (AERMOD) is based on Gaussian dispersion models but includes advancements such as boundary layer scaling formulations, surface and elevated emission points, interactions of plumes with buildings and terrain, and source geometry. Several evaluations of the performance of AERMOD against field study data over averaging times from 1 hour to 1 year found the model was relatively unbiased in estimating upper-percentile 1-hour concentration values. Lagrangian puff

dispersion models, such as CALPUFF, have been developed as an alternative to Gaussian dispersion models. CALPUFF models SO_2 as a tracer and then uses a Lagrangian step algorithm to model non-steady-state dynamics, using time-varying winds specified by meteorological models. CALPUFF simulations were found to improve in accuracy with increasing integration times. Uncertainties in model predictions are influenced by uncertainties in model input data, particularly emissions and meteorological conditions (e.g., wind).

1.4.2 Assessment of Human Exposure

Multiple techniques can be used to assign exposure for epidemiologic studies, including evaluation of data from central site monitoring, personal SO_2 monitoring, and using various modeling approaches (Section 3.3). Each has strengths and limitations, as summarized in Table 3-1. Central site monitors are intended to represent population exposure, in contrast to near-source monitors, which are intended to capture high concentrations in the vicinity of a source and are not typically used as the primary data source in urban-scale epidemiologic studies. Central site monitors may provide a continuous record of SO_2 concentrations over many years, but they do not fully capture the relatively high spatial variability in SO_2 concentration across an urban area. Personal SO_2 monitors can capture the study participants' activity-related exposure across different microenvironments, but low ambient SO_2 concentrations often result in a substantial fraction of the samples below the limit of detection for averaging times of 24 hours or less. The time and expense involved to deploy personal monitors make them suitable for panel epidemiologic studies and exposure validation studies. Models can be used to estimate exposure for individuals and large populations when personal exposure measurements are unavailable. Modeling approaches include estimating concentration surfaces and time-activity patterns and running microenvironment-based models that combine air quality data with time-activity patterns. In general, more complex approaches provide more detailed exposure estimates but require additional input data, assumptions, and computational resources. Depending on the model type, there is the potential for bias and reduced precision due to model misspecification, missing sources, smoothing of concentration gradients, and complex topography. Evaluation of model results helps demonstrate the suitability of that approach for particular applications.

New studies of the relationship between indoor and outdoor SO_2 concentrations have focused on publicly owned buildings rather than residences (Section 3.4.1.2). The results of these studies are consistent with results of previous studies showing that indoor:outdoor ratios and slopes cover an extremely wide range, from near zero to near one. Differences in results among studies are due to building characteristics (e.g., forced

ventilation, building age, and building type), personal activities such as opening windows and doors, and SO_2 measurement limitations. When reported, correlations between indoor and outdoor concentrations were relatively high (>0.75), suggesting that variations in outdoor concentration drive indoor concentrations, particularly considering the lack of indoor SO_2 sources. These high correlations were observed across seasons and geographic locations. The bulk of the evidence for personal-ambient SO_2 relationships was available at the time of the 2008 ISA for Sulfur Oxides (U.S. EPA, 2008d) and showed a wide range of correlations between ambient concentration and personal exposure, in part due to a large fraction of samples below the method detection limit (MDL) in several studies (Section 3.4.1.3). When nearly all of the personal samples are below the MDL, no correlation can be observed. However, when the bulk of the personal samples are above the MDL, personal exposure is moderately correlated with ambient concentration.

"Exposure error" refers to the bias and uncertainty associated with using concentration metrics to represent the actual exposure of an individual or population [(Lipfert and Wyzga, 1996) Section 3.2]. Exposure error has two components: (1) exposure measurement error derived from uncertainty in the metric being used to represent exposure, and (2) use of a surrogate target parameter of interest in the epidemiologic study in lieu of the true exposure, which may be unobservable (Section 3.2.1). Factors that could contribute to error in estimating exposure to ambient SO_2 include time-location-activity patterns, spatial and temporal variability in SO_2 concentrations, and proximity of populations to monitoring sites and sources (Section 3.4.2). Activity patterns vary both among and within individuals, resulting in corresponding variations in exposure across a population and over time. Variation in SO_2 concentrations among different microenvironments means that the amount of time spent in each location, as well as exertion level, will influence an individual's exposure to ambient SO_2. Time spent in different locations has also been found to vary by age, with younger and older age groups spending a greater percentage of time outdoors than adults of typical working age (18−64 years). These variations in activity pattern contribute to differences in exposure and, if uncharacterized, introduce error into population-averaged exposure estimates.

Uncharacterized spatial and temporal variability in SO_2 concentrations can contribute to exposure error in epidemiologic studies. SO_2 has low to moderate spatial correlations among ambient monitoring sites across urban geographic scales; thus, using central site monitor data for epidemiologic exposure assessment introduces exposure error into the resulting health effect estimate. Spatial variability in the magnitude of concentrations may affect cross-sectional and large-scale cohort studies by assigning exposures from one or a small number of sites that do not capture all of the spatial variability within a city.

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

Proximity of populations to ambient monitoring sites may influence how well human exposure is represented by measurements at the monitors, although factors other than distance play an important role as well. While many SO_2 monitoring sites are located near dense population centers, other sites are located near sources and may not fully represent SO_2 concentrations experienced by populations in epidemiologic studies. Use of these near-source monitoring sites introduces exposure error into health effect estimates, although this error can be mitigated by using average concentrations across multiple sites in an urban area.

Exposure to copollutants, such as other criteria pollutants, may result in confounding of health effect estimates. For SO_2, daily concentrations generally exhibit low correlations (median <0.4) with other daily NAAQS pollutant concentrations at collocated monitors (Figure 3-5, Section 3.4.3). However, a wide range of copollutant correlations has been observed across different monitoring sites, from moderately negative to moderately positive. In studies in which daily SO_2 correlations with NO_2 and CO were observed to be high, it is possible the data were collected before a rule to reduce sulfur content in diesel fuel (66 FR 5002) took effect in 2006 and 2007. The minority of sites with stronger correlations may introduce a greater degree of confounding into epidemiologic results. A similar impact is expected for epidemiologic studies of long-term SO_2 exposure, which also report a wide range of copollutant correlations.

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

Choice of exposure estimation method also influences the impact of exposure error on epidemiologic study results. Central site monitors offer a convenient source of time-series data, but fixed-site measurements do not account for the effects of spatial variation in SO_2 concentration, differences between indoor and outdoor exposure to ambient SO_2, and varying activity patterns on personal exposure to SO_2. Personal exposure measurements, such as those made in panel epidemiologic studies, provide accurate and specific exposure estimates, but sample size is often small and only a limited set of health outcomes can be studied. Modeled concentrations or exposures offer alternatives to measurements, with the advantage of estimating exposures over a wide range of scales, populations, and scenarios, particularly for locations lacking monitoring data. However, depending on the model type, there is the potential for bias and reduced precision due to model misspecification, missing sources, smoothing of concentration gradients, and complex topography. Model estimates are most informative when compared to an independent set of measured concentrations or exposures. The various sources of exposure error and their potential impact are considered in the evaluation of epidemiologic study results in this ISA.

1.5 Dosimetry and Mode of Action of Sulfur Dioxide

This ISA summarizes information on the dosimetry of inhaled SO_2, including the processes of absorption, distribution, metabolism, and elimination, as well as information on the mode of action of inhaled SO_2, covering the processes by which inhaled SO_2 initiates a cascade of molecular and cellular responses and the organ-level responses that follow. (Chapter 4). Together, these sections provide the foundation for understanding how exposure to inhaled SO_2 may lead to health effects. This understanding may provide biological plausibility for effects observed in the epidemiologic studies.

1.5.1 Dosimetry of Inhaled Sulfur Dioxide

Dosimetry of inhaled SO_2 refers to the measurement or estimation of the amount of SO_2 and its reaction products reaching and/or persisting at specific sites within the respiratory tract and systemically after exposure. Factors affecting the transport and fate of SO_2 in the respiratory tract include respiratory tract morphology, respiratory functional parameters, and physicochemical properties of SO_2 and of epithelial lining fluid (ELF). Health effects may be due to inhaled SO_2 or its chemical reaction products, including sulfite and S-sulfonates. Few studies have investigated SO_2 dosimetry since the 2008 ISA for Sulfur Oxides (U.S. EPA, 2008d), with most studies conducted prior to the 1982 AQCD (U.S. EPA, 1982a) and the 1986 Second Addendum (U.S. EPA, 1986b).

Because SO_2 is highly soluble in water, it is readily absorbed in the nasal passages of both humans and laboratory animals under resting conditions (Section 4.2.2). During nasal breathing, the majority of available data suggests 95% or greater SO_2 absorption occurs in the nasal passages, even under ventilation levels comparable to that during exercise. With increasing physical activity, there is an increase in ventilatory rate and a shift from nasal to oronasal breathing, resulting in greater SO_2 penetration into the lower respiratory tract. Even at rest, differences have been observed by age, sex, disease status, and body mass index in the fraction of oral versus nasal breathing (Section 4.1.2). Children inhale a larger fraction of air through their mouth than adults, and males tend inhale a larger fraction of air through their mouth than females (across all ages). Individuals with allergies or upper respiratory infections experience increased nasal resistance, and thus, increased fraction of oral breathing. Obesity, especially in boys, also contributes to increased nasal resistance and an increased oral fraction of breathing relative to normal weight children. Due to their increased amount of oral breathing, these individuals may be expected to have greater SO_2 penetration into the lower respiratory tract than healthy, normal weight adults. Children may also be expected to have a greater intake dose of SO_2 per body mass than adults.

Following absorption in the respiratory tract, SO_2 rapidly forms a mixture of bisulfite and sulfite, with the latter predominating. As much as 15−18% of the absorbed SO_2 may be desorbed and exhaled following cessation of exposure. Although some SO_2 products rapidly move from the respiratory tract into the blood and are distributed about the body, experiments using radiolabeled ^{35}S indicate that the majority of sulfur in SO_2-derived products in the body at any given time following exposure is found in the respiratory tract and may be detected there for up to a week following inhalation (Section 4.2.3). The distribution and clearance of inhaled SO_2 from the respiratory tract may involve several intermediate chemical reactions and transformations, particularly the formation of sulfite and S-sulfonates. Sulfite is metabolized into sulfate, primarily in the liver, which has higher sulfite oxidase levels than the lung or other body tissues (Section 4.2.4). Sulfite oxidase activity is highly variable among species with liver sulfite oxidase activity in rats being 10−20 times greater than in humans. Urinary excretion of sulfate is rapid and proportional to the concentration of SO_2 products in the blood (Section 4.2.5). S-sulfonates are cleared more slowly from the circulation with a clearance half-time of days.

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

(19−50 years) females and males, respectively, and by 500 times or more in young children (1−3 years)]. Endogenous sulfite production is two or more orders of magnitude higher than inhalation-derived sulfite levels for both children and adults, even for full day exposures to 75 ppb SO_2 (the level of the 1-hour NAAQS). Ingestion rates of sulfite added to foods vary widely; however, in general, sulfite ingestion is expected to exceed sulfite intake from inhalation in adults and children even for full day exposures to 75 ppb SO_2. However, inhalation-derived SO_2 products accumulate in respiratory tract tissues, whereas sulfite and sulfate from ingestion or endogenous production do not.

1.5.2 Mode of Action of Inhaled Sulfur Dioxide

Mode of action refers to a sequence of key events, endpoints, and outcomes that result in a given toxic effect. The mode of action discussion in Section 4.3 of this ISA updates the basic concepts derived from the SO_2 literature presented in the 1982 AQCD (U.S. EPA, 1982a) and the 2008 ISA for Sulfur Oxides (U.S. EPA, 2008d) and introduces the recent relevant literature. The main effects of SO_2 inhalation are seen at the sites of absorption (i.e., the respiratory tract) and include (1) activation of sensory nerves in the respiratory tract resulting in a neural reflex response, (2) injury to airway mucosa, and (3) increased airway hyperreactivity and allergic inflammation. Effects outside the respiratory tract may occur at very high concentrations of inhaled SO_2.

Reactive products formed as a result of SO_2 inhalation are responsible for a variety of downstream key events, which may include activation of sensory nerves in the respiratory tract, release of inflammatory mediators, and modulation of allergic inflammation or sensitization. These key events may collectively lead to several endpoints, including bronchoconstriction and airway hyper-responsiveness (AHR). A characteristic feature of individuals with asthma is an increased propensity of their airways to narrow in response to bronchoconstrictive stimuli relative to nonatopic individuals without asthma. Thus, bronchoconstriction is characteristic of an asthma attack. However, individuals without asthma may also experience bronchoconstriction in response to SO_2 inhalation; generally this occurs at higher concentrations (>1,000 ppb) than in an individual with asthma. Additionally, SO_2 exposure may increase airway responsiveness to subsequent exposures of other stimuli such as allergens or methacholine. These pathways may be linked to the epidemiologic outcome of asthma exacerbation.

The strongest evidence for the mode of action for respiratory effects following short-term exposure comes from controlled human exposure studies. SO_2 exposure resulted in increased airway resistance due to bronchoconstriction in in adults, both with and without

asthma. In adults without asthma, this response occurred primarily as a result of activation of sensory nerves in the respiratory tract resulting in neural reflex responses (Section 4.3.1). This is mediated by cholinergic parasympathetic pathways involving the vagus nerve. However, in adults with asthma, evidence indicates that the response is only partially due to vagal pathways and that inflammatory mediators such as histamine and leukotrienes also play an important role. Studies in experimental animals also demonstrate that SO_2 exposure activates reflexes that are mediated by cholinergic parasympathetic pathways involving the vagus nerve. However, noncholinergic mechanisms (i.e., neurogenic inflammation) may also be involved.

Evidence demonstrates that SO_2 exposure modulates allergic inflammatory responses (Section 4.3.2). Enhancement of allergic inflammation (i.e., leukotriene-mediated increases in numbers of sputum eosinophils) has been observed in adults with asthma who were exposed for 10 minutes to 750 ppb SO_2. In an animal model of allergic airway disease, repeated exposure to 2,000 ppb SO_2 led to an enhanced inflammatory response, including allergic inflammation. In naive animals, repeated exposure to SO_2 (as low as 100 ppb) over several days promoted allergic sensitization, inflammation, and AHR when animals were subsequently sensitized and challenged with an allergen. Thus, allergic inflammation and increased airway responsiveness may also link short-term SO_2 exposure to asthma exacerbation.

Evidence for the mode of action for respiratory effects due to long-term SO_2 exposure comes from studies in both naive and allergic experimental animals, which demonstrate allergic sensitization, allergic inflammation, AHR, and morphologic changes suggestive of airway remodeling following exposure to SO_2 (i.e., 2,000 ppb) over several weeks (Section 4.3.3). These changes, however, are mild compared to histopathological changes, such as mucous cell metaplasia and intramural fibrosis, which are generally observed following chronic exposure of naive animals to SO_2 concentrations of 10 ppm (10,000 ppb) and higher. However, in allergic animals, exposure to SO_2 over several weeks leads to morphologic responses indicative of airway remodeling and to AHR. Thus, repeated exposure to SO_2 may lead to the development of allergic airway disease, which shares many features with asthma, and to the worsening of the allergic airway disease. The development of AHR may link long-term exposure to SO_2 to the epidemiologic outcome of new onset asthma.

Although there is some evidence that SO_2 inhalation results in extrapulmonary effects, there is uncertainty regarding the mode of action underlying these responses (Section 4.3.4). Evidence from controlled human exposure studies points to SO_2 exposure-induced activation/sensitization of neural reflexes, possibly leading to altered heart rate (HR) or heart rate variability (HRV). Evidence also points to transport of sulfite

into the circulation. Sulfite is highly reactive and may be responsible for redox stress (possibly through autoxidation or peroxidase-mediated reactions to produce free radicals) in the circulation and extrapulmonary tissues. However, this stress is likely to occur only at very high SO_2 concentrations or during prolonged exposures because circulating sulfite is efficiently metabolized to sulfate in a reaction catalyzed by hepatic sulfite oxidase.

1.6 Health Effects of Sulfur Dioxide

This ISA evaluates relationships between an array of health effects and short-term and long-term exposures to SO_2 as examined in epidemiologic, controlled human exposure, and animal toxicological studies. Short-term exposures are defined as those with durations of minutes up to 1 month, with most studies examining effects related to exposures in the range of 1 hour to 1 week. Long-term exposures are defined as those with durations of more than 1 month to years. Drawing from the health effects evidence described in detail in Chapter 5, information on dosimetry and modes of action presented in Chapter 4, as well as issues regarding exposure assessment and potential confounding described in Chapter 3 and Section 1.4, the subsequent sections and Table 1-1 present the key evidence that informed the causal determinations for relationships between SO_2 exposure and health effects.

1.6.1 Respiratory Effects

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

Strong scientific evidence indicates that there is a causal relationship between short-term SO_2 exposure and respiratory morbidity, particularly in individuals with asthma, which is consistent with the conclusions of the 2008 ISA for Sulfur Oxides (U.S. EPA, 2008d). This determination is based on the consistency of findings within disciplines, coherence among evidence from controlled human exposure, epidemiologic, and toxicological studies, and biological plausibility for effects specifically related to asthma exacerbation (Table 5-21).

This conclusion is primarily based on controlled human exposure studies included in the 2008 SO_X ISA (U.S. EPA, 2008d) that showed lung function decrements and respiratory symptoms in adults with asthma exposed to SO_2 for 5−10 minutes under increased ventilation conditions; no new controlled human exposure studies have been conducted to

evaluate the effect of SO_2 on respiratory morbidity among individuals with asthma. These studies consistently demonstrated that individuals with asthma experience a moderate or greater decrement in lung function, defined as a ≥100% increase in specific airway resistance (sRaw) or ≥15% decrease in forced expiratory volume in 1 sec (FEV_1), frequently accompanied by respiratory symptoms, following peak exposures of 5−10 minutes with elevated ventilation rates at concentrations of 400−600 ppb (Section 5.2.1.2). A fraction of individuals with asthma (~5−30%) was observed in these studies to have moderate decrements in lung function at lower SO_2 concentrations (200−300 ppb; Table 5-2). Lung function decrements at these lower concentrations are less likely to be accompanied by respiratory symptoms. Some studies have evaluated the influence of asthma severity on response to SO_2, but the most severe asthmatics have not been tested, and thus, their response is unknown. Adults with moderate to severe asthma demonstrated larger absolute changes in lung function during exercise in response to SO_2 than adults with mild asthma, although this difference was attributed to a larger response to the exercise component of the protocol rather than to SO_2 itself. While adults with moderate to severe asthma may have similar responses to SO_2 as healthy adults (although at lower concentrations), they have less reserve capacity to deal with an insult compared with individuals with mild asthma; therefore, the impact of SO_2-induced decrements in lung function is greater in individuals with asthma than healthy adults. Although there are no laboratory studies of children exposed to SO_2, a number of studies have evaluated airway responsiveness of children and adults to a bronchoconstrictive stimulus. These studies indicate that school-aged children, particularly boys and perhaps obese children, are expected to have greater responses (i.e., greater lung function decrements) following exposure to SO_2 than adolescents and adults.

These findings are consistent with the current understanding of dosimetry and modes of action (Section 1.5). Due to their increased fraction of oral breathing, individuals with asthma may be expected to have greater SO_2 penetration into the lower respiratory tract than healthy adults. Reactive products formed as a result of SO_2 inhalation, particularly sulfites and S-sulfonates, are responsible for a variety of downstream key events, which may include activation of sensory nerves in the respiratory tract resulting in a neural reflex response, release of inflammatory mediators, and modulation of allergic inflammation. These key events may lead to several endpoints including bronchoconstriction and AHR, resulting in the outcome of asthma exacerbation.

Epidemiologic evidence also provides support for a causal relationship, including additional studies that add to the evidence provided by the 2008 ISA for Sulfur Oxides (U.S. EPA, 2008d). Studies of asthma hospital admissions and emergency department (ED) visits report positive associations with short-term SO_2 exposures, particularly for children (i.e., <18 years of age), with additional evidence from studies that examine

potential copollutant confounding that associations are generally unchanged in copollutant models involving PM and other criteria pollutants (Section 5.2.1.2, Figure 5-2). There is also some supporting evidence for positive associations between short-term SO_2 exposures and respiratory symptoms among children with asthma (Section 5.2.1.2). Epidemiologic evidence of associations between short-term SO_2 exposures and lung function or respiratory symptoms among adults with asthma is less consistent (Section 5.2.1.2). Epidemiologic studies of cause-specific mortality that report consistent positive associations between short-term SO_2 exposures and respiratory mortality provide support for a potential continuum of effects (Section 5.2.1.8).

There is some support for other SO_2-related respiratory effects including exacerbation of chronic obstructive pulmonary disease (COPD) in individuals with COPD and other respiratory effects including respiratory infection, aggregated respiratory conditions, and respiratory mortality in the general population (Section 5.2.1.3, Section 5.2.1.4, Section 5.2.1.5, and Section 5.2.1.6). The limited and inconsistent evidence for these nonasthma-related respiratory effects does not contribute heavily to the causal determination.

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

Overall, the evidence is suggestive of, but not sufficient to infer, a causal relationship between long-term SO_2 exposure and respiratory effects, mainly the development of asthma in children (Section 5.2.2). This represents a change from the conclusion in the 2008 ISA for Sulfur Oxides (U.S. EPA, 2008d) that the evidence was "inadequate to infer a causal association." There is a limited number of recent longitudinal epidemiologic studies that evaluate associations between asthma incidence among children and long-term SO_2 exposures, with the overall body of evidence lacking consistency. The evidence from longitudinal studies showing increases in asthma incidence is coherent with findings from animal toxicological studies that provide a pathophysiologic basis for the development of asthma. In naive newborn animals, repeated SO_2 exposure over several weeks resulted in immune responses and airway inflammation, key steps in allergic sensitization. In allergic newborn animals, studies with several days or several weeks of repeated SO_2 exposure found enhanced airway inflammation and some evidence of airway remodeling and AHR. The combined epidemiologic and animal toxicological evidence provides support for an independent effect of long-term exposure to SO_2 on the development of asthma in children, but key uncertainties remain, including exposure measurement error and the potential for copollutant confounding. Some evidence of a link between long-term exposure to SO_2 and respiratory symptoms and/or respiratory allergies among children further supports a possible relationship between long-term SO_2

exposure and the development of asthma. Details of the causal determination are provided in Table 5-24.

1.6.2 Health Effects beyond the Respiratory System

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

Overall, the available evidence is inadequate to infer the presence or absence of a causal relationship between short-term exposure to SO_2 and cardiovascular health effects (Table 5-34, Section 5.3.1). This conclusion is consistent with that of the 2008 ISA for Sulfur Oxides (U.S. EPA, 2008d), which concluded "the evidence as a whole is inadequate to infer a causal relationship." Although multiple epidemiologic studies report positive associations between short-term exposure to SO_2 and a variety of cardiovascular outcomes, the results are inconsistent across the specific cardiovascular outcomes, and the associations are generally attenuated after copollutant adjustment. There is some experimental evidence in humans and animals for SO_2-induced effects on the autonomic nervous system and inflammation and other effects in tissues distal to the absorption site. However, the limited and inconsistent evidence from the available experimental studies does not demonstrate potentially biologically plausible mechanisms for, and is not coherent with, cardiovascular effects such as triggering a myocardial infarction. Evidence for other cardiovascular and related metabolic effects is inconclusive.

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

Overall, the evidence is inadequate to infer the presence or absence of a causal relationship between long-term exposure to SO_2 and cardiovascular health effects Table 5-35, Section 5.3.2). The relationship between long-term SO_2 exposure and cardiovascular outcomes was not evaluated in the 2008 ISA for Sulfur Oxides (U.S. EPA, 2008d). Despite a number of epidemiologic studies that report positive associations between long-term exposure to SO_2 concentrations and cardiovascular disease and stroke, the evidence for any one endpoint is limited and inconsistent. Exposure measurement error and the potential for copollutant confounding are uncertainties in the interpretation of the evidence. Additionally, there is insufficient experimental evidence to provide

coherence or biological plausibility for an independent effect of long-term exposure to SO_2 on cardiovascular health.

1.6.2.3 Reproductive and Developmental Effects

Overall the evidence is inadequate to infer the presence or absence of a causal relationship between exposure to SO_2 and reproductive and developmental outcomes (Table 5-38, Section 5.4), consistent with the conclusion reached in the 2008 ISA for Sulfur Oxides (U.S. EPA, 2008d).

There are several recent well-designed, well-conducted studies that indicate an association between SO_2 and reproductive and developmental health outcomes, including fetal growth metrics, preterm birth, birth weight, and fetal and infant mortality. However, a number of uncertainties are associated with the observed relationship between exposure to SO_2 and birth outcomes, such as timing of exposure windows, exposure error, and spatial and temporal heterogeneity. Few studies have examined other health outcomes, such as fertility, effects on pregnancy (e.g., pre-eclampsia, gestational diabetes), and developmental effects, and there is little coherence or consistency among epidemiologic and toxicological studies for these outcomes. There is limited toxicological evidence at relevant dose ranges of SO_2, making it difficult to evaluate the potential modes of action for reproductive and developmental effects of ambient SO_2. Studies published since the 2008 SO_X ISA (U.S. EPA, 2008d) have not substantially reduced any of the uncertainties identified in the previous ISA, including exposure measurement error and the potential for copollutant confounding; therefore, the evidence is inadequate to infer the presence or absence of a causal relationship between exposure to SO_2 and reproductive and developmental outcomes.

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

Multicity studies evaluated since the completion of the 2008 ISA for Sulfur Oxides continue to provide consistent evidence of positive associations between short-term SO_2 exposures and total mortality (Section 5.5.1). Although the body of evidence is larger than at the time of the last review, key uncertainties and data gaps still remain, which contribute to the conclusion that the evidence for short-term SO_2 exposures and total mortality is suggestive of, but not sufficient to infer, a causal relationship (Table 5-41). This conclusion is consistent with that reached in the 2008 SO_X ISA (U.S. EPA, 2008d). Overall, recent multicity studies evaluated have further informed key uncertainties and data gaps in the SO_2-mortality relationship identified in the 2008 SO_X ISA including

confounding, modification of the SO_2-mortality relationship, potential seasonal differences in SO_2-mortality associations, and the shape of the SO_2-mortality C-R relationship. However, questions remain regarding whether SO_2 has an independent effect on mortality, and these lingering questions can be attributed to the limited number of studies that examined potential copollutant confounding, the relative lack of copollutant analyses with $PM_{2.5}$, and the evidence indicating attenuation of SO_2-mortality associations in copollutant models with NO_2 and PM_{10}. Additionally, a biological mechanism has not been characterized to date that could lead to mortality as a result of short-term SO_2 exposures.

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

The overall evidence is inadequate to infer the presence or absence of a causal relationship between long-term exposure to SO_2 and total mortality among adults (Table 5-43, Section 5.5.2), consistent with the conclusion reached in the 2008 ISA for Sulfur Oxides (U.S. EPA, 2008d). Recent evidence is generally consistent with the evidence included in the ISA, although some recent cohort epidemiologic studies provide evidence for improved consistency in the association between long-term exposure to SO_2 and both respiratory and total mortality. However, none of these recent studies help to resolve the uncertainties identified in the 2008 SO_X ISA related to exposure measurement error, copollutant confounding, or the geographic scale of the analysis.

1.6.2.6 Cancer

The overall evidence for long-term SO_2 exposure and cancer is inadequate to infer the presence or absence of a causal relationship (Table 5-44, Section 5.6), the same conclusion reached in the 2008 ISA for Sulfur Oxides (U.S. EPA, 2008d). Recent studies include evidence on lung cancer as well as other cancer types. Although some studies of SO_2 concentrations and lung cancer mortality have reported null results, other studies that included various cofounders and copollutants reported positive associations. Positive associations were also observed in a study of SO_2 concentrations and bladder cancer mortality but not in ecological studies of bladder cancer incidence. Limited supportive evidence for mode of action is available from genotoxicity and mutagenicity studies, but 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[a] and Causal Determination		SO_2 Concentrations Associated with Effects
Respiratory Effects and Short-Term Exposure (Section 5.2.1): Causal relationship *No change in causal determination from the 2008 SO_X ISA (U.S. EPA, 2008d); new evidence is consistent with previous determination.*		
Key evidence (Table 5-21)	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_2 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_2 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_2 exposure and asthma exacerbation.	Overall study ambient means: *Controlled human exposure studies of decreased lung function:* 200−600 ppb, with a subset analysis of responders showing statistically significant responses at 300 ppb *Controlled human exposure studies of increased respiratory symptoms:* 400−1,000 ppb *Epidemiologic studies:* 1-h max: 9.6−11 ppb 24-h avg: 1.0−37 ppb *Animal studies:* 100 ppb
Respiratory Effects and Long-Term Exposure (Section 5.2.2): Suggestive of, but not sufficient to infer, a causal relationship *Change in causal determination from the 2008 SO_X ISA (U.S. EPA, 2008d) (inadequate to infer a causal relationship) due to new, but limited, evidence.*		
Key evidence[b] (Table 5-24)	Evidence from epidemiologic studies is generally supportive but not entirely consistent for increases in asthma incidence and prevalence related to SO_2 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.	Overall epidemiologic study ambient means: 2-4 ppb Animal toxicological studies: 2,000 ppb

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[a] and Causal Determination		SO_2 Concentrations Associated with Effects
Cardiovascular Effects and Short-Term Exposure (Section 5.3.1) Inadequate to infer a causal relationship *No change in causal determination from the 2008 SO_X ISA (U.S. EPA, 2008d); new evidence is consistent with previous determination.*		
Key evidence[b] (Table 5-34)	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_2 exposure and cardiovascular effects.	Overall epidemiologic study ambient 24-h avg means: 1.2−30 ppb
Cardiovascular Effects and Long-Term Exposure (Section 5.3.2) Inadequate to infer a causal relationship *Not included in the 2008 SO_X ISA (U.S. EPA, 2008d).*		
Key evidence[b] (Table 5-35)	Results of epidemiologic studies of long-term SO_2 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_2 exposure and cardiovascular effects.	Overall epidemiologic study ambient means: 1.3−1.7 ppb
Reproductive and Developmental Effects and Exposure (Section 5.4) Inadequate to infer a causal relationship *No change in causal determination from the 2008 SO_X ISA (U.S. EPA, 2008d); new evidence is consistent with previous determination.*		
Key evidence[b] (Table 5-38)	Consistent positive associations are observed with near-birth exposures to SO_2 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_2 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.	Overall epidemiologic study ambient means: 1.9−13 ppb

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[a] and Causal Determination		SO_2 Concentrations Associated with Effects
Total Mortality and Short-Term Exposure (Section 5.5.1) Suggestive of, but not sufficient to infer, a causal relationship *No change in causal determination from the 2008 SO_X ISA (U.S. EPA, 2008d); new evidence is consistent with previous determination.*		
Key evidence[b] (Table 5-41)	There is consistent epidemiologic evidence from multiple high-quality studies at relevant SO_2 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_2-related mortality; thus, chance, confounding, and other biases cannot be ruled out.	Overall epidemiologic study ambient 24-h avg means: *U.S., Canada, South America, Europe:* 0.4−28 ppb *Asia:* 0.7−>200 ppb
Total Mortality and Long-Term Exposure (Section 5.5.2) Inadequate to infer a causal relationship *No change in causal determination from the 2008 SO_X ISA (U.S. EPA, 2008d); new evidence is consistent with previous determination.*		
Key evidence[b] (Table 5-43)	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_2 exposure and long-term respiratory or cardiovascular health effects to support an association with mortality from these causes.	Overall epidemiologic study ambient means: 1.6−24 ppb

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[a] and Causal Determination		SO_2 Concentrations Associated with Effects
Cancer and Long-Term Exposure (Section 5.6) Inadequate to infer a causal relationship *No change in causal determination from the 2008 SO_X ISA (U.S. EPA, 2008d); new evidence is consistent with previous determination.*		
Key evidence[b] (Table 5-44)	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_2 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_2 = sulfur dioxide; SO_X = sulfur oxides.

[a]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.

[b]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_2. Spatial and temporal heterogeneity may introduce exposure error in long-term effects. For studies of reproductive and developmental outcomes, associations with exposure to SO_2 at particular windows during pregnancy are inconsistent between studies. Additionally, although SO_2 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.

1

1.7 Policy-Relevant Considerations

As described in the Preamble to the ISAs (U.S. EPA, 2015b) and Section 1.1, this ISA informs policy-relevant issues that are aimed at characterizing quantitative aspects of relationships between ambient SO_2 exposure and health effects and the impact of these relationships on public health. To that end, this section integrates information from the ISA to describe SO_2 exposure durations and patterns related to health effects, the shape of the concentration-response relationship, regional heterogeneity in relationships, the adverse nature of health effects, and at-risk populations and lifestages. In addressing these policy-relevant issues, this section focuses on respiratory effects associated with short-term exposures, for which the evidence indicates there is a causal relationship.

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

Effects have been observed in controlled human exposure studies after SO_2 exposures as brief as 5−10 minutes. Consistent associations between SO_2 concentrations and asthma hospital admissions and ED visits that are generally unchanged in copollutant models have been demonstrated in epidemiologic studies using daily exposure metrics (24-h avg and 1-h daily max), although the observed effects could be related to very short duration (5−10 minutes) peak exposures experienced during the day.

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

1.7.2 Concentration-Response Relationships and Thresholds

Characterizing the shape of concentration-response relationships for health effects associated with SO_2 exposure aids in quantifying the public health impact of SO_2 exposure. A key issue is often whether the relationship is linear across the full range of ambient concentrations or whether there are deviations from linearity, and if so, at what concentrations they occur. Another important issue is the evidence regarding potential thresholds for key effects. Such thresholds may indicate exposures below which adverse health outcomes are not elicited. Lack of a discernable threshold in the evidence for

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

Results from controlled human exposure studies indicate wide interindividual variability in response to SO_2 exposures, with peak (5 to 10 minutes) exposures at concentrations as low as 200−300 ppb eliciting lung function decrements in some individuals with asthma. A clear increase in the magnitude of lung function decrements was observed with increasing exposure concentrations between 200 and 1,000 ppb during 5−10 minute SO_2 exposures. The limited epidemiologic research on concentration-response functions relating SO_2 concentrations to respiratory health morbidity does not provide evidence for a deviation from linearity or a discernable population-level threshold.

1.7.3 Regional Heterogeneity in Effect Estimates

The 2008 ISA for Sulfur Oxides (U.S. EPA, 2008d) discussed spatial variability in SO_2 concentrations and its impact on effect estimates from epidemiologic studies. Correlations between monitors ranged from very low to very high, suggesting that SO_2 concentrations at some monitoring sites may not be highly correlated with the community average concentration. Of particular concern for SO_2 is the predominance of point sources, resulting in an uneven distribution of SO_2 concentrations across an urban area. Factors contributing to differences among monitoring sites include proximity to sources, terrain features, and uncertainty regarding the measurement of low SO_2 concentrations.

Spatial and temporal variability in SO_2 concentrations can contribute to exposure error in epidemiologic studies, whether such studies rely on central site monitor data or concentration modeling for exposure assessment. SO_2 has low to moderate spatial correlations between ambient monitoring sites across urban geographic scales; thus, using central site monitor data for epidemiologic exposure assessment introduces exposure error into the resulting effect estimate. Spatial variability in the magnitude of concentrations may affect cross-sectional and large-scale cohort studies by undermining the assumption that intraurban concentration and exposure differences are less important than interurban differences. This issue may be less important for time-series studies, which rely on day-to-day temporal variability in concentrations to evaluate health effects. Low correlations between monitors contribute to exposure error in time-series studies, including bias toward the null and wider confidence intervals.

1.7.4 Public Health Significance

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

1.7.4.1 Characterizing Adversity of Health Effects

Both the World Health Organization (WHO) and the American Thoracic Society (ATS) have provided guidance in describing what health effects may be considered adverse. WHO defines health as "the state of complete physical, mental, and social well-being and not merely the absence of disease or infirmity" (WHO, 1948). By this definition, changes in health outcomes that are not severe enough to result in a diagnosis of a clinical effect or condition can be considered adverse if they affect the well-being of an individual. ATS also has considered a wide range of health outcomes in defining adverse effects. Distinguishing between individual and population risk, ATS described its view that small air pollution-related changes in an outcome observed in individuals might be considered adverse on a population level. This is because a shift in the distribution of population responses resulting from higher air pollution exposure might increase the proportion of the population with clinically important effects or at increased risk of a clinically important effect that could be caused by another risk factor (ATS, 2000). Increases in ambient SO_2 concentrations are associated with a broad spectrum of health effects related to asthma, including those characterized as adverse by ATS such as ED visits and hospital admissions.

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

The primary NAAQS are intended to protect public health with an adequate margin of safety. In so doing, protection is provided for both the population as a whole and those groups potentially at increased risk for health effects from exposure to the air pollutant for which each NAAQS is set (Preface to this ISA). Hence, the public health significance of health effects related to SO_2 exposure also is informed by whether specific lifestages or groups in the population are identified as being at increased risk of SO_2-related health effects.

At-risk populations or lifestages can be characterized by specific biological, sociodemographic, or behavioral factors, among others. Since the 2008 ISA for Sulfur Oxides (U.S. EPA, 2008d), the U.S. EPA has used a framework for drawing conclusions about the role of such factors in modifying risk of health effects of air pollution exposure [Table III of the Preamble to the ISAs (U.S. EPA, 2015b)]. Similar to the causal framework, conclusions about at-risk populations are based on judgments of the consistency and coherence of evidence within and across disciplines (Chapter 6). Briefly, the evaluation is based on studies that compared exposure or health effect relationships among groups that differ according to a particular factor (e.g., people with and without asthma) and studies conducted in a population or animal model with a particular factor or pathophysiological condition. Where available, information on exposure, dosimetry, and modes of action is evaluated to assess coherence with health effect evidence and inform how a particular factor may contribute to SO_2-related risk of health effects (e.g., by increasing exposure, increasing biological effect for a given dose).

There is adequate evidence that people with asthma are at increased risk for SO_2-related health effects (Section 6.3.1), which is consistent with the findings of the 2008 ISA for Sulfur Oxides (U.S. EPA, 2008d). The conclusions are based on findings for short-term SO_2 exposure and respiratory effects (specifically lung function decrements), for which a causal relationship has been determined (Section 5.2.1.9). There are a limited number of epidemiologic studies evaluating SO_2-related respiratory effects that include stratification by asthma status, but there is evidence for respiratory-related hospital admissions and emergency department visits (Section 5.2.1.2). Further support for increased risk in individuals with asthma is provided by biological plausibility drawn from modes of action. Children with asthma may be particularly at increased risk relative to adults with asthma due to their increased responsiveness to methacholine, increased ventilation rates relative to body mass, and increased proportion of oral breathing, particularly among boys. Among children in the U.S., asthma is the leading chronic illness (9.5% prevalence) and largest reason for missed school days.

There is also evidence suggestive of increased risk for children and older adults relative to other lifestages (Section 6.5.1). Although the 2008 ISA for Sulfur Oxides (U.S. EPA, 2008d) discussed several studies indicating stronger associations between SO_2 and respiratory outcomes for these lifestages, the recent evidence is not entirely consistent with previous studies. For children, studies comparing SO_2-associated respiratory outcomes reported mixed results. For adults, recent evidence generally found similar associations for SO_2-related respiratory outcomes or mortality across age groups, although those over 75 years of age were more consistently at increased risk. In addition, there was insufficient toxicological evidence regarding the effect of lifestage on

respiratory responses to SO_2 to support observations made across epidemiologic studies that evaluated lifestage.

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

Several aspects of the current evidence are important for considering the public health significance of SO_2-related health effects. One aspect is adversity of the health effects, which may include health effects that are clearly adverse such as ED visits and hospital admissions for asthma and asthma exacerbation. Magnitude of the affected population is also important. As noted above, in the case of SO_2-related health effects, the potentially affected population is large, given the number of people with asthma in the U.S.
The roles of co-occurring risk factors or combined higher SO_2 exposure and health risk in influencing the risk of SO_2-related health effects is not well understood. The large proportions of children and older adults in the U.S. population and the high prevalence of asthma in children may translate into a large number of people affected by SO_2, and thus, magnify the public health impact of ambient SO_2 exposure.

1.8 Summary and Health Effects Conclusions

This ISA is a comprehensive evaluation and synthesis of the policy-relevant science regarding the potential health effects of ambient sulfur oxides, focusing on SO_2. The ISA development process involves review of the scientific literature, selecting and evaluating relevant studies, and evaluating the weight of evidence to reach causal determinations regarding the likelihood of independent health effects of SO_2. Information is included in the ISA on sources of SO_2, atmospheric chemistry of SO_2 and other sulfur-containing compounds, ambient concentrations of SO_2 nationwide and in urban areas, and modeling approaches for estimating SO_2 concentrations. Approaches for characterizing exposure to ambient SO_2, including monitoring and modeling, together with factors affecting ambient exposure, are described in terms of their potential impact on epidemiologic study results. Dosimetry of SO_2 and potential modes of action are discussed to provide context for the consideration of potential health effects of SO_2, including respiratory effects, cardiovascular effects, reproductive and developmental effects, cancer, and mortality.

Consistent with the findings of the 2008 ISA for Sulfur Oxides (U.S. EPA, 2008d), studies continue to support the conclusion that there is a causal relationship between short-term SO_2 exposure and respiratory effects. This causal determination is based on consistency of findings within disciplines, coherence among multiple lines of evidence,

and biological plausibility indicating that there is a causal relationship between short-term SO_2 exposure and respiratory effects in individuals with asthma. The primary evidence for this conclusion comes from controlled human exposure studies that showed lung function decrements and respiratory symptoms in adult individuals with asthma exposed to SO_2 for 5−10 minutes under increased ventilation conditions. Supporting evidence was provided by epidemiologic studies that reported positive associations between short-term SO_2 exposures and asthma hospital admissions and ED visits that were generally unchanged in copollutant models involving PM and other criteria pollutants.

For both long-term exposure and respiratory effects, as well as short-term exposure and total mortality, the evidence is suggestive of, but not sufficient to infer, a causal relationship. In both cases, there is some evidence of an association between SO_2 exposure and health outcomes, but the evidence is inconsistent and uncertainties remain, including exposure error and copollutant confounding. The evidence was considered to be inadequate to infer the presence or absence of a causal relationship for other health effects, including cardiovascular morbidity (short- and long-term exposure), reproductive and developmental effects, total mortality (long-term exposure), and cancer. For these outcome categories, the evidence generally was not consistent across specific outcomes, showed a potential for copollutant confounding, and was lacking in biological plausibility.

In considering the effects of SO_2 on various populations and lifestages, there is adequate evidence that people with asthma are at increased risk for SO_2-related health effects, as well as suggestive evidence for increased risk among children and older adults. The large proportions of children and older adults in the U.S. population and the high prevalence of asthma in children may translate into a large number of people affected by SO_2, and thus, magnify the public health impact of ambient SO_2 exposure.

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

2.1 Introduction

The Clean Air Act requires the U.S. Environmental Protection Agency (U.S. EPA) to periodically review the air quality criteria and the national ambient air quality standards (NAAQS) for sulfur oxides (SO_X), which is one of the six criteria air pollutants, and revise the standards as may be appropriate. Sulfur oxides are a group of closely related sulfur-containing gaseous compounds [e.g., sulfur dioxide (SO_2), sulfur monoxide (SO), disulfur monoxide (S_2O), and sulfur trioxide (SO_3)], and the NAAQS are currently set using SO_2 as the indicator species. Of the sulfur oxides, SO_2 is the most abundant in the atmosphere, the most important in atmospheric chemistry, and the one most clearly linked to human health effects (U.S. EPA, 2008d). As in previous reviews, the presence of sulfur oxides other than SO_2 in the atmosphere has not been demonstrated (U.S. EPA, 1996b; HEW, 1969). Therefore, the emphasis in this chapter is on SO_2. Note that the mechanism of particle-phase SO_4^{2-} formation is briefly described in Section 2.3 [for more detail, see Seinfeld and Pandis (2006), Finlayson-Pitts and Pitts (2000), and other atmospheric chemistry texts]. The health effects of sulfate aerosol and other particle-phase sulfur compounds are discussed in the ISA for Particulate Matter (U.S. EPA, 2009a).

Sulfur dioxide is both a primary gas-phase pollutant (when formed during fuel combustion) and a secondary pollutant [the product of atmospheric gas- or droplet-phase oxidation of reduced sulfur compounds (sulfides)]. Fossil fuel combustion is the main anthropogenic source of primary SO_2, while volcanoes and landscape fires (wildfires as well as controlled burns) are the main natural sources of primary SO_2. Industrial chemical and pulp and paper production, natural biological activity (plants, fungi, and prokaryotes), and volcanoes are among many sources of reduced sulfur compounds that ultimately lead, through various oxidation reactions in the atmosphere, to the formation of secondary SO_2.

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

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

2.2 Anthropogenic and Natural Sources of Sulfur Dioxide

This section briefly describes the main U.S. anthropogenic and natural sources of SO_2 emissions. Emissions estimates for natural and anthropogenic sulfide emissions for the U.S. alone are not available in the literature. Therefore, a brief discussion of the sulfur cycle and estimates of the contribution of sulfides at the global scale, all of which can be found in the literature, are provided. Section 2.2.1 describes the main categories of anthropogenic SO_2 emissions, while Section 2.2.2 presents the geographic distribution of SO_2 sources across the U.S. The declining trend in anthropogenic SO_2 emissions is discussed in Section 2.2.3. Natural sources of SO_2 are discussed in Section 2.2.4. Indirect production of SO_2 through oxidation of reduced sulfur compounds emitted from geologic and biological sources is discussed in Section 2.2.5.

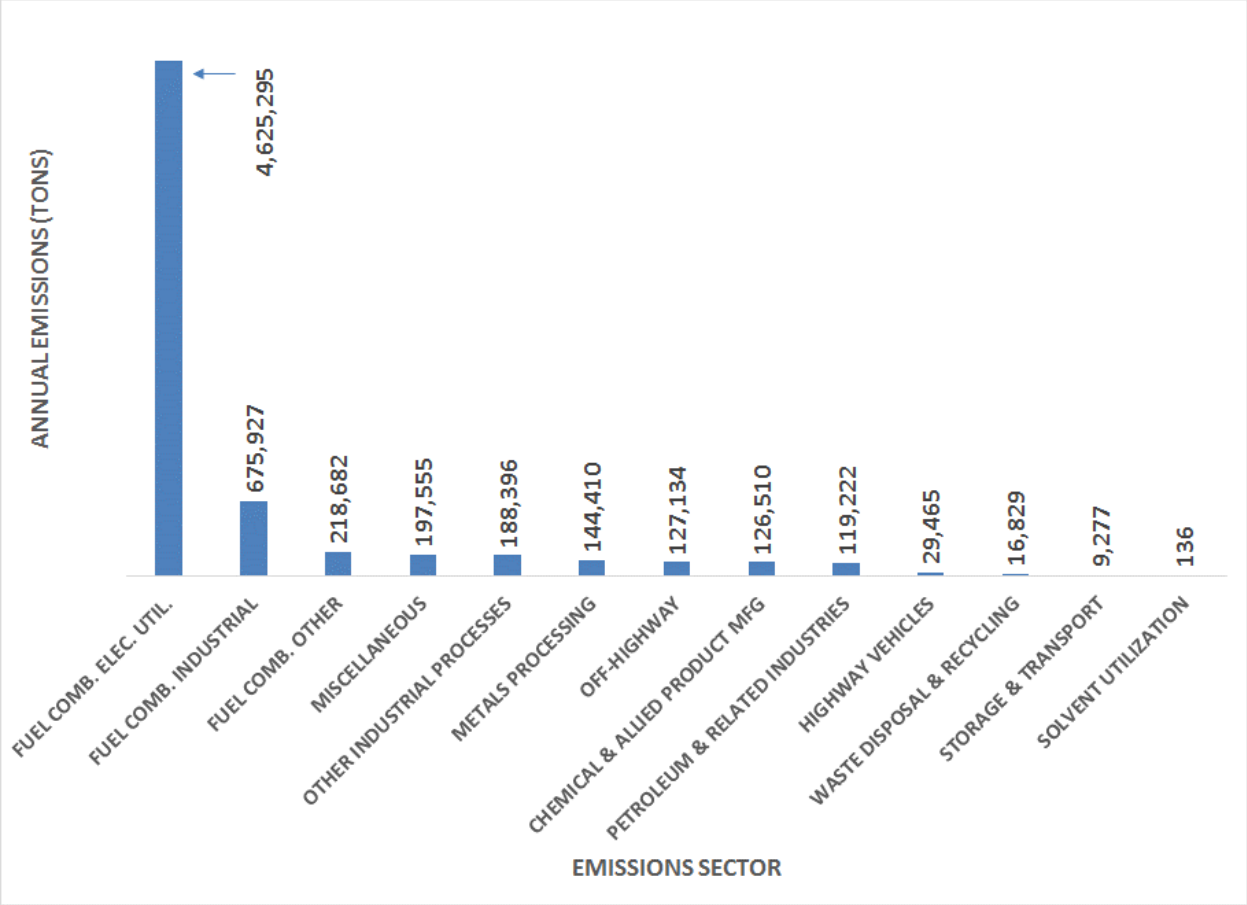
Sulfur is present to some degree in all fossil fuels, especially coal, and occurs as reduced organosulfur compounds. Coal also contains sulfur in mineral form (pyrite or other metallo-sulfur minerals) and in elemental form (Calkins, 1994). Of the most common types of coal (anthracite, bituminous, subbituminous, and lignite), sulfur content varies between 0.4 and 4% by mass. Fuel sulfur is almost entirely converted to SO_2 (or SO_3) during combustion, making accurate estimates of SO_2 combustion emissions possible based on fuel composition and combustion rates.

The mass of sulfur released into the environment by anthropogenic sources is comparable to natural sources (Brimblecombe, 2003). In addition to volcanic and other geologic SO_2 emissions, naturally occurring SO_2 is derived from the oxidation of sulfides emitted by low flux “area” sources, such as the oceans and moist soils. Anthropogenic emissions of sulfur are primarily in the form of SO_2, emerging from point sources in quantities that may substantially affect local and regional air quality.

2.2.1 U.S. Anthropogenic Sources

The largest SO_2-emitting sector within the U.S. is electricity generation based on coal combustion (4,625,295 tons). The mass of emissions produced by the Fuel Combustion in Electrical Utilities sector [i.e., coal-fired electric generating units (EGUs)] exceeds those produced by the next largest sector [the Fuel Combustion—Industrial sector (i.e., coal-fired boilers)] by nearly a factor of 7, and EGUs emit approximately 2.5 times

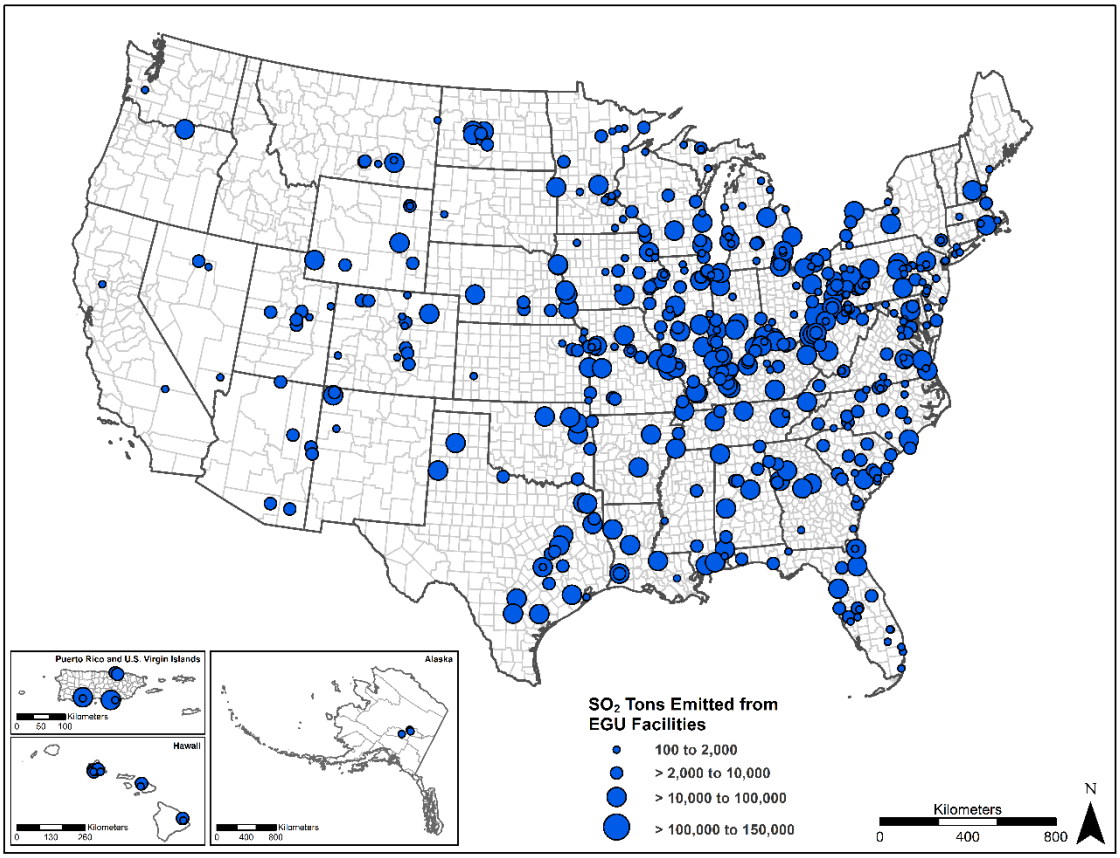
as much SO_2 as all other sources combined. Figure 2-1 provides a sector comparison of annual emissions [in tons] found in the U.S. EPA 2011 National Emissions Inventory (NEI) (U.S. EPA, 2013a).



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.

Because EGUs comprise the largest NEI source category, the spatial distribution of SO_2-emitting EGUs is presented here (U.S. EPA, 2013a). Most EGU sources are located in the eastern half of the continental U.S., as indicated in Figure 2-2. There is a particularly high concentration of EGUs in the Ohio River valley, upper Midwest, and along the Atlantic coast. Many of the monitoring sites with elevated SO_2 concentrations are located in these same areas (Figure 2-11).



Note: EGU = electric power generating unit; SO_2 = 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.

Industrial fuel combustion is the second largest source nationwide, emitting 675,927 tons per year (tpy), followed by other fuel combustion (218,682 tpy). Miscellaneous (197,555 tpy) is the fourth-largest source and includes SO_2 emissions by fire used in landscape management and agriculture as well as wildfires (U.S. EPA, 2013a). Wildfires, as a natural source of SO_2 emissions, are discussed in Section 2.2.4.3.

The commercial marine sector falls within the off-highway category (127,134 tpy), after EGUs and Industrial Fuel Combustion U.S. EPA (2013a). Wang et al. (2007) modeled SO_2 emissions from commercial marine activity based on a combination of historical shipping data and marine traffic predictions based on port sizes and probable routes using data from 2002. A 200 nautical mile boundary was imposed around the marine, lake, and

river international borders of the U.S. Thirty-eight percent of emissions were estimated for the East Coast of the U.S. related to commercial marine shipping. Twenty percent were estimated for the West Coast, and 26% of emissions were estimated for the Gulf Coast. Smaller quantities were estimated elsewhere (10% for Alaska, 3% for Hawaii, and 2% for the Great Lakes). Interior waterway activity was not included in the Wang et al. (2007) paper. In 2010, the International Maritime Organization introduced Emissions Control Areas (ECA) around U.S., Canadian, and French waters under the International Convention for the Prevention of Pollution from Ships (Office of Transportation and Air Quality, 2010). The ECA is a 200 nautical mile buffer around the maritime borders, in which fuels cannot contain more than 1,000 ppm sulfur as of 2015. The fuel sulfur regulation was first lowered from 15,000 to 10,000 ppm in 2010. These reductions are expected to be accomplished by maritime vessels switching fuel sources when they cross the 200 nautical mile buffer to approach their port. Office of Transportation and Air Quality (2010) estimates that this reduction in the amount of sulfur in marine fuels used within the 200 nautical mile buffer results in an 85% reduction in SO_2 emissions from the commercial marine sector.

Monitoring data that can indicate the effects of the ECA on air quality near ports is very limited. The SLAMS monitoring network used to implement the SO_2 NAAQS (discussed in Section 2.4.1.1) does not include any monitors located at ports. However, as part of its Clean Air Action effort, the San Pedro Bay Ports in California, operate a network of ambient monitors at the ports of Los Angeles and Long Beach (the two busiest ports in the U.S.). The network includes six monitors, four sites in located at the Port of Los Angeles and two sites located at the Port of Long Beach. A map of the network is available at http://caap.airsis.com/MapView.aspx. The latest reports from these two ports show SO_2 concentration well below the NAAQS. At the Port of Los Angeles, the 3 year average of the 99th percentile 1-h daily max for the latest reported period (May 2013−April 2016) ranged from 17 ppb to 23 ppb at the four Port of Los Angeles sites (Leidos Inc, 2016). At the Port of Long Beach, the 3 year average of the 99th percentile 1-h daily max for the latest reported period (January 2013−December 2015) ranged from 13 ppb to 20 ppb at the two Port of Long Beach sites (Leidos Inc, 2016).

National SO_2 emissions sector summaries cannot offer insight concerning the local influence of individual SO_2-emitting facilities. In addition to fossil fuel-fired steam electricity plants, other types of large emissions facilities that may be few in number include copper smelters, coal cleaning plants, kraft pulp mills, Portland Cement plants, iron and steel mill plants, sulfuric acid plants, petroleum refineries, and chemical processing plants. For example, the Metals Processing sector represents less than 2.2% of total emissions from the 2011 NEI (U.S. EPA, 2013a), but monitoring sites that have

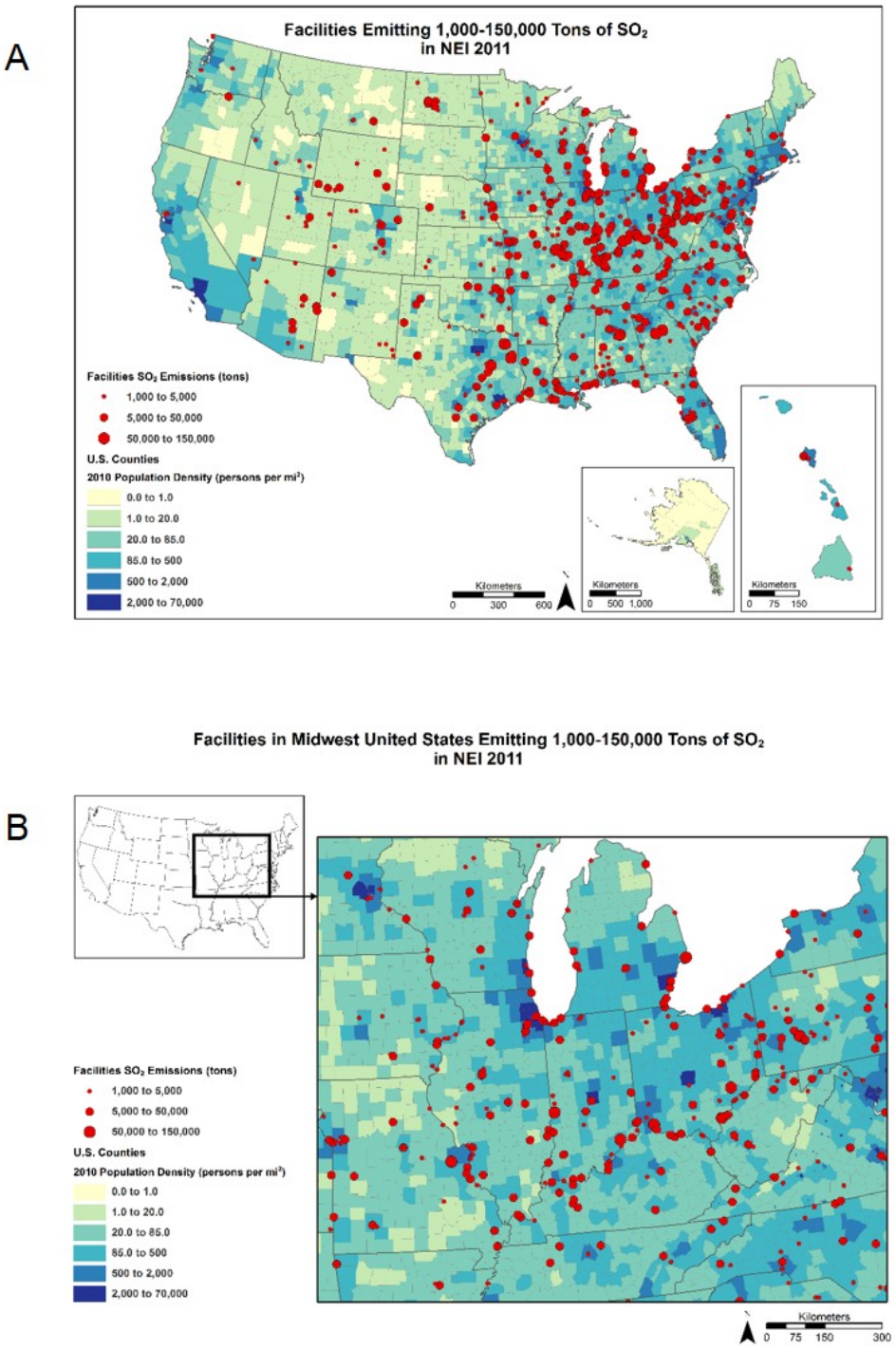
recorded some of the highest 1-h daily max SO_2 concentrations in the U.S. are located near copper smelters in Arizona (Section 2.5.2 and Section 2.5.4; Figure 2-11).

2.2.2 National Geographic Distribution of Large Sources

Figure 2-3 shows the geographic distribution of continental U.S. facilities emitting more than 1,000 tpy SO_2, with an enlargement of the Midwest states including the Ohio River Valley, where a large number of these SO_2-emitting sources are located.

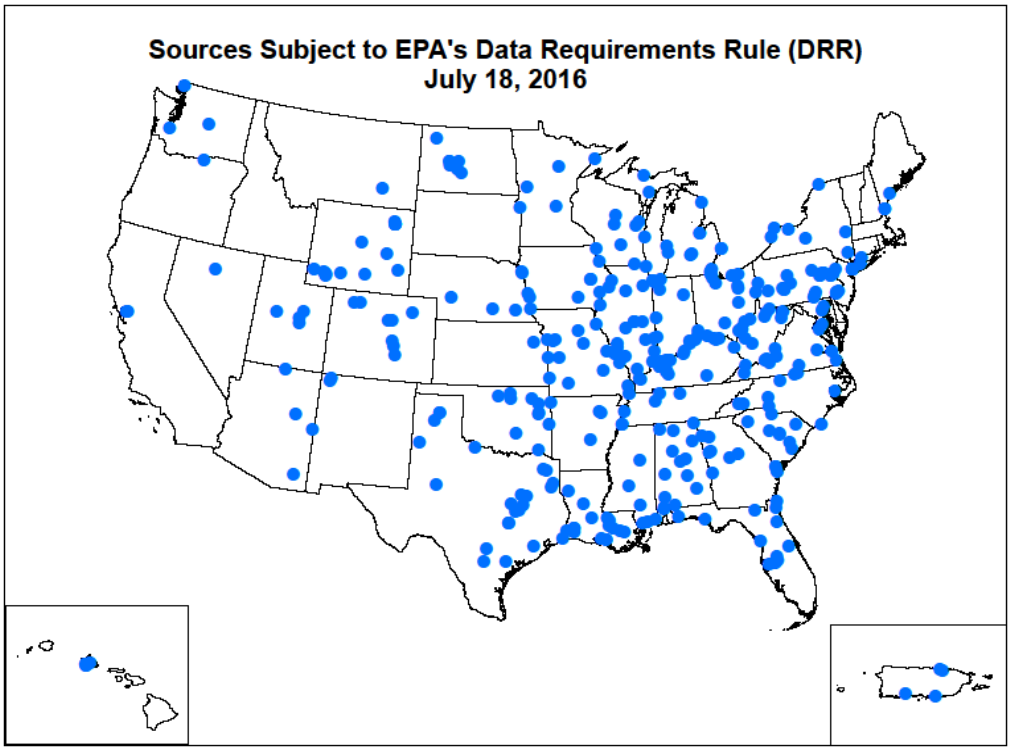
U.S. EPA Sulfur Dioxide Data Requirements Rule

Another source of information of large sources of SO_2 emissions is air agency submissions in response to a regulatory requirement concerning characterization of ambient SO_2 concentrations in areas with large sources of SO_2 emissions to help implement the 1-hour SO_2 NAAQS (CFR, 51.1202−51.1203; 80 FR50152, August 21, 2015). This regulation requires that, at a minimum, air agencies must characterize air quality around sources that emit 2,000 tons per year or more of SO_2. An air agency may avoid the requirement for air quality characterization near a source by adopting enforceable emission limits that ensure that the source will not emit more than 2,000 tpy. This final rule gives air agencies the flexibility to characterize air quality using either modeling of actual source emissions or using appropriately sited ambient air quality monitors. Under this requirement, air agencies submitted to the relevant EPA Regional Administrator a final list identifying the sources in the state around which SO_2 air quality is to be characterized. The list included sources with emissions above 2,000 tpy SO_2. The EPA Regional Offices or air agencies included additional sources on this list that they deemed necessary. The final list included 377 sources (https://www.epa.gov/so2-pollution/so2-data-requirements-rule-source-list). Figure 2-4 shows the locations of those sources.



Note: NAAQS = national ambient air quality standards; NEI = National Emissions Inventory; SO_2 = 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

Anthropogenic emissions of SO_2 in the U.S. have shown dramatic declines since the 1970s, and emissions reductions have accelerated since the 1990 amendments to the Clean Air Act were enacted (USC Title 42 Chapter 85). Table 2-1 gives the annual SO_2 emissions, percentage of the U.S. SO_2 total emissions, and change in emissions rate from 2004 to 2011. Figure 2-5 illustrates the emissions trends by sector from 1970 to 2011 in relation to the timeline over which the NAAQS for SO_2 and the Clean Air Act control programs [Acid Rain Program (ARP), NO_X Budget Program (NBP), and Clean Air Interstate Rule (CAIR)] have been implemented. Exceptions to the steep decline in SO_2 emissions in the listed sectors are the marked increases in emissions from the commercial storage and transport sectors and from miscellaneous, i.e. landscape fires. However,

commercial storage and transport contributes only 0.1% of total 2011 SO_2 emissions. Landscape fires are a larger contributor to the NEI (3%) and are discussed further in Section 2.2.4.3.

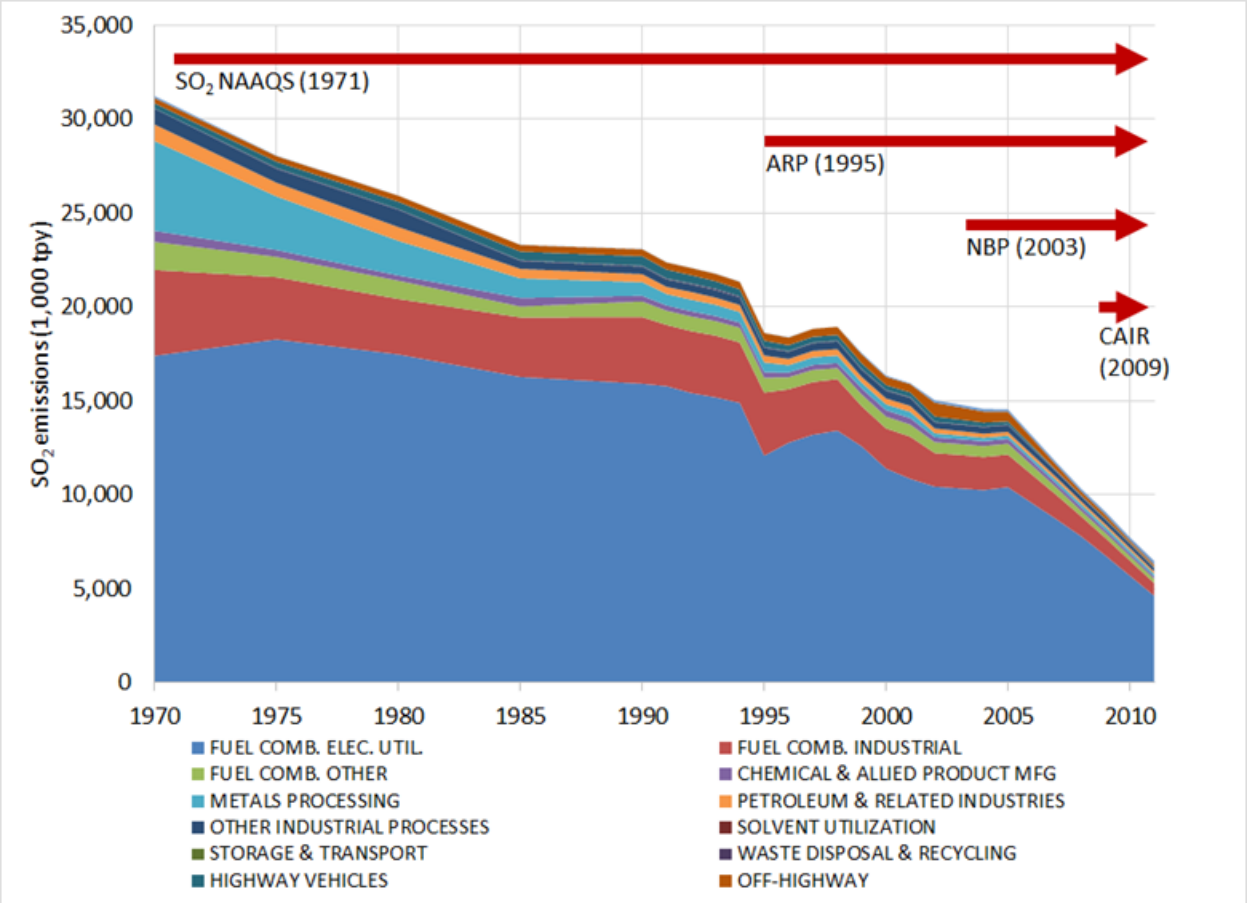
Hand et al. (2012) studied reductions in EGU-related annual SO_2 emissions during the period 2001−2010. They found that emissions decreased throughout the U.S. by 6.2% per year, with the largest reductions in the western U.S. at 20.1% per year. The smallest reduction (1.3% per year) occurred in the Great 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_X Budget Program; SO_2 = 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

This section provides an overview of the major natural sources of SO_2 and reduced sulfur compounds that are oxidized in the atmosphere to form SO_2. Section 2.2.4.1 briefly describes the elements of the global sulfur cycle. Section 2.2.4.2 briefly discusses volcanic sources of SO_2 within the U.S. Section 2.2.4.3 discusses SO_2 emissions by U.S. wildfires. Section 2.2.4 concludes with a brief summary of both anthropogenic and natural emissions of reduced sulfur gases that can serve as precursors to SO_2.

2.2.4.1 The Global Sulfur Cycle

The total budget for sulfur, in all its forms, at Earth's surface is on the order of 1.1×10^{16} tons S (Schlesinger, 1997). The sulfur cycle comprises the many chemical and biological processes that continuously interconvert the element between its four main oxidation states (−2, 0, +4, +6). The reduced form of sulfur is present in the environment in hydrogen sulfide, hydrogen disulfide, and a number of organic compounds. Oxidized sulfur is present primarily as SO_2 and sulfate (SO_4^{2-}).

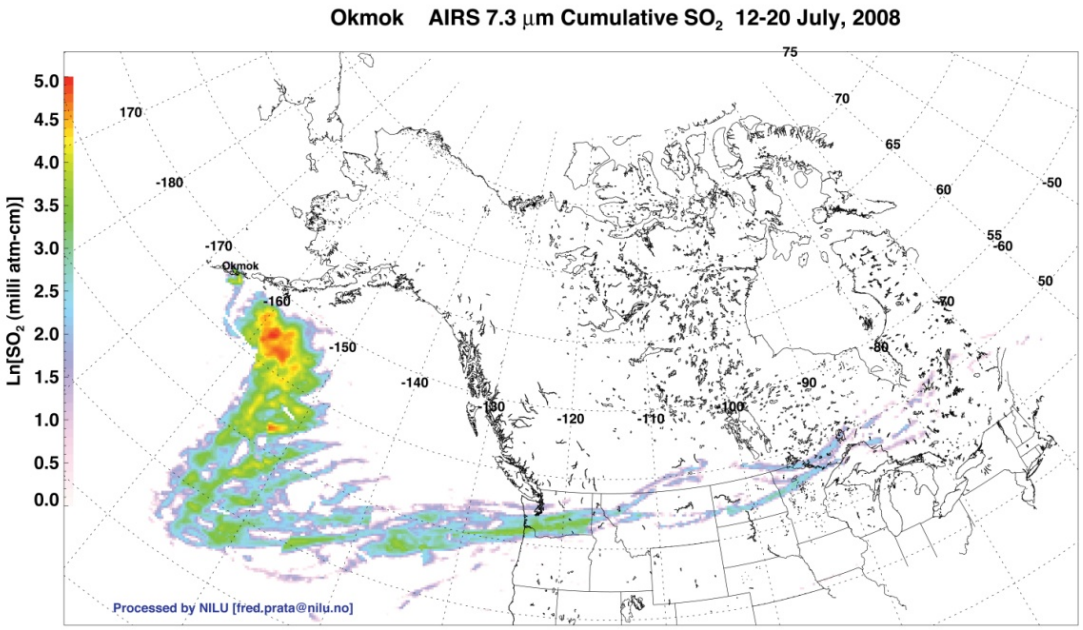
Volcanoes and wildfires are nonbiological natural sources that directly emit SO_2 to the atmosphere. Biological natural sources, together with volcanoes, emit reduced sulfur compounds that subsequently oxidize in the atmosphere to form SO_2. Under anaerobic conditions, various species of plants, fungi, and prokaryotes convert oxidized sulfur into its reduced forms (Madigan et al., 2006). Photosynthetic green and purple bacteria and some chemolithotrophs oxidize sulfides to form elemental sulfur. Some species oxidize elemental sulfur to form SO_4^{2-} and SO_2; others reduce elemental sulfur to sulfides (*dissimilative sulfur reduction*), while others are capable of reducing SO_4^{2-} all the way down to sulfide (*dissimilative SO_4^{2-} reduction*).

2.2.4.2 Volcanoes as a Natural Source of Sulfur Dioxide

Geologic activity, including fumaroles, geysers, and metamorphic degassing, emits a number of gases, including SO_2, carbon dioxide (CO_2), hydrogen sulfide (H_2S), hydrochloric acid, chlorine, and others (Simpson et al., 1999). Eruptive and noneruptive volcanoes are the most important sources of geologic SO_2 emissions. Noneruptive volcanoes outgas at relatively constant rates and appear to be more important than eruptive volcanoes as a source of SO_2. The emissions of eruptive volcanoes are sporadic, and therefore, vary from year to year (Simpson et al., 1999).

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

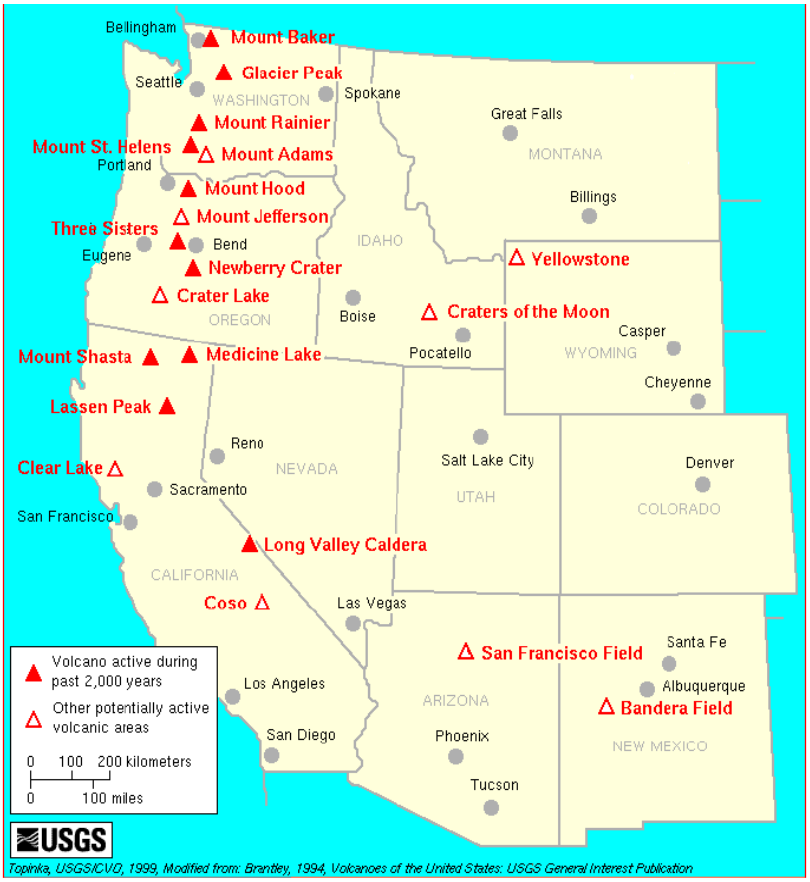
features at 4 and 7.3 μm, which allowed Prata et al. (2010) to calculate the total mass of SO_2 emitted during the eruption as 319,670 ± 11,023 tons.



AIRS = Atmospheric Infrared Sounder; 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).

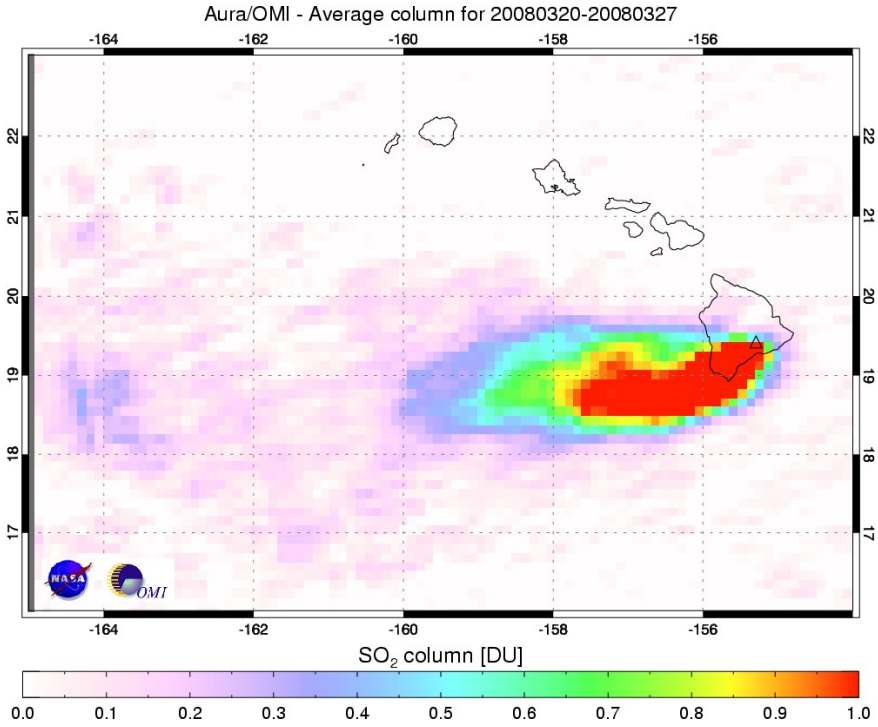
The line of volcanoes begins with the Aleutian Islands in Alaska and extends south and east through the states of Washington, Oregon, California, Arizona, and New Mexico, with outlying geologically active sites in Idaho (Craters of the Moon) and Wyoming (Yellowstone). Figure 2-7 shows the geographic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



Source: USGS (1999). Map courtesy of Lyn Topinka (1999, USGS / CVO), Modified from Steve Brantley (USGS 1994), Volcanos of the United States, USGS General Interest Pulication.

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

The state of Hawaii, located over a "hot spot" in the north-central portion of the Pacific tectonic plate, is a series of volcanic islands with one of the world's most active volcanoes, Kīlauea, located on the Big Island of Hawaii. Kīlauea might typically be described as a noneruptive volcano, emitting SO_2 at a steady rate. In mid-March of 2008, the volcano experienced a small explosion followed by a two- to fourfold increase in SO_2 emissions. The Ozone Monitoring Instrument (OMI) aboard the NASA Aura satellite detected this increase in SO_2 emissions. Figure 2-8 shows the average concentration of SO_2 in the evolving plume for the March 20−27, 2008 period. Persistent easterly trade winds moved the plume westward, away from populated areas.



DU = Dobson units; OMI = Ozone Monitoring Instrument; SO_2 = sulfur dioxide.

Note: A DU is approximately equivalent to a total column concentration of 1 ppbv of SO_2. 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 Kīlauea sulfur dioxide plume during its March 20−27, 2008 eruption.

In another study using SO_2 column densities derived from GOME-2 satellite measurements for the period 2007−2012, Beirle et al. (2013) determined Kīlauea's monthly mean SO_2 emission rates and effective SO_2 lifetimes. For the March through November, 2008 period, the authors reported Kīlauea's SO_2 emission rates as 8,818−20,943 tons/day and the effective SO_2 lifetime as 1−2 days. Several studies have estimated the global SO_2 emissions of sulfur by volcanoes to be in the range of 7.7 x 10^6−2.0 x 10^7 tpy (Chin et al., 2000; Feichter et al., 1996; Pham et al., 1996; Langner and Rodhe, 1991).

2.2.4.3 Wildfires as a Natural Source of Sulfur Dioxide

Sulfur is a component of amino acids in vegetation and is released during combustion, mainly in the form of SO_2. Using satellite data from various sources, including the

Moderate Resolution Imaging Spectroradiometer (MODIS) Thermal Anomalies Product, the Global Land Cover Characteristics 2000 data set, and the MODIS Vegetation Continuous Fields Product in conjunction with the literature to determine fire location and timing, fuel loadings, and emission factors, Wiedinmyer et al. (2006) estimated SO_2 emissions from fires for the U.S. at 176,370 tons in the year 2004. Canadian fires emitted 121,254 tons, and Mexican fires emitted 55,116 tons of SO_2 for the same period. However, wildfire emissions do vary from year to year. Emissions estimates for SO_2 derived from global modeling studies of wildfire range between 5.1×10^6–6.3×10^6 tpy SO_2 (Chin et al., 2000; Feichter et al., 1996; Pham et al., 1996; Langner and Rodhe, 1991).

Projected increases in wildfire frequency and intensity under warming climate conditions imply increasing wildfire-related SO_2 emissions. However, these estimates are highly uncertain due to the lack of data on the sensitivity of emissions composition with respect to the effects of climate change on landscape species composition and burning conditions. For comparison, the 2011 NEI also includes an estimate for agricultural and prescribed burning emissions at 99,208 tpy, which is about half of the estimated SO_2 emissions from wildfires (U.S. EPA, 2013a).

2.2.5 Reduced Sulfur Compounds as Indirect Sources of Sulfur Dioxide

Sulfides, including H_2S, carbonyl sulfide (OCS), carbon disulfide (CS_2), methylmercaptan (CH_3SH), dimethyl sulfide (DMS), and dimethyl disulfide (DMDS), are emitted from energy production, industrial activities, agriculture, and various ecosystems, especially coastal wetland systems, inland soils, and oceans. In addition to SO_2, volcanoes release sulfides, specifically H_2S, OCS, and CS_2. As described in Section 2.3, all of these gases, with the exception of OCS, have short atmospheric lifetimes, given their high rates of reaction with hydroxyl radicals and given the high rates of reaction of nitrate radicals (NO_3) with SO_2 as a reaction product. Table 2-2 provides a list of the natural and anthropogenic sources of the five main organosulfides. Dimethyl sulfide is particularly important, both for the large role it plays as a source of atmospheric sulfur and for its role in initiating the formation of marine clouds.

Table 2-2 Global sulfide emissions in tpy sulfur.

Sources	OCS	CS_2	CH_3SH	DMS	DMDS
Seawater and marshes	3.4×10^5	2.68×10^5	5.22×10^6	3.11×10^7	2.35×10^5
Vegetation and soils		7.72×10^4	1.91×10^6	3.83×10^6	9.57×10^5
Volcanoes	1.21×10^4	1.87×10^4			
Atmospheric oxidation	5.10×10^5				
Biomass burning (all types)	5.07×10^4	2.03×10^3		6.61×10^3	1.31×10^5
Pulp and paper industry	1.07×10^5	8.65×10^4	1.85×10^6	1.61×10^6	3.01×10^5
Rayon/cellulosics manufacture		1.17×10^6	1.52×10^5	1.05×10^5	
Manure			3.64×10^5	7.28×10^5	7.28×10^5
Paddy fields	4.19×10^2	2.97×10^4	8.38×10^2	2.76×10^4	6.28×10^2
Pigment industry	8.16×10^4	2.26×10^5			
Food processing and waste	6.94×10^2			4.38×10^3	3.19×10^4
Gas industry	7.72×10^2		5.29×10^3	9.26×10^2	1.10×10^2
Wastewater	3.75×10^1	1.14×10^3	7.17×10^4	6.17×10^3	2.98×10^4
Aluminum industry	9.70×10^4	4.41×10^3			
Coal combustion	1.80×10^4	3.64×10^2			
Coke production	9.92×10^3	1.54×10^4			
Biofuel combustion	5.16×10^4	2.09×10^3			
Vehicles	6.61×10^3	3.31×10^2			
Shipping	3.31×10^4	1.65×10^3			
Tire wear	1.87×10^3	2.54×10^3			
Tire combustion	3.31	6.61×10^{-2}			
Landfill	8.71×10^1	2.09×10^2	3.75×10^2	2.87×10^2	8.82
Brick making		3.31×10^2			
Total global sources	1.33×10^6	1.90×10^6	9.58×10^6	3.74×10^7	2.41×10^6

CH_3SH = methylmercaptan; CS_2 = carbon disulfide; DMDS = dimethyl disulfide; DMS = dimethylsulfide; OCS = carbonyl sulfide.
Adapted from (Lee and Brimblecombe, 2016).

Dimethyl sulfide (DMS) is the most abundant reduced sulfur gas. It has appreciable anthropogenic sources (pulp and paper production, agricultural operations), but these are dwarfed by the quantity emitted by natural biological activity. Natural emissions of dimethyl sulfide originate with the breakdown of dimethyl sulfoniopropionate, a metabolite of the amino acid, methionine, produced by marine organisms living in upwelling or coastal zones and by anaerobic bacteria in marshes and estuaries. The oxidation of dimethyl sulfide contributes to low-level background SO_2 concentrations in coastal environments. Lee and Brimblecombe (2016) provide a literature-derived global estimate of DMS emissions from seawater and marshland of 3.1 x 10^7 tpy S. Earlier estimates for seawater DMS emissions range widely from 6.1 x 10^6 to 2.4 x 10^7 tpy (Liu et al., 2005; Chin et al., 2000; Feichter et al., 1996; Pham et al., 1996; Langner and Rodhe, 1991). A warming climate may have a complex feedback effect on DMS emissions, influencing both ocean surface temperatures and currents controlling nutrient dispersion that impact the population and location of DMS producing phytoplankton (Kloster et al., 2007).

2.3 Atmospheric Chemistry and Fate

Known sulfur oxides in the troposphere include SO_2 and SO_3 (U.S. EPA, 2008d). SO_3 can be emitted by power plants and factories, but it reacts within seconds with water in the stacks or immediately after release into the atmosphere to form H_2SO_4. Gas-phase sulfuric acid quickly condenses onto existing particles or participates in new particle formation (Finlayson-Pitts and Pitts, 2000). Of those species, only SO_2 is present at concentrations relevant for chemistry in the troposphere, boundary layer, and for human exposures.

This section provides an overview of the primary atmospheric chemistry and removal processes for SO_2 of relevance to atmospheric concentrations at urban scales. Section 2.3.1 describes the photochemical reactions that remove SO_2 from the atmosphere by converting it into compounds that condense into the particle or cloud water phase. Section 2.3.2 describes the aqueous-phase oxidation of SO_2, the major oxidation mechanism in the atmosphere, as well as dry and wet deposition of SO_2.

2.3.1 Photochemical Removal of Atmospheric SO_2

The atmospheric lifetime (τ) of SO_2 with respect to reactions with the OH radical in the troposphere is 7.2 days. The rate constant for the reaction between SO_2 and NO_3 radical is

too small to be of any importance in the reduction of SO_2 concentrations at urban or regional scales. The same is true for the reaction between SO_2 and the hydroperoxyl (HO_2) radical (Sander et al., 2011).

In the stepwise oxidation of SO_2 by OH, SO_2 is oxidized to form SO_3, taking the sulfur atom from the S(IV) to S(VI) oxidation state, producing the bisulfite radical (HSO_3):

$$SO_2 + OH + M \rightarrow HSO_3 + M$$

Equation 2-1

where M is an unreactive gas molecule that absorbs excess, destabilizing energy from the SO_2-OH transition state. This reaction is followed by

$$HSO_3 + O_2 \rightarrow SO_3 + HO_2$$

Equation 2-2

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

$$SO_2 + sCI \rightarrow SO_3 + products$$

Equation 2-3

The unspecified "products" of this reaction are other organic radicals derived from the degradation of the Criegee intermediate (Berndt et al., 2012; Mauldin et al., 2012; Welz et al., 2012). Rate coefficients for the reaction of sCIs with SO_2 have been reported as 4×10^{-15} cm^3/sec (Johnson et al., 2001), approximately 3.5×10^{-11} cm^3/sec (Liu et al., 2014b), and 3.9×10^{-11} cm^3/sec (Welz et al., 2012). Recent studies report rate coefficients greater than 3×10^{-11} cm^3/sec (Friedman et al., 2016; Lee, 2015; Berndt et al., 2012). These reaction rate coefficients far exceed those of the reactions between these intermediates and H_2O. However, hydrolysis of SO_2 could be limited if sCIs that are potential SO_2 oxidants are hydrolyzed via competing reactions (Kim et al., 2015).
The efficiency of Criegee radical hydrolysis is sensitive to the molecular structure of the alkene. Bimolecular hydrolysis rates constants vary by a factor of 1,000 between syn- versus anti-substituted low molecular weight alkenes (Lin and Takahashi, 2016).

Criegee radicals are produced by the reaction of alkenes with O_3 during both night and day. The relative importance of the OH and sCI pathways depends in large measure on the local concentration of alkenes, such as low molecular weight alkenes emitted by motor vehicles and industrial processes as well terpenoids emitted by trees.
The importance of this mechanism as a sink for SO_2 is supported by observations that areas adjacent to SO_2 sources, with high biogenic or industrial VOC concentrations, have elevated organic PM concentrations (Friedman et al., 2016). However, limited information on the identity and concentrations of alkenes at urban scales prevents estimates of the impact of this reaction pathway on urban SO_2 concentrations.

The SO_3 that is generated by either oxidation mechanism (i.e., reaction with OH or via the Criegee reaction mechanism) is a highly reactive species. Water vapor is sufficiently abundant in the troposphere to ensure that SO_3 is quickly converted to gas-phase sulfuric acid, as shown in the equation below (Loerting and Liedl, 2000).

$$SO_3 + H_2O + M \rightarrow H_2SO_4 + M$$

Equation 2-4

Because H_2SO_4 is extremely water soluble, gaseous H_2SO_4 will be removed rapidly by dissolution into the aqueous phase of aerosol particles and cloud droplets. In a study of SO_2 plume transport in and out of foggy conditions, Eatough et al. (1984) observed that roughly 30% of the SO_2 converts to H_2SO_4 particulate each hour when inside a fog bank and roughly 3.1% per hour outside a fog bank. Khoder (2002) observed that conversion from SO_2 to H_2SO_4 increases with increasing relative humidity and increasing O_3, based on a sampling campaign in an urban area of Egypt. Pearson correlation of SO_2-to-H_2SO_4 conversion ratio with relative humidity was 0.81 in the winter and 0.89 in the summer. Hung and Hoffmann (2015) recently conducted spray chamber experiments of SO_2 to H_2SO_4 conversion. They observed that SO_2 deposited to the surfaces of water microdroplets and then underwent rapid oxidation, first to HSO_3^- and HSO_4^-, and then to SO_4^{2-}. Acidic conditions promoted more rapid oxidation of SO_2.

2.3.2 Heterogeneous Oxidation of Sulfur Dioxide

The major sulfur-containing species in clouds are the HSO_3^- and SO_3^{2-} (sulfite) ions that form when SO_2 dissolves in cloud droplets and subsequently undergoes acid dissociation. Both exist in the S(IV) oxidation state, which readily oxidizes in the presence of aqueous-phase oxidizing agents to form the S(VI) anions, HSO_4^- (bisulfate), and SO_4^{2-}. The major species capable of oxidizing S(IV) to S(VI) in cloud water are O_3, peroxides [either hydrogen peroxide (H_2O_2) or organic peroxides], OH radicals, and transition metal ions such as Fe and Cu that catalyze the oxidation of S(IV) to S(VI) by O_2.

The basic mechanism of the aqueous-phase oxidation of SO_2 can be found in numerous texts on atmospheric chemistry [e.g., (Seinfeld and Pandis, 2006; Jacobson, 2002; Finlayson-Pitts and Pitts, 2000; Jacob, 1999)]. Similar initial steps occur in the fluids lining the airways (Section 4.2.1). The steps involved in the aqueous phase oxidation of SO_2 are summarized below (Jacobson, 2002).

Dissolution of SO_2 occurs first,

$$SO_2(g) \Leftrightarrow SO_2(aq)$$

Equation 2-5

followed by the formation and dissociation of sulfurous acid (H_2SO_3).

$$SO_2(aq) + H_2O(l) \Leftrightarrow H_2SO_3 \Leftrightarrow H^+ + HSO_3^- \Leftrightarrow 2H^+ + SO_3^{2-}$$

Equation 2-6

In the pH range commonly found in rainwater (2 to 6), H_2O_2 will oxidize HSO_3^- to SO_4^{2-}.

$$HSO_3^- + H_2O_2 + H^+ \rightarrow SO_4^{2-} + H_2O + 2H^+$$

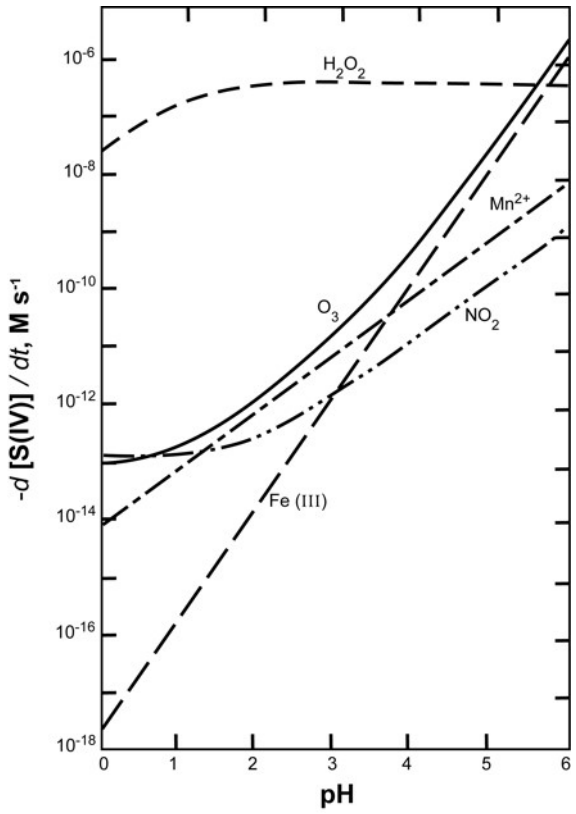
Equation 2-7

The rates of aqueous-phase oxidation of S(IV) to S(VI) as a function of pH are shown in Figure 2-9. For pH values up to about 5.3, H_2O_2 is the predominant oxidant; above pH 5.3, O_3, followed by Fe(III), becomes predominant.

Ambient ammonia (NH_3) vapor readily dissolves in acidic cloud drops to form ammonium (NH_4^+). Because NH_4^+ is very effective in controlling acidity, it amplifies the rate of oxidation of S(IV) to S(VI) and the rate of dissolution of SO_2 in particles and cloud droplets. Therefore, in environments where NH_3 is abundant, SO_2 is subject to fast removal by cloud and fog droplets and ultimately forms ammonium sulfate [$(NH_4)_2SO_4$].

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

In the same way that it is removed from the gas phase by dissolution into cloud droplets, SO_2 can be removed by dry deposition onto wet surfaces (Shadwick and Sickles, 2004; Clarke et al., 1997). For example, in the eastern U.S., SO_2 is responsible for more than 85% of dry sulfur deposition (Sickles and Shadwick, 2007). However, aqueous SO_4^{2-} may be removed through occult deposition of large fog or cloud droplets (Lillis et al., 1999; Pandis and Seinfeld, 1989; Dollard et al., 1983). Scavenging by rain (wet deposition) serves as another removal route. Modeling studies have shown that slightly more than half of SO_2 in both models is lost by gas- and aqueous-phase oxidation, with the remainder of SO_2 loss accounted for by wet and dry deposition (Long et al., 2013; Liu et al., 2012a).



Fe = iron; H_2O_2 = hydrogen peroxide; Mn^{2+} = manganese ion; NO_2 = nitrogen dioxide; O_3 = 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: $[SO_2(g)]$ = 5 ppb; $[NO_2(g)]$ = 1 ppb; $[H_2O_2(g)]$ = 1 ppb; $[O_3(g)]$ = 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.

Sulfur dioxide is known to adhere to and then react on dust particles. Very recent investigations have shown that, for some mineral compositions, SO_2 uptake on dust particles is sensitive to relative humidity, the mineral composition of the particle, and the availability of H_2O_2, the relevant oxidant (Huang et al., 2015b). Once SO_2 is oxidized to H_2SO_4 on the particle surface, glyoxyl, one of the most prevalent organic compounds in the atmosphere, will adhere to the surface and react to form oligomers and organosulfate compounds. This process is enhanced under high humidity conditions (Shen et al., 2016).

2.4 Measurement Methods

This section discusses the federal reference method (FRM) and federal equivalent method (FEM) used for NAAQS compliance as well as the state, local, and tribal monitoring networks across the U.S. used for NAAQS compliance monitoring. Detailed information about monitoring methods, including accuracy, precision, limits of detection, and other operational parameters was published in the 1982 Air Quality Criteria for Particulate Matter and Sulfur Oxides Volume II (U.S. EPA, 1982a) and then updated in Appendix B.6 of the 2008 ISA for Sulfur Oxides—Health Criteria (U.S. EPA, 2008d). The List of Designated Reference and Equivalent Methods (U.S. EPA, 2016f) lists all monitors approved as FRMs or FEMs and provides monitor specifications. A brief summary of that information, along with a discussion of more recent studies evaluating FRMs and FEMs for monitoring SO_2 concentration (Section 2.4.1) or alternative SO_2 monitoring methods (Section 2.4.2), is provided. Section 2.4.3 describes the sampling network.

2.4.1 Federal Reference and Equivalent Methods

Currently, there are two FRMs for the measurement of SO_2—the manual pararosaniline wet-chemistry method and the automated pulsed ultraviolet fluorescence (UVF) method. The manual method was approved as an FRM in the 1970s and was quickly replaced by the flame photometric detection (FPD) method, an FEM because the manual method was too complex and had a slow response even in automated form. The UVF method was designated as an FEM in the late 1970s and ultimately replaced the FPD method. The UVF method is inherently linear and relatively safe whereas the FPD method requires highly flammable hydrogen gas. The UVF method has been the most commonly used method by state and local monitoring agencies since the 1980s. It was added as an FRM as a result of the new 1-hour SO_2 primary NAAQS established in 2010 (75 FR 35520). The UVF method supports the need for a continuous monitoring method, as it can easily provide 1-hour SO_2 measurements. The existing pararosaniline manual method was retained as a FRM, and although cumbersome, the method can provide hourly measurements to support the 1-hour NAAQS.

In the UVF method, SO_2 molecules absorb UV light at one wavelength and emit UV light at longer wavelengths through excitation of the SO_2 molecule to a higher energy electronic state. Once excited, the molecule loses a portion of its energy by collision with another gas molecule and, then by emitting a photon of light at a longer wavelength which returns to its electronic ground state. The intensity of the emitted light is, therefore, proportional to the number of SO_2 molecules in the sample gas. In commercial analyzers,

light from a high-intensity UV lamp passes through a bandwidth filter that allows only photons with wavelengths around the SO_2 absorption peak (near 214 nm) to enter the optical chamber. The light passing through the source bandwidth filter is collimated using a UV lens and passes through the optical chamber, where it is detected on the opposite side of the chamber by the reference detector. A detector is offset from and placed perpendicular to the light path to detect the SO_2 fluorescence. Because the SO_2 fluorescence at about 330 nm is different from its excitation wavelength, an optical bandwidth filter is placed in front of the detector to filter out any stray light from the UV lamp. A lens is located between the filter and the detector to focus the fluorescence onto the active area of the detector and optimize the fluorescence signal. A particulate filter is also placed after the sample inlet to prevent damage, malfunction, and interference from particles in the sampled air.

Studies have compared UVF to sampled SO_2 from impregnated filters for quality assurance. Comparison of 24-h avg concentration measurements obtained with the UVF method and with impregnated filters showed annual-average differences within ±0.07 ppb, based on data obtained between 1993 and 2001 from four Finnish cities (Leppänen et al., 2005). Ferek et al. (1997) evaluated the Teco model UVF (developed at the University of Washington) against carbonate-impregnated filters for measurement of SO_2 concentration in laboratory studies. The Teco UVF measured SO_2 concentrations down to 16 ppt and, on average, produced a positive difference of 7% compared with the filter. The Teco UVF analyzed data at a frequency as high as 1 Hz, but noise was curtailed by averaging up to 10 minutes. The Ferek et al. (1997) study highlighted the Teco UVF but also included other SO_2 measurement techniques in the SO_2 monitor comparison, including gas spectrometry/mass spectrometry, high performance liquid chromatography, and a mist chamber, which produced a maximum of 30% differences for filter-measured SO_2 concentrations of 3−4 ppb averaged over 90 minutes.

2.4.1.1 Minimum Performance Specifications

Minimum performance specifications [in accordance with 40 Code of Federal Regulations (CFR) Part 53] were made more stringent for any new FRM and FEM automated method with the addition of the UVF method as an FRM. The new specifications are provided in Table 2-3. The previous specifications were based on the older, manual, wet-chemistry FRM and were updated to reflect current technology and improved performance in SO_2 instrumentation. The lower detection limit (LDL) for a routine, automated SO_2 analyzer is required to be 2 ppb. As part of the National Core (NCore) monitoring network, new trace-level SO_2 instruments have been developed and added to State and Local Air Monitoring Sites (SLAMS). These new trace-level (i.e., low

LDL) instruments have LDLs of 0.2 ppb or lower. Note that FRMs and FEMs may have more stringent performance characteristics than the minimum performance specifications 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 (*two times the noise*)	0.002 ppm (2 ppb)
Interference equivalent • Each interferent • Total, all interferents	 ±0.005 ppm (5 ppb) —
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 • 80% of upper range limit	 2.0% 2.0%

2.4.1.2 Positive and Negative Interferences

The UVF method has a number of positive and negative interferences. The most frequent source of positive interference is other gases that fluoresce at the same wavelength as SO_2. The most common gases include volatile organic compounds (e.g., xylenes, benzene, toluene) and polycyclic aromatic hydrocarbons (PAHs; e.g., naphthalene). To reduce this source of positive interference, high-sensitivity SO_2 analyzers are equipped with scrubbers or “kickers” to remove these compounds from the air stream

prior to entering the optical chamber. Luke (1997) evaluated a modified pulsed fluorescence SO_2 detector and found positive interference from nitric oxide (NO), CS_2, and several highly fluorescent aromatic hydrocarbons such as benzene, toluene, *o*-xylene, *m*-xylene, *p*-xylene, *m*-ethyltoluene, ethylbenzene, and 1,2,4-trimethylbenzene. The positive artifacts could be virtually eliminated by using a hydrocarbon "kicker" membrane. At a flow rate of 300 standard cm^3/minute and a pressure drop of 645 torr across the membrane, the interference from ppm levels of many aromatic hydrocarbons can be eliminated.

Another source of positive interference is NO, which fluoresces in a region close to that of SO_2. However, in high-sensitivity SO_2 analyzers, the bandpass filter in front of the detector is specifically designed to prevent detection of NO fluorescence at the detector. Care must be exercised when using multicomponent calibration gases containing both NO and SO_2, so that the NO rejection ratio of the SO_2 analyzer is sufficient to prevent NO interference.

The most common source of positive bias in high-sensitivity SO_2 analyzers is stray light in the optical chamber. Because SO_2 can be excited by a broad range of UV wavelengths, any stray light entering the optical chamber with an appropriate wavelength can excite SO_2 in the air stream and increase the fluorescence signal. Additionally, stray light entering the optical chamber with a similar wavelength of SO_2 fluorescence may impinge on the detector and increase the fluorescence signal. Stray light is also minimized with changes in instrument design such as use of light filters, dark surfaces, and opaque tubing.

H_2O is a common source of negative interference in high-sensitivity SO_2 monitors. When excited SO_2 molecules collide with water vapor as well as other common molecules in air (e.g., nitrogen and oxygen), nonradiative deactivation (quenching) can occur. During collisional quenching, the excited SO_2 molecule transfers energy, kinetically allowing the SO_2 molecule to return to a lower energy state without emitting a photon. Collisional quenching decreases the SO_2 fluorescence and results in an underestimation of SO_2 concentration in the air sample. Of particular concern is the variable water vapor content of air. Luke (1997) reported that the response of the detector could be reduced by an amount of approximately 7 to 15% at water vapor mixing ratios of 1 to 1.5 mole percent [relative humidity (RH) = 35 to 50% at 20 to 25°C and 1 atmosphere for a modified pulsed fluorescence detector (Thermo Environmental Instruments, Model 43s)]. Condensation of water vapor in sampling lines must be avoided, as water on the inlet surfaces can absorb SO_2 from the sample air. Condensation is normally prevented by heating sampling lines to a temperature above the expected dew point and to within a few degrees of the controlled optical bench temperature. Some monitors are equipped with a

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

2.4.2 Alternative Sulfur Dioxide Measurements

A number of optical methods for measuring SO_2 are available. They include laser induced fluorescence (LIF), cavity ring-down spectroscopy (CRDS), differential optical absorption spectrometry (DOAS), and UV absorption. There are also methods based on mass spectroscopy or mass spectrometry [e.g., chemical ionization mass spectroscopy (CIMS) and atmospheric pressure ionization mass spectrometry (APIMS)]. These methods are often too expensive and complex for routine monitoring applications and are more suitable for source monitoring. However, approaches to reduce interferences and increase SO_2 selectivity could be extended to FRM and FEM instrumentation. The LIF, CRDS, and DOAS methods will be discussed below as they have the potential to provide trace-level SO_2 measurements or have shown good agreement with UVF instrumentation.

LIF is a technique that can provide high sensitivity for ambient SO_2 measurements and reduces interferences with species that fluoresce at the same wavelength as SO_2. Both tunable and nontunable laser sources have been evaluated. Matsumi et al. (2005) evaluated a LIF method using a tunable laser at an SO_2 absorption peak at 220.6 nm and trough at 220.2 nm. The difference between the signals at the two wavelengths is used to estimate the SO_2 concentration. This technique has a sensitivity of 5 ppt in 60 sec. Simeonsson et al. (2012) evaluated a direct LIF technique using a nontunable laser source at an absorption wavelength of 223 nm, which coincides with the SO_2 absorption peak. This technique has a high sensitivity with LDL of 0.5 ppb. Both the tunable and nontunable instruments have low LDL ($\leq$0.5 ppb); therefore, they can provide trace-level SO_2 measurements.

CRDS is an optical absorption method based on measurement of the rate of light absorption through a sample. CRDS has successfully been used to measure ambient NO_2 and NO with high sensitivity. Medina et al. (2011) compared a CRDS-tunable laser method to the routinely used pulsed ultraviolet fluorescence (UVF) method for measuring SO_2. At an absorption wavelength of 308 nm, the CRDS had an LDL of 3.5 ppb, which was higher than those for routine and trace-level UVF SO_2 monitors (e.g., Thermo Scientific 43i and Thermo Scientific 43i-TLE). However, the response time was faster compared to the UVF methods (a few seconds vs. 80 sec). To reduce interferences, a ferrous sulfate scrubber was used to remove NO_2 and O_3, and a denuder was used to zero SO_2 levels. Improvements could be made to increase the sensitivity to about 1 ppb by changing the placement of the mirrors to optimize laser light reaching the cavity or using

a better detection system. Additionally, improving the mirror reflectivity could improve the sensitivity to about 0.1 ppb, similar to the detection levels of trace-level SO_2 monitors.

DOAS is an optical remote sensing method based on the absorption of light in the UV-visible wavelength region to measure atmospheric pollutants. Kim and Kim (2001) compared SO_2 concentrations measured using a DOAS system with daily mean SO_2 concentrations measured by an in situ monitor in Seoul, Korea during a 13-month period. In this study, the DOAS typically reported SO_2 concentrations around 10−40% above the in situ technique, but SO_2 concentrations measured by the DOAS were sometimes 100−200% below those measured with the in situ monitor. Across all measurements, the daily mean SO_2 concentration was 36% higher from the DOAS compared with the in situ monitor. Discrepancies between the two methods were attributed to ability to respond to meteorological factors. The DOAS was reported to have an LDL of 0.07 ppb, compared with 1 ppb reported for the in situ method. A newer technique called multiaxis differential optical absorption spectroscopy (MAX-DOAS) has been developed that offers increased sensitivity in measuring SO_2 (Honninger et al., 2004). MAX-DOAS is based on the measurement of scattered sunlight at multiple viewing directions and can obtain both surface concentrations and vertical column density of SO_2. Wang et al. (2014b) compared MAX-DOAS SO_2 column measurements in the 305 to 317.5 nm absorption wavelength to surface SO_2 measurements from a modified UVF SO_2 monitor (Thermo Environmental Instruments Model 43C) and found good agreement (r = 0.81, slope = 0.90).

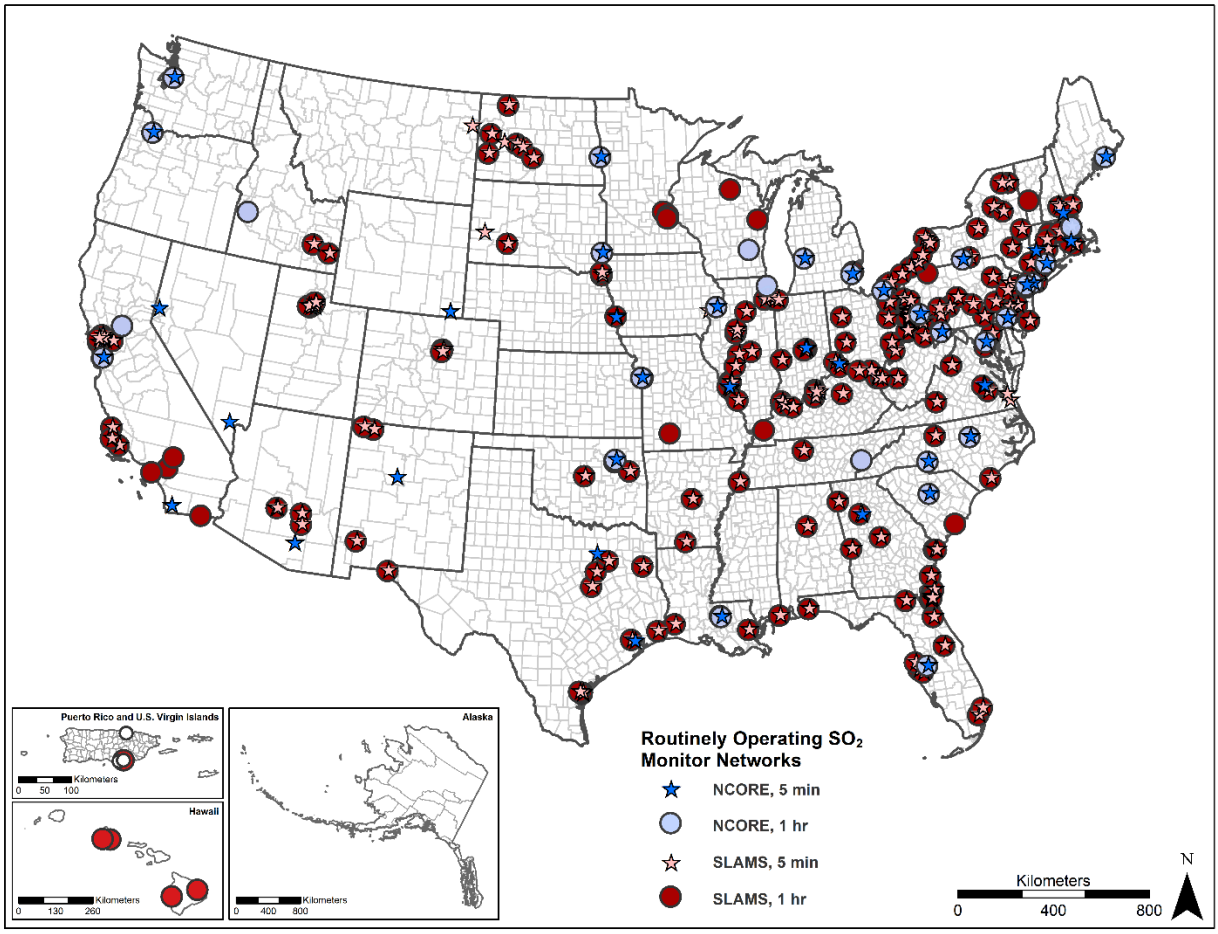
Remote sensing by satellites (e.g., OMI, infrared atmospheric sounding interferometer, etc.) is an emerging technique for measuring SO_2 as well as other pollutants. This technique can be used for a variety of applications, including air quality management (e.g., augmenting ground-based monitors, assessing emissions inventories), studying pollutant transport, assessing emissions reductions, and evaluating air quality models. Remote sensing methods employ a retrieval system using a combination of solar backscatter or thermal infrared emission spectra and mathematical algorithms to estimate pollutant concentrations. Remote sensing from space is particularly challenging for SO_2 measurements for two reasons: (1) air scattering causes SO_2 to have a low optical thickness (three orders of magnitude lower than O_3), so that only large SO_2 sources can be observed (Bogumil et al., 2003) and (2) emissions reductions programs have led to lower SO_2 emissions from stationary sources, making it more difficult to see anthropogenic SO_2 emissions (Streets et al., 2014). The majority of remote sensing studies have focused on large natural sources (e.g., volcanoes), large anthropogenic sources (e.g., coal-burning power plants, smelters), fuel extraction from oil sands, and newly constructed coal-burning facilities with high, uncontrolled SO_2 emissions

(Boynard et al., 2014; McCormick et al., 2014; Streets et al., 2014; Clarisse et al., 2012; McLinden et al., 2012; Fioletov et al., 2011; Nowlan et al., 2011; Bobrowski et al., 2010; Li et al., 2010; Khokhar et al., 2008; Carn et al., 2007).

2.4.3 Ambient Sampling Network Design

Compliance with NAAQS is primarily carried out through the SLAMS network, although modeling may also be used to characterize air quality for implementation purposes (75 FR 35520). There are 438 SLAMS sites reporting 1-hour SO_2 concentrations to the Air Quality System (AQS), U.S. EPA's repository for detailed air pollution data that is subject to quality control and assurance procedures. In addition to their use in compliance evaluations, some of these sites function as central monitoring sites for use in epidemiological studies. The SLAMS network also reports either the maximum 5-minute concentration in the hour (one of twelve 5-minute periods within an hour) or all twelve 5-minute average SO_2 concentrations within the hour. Siting requirements for monitors in the SLAMS network can be found in 40 CFR Part 58, Appendix E.

The SLAMS network includes the NCore monitoring network, which began January 1, 2011 and consists of 80 sites (63 urban and 17 rural). NCore is a multipollutant measurement network and includes SO_2 measurements as well as measurements for other gaseous pollutants (O_3, CO, NO_X, oxides of nitrogen), $PM_{2.5}$, $PM_{10-2.5}$, and meteorology. NCore is focused on characterizing trends in pollutants, understanding pollutant transport in urban and rural areas, and evaluating data with respect to the NAAQS. Figure 2-10 shows the locations of these monitoring networks across the U.S. The Clean Air Status and Trends Network (CASTNet) also measures ambient SO_2. However, these data are not used for NAAQS compliance purposes and are obtained predominantly in National Parks or other ecologically sensitive sites. Because CASTNet monitors are not deployed in populated areas, they are not useful in evaluating the health effects of SO_2. This network provides weekly averages of total sulfur (dry SO_2, dry SO_4^{2-}, and wet SO_4^{2-}) in about 90 sites located in or near rural locations to assess long-term trends in acidic deposition due to emission reduction programs. CASTNet data are presented in the Integrated Science Assessment for Oxides of Nitrogen and Sulfur—Ecological Criteria (U.S. EPA, 2008b).



NCORE = National Core; SLAMS = State and Local Air Monitoring Sites; SO_2 = 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.

The minimum monitoring requirements for the SLAMS network are outlined in 40 CFR Part 58, Appendix D. SO_2 monitors at SLAMS sites represent four main spatial scales: (1) microscale—areas in close proximity, up to 100 m from a SO_2 point or area source, (2) middle scale—areas up to several city blocks, with linear dimensions of about 100 to 500 m, (3) neighborhood scale—areas with linear dimensions of 0.5 to 4 km, and (4) urban scale—urban areas with linear dimensions of 4 to 50 km. Microscale, middle-scale, and neighborhood-scale sites are used to determine maximum hourly SO_2 concentrations because these sites are close to stationary point and area sources, whereas neighborhood- and urban-scale sites are used as central monitoring sites to characterize population exposures and trends, such as in epidemiologic studies (Section 3.2.1).

Urban-scale sites can also be used to determine background concentrations in areas where monitors are located upwind of a local source. There are also a number of regional-scale monitoring sites, representing length scales of tens to hundreds of kilometers, typically in rural areas of uniform geography without large SO_2 sources. These sites can be used to determine the amount of regional pollution transport and to support secondary NAAQS.

Stationary sources are the primary emission sources of SO_2. Prior to the revised SO_2 primary NAAQS in 2010, U.S. EPA evaluated about 488 SO_2 monitoring sites in operation during 2008 and found that the network was not adequately focused to support the revised NAAQS (U.S. EPA, 2009d). To address this deficiency, U.S. EPA promulgated minimum monitoring requirements based on a near-source monitoring approach. The Population Weighted Emissions Index (PWEI), which is based on population and emissions inventory data at the core-based statistical area (CBSA) level, was introduced to assign the appropriate number of monitoring sites in a given CBSA (75 FR 35520). The PWEI accounts for SO_2 exposure by requiring monitor placement in urban areas where population and emissions may lead to higher potential for population exposure to maximum hourly SO_2 concentrations. The PWEI value is calculated by multiplying the population of each CBSA by the total amount of SO_2 emissions (in tons per year) in a given CBSA, using the most recent census data (or estimates) and combining the most recent county-level emissions data (from the National Emissions Inventory) for each county in each CBSA, respectively. This value is then divided by 1 million, resulting in a PWEI value with units of million person-tons per year. A minimum of three SO_2 monitoring sites is required for any CBSA with a PWEI value greater than or equal to 1,000,000. For any CBSA with a PWEI value greater than or equal to 100,000 but less than 1,000,000, a minimum of two SO_2 monitoring sites is required. Lastly, a minimum of one SO_2 monitoring site is required for any CBSA with a PWEI value greater than or equal to 5,000 but less than 100,000. The monitors sited within a CBSA based on the PWEI criterion should also be, at minimum, one of the following monitoring site types: population exposure, highest concentration, source impacted, general background, or regional transport.

Another minimum monitoring requirement for the revised NAAQS involves the quantity of monitoring sites in a given state, which is based on the state's contribution to the NEI for SO_2. This requirement was designed to offer some flexibility in monitoring site placement, either inside or outside of a CBSA, independent of the PWEI criteria. Additionally, all monitoring sites in the network must be placed at locations where maximum peak hourly SO_2 concentrations are expected. Monitoring sites in the NCore network are not source oriented, and therefore, do not necessarily count towards the minimum monitoring requirements for SO_2. However, if an NCore SO_2 monitoring site is

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

2.5 Environmental Concentrations

This section provides an overview of SO_2 ambient and background concentrations. SO_2 data discussed in this section were obtained from the AQS. Section 2.5.1 introduces different SO_2 metrics used for NAAQS compliance and epidemiologic applications. Ambient concentrations of SO_2 are then discussed on various spatial and temporal scales. Spatial variability is discussed in Section 2.5.2, which is divided into two sections discussing large-scale variability (i.e., nationwide) and small-scale variability (i.e., urban areas). Temporal variability is then discussed in Section 2.5.3, extending from multiyear trends to subhourly variations. The relationships between 5-minute hourly max and 1-hour concentrations are described in Section 2.5.4. Background SO_2 concentrations from natural sources are subsequently discussed in Section 2.5.5.

2.5.1 Sulfur Dioxide Metrics and Averaging Time

Different metrics are used to represent ambient SO_2 concentrations for epidemiologic analysis and NAAQS compliance. As discussed in Section 2.5.4, hourly and 5-minute concentration data are routinely reported to U.S. EPA's AQS data repository by state, local, and tribal agencies. Metrics can be derived from these hourly and 5-minute data to represent concentration and exposure levels on different time scales. Table 2-4 provides information on how different SO_2 metrics are derived. Daily metrics include the 24-h avg SO_2 concentration and the 1-h daily max SO_2 concentration. Hourly metrics include the 5-minute hourly max concentration reported during a given hour and the 1-h avg concentration. Metrics derived using maximum concentration statistics (i.e., 1-h daily max or 5-minute hourly max) provide insight about peak ambient concentrations occurring over a given hour or day.

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

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

Metric	Aggregation Time	Averaging Time Description
24-h avg	Daily	Daily mean of 1-h avg SO_2 concentrations
1-h daily max	Daily	Maximum 1-h SO_2 concentration reported during the day
1-h avg	Hourly	Hourly mean SO_2 concentrations reported during the day
5-min hourly max	Hourly	Maximum 5-min SO_2 concentration reported during 1 h

avg = average; max = maximum; SO_2 = sulfur dioxide.

AQS SO_2 data used to compute national statistics meet the data quality and completeness criteria listed in Table 2-5. Three additional criteria were applied for the 5-minute data to reduce the influence of outliers. The 5-minute data had to correspond to an hourly data concentration, the mean of the 5-minute data could be no more than 120% of the hourly mean, and the 5-minute hourly max concentration had to fall within 1 to 12 times the 1-h avg concentration. Although negative values may be entered into the AQS database, they were excluded from this analysis. Concentrations below the monitor detection limit were included as they likely represent true low values. Based on these criteria, statistics were computed for data from a total of 380 sites across the U.S. for 5-minute hourly max SO_2 concentrations and for data from a total of 438 sites for the 1-h daily max, 24-h avg, and 1-h avg SO_2 metrics. 13% of sites did not have 5-minute data for comparison with 1-hour data.

2.5.2 Spatial Variability

This section provides a brief overview of national- and urban-scale SO_2 spatial variability and discusses how variations in ambient SO_2 concentrations influence human exposure in different geographical regions.

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

AQS SO_2 data used to compute national statistics (to meet the data quality and completeness criteria)	
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_2 concentrations measured at AQS monitoring sites during 2003–2005 were reported. Nationwide statistics of 5-minute hourly max SO_2 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_2 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_2 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_2 summary data provide a snapshot of recent concentrations and, compared with those presented in the 2008 SO_X 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_X 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_2 concentrations in the upper range of the distribution (99th percentile) covered a wide range of concentrations

but were never greater than the primary NAAQS level of 75 ppb. Across all metrics, large differences were observed between mean and 99th percentile concentrations, particularly for the SO_2 1-h daily max and 5-minute hourly max data. Such large differences between mean and 99th percentile concentrations are consistent with the highly variable nature of SO_2, which is characterized by periodic peak concentrations superimposed on a relatively low background concentration. Higher concentrations in the 1-h daily max distribution compared with the 5-minute hourly max distribution were likely attributable to the omission of high 5-minute concentrations from the 58 monitoring sites without 5-minute data.

The absolute highest 1-h daily max SO_2 concentration in 2013−2015 was 2,071 ppb. 99th percentile 1-h daily max concentrations over 200 ppb were reported at this site and other sites near active volcanoes in Hawaii Table 2-6), which are discussed further in Section 2.5.5. Other reports of 99th percentile, 1-h daily max concentrations greater than 200 ppb occurred at three monitoring sites near a copper smelter in Gila County, AZ, as mentioned in Section 2.2.2. In addition, sites where the 99th percentile 1-h daily max concentration was greater than 75 ppb were located in North Dakota, Illinois, Iowa, Wisconsin, Arizona, Missouri, Indiana, Tennessee, Ohio, Kentucky, Louisiana, and Pennsylvania, often near coal-fired EGUs. As shown in the nationwide map in Figure 2-11, the majority of monitoring sites across the U.S. report 99th percentile, 1-h daily max concentrations below the primary NAAQS level of 75 ppb. The 99th percentile of 24-h avg concentrations, which are often used as exposure metrics in epidemiologic studies, followed a similar pattern, with most elevated values located in the industrial Midwest (Figure 2-12).

2.5.2.2 Urban Spatial Variability

Air quality measurements from centrally located, urban monitoring sites are often used to represent community-scale exposure in epidemiologic analyses. However, central site exposure estimates may not fully capture variations in pollutant concentrations over urban scales. SO_2 spatial variability was characterized in six focus areas: Cleveland, OH; Pittsburgh, PA; New York City, NY; St. Louis, MO; Houston, TX; and Gila County, AZ. These focus areas were selected based on (1) their relevance to current health studies (i.e., areas with peer-reviewed, epidemiologic analysis), (2) the existence of four or more monitoring sites located within the area boundaries, and (3) the presence of several diverse SO_2 sources within a given focus area boundary.

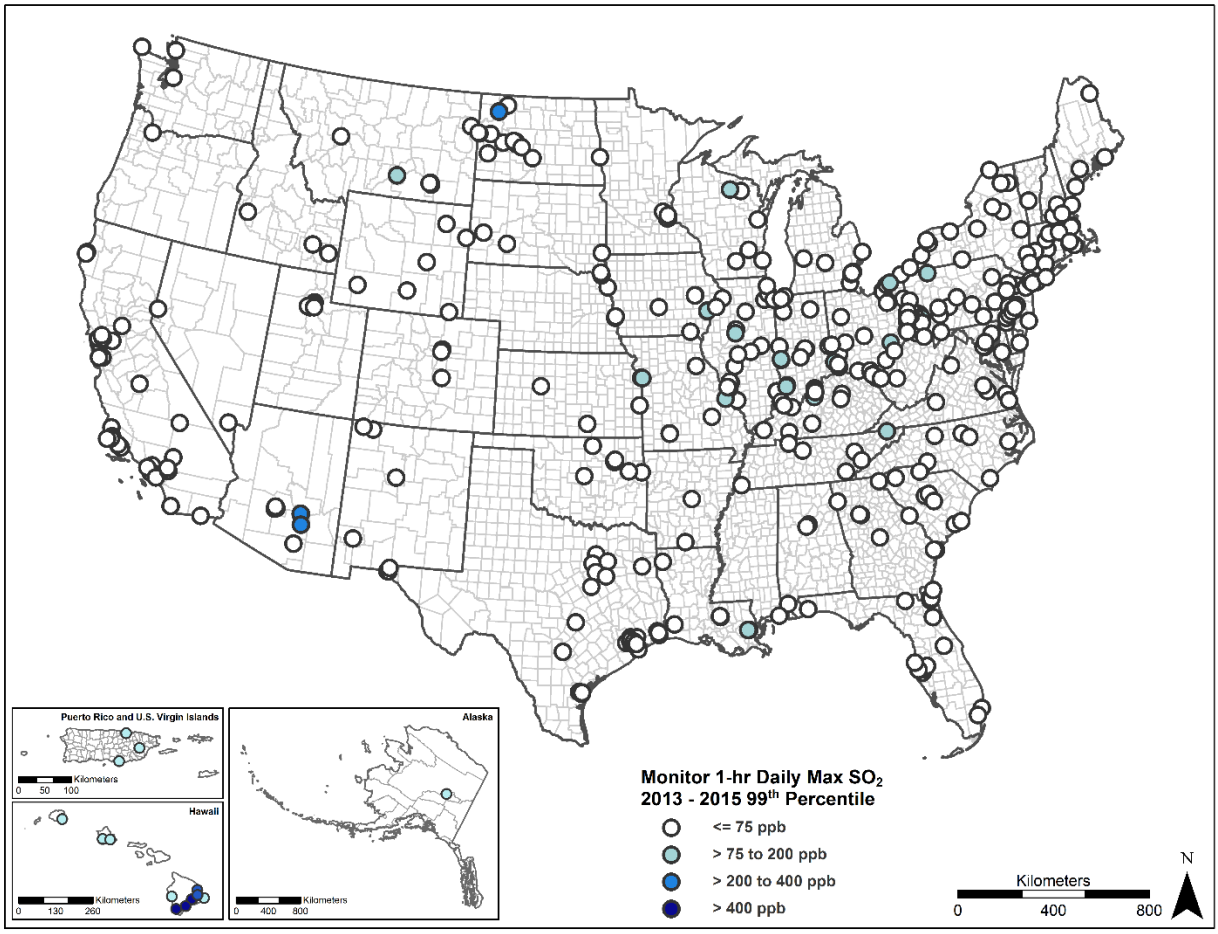
Table 2-6 National statistics of sulfur dioxide concentrations (parts per billion) from Air Quality System monitoring sites, 2013−2015.[a]

Year	N of Obs	Mean	5%	10%	25%	50%	75%	90%	95%	98%	99%	Max	AQS Max ID[b]
5-min hourly max													
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
1-h avg													
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
1-h daily max													
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
24-h avg													
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.

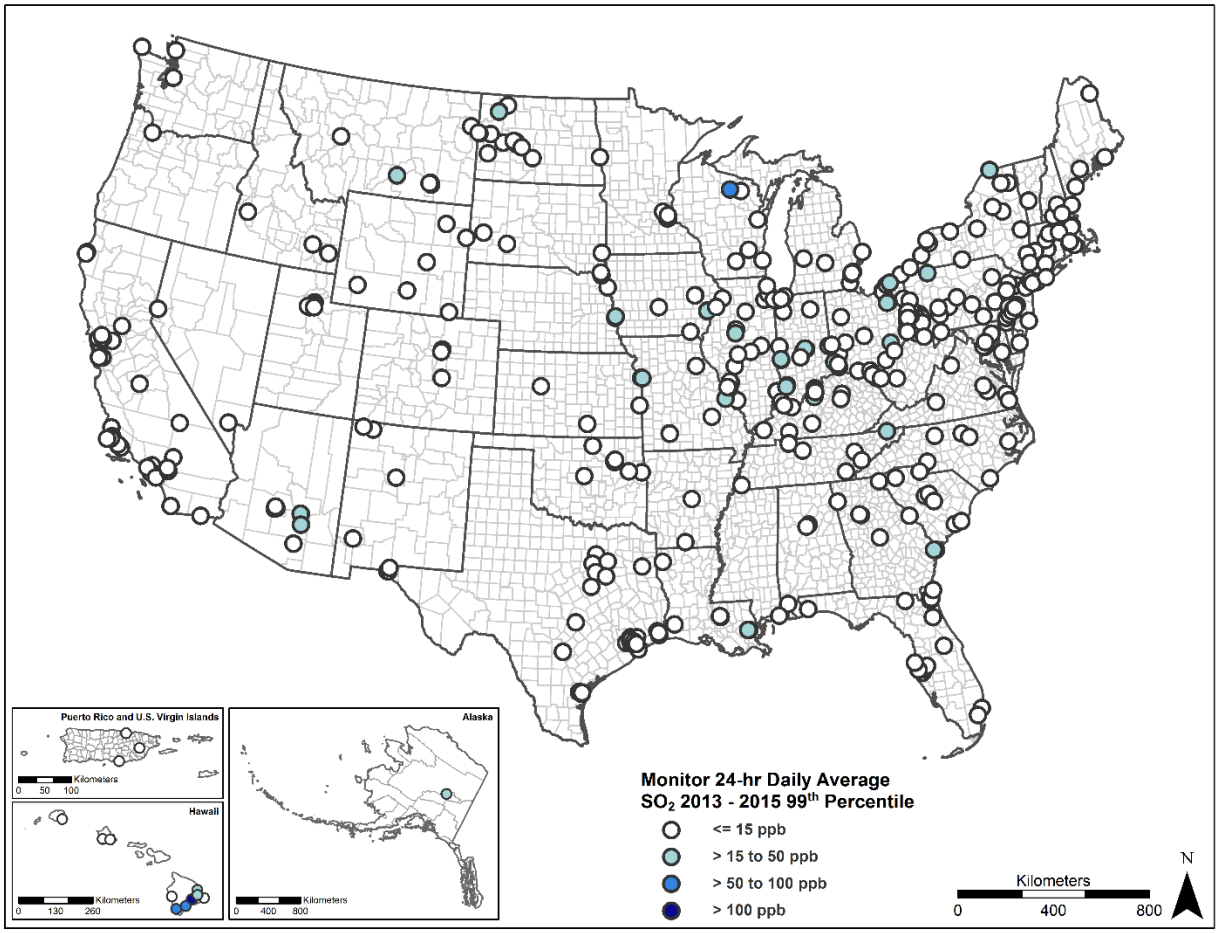
[a]Data below 0 ppb have been trimmed from the data set.

[b]AQS site ID number reporting the highest 3-yr concentration across the U.S.



Max = maximum; SO_2 = 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.

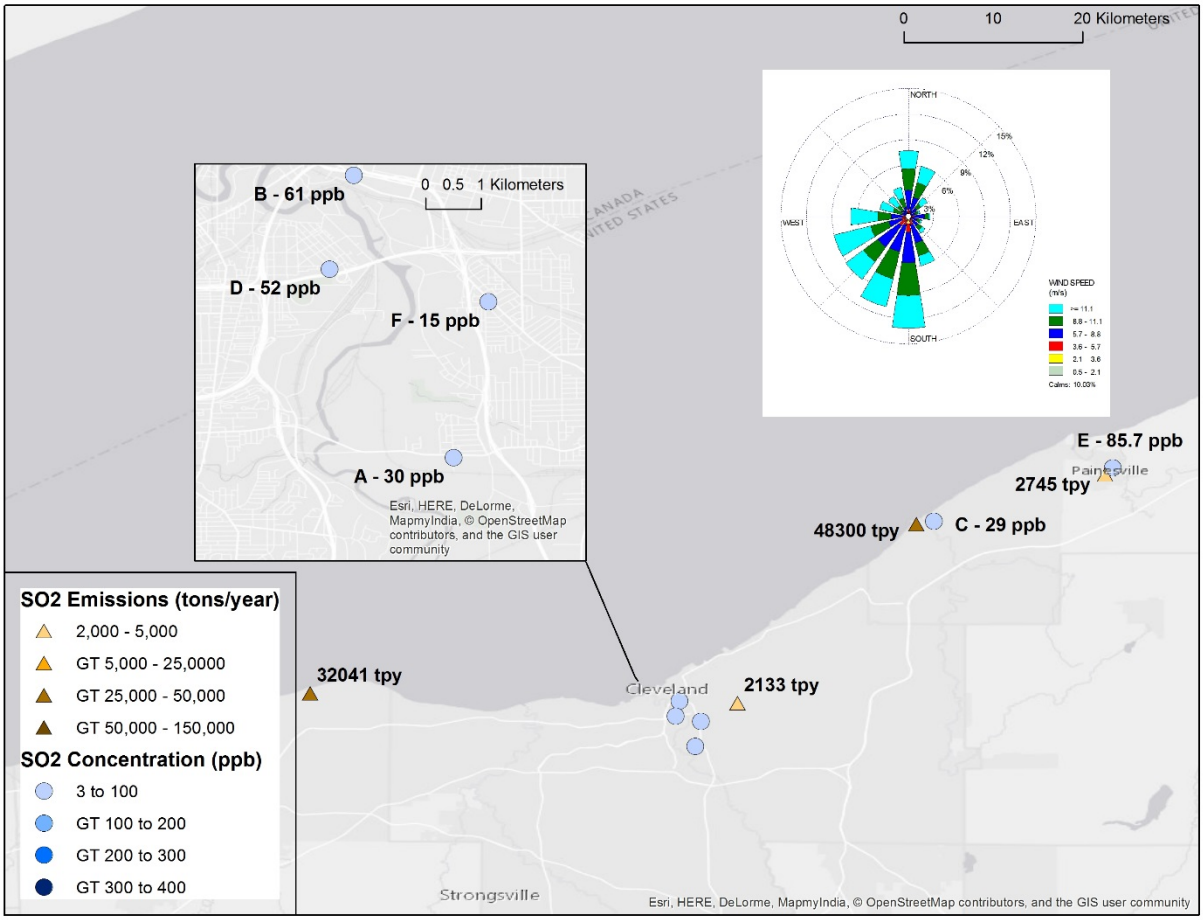


Note: The 24-h avg concentration is a metric often used in epidemiologic studies.
SO_2 = sulfur dioxide.

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

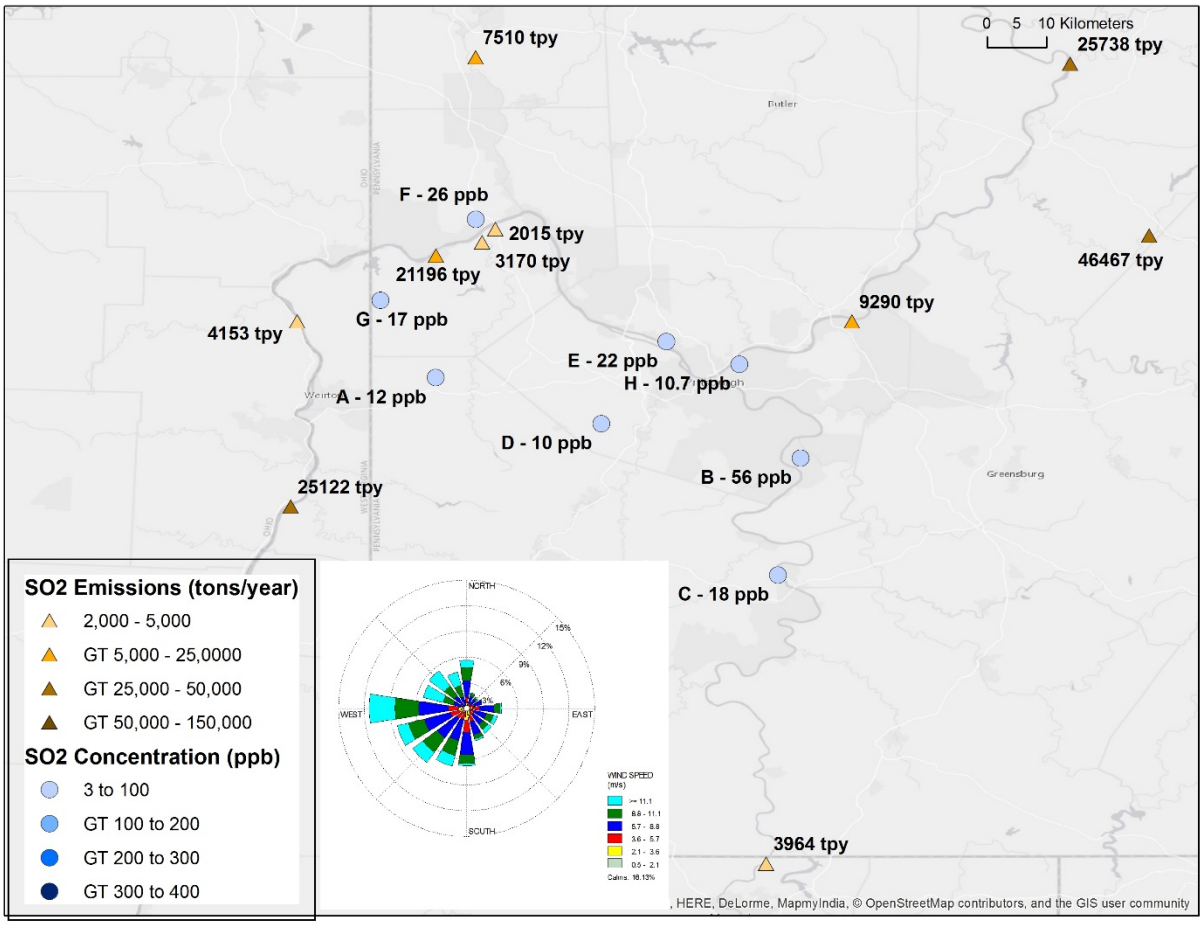
Maps of individual focus areas indicating 99th percentile 5-minute hourly max concentrations at monitoring sites and emissions from large point sources and their locations are presented in Figure 2-13 through Figure 2-18. As shown by the maps, up to 12 SO_2 monitoring sites are located in individual focus areas. Monitoring sites in each focus area are located at various distances from SO_2 sources. Due to the relatively short atmospheric lifetime of SO_2, monitoring sites within close proximity of large point sources (e.g., electric generating units, industrial sources, copper smelting facilities, shipping ports) are expected to detect higher SO_2 concentrations than those further downwind. However, other variables, particularly stack height and wind speed and direction, influence concentrations observed near sources. For example, Sites C and E in

Cleveland are both adjacent to large sources, but Site C has a much lower concentration than Site E despite the source near Site C emitting much more SO_2 than the source near Site E.



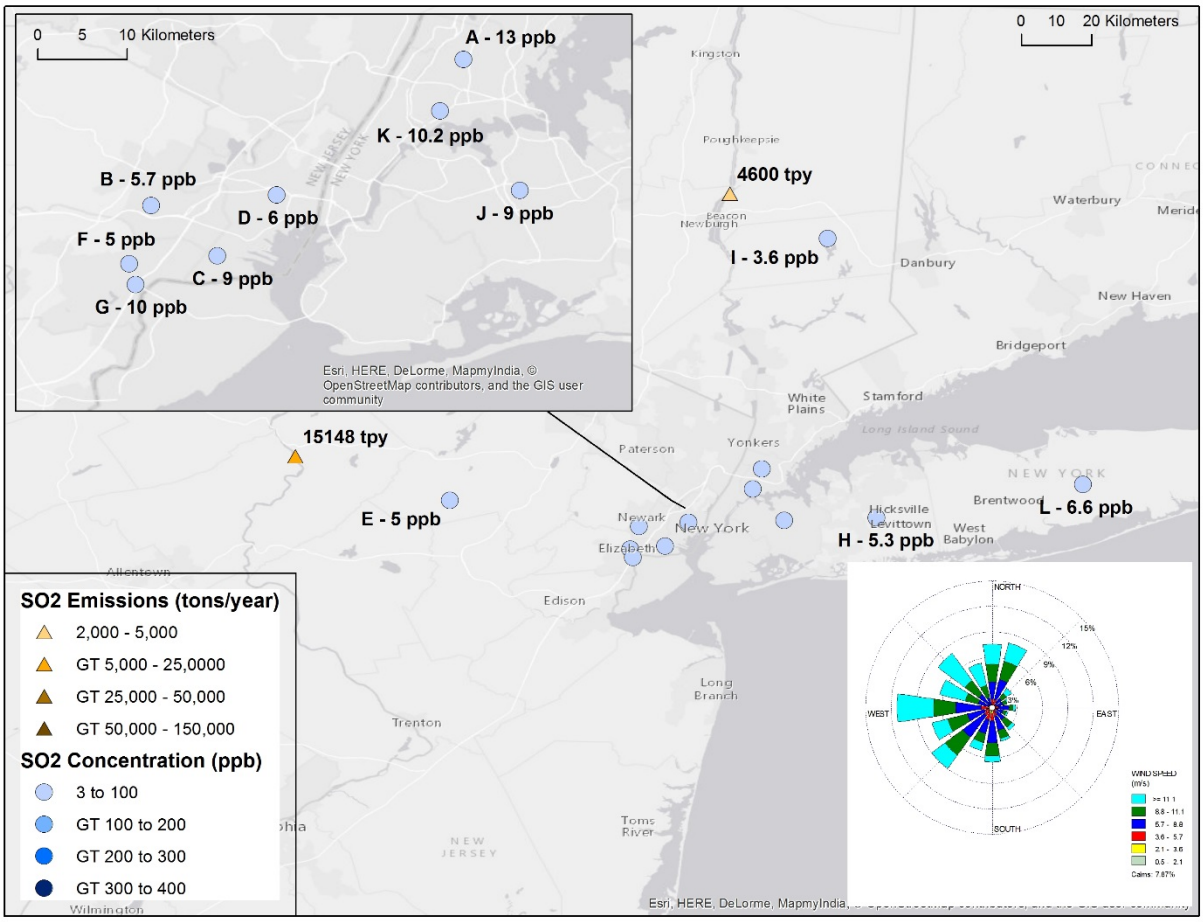
Note: Blue circles denote monitoring sites included in the U.S. Air Quality Monitoring System. Yellow triangles denote sources emitting 2,000 tons/yr or more according to the 2011 U.S. National Emissions Inventory. The inset, upper right, displays a wind rose of average wind speed and direction for data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

Figure 2-13 Map of the Cleveland, OH focus area showing emissions from large sources and the 99th percentile 5-minute hourly max concentration at ambient monitors during 2013−2015.



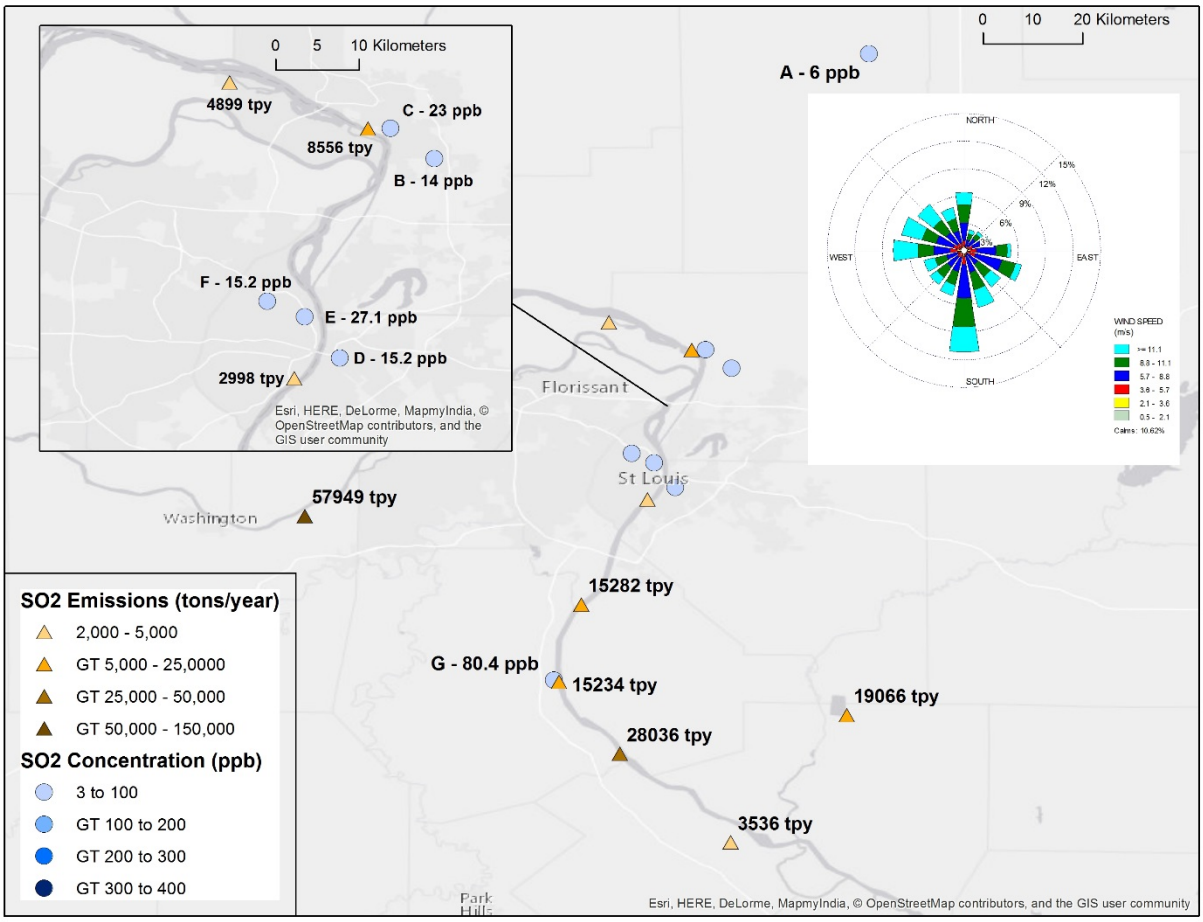
Note: Blue circles denote monitoring sites included in the U.S. Air Quality Monitoring System. Yellow triangles denote sources emitting 2,000 tons/yr or more according to the 2011 U.S. National Emissions Inventory. The inset, lower center, displays a wind rose of average wind speed and direction for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

Figure 2-14 Map of the Pittsburgh, PA focus area showing emissions from large sources and the 99th percentile 5-minute hourly max concentration at ambient monitors during 2013−2015.



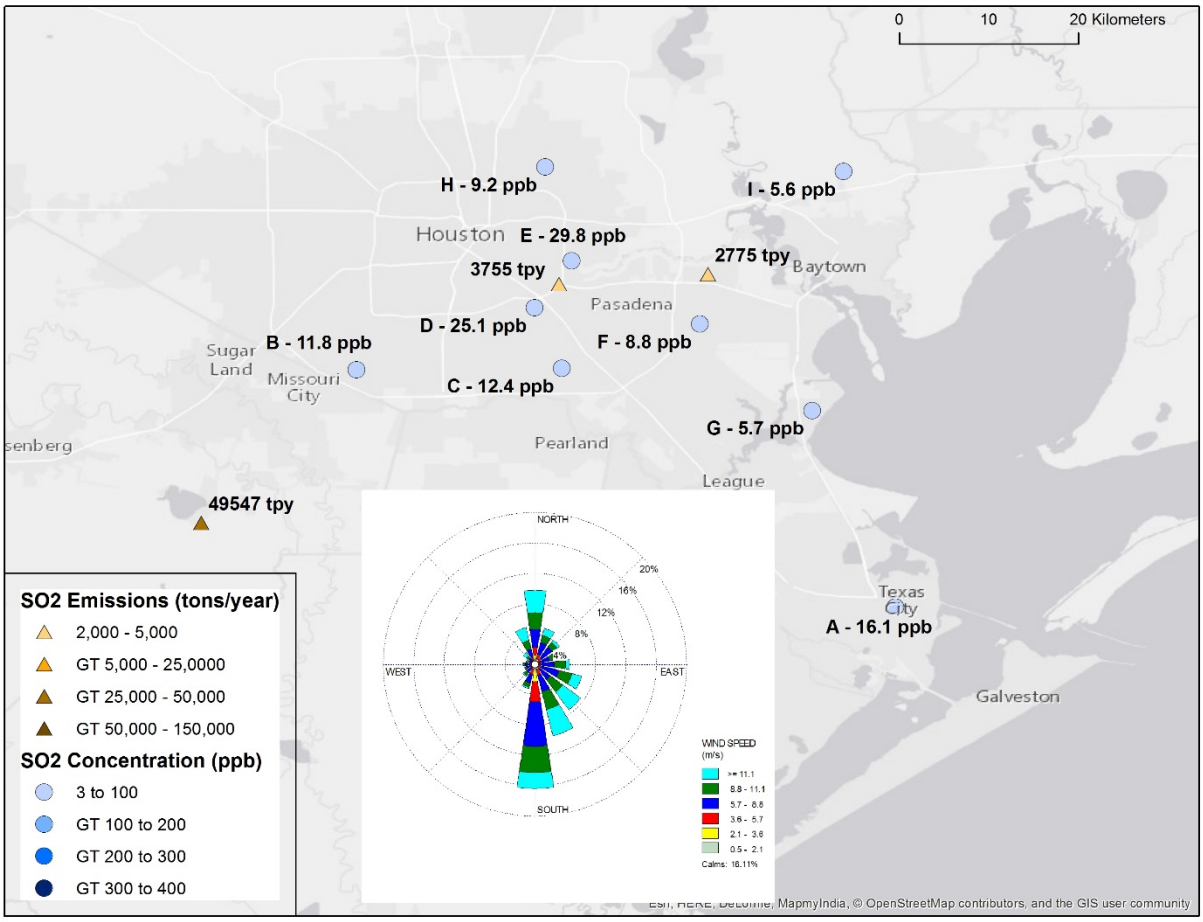
Note: Blue circles denote monitoring sites included in the U.S. Air Quality Monitoring System. Yellow triangles denote sources emitting 2,000 tons/yr or more according to the 2011 U.S. National Emissions Inventory. inset, upper right, displays a wind rose of average wind speed and direction for data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



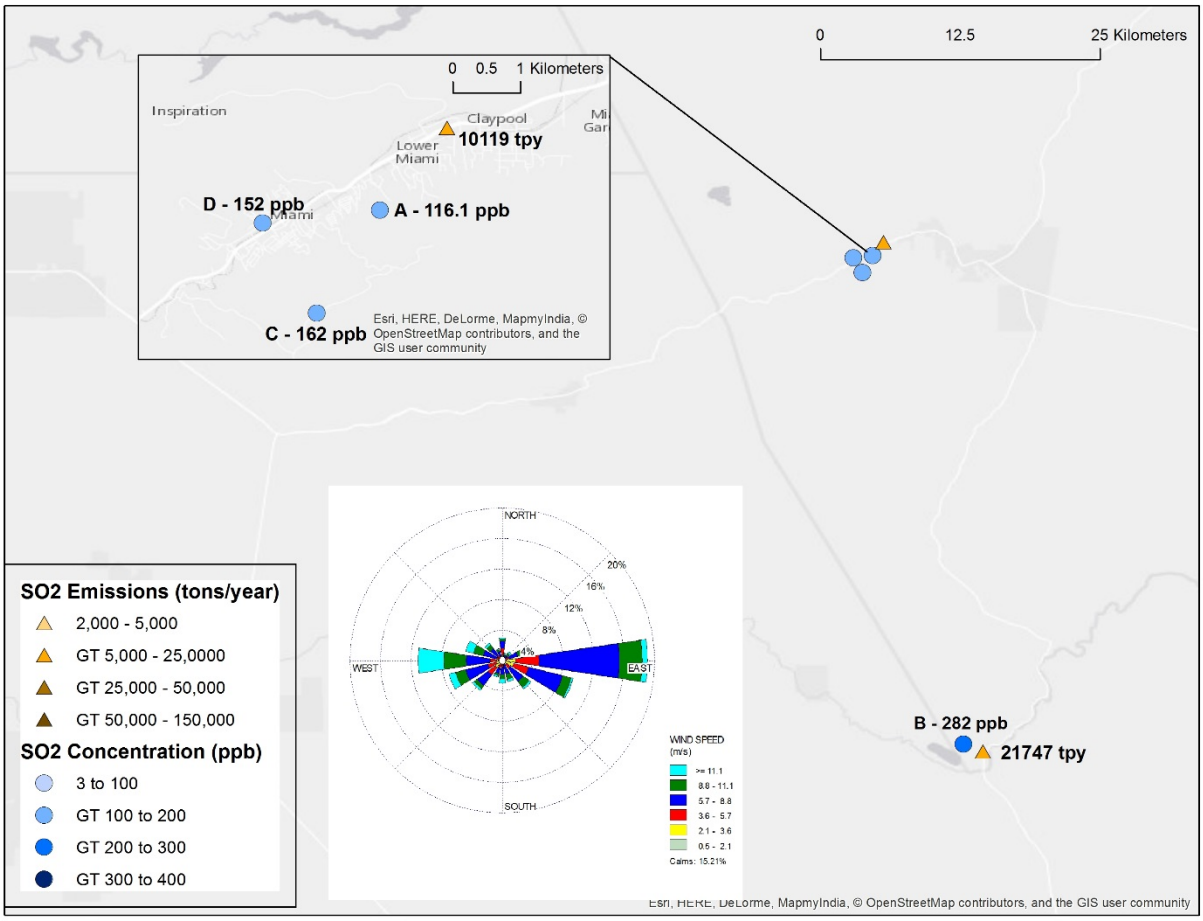
Note: Blue circles denote monitoring sites included in the U.S. Air Quality Monitoring System. Yellow triangles denote sources emitting 2,000 tons/yr or more according to the 2011 U.S. National Emissions Inventory. The inset, upper left, displays a wind rose of average wind speed and direction for data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

Table 2-7 provides the distribution of 1-h daily max SO_2 concentrations and monitor type (standard vs. trace level monitor) reported at individual AQS sites in the six focus areas. Concentrations reported at these sites were similar to nationwide SO_2 concentrations discussed earlier in this section (Section 2.5.2.1). For all but one individual monitoring site, median concentrations were below 15 ppb. The one exception was the monitoring site in the Gila County, AZ focus area, for which the median concentration was 39 ppb. This particular monitoring site (Site B) is located within 1 km of a copper smelting plant

with markedly high annual SO_2 emissions [greater than 20,000 tpy SO_2 (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.[a]

Site Label	AQS Monitoring Site ID	N of Obs	Mean	Min	10%	25%	50%	75%	90%	99%	Max	Monitor Type
Cleveland-Elyria-Mentor, OH												
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
Pittsburgh, PA												
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
New York-Northern New Jersey-Long Island, NY-NJ-PA												
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.[a]

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
St. Louis, MO-IL												
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
Houston-Sugar Land-Baytown, TX												
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.[a]

Site Label	AQS Monitoring Site ID	N of Obs	Mean	Min	10%	25%	50%	75%	90%	99%	Max	Monitor Type
Gila County, AZ												
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.
[a]Monitor values below 0 ppb have been trimmed from the data set.

More substantial site-to-site differences were observed in the 99th percentile of SO_2 concentrations. Across these monitoring sites, 99th percentile concentrations ranged from 5.8 to 247.2 ppb, with the majority of sites exhibiting 99th percentile concentrations at or below 37.5 ppb. Relatively high 99th percentile concentrations were reported at monitoring sites within 5 km of a large SO_2 point source, particularly in Gila County, AZ. Relatively high 99th percentile concentrations were also observed in the Cleveland, OH and Pittsburgh, PA focus areas. These data were in agreement with previous studies, which generally observed higher urban SO_2 concentrations near local industrial/combustion sources related to oil-burning units, diesel truck traffic, and EGUs (Clougherty et al., 2013; Wheeler et al., 2008).

Over the past decade, the number of AQS monitoring sites reporting 5-minute SO_2 concentrations has substantially increased. At the time of the 2008 SO_X ISA (U.S. EPA, 2008d), a total of 98 monitoring sites periodically reported 5-minute hourly max concentrations. To date, approximately 380 sites report 5-minute data, including urban sites within focus areas, sites near city centers, and sites near SO_2 sources (see Figure 2-10 in Section 2.4.3).

Similar analyses of 5-minute hourly max concentrations were performed on more recent data reported at individual monitoring sites in the six focus areas. Table 2-8 shows the range in 5-minute hourly max SO_2 concentrations reported at individual monitors, within the six focus areas in the 2013−2015 time frame. Median 5-minute hourly max concentrations are below 5 ppb, while maximum concentrations range from 15 to 1,241 ppb.

Table 2-8 5-minute sulfur dioxide concentrations by Air Quality System monitoring sites in select focus areas, 2013–2015.[a]

Site Label	AQS Monitoring Site ID	N of Obs	Mean	Min	10%	25%	50%	75%	90%	99%	Max	Monitor Type
Cleveland-Elyria-Mentor, OH												
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
Pittsburgh, PA												
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
New York-Northern New Jersey-Long Island, NY-NJ-PA												
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.[a]

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
St. Louis, MO-IL												
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
Houston-Sugar Land-Baytown, TX												
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.[a]

Site Label	AQS Monitoring Site ID	N of Obs	Mean	Min	10%	25%	50%	75%	90%	99%	Max	Monitor Type
Gila County, AZ												
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.
[a]Monitor values below 0 ppb have been trimmed from the data set.

To evaluate the extent of SO_2 spatial variability over urban geographical scales, concentration correlations between monitoring site pairs were calculated in each of the six focus areas. To estimate the degree to which concentrations at two different monitoring sites followed similar temporal trends, pairwise comparisons were evaluated using Pearson correlations. Across the six focus areas, Pearson correlations ranged from 0 to 1.0 for 24-h avg data. Correlations close to 1 represent strong correspondence over time between pairwise monitoring site concentrations, while values close to 0 represent poor correspondence between concentrations. Figure 2-19 and Figure 2-20 respectively show scatterplots of pairwise correlations of 24-h avg and 5-minute hourly max SO_2 concentrations versus distance between monitoring site pairs. 24-h avg concentrations are presented due to their frequent use in epidemiologic studies, while 5-minute hourly max concentrations are a metric of interest for short-duration exposures. Given the meandering nature of SO_2 plumes and potential for plume touchdown several kilometers from the stack (Turner, 1970), low correlation among monitoring sites would be expected in most cases for the 5-minute hourly max data.

Inter-site pairwise comparisons in Figure 2-19 suggest high spatial variability of the 24-h avg SO_2 concentration time series. In every focus area except for New York (discussed below), low to moderate inter-site pairwise correlations of 24-h avg SO_2 concentration data were observed, with the majority of Pearson correlations below 0.6. Inter-site pairwise correlations tended to decrease with distance. Even within relatively short distances (up to 15 km), most inter-site pairwise correlations were low, reflecting the variable nature of ambient SO_2 across urban spatial scales, possibly due to short atmospheric residence time, variable meteorology, and the episodic nature of the emissions as discussed in Section 2.2.

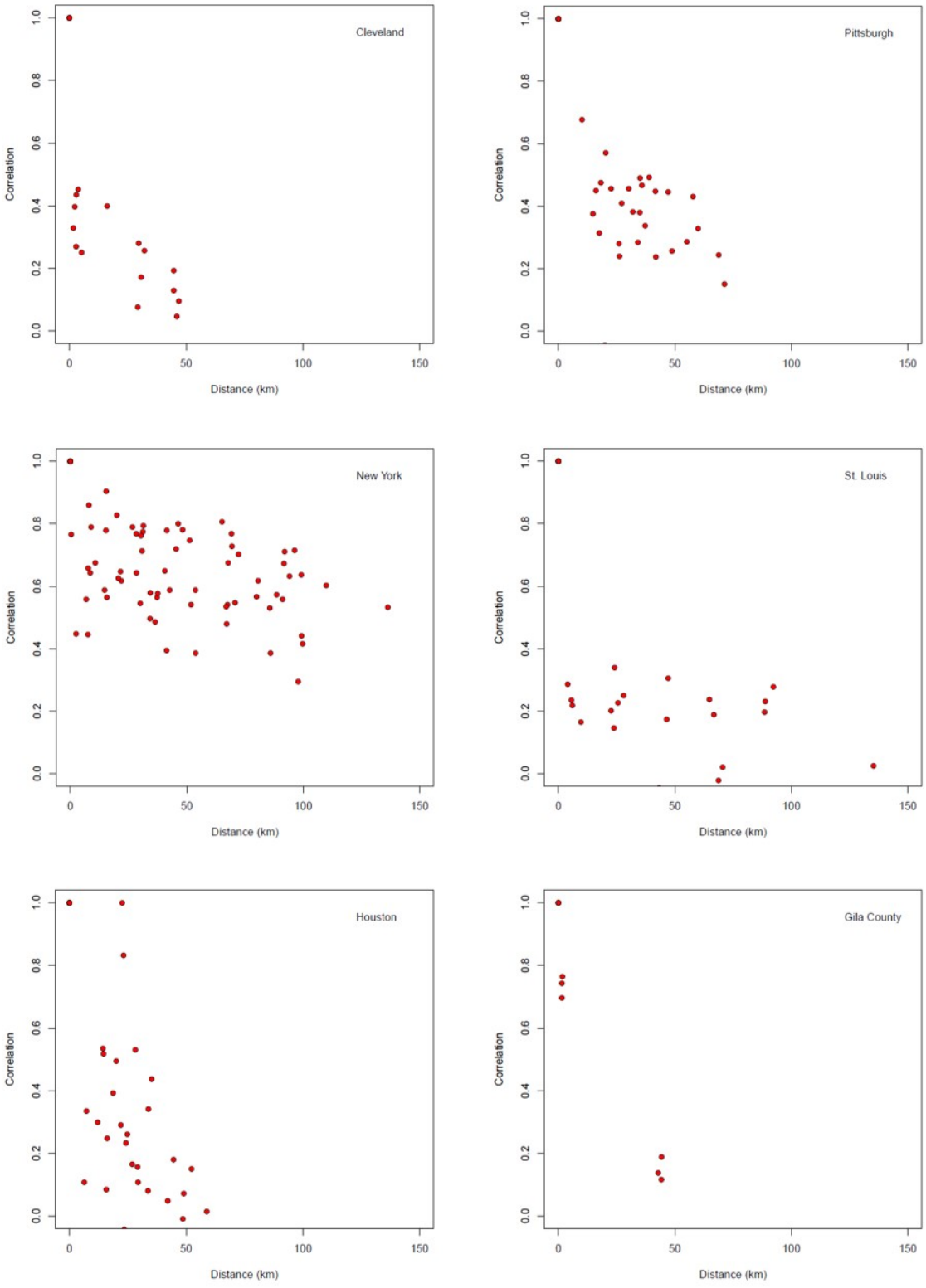


Figure 2-19 Pairwise correlations of 24-h avg sulfur dioxide versus distance between monitoring site pairs in six focus areas, 2013–2015.

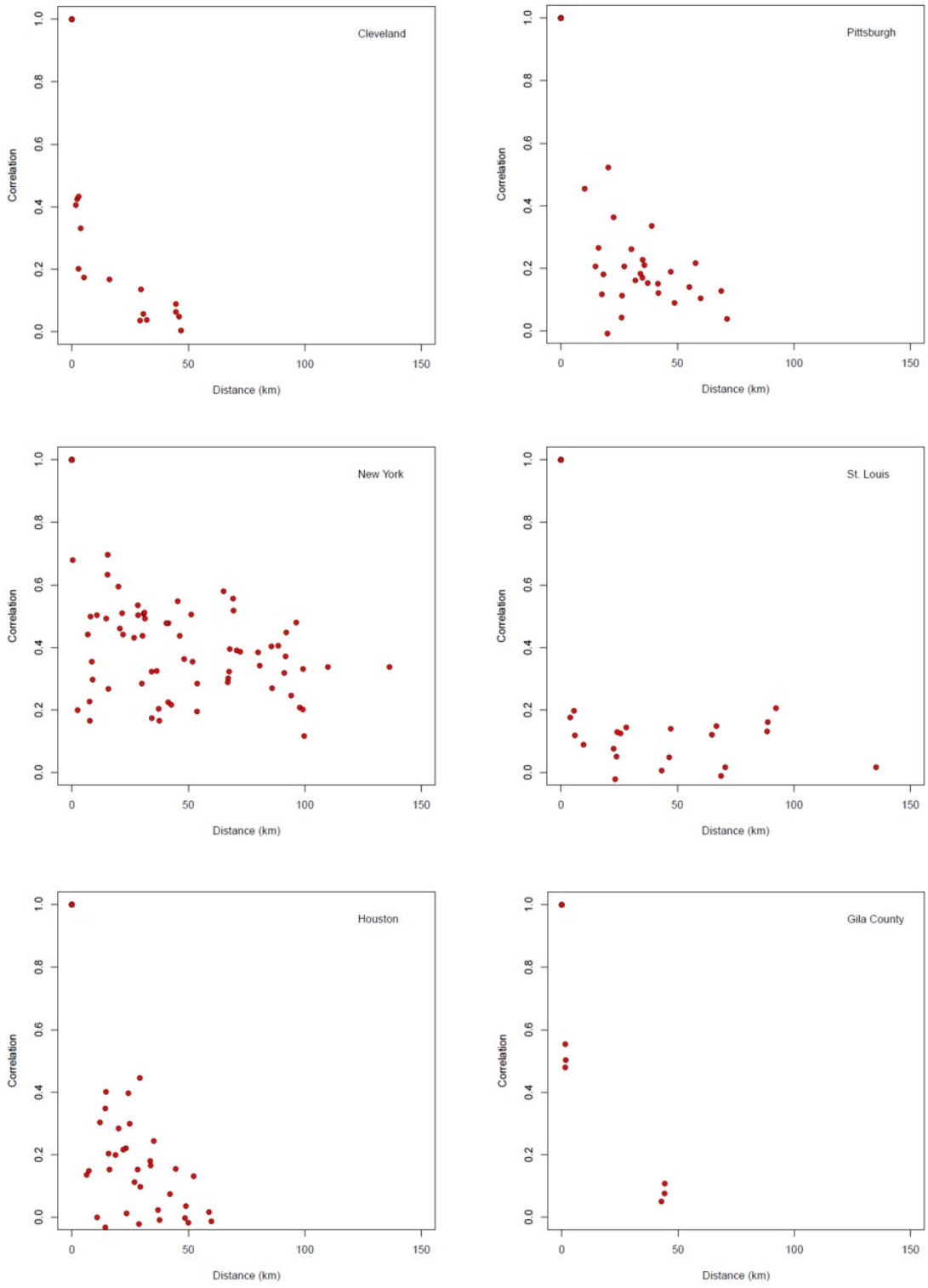


Figure 2-20 Pairwise correlations of 5-minute hourly max data versus distance between monitoring sites in six focus areas, 2013–2015.

In comparison, 5-minute hourly max SO_2 concentrations had somewhat higher spatial variability across urban spatial scales (Figure 2-20). In most cases, inter-site pairwise correlations of 5-minute hourly max concentrations are lower (less than 0.4) and decline more dramatically with distance than inter-site pairwise correlations of 24-h avg concentrations. Greater spatial variability in 5-minute hourly max concentrations may be explained by the fact that maximum metrics tend to capture peak SO_2 events that are likely more variable across urban areas than 24-h avg concentrations.

While spatial variability is evident to some degree in all urban areas, the extent of this variability is location dependent. For example, pairwise correlations in Cleveland, OH and St Louis, MO indicate strong SO_2 spatial heterogeneity. In comparison, pairwise correlations in New York City, NY are generally high and uniform across more than 100 km despite sometimes large distances between monitoring sites. Stronger pairwise correlations in New York City, NY may be related to similar temporal source patterns, given that the focus area's smaller power plants (<2,000 tpy SO_2 emissions), including gas-coal cogeneration facilities in Brooklyn, NY and Sayreville, NJ; an oil-burning facility in Queens, NY; a coal-fired power plant in Jersey City, NJ; and numerous homes using oil-burning heat likely have similar periods of high operation across the metropolitan area. This is analogous to observations about similarities in traffic patterns across large distances that promote higher correlation despite distance between the sources (Sarnat et al., 2010). Conversely, high spatial variations in Cleveland, OH and St. Louis, MO may be explained by the presence of a limited number of sources (>2,000 tpy) located at unevenly distributed sites across the metropolitan area.

In summary, SO_2 concentrations vary substantially across urban spatial scales as evidenced by poor to moderate inter-site pairwise correlations observed in SO_2 data in six focus areas. Spatial heterogeneity in urban-scale SO_2 concentrations and their temporal patterns may be explained by the presence of multiple, unevenly distributed SO_2 sources, meteorological factors that lead to varying degrees of SO_2 dilution, or removal through cloud/fog chemistry and deposition. Additionally, in this analysis, metrics representing maximum SO_2 concentrations generally exhibited more spatial heterogeneity than 24-h avg metrics.

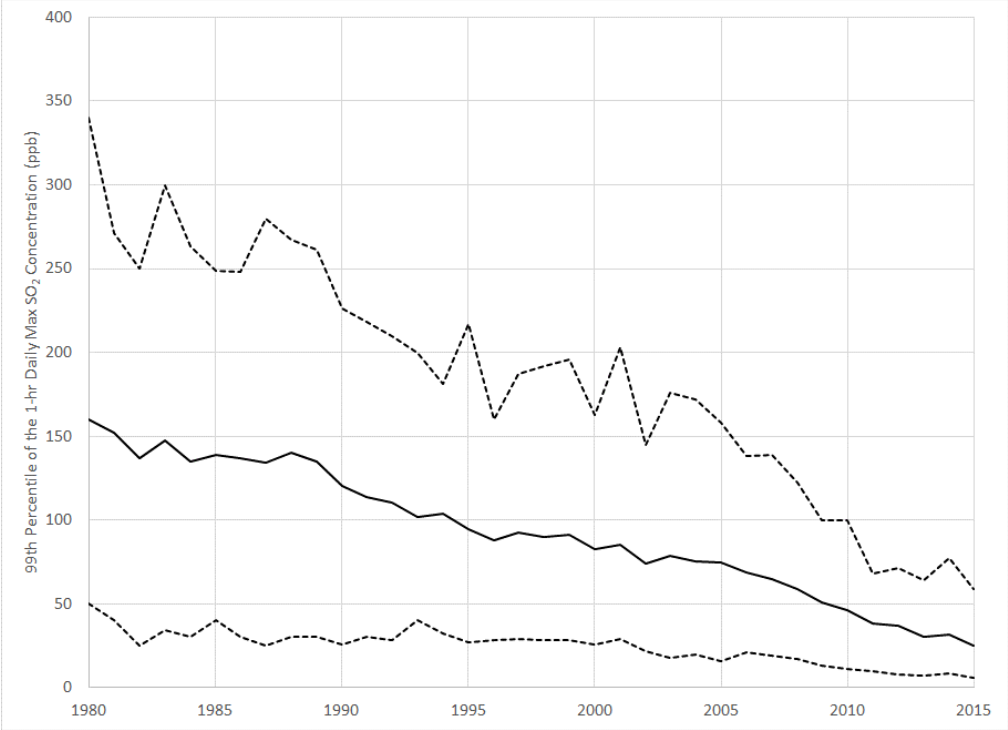
2.5.3 Temporal Variability

Temporal variations in outdoor SO_2 concentrations affect the magnitude, duration, and frequency in which humans are exposed to SO_2. In this section, different types of

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

2.5.3.1 Long-Term Trends

Trends in SO_2 concentrations reported at AQS monitoring sites across the U.S. from 1980 to 2015 are shown in Figure 2-21 for the annual 99th percentile of the 1-h daily max SO_2 concentration. Information on SO_2 concentration trends at individual, local air monitoring sites can be found at https://www.epa.gov/air-trends/sulfur-dioxide-trends (U.S. EPA, 2012b).



SO_2 = 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 1990−2015.

The steady decline in SO_2 concentrations over the past 25 years is largely attributed to emissions reductions at EGUs due to the Acid Rain and NO_X Budget Programs, and the Clean Air Interstate Rule (CAIR) implemented under the Clean Air Act Amendments of 1990 (USC Title 42 Chapter 85). The goal of the Acid Rain Program was to reduce power plant SO_2 emissions by 8.95 x 10^6 tons from 1980 levels. Reductions in SO_2 emissions commenced in 1996 and continued into the 2000s, resulting in dramatic decreases in total, nationwide SO_2 emissions and concentrations (Figure 2-5). The NO_X Budget Program and CAIR led to further reductions in SO_2 emissions. From 1990−2014, the annual 99th percentile average of 1-h daily max SO_2 concentration has decreased by 76% nationally.

Substantial declines in SO_2 concentration over the past decades have also been observed on regional scales. Blanchard et al. (2013) reported an average decline of 7.6% per year (±1.6%) in SO_2 emissions from 1999−2010 across four southeastern U.S. states (Alabama, Florida, Georgia, Mississippi), primarily due to reductions in power plant emissions, which account for approximately 75% of total SO_2 emissions in the southeastern U.S. region. This decline corresponded to large reductions in annual SO_2 concentrations (between 5.1 and 9.7% per year) reported at monitoring sites across these four states.

2.5.3.2 Seasonal Trends

In the 2008 SO_X ISA (U.S. EPA, 2008d), month-to-month trends for SO_2 were observed across a number of metropolitan areas, and these seasonal profiles varied by location. Some cities, such as Steubenville, OH and Phoenix, AZ showed clear wintertime maxima, while other urban areas (Philadelphia, PA; Los Angeles, CA; Riverside, CA) exhibited higher SO_2 concentrations during summer months. Differences in seasonal profiles were attributed to variations in source emissions, topography, and meteorological conditions among different areas.

Month-to-month variability based on more recent 1-h daily max concentrations (2013−2015) is shown for the six focus areas introduced earlier in this chapter (Section 2.5.2.2). Figure 2-22 displays the range of SO_2 concentrations reported at all monitoring sites within each focus area.

The data indicate that 1-h daily max SO_2 concentrations vary across seasons, especially in the higher concentrations within monthly SO_2 concentration distributions. Among the five urban focus areas, median concentrations (50th percentile: black line) varied by no more than 6 ppb throughout the year, while the median concentration in the Gila County, AZ focus area varied by 30 ppb. Large variations across all focus areas are observed in

the upper end (greater than 75th percentile) of SO_2 concentrations. Notably, mean monthly SO_2 concentrations were higher and more variable than median values, indicating that the distribution is skewed by high, infrequent observations.

Recent data further demonstrate that seasonal profiles vary by location. While each focus area exhibits some degree of seasonal variation, no consistent seasonal profile was observed across the focus areas. For example, springtime maxima in 1-h daily max SO_2 are evident in Cleveland, OH and Gila County, AZ, corresponding to focus areas with the highest SO_2 concentrations. Alternatively, New York City, NY, Houston, TX, and Pittsburgh, PA show clear wintertime maxima.

Month-to-month variations in SO_2 concentrations are consistent with month-to-month emissions patterns (Lee et al., 2011a) and the atmospheric chemistry of SO_2. Summertime minima, observed in the New York City, NY, and Houston, TX, focus areas, may correspond to enhanced oxidation of SO_2 to SO_4^{2-} by photochemically derived atmospheric oxidants that are more prevalent during the humid summer (Khoder, 2002). The difference in seasonality among these cities suggest that SO_2 can be substantially variable across local and regional scales.

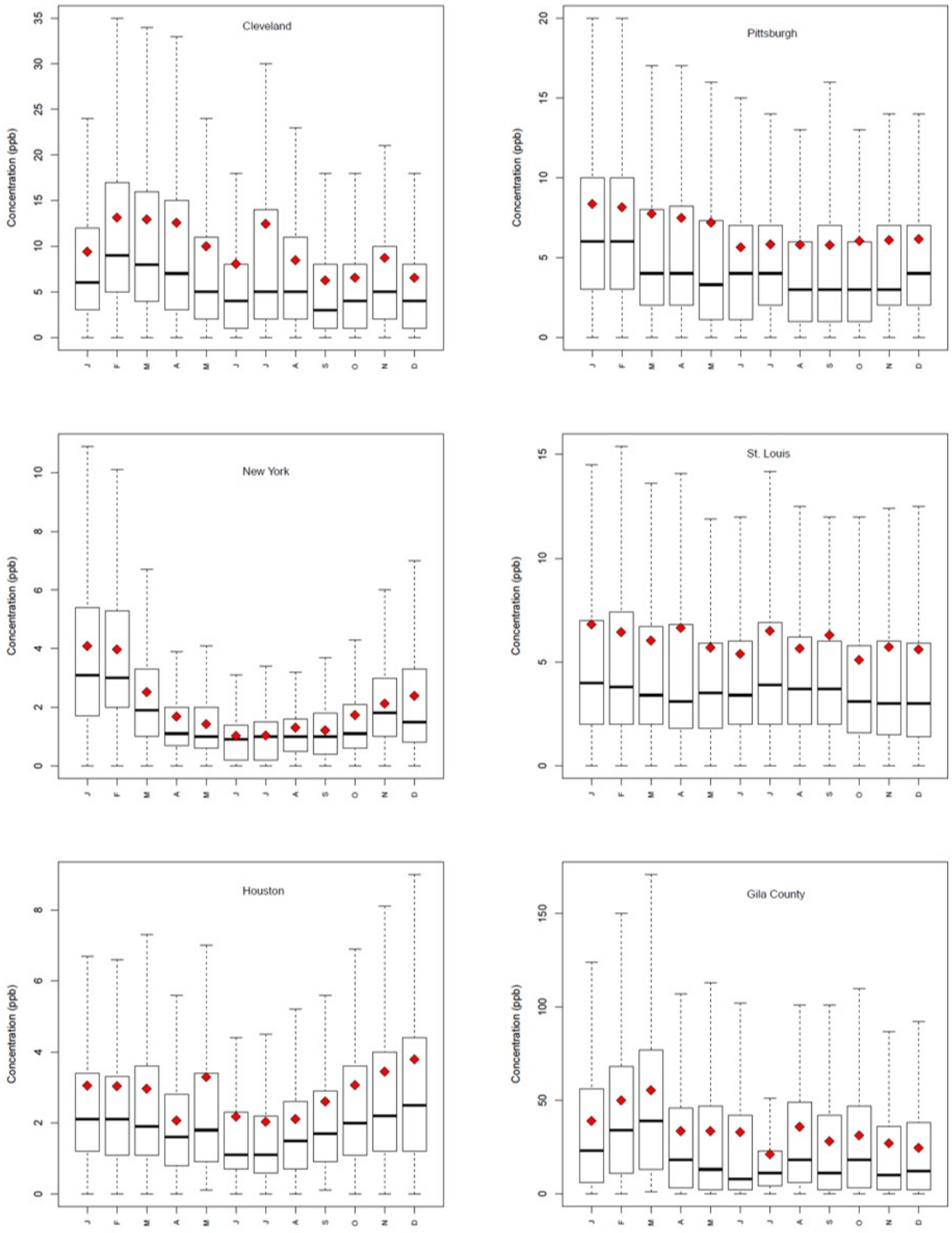


Figure 2-22 Sulfur dioxide month-to-month variability based on 1-h daily max concentrations at Air Quality System sites in each core-based statistical area, 2013–2015.

2.5.3.3 Diel Variability

The 2008 SO_X ISA (U.S. EPA, 2008d) explored nationwide patterns in diel variability of SO_2 concentrations (i.e., variability of SO_2 concentrations across a 24-hour period), and found clear daytime maxima and nighttime minima, with larger day-night differences with increasing SO_2 concentrations. Daytime maxima were attributed to entrainment of SO_2 from elevated point sources (e.g., power plants and industrial sources) into the mixed boundary layer, which expands due to rising surface temperatures.

Diel patterns were investigated in the focus areas using 1-h avg and 5-minute hourly max SO_2 data for the 2013−2015 time frame. Figure 2-23 and Figure 2-24 show variations in 1-h avg and 5-minute hourly max SO_2 concentrations in the six focus areas.

Consistent with the nationwide diel patterns reported in the 2008 SO_X ISA (U.S. EPA, 2008d), SO_2 concentrations in the six focus areas were generally low during nighttime and approach maxima values during daytime hours (Figure 2-23 and Figure 2-24). In Pittsburgh, PA; New York City, NY; St. Louis, MO; Houston, TX; and Gila County, AZ, daytime maxima occurred during early morning hours (6:00 to 9:00 a.m. LST). In Cleveland, OH, SO_2 tended to peak later in the morning or in some cases early- to mid-afternoon.

The timing and duration of daytime SO_2 peaks in the six focus areas were likely a result of a combination of source emissions and meteorological parameters. The 2008 SO_X ISA (U.S. EPA, 2008d) concluded that higher daytime SO_2 likely reflected an increase in power plant emissions coupled with an increase in entrainment of these elevated emissions into the lower atmosphere as the mixed layer expands throughout the day. Distinct morning peaks may have been related to stable atmospheric conditions, which tend to trap atmospheric pollution near the ground, resulting in an overall increase in ground-level pollution.

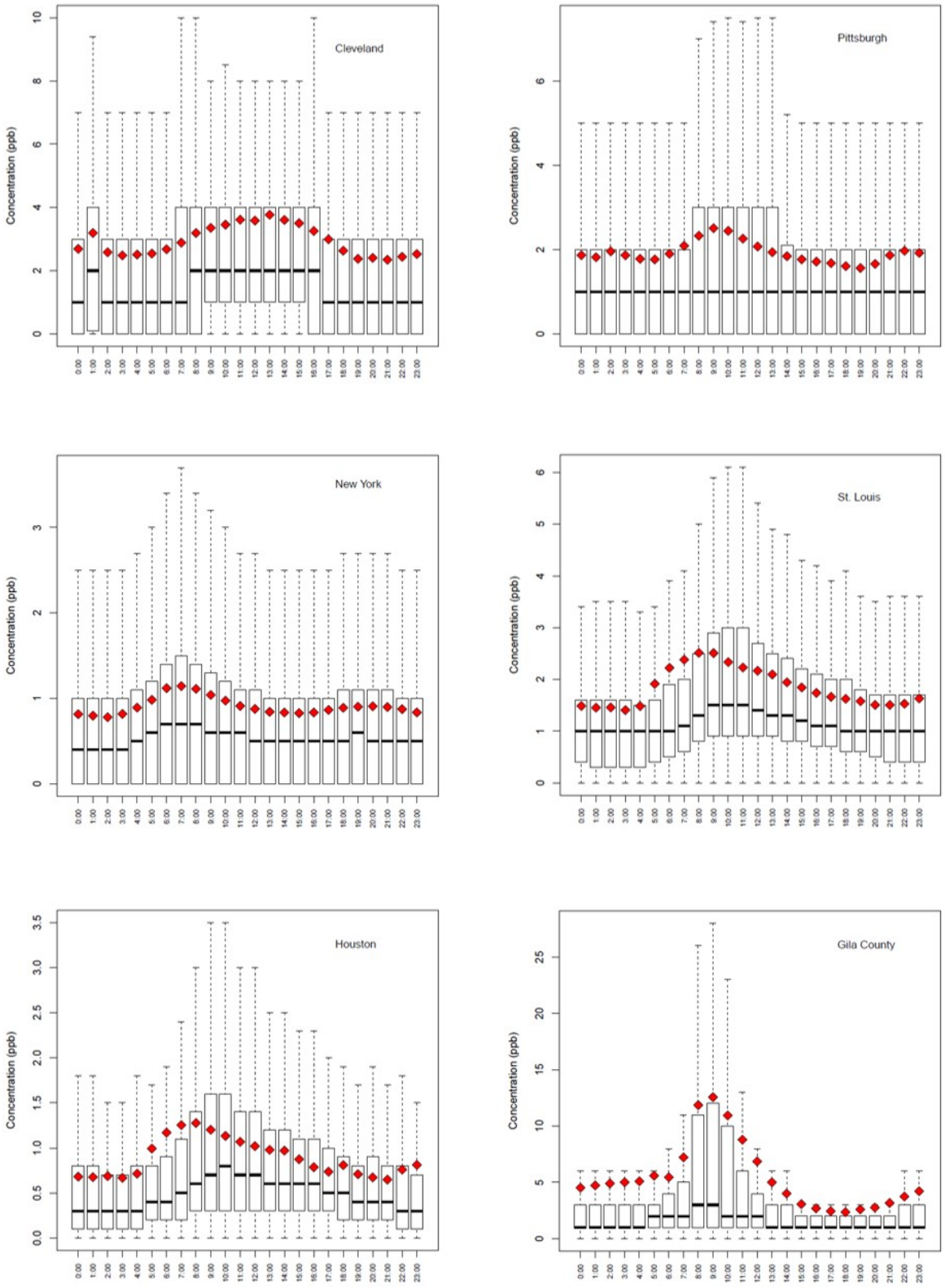


Figure 2-23 Diel variability based on 1-h avg sulfur dioxide concentrations in the six focus areas, 2013–2015.

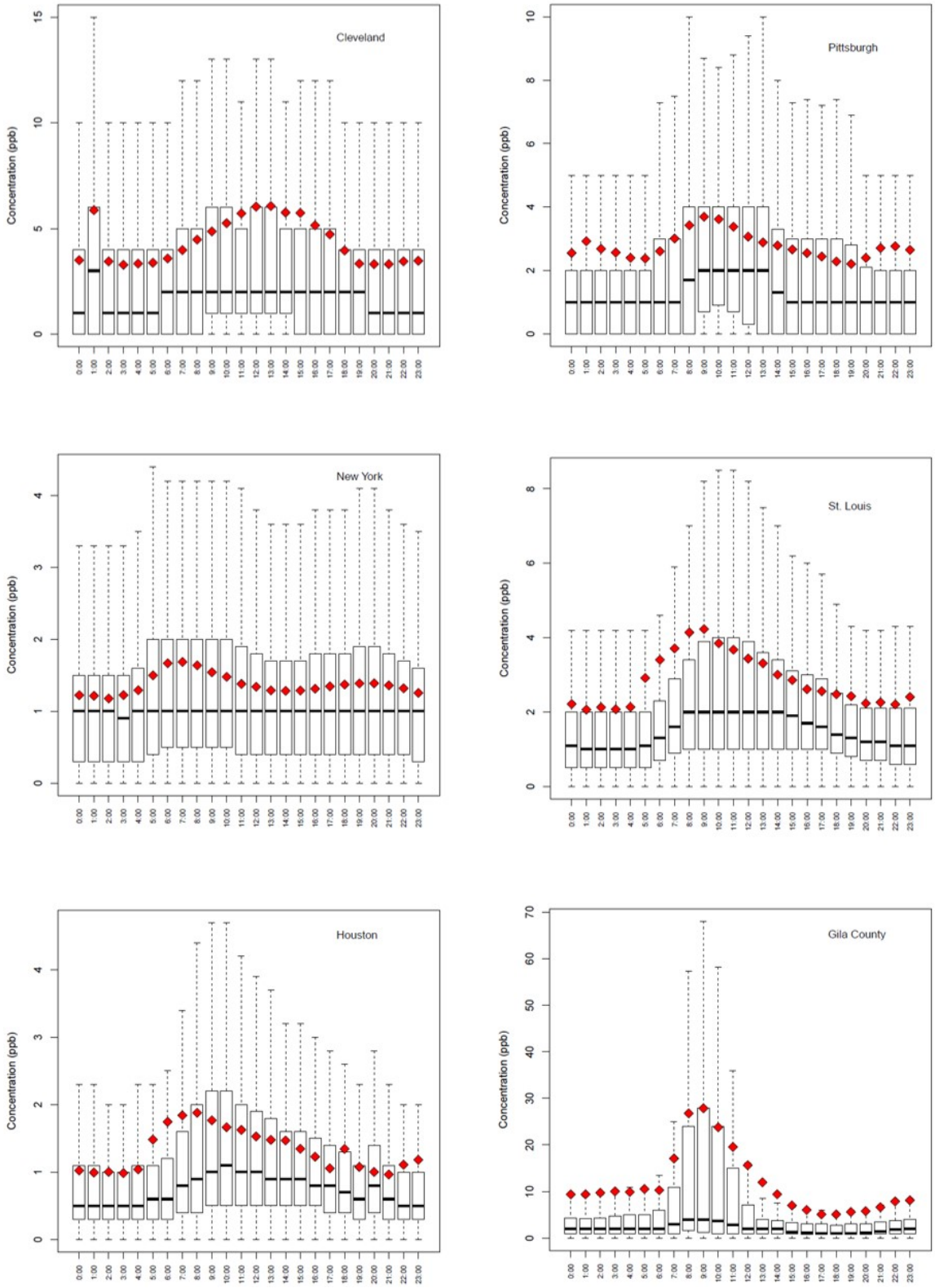
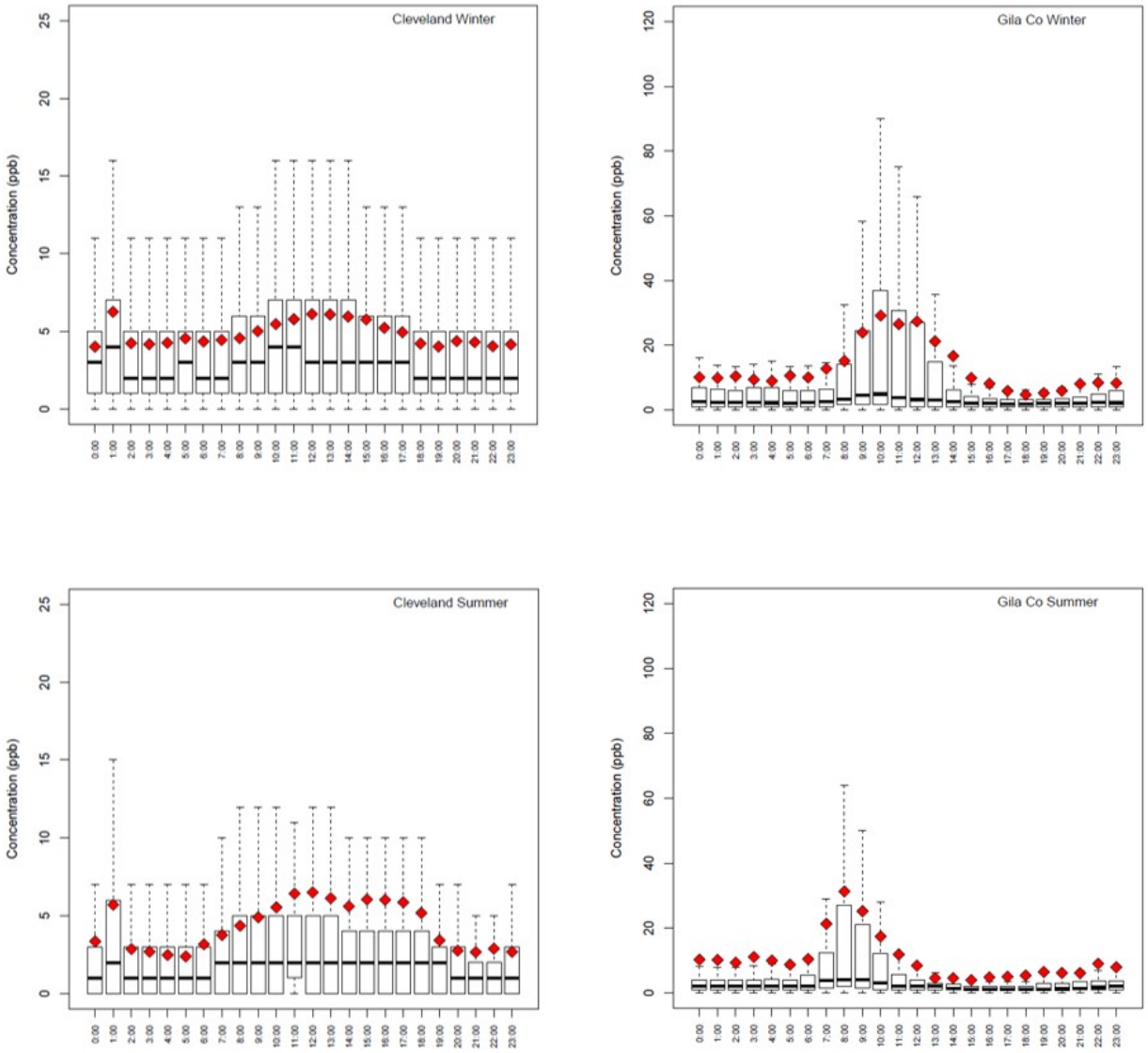


Figure 2-24 Diel trend based on 5-minute hourly max data in the six focus areas, 2013–2015.

Notably, SO_2 concentrations were all well below the primary NAAQS level during all hours of the day in every focus area except Gila County, AZ. In all focus areas, median 5-minute hourly max and 1-h avg concentrations were less than 5 ppb. SO_2 concentrations were for the most part below 15 ppb for all but Gila County, AZ, even when examining the upper end of the distribution of 5-minute hourly max concentrations. For Gila County, AZ, the 95th percentile of 5-minute hourly max and 1-h avg SO_2 concentrations exceeded 65 ppb and 25 ppb, respectively.

Diel SO_2 concentration patterns may be influenced by seasonal factors. Diel plots of 5-minute hourly max for winter and summer are presented for Cleveland, OH and Gila County, AZ in Figure 2-25. A clear contrast can be seen between the two locations. Cleveland, OH exhibited very little change in diel patterns between the cold and warm seasons. In contrast, the mode of the diel pattern occurred earlier in summer compared with winter for Gila County, AZ. Factors that may influence the mode of the diel pattern include peak smelter operation times and atmospheric mixing. For example, seasonal differences in solar radiation prolong nighttime inversion periods during the winter. Transport to downwind monitoring sites may be impeded by stable conditions. Moreover, increased solar radiation during the summer enhances mixing, increasing the probability of plume touchdown (Slade, 1968b). The median and average 5-minute hourly max SO_2 concentrations were also somewhat lower during the summer compared with winter in Gila County, AZ. O_3 production in the summer may have promoted oxidation of SO_2 (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

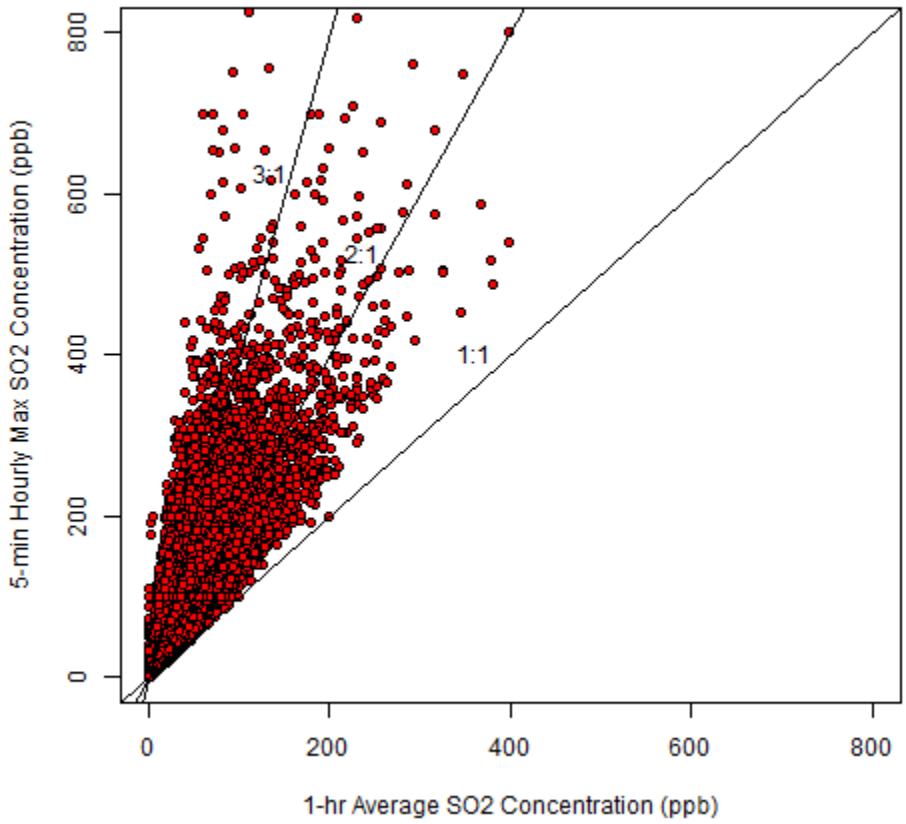
Peak concentrations within an SO_2 plume can greatly exceed the mean concentration at the plume centerline, so that exposure to the peak may be much greater than an hourly or daily SO_2 measurement. Plume dispersion is a Gaussian process, but the plume meanders so that the peak at any instant in time exceeds the mean of the plume centerline found by averaging over some longer time period, such as 1 hour or 1 day (Slade, 1968a; Gifford, 1960). Several studies (Dourado et al., 2012; Schauberger et al., 2012; Venkatram, 2002; Turner, 1970) have characterized the peak-to-mean ratio (PMR), showing that the ratio increases with longer averaging time. Venkatram (2002) used dispersion modeling to illustrate the stochasticity of the dispersion process, where the mean over a longer time period is determined by an ensemble average across simulations. At a fixed location, the results of Venkatram (2002) imply that exposure to the plume peak occurs with varying probabilities based on the time scale used to represent the instantaneous plume, the time scale over which the average is computed, the intermittency of atmospheric turbulence, and atmospheric stability.

The PMR has been computed in the literature as a function of the ratio of the mean-to-peak concentration integration times raised to some power in the range of 0.2 to 0.5 (Venkatram, 2002) or 0 to 0.68 (Schauberger et al., 2012), with the increasing exponent corresponding to increased atmospheric instability. When 5-minute hourly max data are compared with 1-h avg data, the mean-to-peak integration time ratio is 60 minutes-to-5 minutes = 12. A peak-to-mean ratio of 1 to 5.4 would be expected using the wider range of exponents (i.e., 12^0 to $12^{0.68}$).

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

PMRs were used extensively in the previous SO_2 NAAQS review to evaluate the distribution of 5-minute hourly max concentrations corresponding to a given 1-h avg SO_2 concentration (U.S. EPA, 2009b). PMRs are determined by dividing the 5-minute hourly max concentration by the 1-h avg concentration. Using this approach, a PMR of 1 demonstrates that 5-minute hourly max and 1-h avg concentrations are equivalent. A high PMR value (up to a maximum value of 12 in this case) indicates that the 5-minute hourly max concentration is higher than the 1-h avg concentration. For example, a PMR of 2 (shown as 2:1 on Figure 2-26 and Figure 2-27) indicates that 5-minute hourly max concentration is 2 times higher than the 1-h avg concentration. PMR values of 1 (1:1) through (3:1) are displayed as lines in Figure 2-26 and Figure 2-27. Median PMRs obtained from comparing the 5-minute hourly max with the 1-h avg AQS data at sites

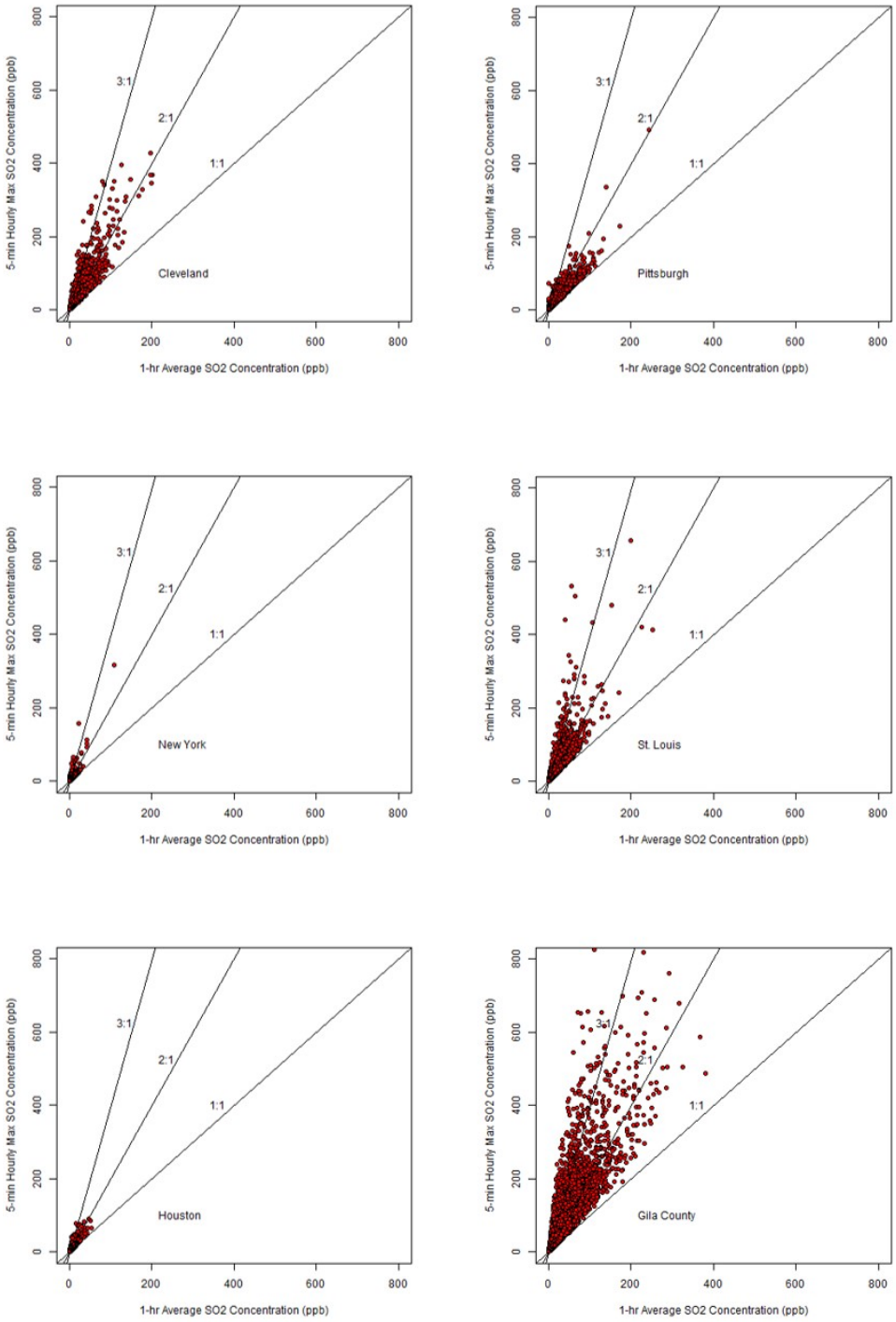
where both measures were available simultaneously, and neglecting concentrations below 0 ppb, had a range of 1 to 5.5 with a median of 1.3, in reasonable agreement with the predicted range of 1 to 5.4 for the PMR.



SO_2 = 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_2 = 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.

Table 2-9 displays the range of temporal correlations between corresponding 5-minute hourly max and 1-h avg concentrations and the range of PMRs computed from SO_2 measurements reported at these monitoring sites within the six focus areas shown in Figure 2-27. Similar to results in the 2008 SO_X ISA (U.S. EPA, 2008d), 5-minute hourly max concentrations tend to correlate well with 1-h avg metrics, suggesting that 1-h avg metrics, in most cases, adequately represent changes in 5-minute hourly max data over time. However, 5-minute hourly max concentrations tend to be higher than 1-h avg concentrations. PMRs were skewed higher for the Gila County focus area and slightly higher for the New York City focus area. However, overall 1-h daily max concentrations in New York were relatively low (highest 99th percentile 1-h daily max was 16.5 ppb), so a PMR of 2 or 3 would lead to a 5-minute hourly max of 33 or 49.5 ppb. In contrast, the 1-h daily max concentrations in Gila County were much higher (highest 99th percentile 1-h daily max was 247 ppb), which would lead to 5-minute hourly max concentrations of 494 ppb if the PMR were 2 and of 741 ppb if the PMR were 3.

2.5.5 Background Concentrations

With the exception of periodic volcanic eruptions in Hawaii, natural and international transboundary sources of SO_2 make only minor contributions to the total atmospheric burden of SO_2 in the U.S. Section 2.2.4 and Section 2.2.5 describe those sources contributing to background SO_2.

No new studies have appeared that attempt to estimate background SO_2 concentrations since the 2008 SO_X ISA (U.S. EPA, 2008d). The 2008 SO_X ISA discussed a global scale three-dimensional modeling study that estimated annual mean SO_2 concentrations in surface air including both anthropogenic and natural sources, using the MOZART-2 (Model of Ozone and Related Chemical Tracers) Horowitz et al. (2003). Sources included in the study included emissions from fossil and biofuel combustion, biomass burning, biogenic and soil emissions, and oceanic emissions. Background SO_2 concentration estimates were below 0.01 ppb over much of the U.S. Maximum background concentrations of SO_2 are 0.03 ppb. In the U.S. Northwest, geothermal sources of SO_2 are responsible for 70 to 80% of the background SO_2 concentration; even so, total SO_2 concentrations are still on the order of ~2 ppb or less. In these simulations, background contributed less than 1% to SO_2 concentrations in surface air in 2001 throughout much of the contiguous U.S.

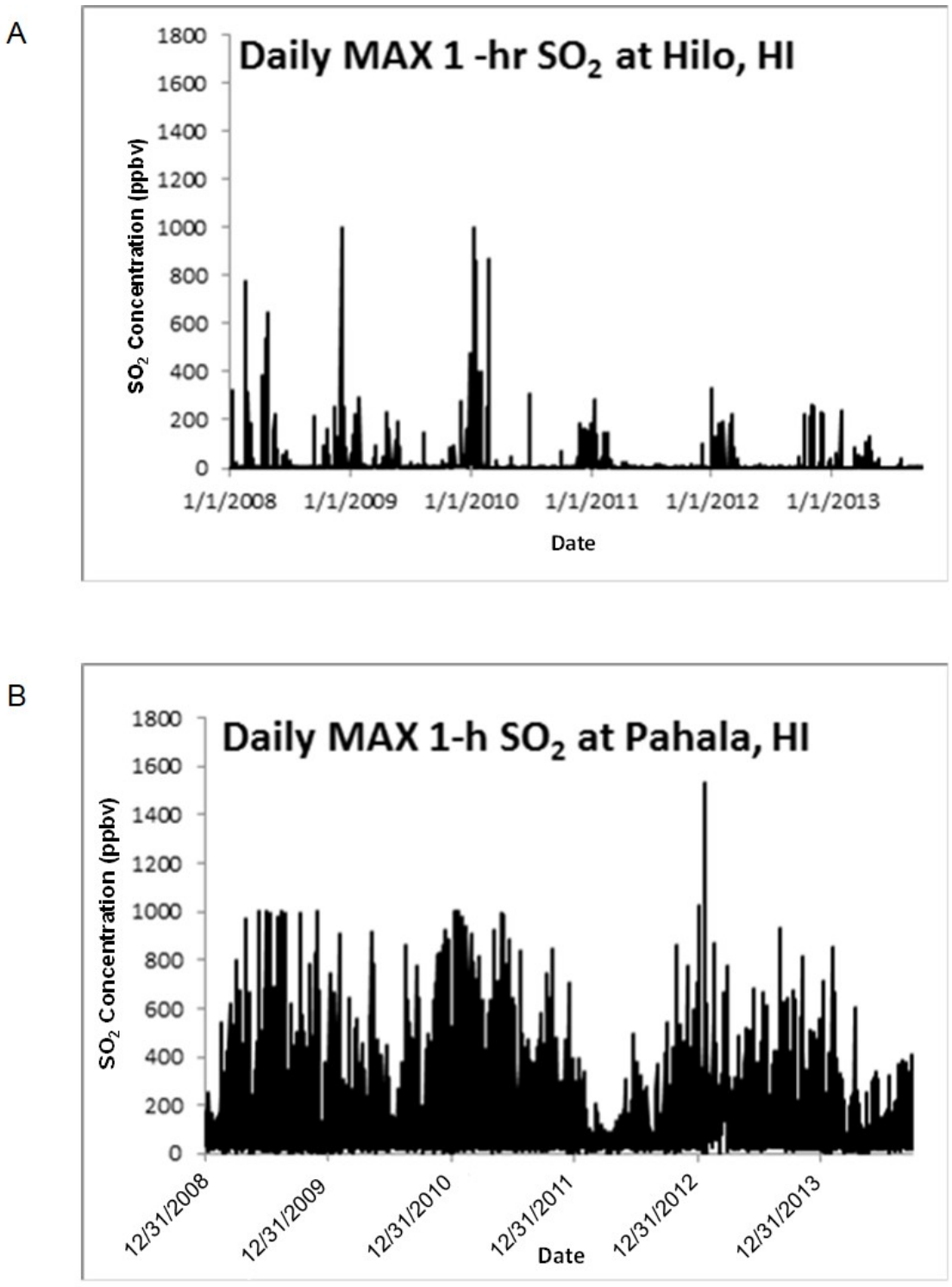
Table 2-9 Pearson correlation coefficient and peak-to-mean ratio for maximum sulfur dioxide concentrations in the six focus areas, 2013−2015.

Focus Area	N Monitoring Sites	Correlation Coefficient	Median PMR[a]
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.
[a]Median PMR = 5 min max/1-h avg. The range of data represents median PMR across each site within the focus area.

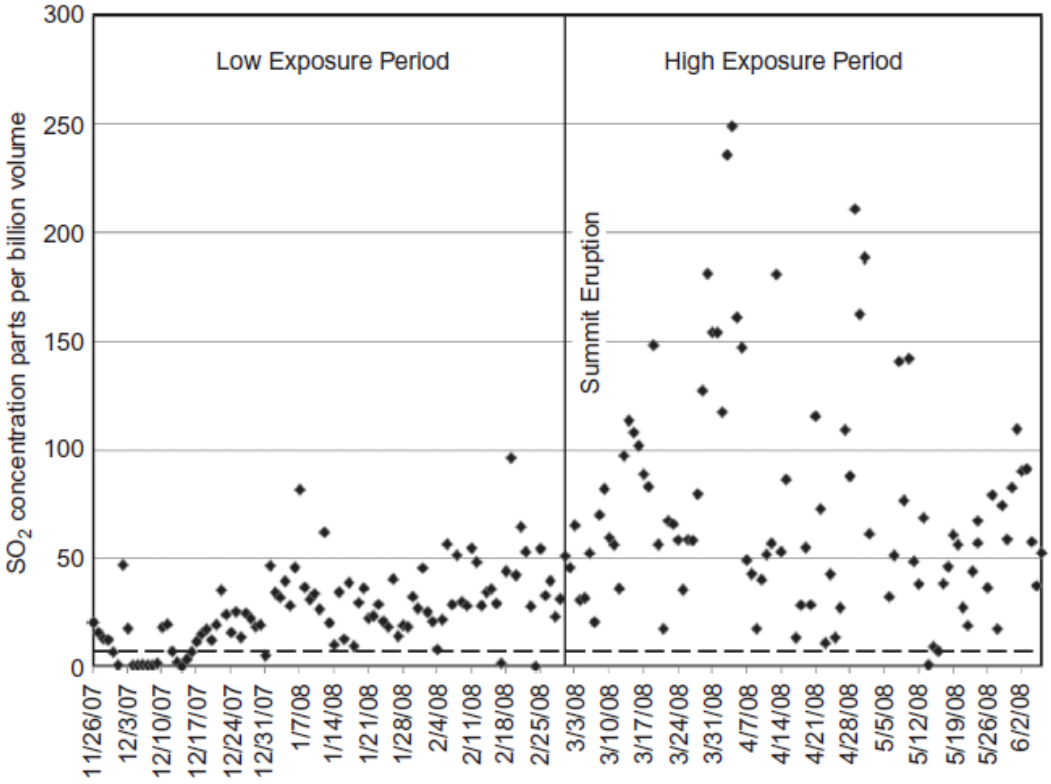
Satellite-borne instruments have mapped large SO_2 sources globally and have obtained data showing intercontinental transport. Fioletov et al. (2013) identified a number of "hotspots" for continuous SO_2 emissions, both anthropogenic and volcanic (e.g., industrial sources in China, Russia, the U.S., the Gulf of Mexico and Saudi Arabia; volcanic sources in Kīlauea, HI and Anahatan in the Marianas). Clarisse et al. (2011) showed evidence for transport of SO_2 from Asia to Alaska and Canada. In one such episode in November 2010, there was a clearly defined plume crossing the Pacific.

As described in Section 2.2.4.2, volcanic sources of SO_2 in the U.S. are found in the Pacific Northwest, Alaska, and Hawaii. The most important domestic effects from volcanic SO_2 occur on the Hawaiian Islands. Nearly continuous venting of SO_2 from Mauna Loa and Kīlauea produces SO_2 in high concentrations that can affect populated areas on the Big Island of Hawaii (as well as others in the chain, depending on wind conditions). Figure 2-28A shows the 2008−2013 time series for 1-h daily max SO_2 concentrations at Hilo, HI, (population of approximately 40,000), which is located about 50 km northeast of Kīlauea. Figure 2-28B shows the same time series at Pahala (population ~1,300) which is located about 30 km southeast of Kīlauea (Longo et al., 2010). As demonstrated by these figures, 1-h daily max SO_2 concentrations can reach levels greater than 1,000 ppb. Figure 2-29 shows a 6-month concentration time series for the Ka'u District, one of the other communities scattered throughout the southern half of the island that are also exposed to high SO_2 concentrations (Longo et al., 2010).



SO_2 = sulfur dioxide.

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



SO_2 = sulfur dioxide.

Note. The dashed line represents the World Health Organization 24-h avg SO_2 guideline = 7.5 ppbv (WHO, 2006).

Data source: SO_2 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

This section discusses various modeling techniques to estimate ambient concentrations of SO_2. Different types of models are discussed in terms of their capabilities, strengths, and limitations. Section 2.6.1 focuses on dispersion models, which are the most widely used and the most relevant for modeling the influence of large point sources on local-scale SO_2 concentrations in the urban and other near-field environments. Section 2.6.2 briefly discusses chemical transport models (CTMs) that can be used to model SO_2 concentrations at regional and national scales.

2.6.1 Dispersion Modeling

Atmospheric transport and dispersion (ATD) models are important mathematical tools for simulating the fate of air pollutants in support of a wide variety of environmental assessments. ATD models can be used to estimate SO_2 concentration for regulatory purposes if monitoring data are not available or sufficient (75 CFR 35520). Using equations that represent the physical and chemical atmospheric processes that govern dispersal and fate, ATD models provide an estimate of the concentration distribution, both temporally and spatially, of pollutants emitted from sources such as industrial facilities, roadways, and urban areas. The processes that are most important vary depending on the particular model application. The models must specifically account for the characteristics of the source or sources of the pollutant (e.g., buoyant releases), the meteorological conditions, the surrounding surfaces and complexities (e.g., buildings, terrain, and trees), the background concentrations from sources not considered directly in the modeling and the chemical transformations of the pollutant in the atmosphere.

Dispersion models are particularly important to pollutant studies where monitoring is not practical or sufficient. For pollutants such as SO_2 where spatial distributions of 1-h avg concentrations associated with large sources often contain extreme gradients, the siting of individual monitors to capture high ground-level concentrations over a wide variety of sources and meteorological conditions would be challenging at best. Extensive arrays of monitors are impractical. Thus, the implementation program for the 2010 primary SO_2 NAAQS allows for air quality modeling to be used in place of monitoring to characterize air quality, and for such air quality information to be used in the process for informing final designation decisions (75 FR 35520). The SO_2 NAAQS is currently the only criteria pollutant standard for which modeling may be used to characterize air quality for the purpose of the area designation process. In addition, modeling is critical to the assessment of the impact of future sources or proposed modifications where monitoring cannot inform. Also, modeling is helpful in the design and implementation of mitigation techniques for addressing existing pollution problems and for compliance evaluations.

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

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

In the U.S., steady-state Gaussian models are the most common dispersion models used for primary pollutants like SO_2 (U.S. EPA, 2010a). These models may be used to determine compliance with standards and primary pollutant impacts from new or proposed sources. The same is true for these types of analyses in other countries. For example, ADMS (Carruthers et al., 1995), HPDM (Hanna and Chang, 1993), OML (Olesen et al., 1992), and several other steady-state Gaussian-based models have been recommended by the European Environment Agency (van Aalst et al., 1998) for applications involving SO_2 from smoke stacks. Other examples in which Gaussian-type models are found to be applicable for near-field applications are by the U.K. Department of Environment, Food, and Rural Affairs (Williams et al., 2011) and by the New Zealand Ministry of the Environment (Bluett et al., 2004). The primary concerns for many of these compliance-type applications are the magnitude, location, and frequency of high concentrations and the strong gradients of concentrations found near sources. Often the highest concentrations are found within a few kilometers and sometimes within tens of meters of the source. Near-field or near-to-the-source dispersion is the real strength of steady-state modeling.

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

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

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

One limitation of the Gaussian approach is the assumption of steady conditions over a 1-hour modeling period and over the plume transport distance to the receptors. The model is recommended for receptors up to 50 km from a source when steady conditions are appropriate (U.S. EPA, 2005b). However, this can be challenging, especially for light winds. Under low wind conditions, there are concerns that AERMOD can overestimate measured SO_2 concentrations without adjustment for empirical relationships between wind and concentration (Paine et al., 2015). Recent updates to AERMOD have been made by the U.S. EPA to address those concerns (80 FR 45340). AERMOD is also limited in its treatment of SO_2 chemistry, using a method much simpler than the more rigorous simulation of atmospheric transformation of SO_2 found in models such as CMAQ or SCICHEM (Chowdhury et al., 2012). AERMOD uses a simple 4-hour half-life assumption for reducing SO_2 concentration in the plume with travel time (Turner, 1964). This approach yields results consistent with the SO_2 residence time estimates by Hidy (1994) and Seinfeld and Pandis (2006). Therefore, for conditions and sources where the highest hourly concentrations are expected to be relatively close to the source, chemistry is not expected to play a major role in determining compliance with primary standards.

Lagrangian puff dispersion models, such as CALPUFF, have been developed as an alternative to Gaussian dispersion models, such as AERMOD. CALPUFF models SO_2 as particles and then uses a Lagrangian step algorithm to model nonsteady-state dynamics, using time-varying winds specified by meteorological models, such as MM5 [e.g., Atabi et al. (2016), Abdul-Wahab et al. (2011), Souto et al. (2014), Lee et al. (2014), Zhang et al. (2015a)]. The nonsteady-state approach offered by Lagrangian puff dispersion models may be considered an alternative to Gaussian dispersion models that do not account for time dependence. Comparisons have been conducted between Lagrangian models such as CALPFUFF and Gaussian plume models such as AERMOD. CALPUFF predictions of

24-hour SO_2 concentrations at an oil refinery in Sohar, Oman compared within 36% of measurements (Abdul-Wahab et al., 2011). Comparison of CALPUFF and AERMOD to SO_2 measurements at a gas refinery in South Pars, Qatar showed that, while CALPUFF and AERMOD both typically underestimated SO_2 measurements, CALPUFF predictions were usually closer to measured SO_2 concentrations compared with AERMOD (Atabi et al., 2016). However, Rood (2014) observed that Lagrangian puff models and Gaussian dispersion models both underpredicted 1-h and 9-h avg concentrations, but the magnitude of bias was larger in the Lagrangian puff models applied at a field site in Colorado with variable winds and natural topography. Holnicki et al. (2016) noted that the model performance improved with longer averaging times and that the 1-h avg concentration predicted by CALPUFF was less accurate than predictions for annual average concentrations, when compared to SO_2 measurements. However, recent dispersion modeling results were compared between CALPUFF and AERMOD for the Section 126 Petition from New Jersey for the Portland Generating Station (76 FR 69052) where CALPUFF overestimated 1-h daily max SO_2 observations taken in Columbia, NJ by 226%, while AERMOD overestimated the same observations by 14%.

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

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

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

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

For models intended for application to compliance assessments (e.g., related to the 1-h daily max SO_2 standard), the model's ability to capture the high end of the concentration distribution is important. Measures such as robust highest concentration (RHC) (Cox and Tikvart, 1990), and exploratory examinations of quantile-quantile plots (Chambers et al., 1983) are useful. The RHC represents a smoothed estimate of the top values in the distribution of hourly concentrations. In contrast, for dispersion modeling in support of health studies where the model must capture concentrations at specified locations and time periods, additional measures of bias and scatter are important.

The intended use of a model and the objective of a model evaluation guide the selection of evaluation criteria. Frost (2014) considered model performance for AERMOD, applied to the study of 1 year of SO_2 emissions from three coal-fired EGUs. The authors found good agreement (judged to be within a factor of two of the 99th percentile SO_2 design value) for the majority of the data but noted performance outside a factor of two for the top 5% of measured 1-h avg concentrations. However, Rehbein et al. (2014) found that the model fell within a factor of two of the monitoring data even at high concentrations for a model validation outside a nickel smelting facility in Sudbury, Ontario, Canada. U.S. EPA also conducted evaluations of prognostic meteorological data in AERMOD (U.S. EPA, 2015a), including the facility modeled by Frost (2014). These evaluations included data analysis adhering to the U.S. EPA Protocol for Best Performing Models, which includes a scientific and operational component of model performance (U.S. EPA, 1992). SO_2 concentrations modeled by AERMOD were within a factor of two of observations in all but one simulation when using the metrics of the protocol. Meteorological parameters were modeled with FB within 20% of observations (U.S. EPA, 2015a).

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

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

With the adoption of the 2010 1-h daily max SO_2 standard, there is renewed interest in AERMOD's abilities to simulate near-field maximum short-term concentrations. A number of specific areas for model improvement were discussed at the 10th and 11th Modeling Conference on Air Quality in 2012 (U.S. EPA, 2012a) and 2015 (U.S. EPA, 2016a). Among them were concerns about simulations in stable conditions with light and meandering winds, use of prognostic meteorological data, modeling of emissions from haul roads, plume chemistry, and building downwash. Proposed improvements include an adjusted friction velocity model for stable/low wind conditions in AERMET, a new model for dispersion options in AERMOD, and an option for buoyant line sources in AERMOD (U.S. EPA, 2016a). Research in many of these areas is underway, and improvements to AERMOD have been made based on the outcomes of those conferences, largely as part of EPA rulemaking to revise the *Guideline*. While the stochastic nature of the atmosphere will always preclude the development of a perfect model, improvements to the model formulations will continue with the goal of estimating hourly average concentrations while reducing model uncertainty and expanding applicability.

2.6.2 Chemical Transport Models

Chemical transport models are an important tool for characterizing regional- and national-scale air quality. The scales at which they typically operate are too large to satisfactorily capture meteorological and chemical processes involving SO_2 at the local or near-source scale. The dispersion models discussed previously are thus preferable for characterizing SO_2 concentrations at these scales.

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

primary species such as SO_2, NO_2, NH_3, VOCs, and primary PM, and by meteorological fields produced by other numerical weather prediction models. Values for meteorological variables such as winds and temperatures are taken from a meteorological model that is nudged by operational analyses, re-analyses, or general circulation models. In most cases, these are off-line meteorological predictions, thus they are not modified by radiatively active species generated by the air quality model. Work to integrate meteorology and chemistry was initiated in the mid-1990s [by Lu et al. (1997a) and Lu et al. (1997b) and references therein], although limits to computing power prevented widespread application. More recently, new integrated models of meteorology and chemistry are available; see, for example, the Weather Research and Forecast model with chemistry (WRF-Chem; http://ruc.noaa.gov/wrf/wrf-chem/) and WRF-CMAQ (Wong et al., 2012).

Biases in SO_2 concentrations predicted by CTMs can occur as a result of error in model representation of atmospheric processes converting SO_2 to H_2SO_4 and in removal processes. For example, overestimates of cloud-based reactions converting SO_2 to H_2SO_4 have been shown to negatively bias SO_2 concentration estimates in CMAQ v4.6 (Mueller et al., 2011). Improvements to modeling these processes, such as capturing metal catalysis of the $SO_2 \rightarrow H_2SO_4$ conversion process, have been included in CMAQ v5.0.2 to improve model estimates of SO_2 and SO_4^{2-} (Alexander et al., 2009). Therefore, when using CMAQ to estimate exposure to SO_2, attention must be given to the version of the model so that any inherent biases are understood.

The Air Quality Model Evaluation International Initiative (AQMEII) was developed by scientists in Europe and North America to evaluate several CTMs against each other using common input data sets (Rao et al., 2011). Pouliot et al. (2015) assembled emissions input data for European and North American simulations performed over two phases of the AQMEII study and found a 12% reduction in SO_2 emission estimates for 2006 in both Europe and North America. These differences were attributed to differences in methodologies used to estimate emissions and to differences in input data that influence the CTM output. In a comparison of CTM models of SO_2 with surface measurements in Europe, the Modeling Atmospheric Composition and Climate (MACC) model reanalysis overestimated surface SO_2 concentrations by 40% in winter and underestimated surface SO_2 levels by 63% in summer (Giordano et al., 2015). In North America, MACC underestimated SO_2 in summer by 81%. MACC results were higher than regional CTMs in the winter for North America, and seasonal variability was not well captured ($r = 0.16$ in summer and $r = 0.19$ in winter). These errors were thought to relate to the differences in the lifetime of SO_2 transported from the domain borders to the domain center being shorter than the timescale of the model bias.

2.7 Summary

Of the sulfur oxides, SO_2 is the most abundant in the atmosphere, the most important in atmospheric chemistry, and the one most clearly linked to human health effects. Thus, the NAAQS are currently set using SO_2 as the indicator species. As a consequence of several U.S. air quality regulatory programs, emissions of SO_2 have declined by approximately 72% for all NEI source categories during the time period 1990−2011 (Section 2.2). Coal-fired EGUs remain the dominant anthropogenic source by nearly an order of magnitude above the next highest source (coal-fired boilers), emitting 4.6 x 10^6 tons SO_2 annually, according to the 2011 NEI. Natural sources include volcanoes, wildfires, and biogenic sulfides that are intermittent and of limited spatial extent.

Beyond the size of the emissions source, the important variables that determine the concentration of SO_2 downwind of a source are the photochemical removal processes occurring in the emissions plume (Section 2.3) and local meteorology. The gas-phase oxidation of SO_2 by hydroxyl radical is slow in comparison to aqueous-phase oxidation in cloud and fog droplets. Clouds and fog can reduce local SO_2 concentrations by converting it to H_2SO_4 in the droplet phase. Another gas-phase oxidation mechanism involves a Criegee intermediate biradical that participates in converting SO_2 to SO_3. The Criegee-based SO_2 oxidation mechanism may amplify the rate of SO_2 removal in areas with high concentrations of Criegee precursors (i.e., low molecular weight organic gases, such as biogenic compounds, and unsaturated hydrocarbons) present downwind of industrial sites and refineries. The atmospheric SO_2 oxidation processes, coupled with variable meteorological conditions, including wind, atmospheric stability, humidity, and cloud/fog cover, influence the observed SO_2 concentrations at urban monitoring sites.

Changes were undertaken to the existing U.S. EPA monitoring network as a result of the new 1-h daily max primary NAAQS standard promulgated in 2010 (Section 2.4). First, the automated pulsed ultraviolet fluorescence (UVF) method, the method most commonly used by state and local monitoring agencies for NAAQS compliance, was designated as a FRM. Second, new SO_2 monitoring guidelines require states to report 5-minute data in light of health effects evidence on lung function decrements among exercising individuals with asthma following a 5−10 minute exposure of SO_2 above 200 ppb (Section 5.2.1.2). There are 380 monitoring sites across the U.S. reporting 5-minute data. Analysis of environmental concentrations of SO_2 data reported in this chapter reflect the monitoring network changes, particularly the analysis of the recent 5-minute data.

On a nationwide basis, the average 1-h daily max SO_2 concentration reported during 2013−2015 is 5.4 ppb (Section 2.5.2.1). However, peak concentrations (99th percentile)

of the 1-h daily max SO_2 concentrations can be greater than 75 ppb at some monitoring sites located near large anthropogenic or natural sources (e.g., volcanoes). SO_2 concentration is highly variable across urban spatial scales (Section 2.5.2.2), exhibiting moderate to poor correlations between SO_2 concentrations measured at different monitoring sites across a metropolitan area. This high degree of urban spatial variability may not be fully captured by central site monitoring estimates.

Long-term concentration trends show a steady decline in the mean, 10th, and 90th percentile of the site-specific 99th percentile of the 1-h daily max SO_2 concentrations (Section 2.5.3). The data show a 76% decline in 99th percentile 1-h daily max SO_2 concentration over the period 1990−2015. Seasonal trends were examined for six focus areas, and only New York and, to a lesser extent, Houston, exhibited strong intra-annual trend in which cool season 1-h daily max SO_2 concentrations were higher than warm season 1-h daily max SO_2 concentrations. Diel patterns in 1-h avg SO_2 concentration mostly shows daytime concentrations peak in the morning or midday, and the time of the peak can vary by location and may be influenced by seasonal conditions.

Peak concentrations within an SO_2 plume can greatly exceed the mean concentration at the plume centerline, so that exposure to the peak may greatly exceed an hourly or daily SO_2 measurement (Section 2.5.4). PMRs obtained from comparing the 5-minute hourly max with the 1-h avg AQS data at sites where both measures were available simultaneously had a range of 1 to 5.5 with a median of 1.3. In a city with low SO_2 concentrations, a high PMR may still be related to elevated 5-minute hourly max SO_2 concentration. For example, overall 1-h daily max concentrations in the New York focus area were relatively low (highest 99th percentile 1-h daily max was 16.5 ppb), so a PMR of 2 or 3 would lead to a 5-minute hourly max of 33 or 49.5 ppb. In contrast, the 1-h daily max concentrations in Gila County were much higher (highest 99th percentile 1-h daily max was 247 ppb), which would suggest 5-minute hourly max concentrations of 504 ppb if the PMR were 2 and of 741 ppb if the PMR were 3.

Contributions to background concentrations include natural emissions of SO_2 and photochemical reactions involving reduced sulfur compounds of natural origin, as well as the transport of sulfur compounds from outside of the U.S. (Section 2.5.5). In the U.S. Northwest, geothermal sources of SO_2 are responsible for 70 to 80% of the background SO_2 concentration; even so, total SO_2 concentrations are still on the order of ~2 ppb or less. In model simulations, background contributed less than 1% to SO_2 concentrations in surface air in 2001 throughout much of the contiguous U.S. Even with ambient concentrations for 2013−2015 that were roughly half the magnitude of those measured around 2001, the estimated background SO_2 would contribute only 2% to ambient SO_2 concentrations in most of the contiguous U.S.

Atmospheric modeling includes dispersion and chemical transport models to estimate SO_2 concentrations in locations where monitoring is not practical or sufficient (Section 2.6). Because existing ambient SO_2 monitors may not be sited in locations to capture peak 1-h daily max concentrations, the implementation program for the 2010 primary SO_2 NAAQS allows for air quality modeling to be used to characterize air quality for informing designation decisions (75 FR 35520). Modeling is critical to assessing the impact of future sources or proposed modifications when monitoring cannot be informative, and for designing and implementing mitigation techniques.

Chapter 3 Exposure to Ambient Sulfur Dioxide

3.1 Introduction

The 2008 SO_X ISA (U.S. EPA, 2008d) evaluated ambient SO_2 concentrations and exposure assessment in multiple microenvironments, presented methods for estimating personal and population exposure via monitoring and modeling, analyzed relationships between personal SO_2 exposure and ambient SO_2 concentrations, and discussed the implications of using ambient SO_2 concentrations to estimate exposure in epidemiologic studies. This chapter summarizes that information and presents new information regarding exposure to ambient SO_2. The chapter will focus on the inhalation exposure route for SO_2 from the key sources described in Chapter 2 because the presence of other SO_X species in the atmosphere has not been demonstrated, as discussed previously. Exposure to particulate sulfate formed by oxidation of SO_2 is considered in the PM ISA (U.S. EPA, 2009a). Sections within the chapter are organized to first present broad exposure concepts applicable to air pollution in general, followed by SO_2-specific material. Topics addressed in the chapter include methodological considerations for use of exposure data, and exposure assessment and epidemiologic inference. Many new studies are included in this chapter to better characterize exposure and understand exposure error. This material provides context for interpreting the epidemiologic studies described in Chapter 5.

3.2 Conceptual Overview of Human Exposure

3.2.1 Exposure Metrics

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

The *concentration* of an air pollutant is defined as the mass or volume of the pollutant in a given volume of air (e.g., $\mu g/m^3$ or ppb). Concentrations observed in outdoor locations are referred to as ambient concentrations. The term *exposure* refers to contact with a specific pollutant concentration over a certain period of time (Zartarian et al., 2005), in single or multiple locations. For example, contact with a concentration of 10 ppb SO_2 for 1 hour would be referred to as a 1-hour exposure to 10 ppb SO_2, and 10 ppb is referred to

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

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

Because personal exposures are not routinely measured, the term *surrogate* is used in this chapter to describe a quantity meant to estimate or represent exposure, such as an SO_2 concentration measured at a central site monitor (Sarnat et al., 2000). When surrogates are used for exposure assignment in epidemiologic studies, exposure misclassification or exposure error can result. *Exposure misclassification* refers to exposure error for categorical variables, such as diseased and nondiseased individuals. Exposure misclassification due to exposure assignment methods and spatial and temporal variability in pollutant concentrations may be either differential (i.e., systematic), or nondifferential (i.e., random). An example of differential misclassification is the use of geocoding to estimate air pollution exposure by proximity to roadways, because concentrations are different upwind and downwind of a major roadway (Lane et al., 2013; Singer et al., 2004). Nondifferential misclassification refers to the situation where exposure characterization is similarly accurate across all groups.

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

Exposure error refers to the bias and uncertainty associated with using concentration metrics to represent the actual exposure of an individual or population (Lipfert and

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

3.2.2 Conceptual Model of Personal Exposure

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

An individual's time-integrated total exposure to SO_2 can be described based on a compartmentalization of the person's activities throughout a given time period:

$$E_T = \int C_j \, dt$$

Equation 3-1

where E_T = total exposure over a time period of interest, C_j = airborne SO_2 concentration at microenvironment j, and dt = portion of the time period spent in microenvironment j. Total exposure can be decomposed into a model that accounts for exposure to SO_2 of ambient (E_a) and nonambient (E_{na}) origin of the form:

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

Equation 3-2

Although indoor combustion of sulfur-containing fuels, particularly kerosene, is a nonambient source of SO_2 (see Section 3.4.1), these sources are specific to individuals and may not be important sources of population exposure. This ISA focuses on the ambient component of exposure because this is more relevant to the NAAQS review. Assuming steady-state outdoor conditions, E_a can be expressed in terms of the fraction of time spent in various outdoor and indoor (including enclosed microenvironments such as vehicles) microenvironments (U.S. EPA, 2006; Wilson et al., 2000):

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

Equation 3-3

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

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

Equation 3-4

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

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

Equation 3-5

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

use concentration measured at a central site monitor to represent ambient concentration; thus α, the ratio between personal exposure to ambient SO_2 and the ambient concentration of SO_2, is defined as:

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

Equation 3-6

Combining Equation 3-5 and Equation 3-6 yields:

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

Equation 3-7

where α varies between 0 and 1. Estimates of α for SO_2 are provided in Section 3.4.1.3. If a person's exposure occurs in a single microenvironment, the ambient component of a microenvironmental SO_2 concentration can be represented as the product of the ambient concentration and F_{inf}. Time-activity data and corresponding estimates of F_{inf} for each microenvironmental exposure are needed to compute an individual's α with accuracy (U.S. EPA, 2006). In epidemiologic studies, α is assumed to be constant in lieu of time-activity data and estimates of F_{inf}, which varies with building- and meteorology-related air exchange characteristics (Section 3.4.1.1). If important local outdoor sources and sinks exist that are not captured by central site monitors, then the ambient component of the local outdoor concentration may be estimated using dispersion models, land use regression (LUR) models, receptor models, fine-scale chemical transport models (CTMs), or some combination of these techniques. These techniques are described in Section 3.3.2.

3.2.3 Exposure Considerations Specific to Sulfur Dioxide

The inhalation exposure pathway relevant for SO_2 is influenced by sources, chemistry, meteorology, and ambient concentrations, described in detail in Chapter 2 and summarized briefly here. The vast majority of SO_2 is emitted by coal-fired EGUs (Section 2.2); the point source nature of these emissions contributes to the relatively high spatial variability of SO_2 concentrations (both ambient and exposure) compared with pollutants such as PM and O_3 (Section 2.5; Section 3.4.2.2). Another contributing factor to spatial variability is the dispersion and oxidation of SO_2 in the atmosphere (Section 2.3), resulting in decreasing ambient SO_2 concentrations with increasing distance from the source. SO_2 travels as a plume, which may or may not impact portions of an urban area depending on meteorological conditions. Ambient SO_2 concentrations do not exhibit consistently strong temporal variability over daily or seasonal time scales

(Section 2.5); however, in some areas, concentrations are low during nighttime and show a daytime maximum, affecting temporal exposure patterns. Due to the relative lack of indoor SO_2 sources, personal SO_2 exposure is expected to be dominated by ambient exposure (Section 3.4.1.3).

3.3 Methodological Considerations for Use of Exposure Data

This section describes techniques that have been used to measure microenvironmental concentrations of SO_2 that serve as surrogates for personal SO_2 exposures in epidemiologic studies. Previous studies from the 2008 SO_X ISA (U.S. EPA, 2008d) are described along with newer studies.

3.3.1 Measurements

3.3.1.1 Central Site Monitoring

Central site monitors are sited for the purpose of determining whether attainment goals are met under the Clean Air Act. However, central site monitoring ambient SO_2 concentration data are also often used in epidemiologic studies as a surrogate for exposure to SO_2, as discussed in Section 3.4.4. Methods, errors, and uncertainties regarding measurements made by central site monitors are described in Section 2.4. The effect of errors and uncertainties due to instrumentation issues depends on epidemiologic study design, as described further in Section 3.4.4. Various uses of these data are possible depending on the design of the epidemiologic study. Short-term (e.g., daily, hourly) data can be used for time-series studies and long-term (e.g., annual average) data for longer term studies. For a given CBSA, central site monitors are sited at a fixed location based on the number of people living in the CBSA and the sources of SO_2 emissions (40 CFR 58, Appendix D). Even in CBSAs with multiple monitors, the monitors do not fully capture spatial variability in SO_2 concentration across the study area.

3.3.1.2 Personal Monitoring Techniques

Personal SO_2 monitors have been used in studies characterizing relationships between indoor and outdoor SO_2 concentrations and relationships between personal exposure to SO_2 and ambient SO_2 concentrations (Section 3.4.1.3). Additionally, personal monitoring

is used infrequently in the epidemiologic studies described in Chapter 5. As described in the 2008 SO_X ISA (U.S. EPA, 2008d), both active and passive samplers have been used to measure personal SO_2 exposures. The Harvard-EPA annular denuder system is an active sampler initially developed to measure particles and acidic gases simultaneously (Brauer et al., 1989; Koutrakis et al., 1988). The system draws air at 4 L/minute past an impactor to remove particles and then through an annular denuder coated with sodium carbonate to trap SO_2 and other acidic gases. Gases collected within the denuder are extracted with ultrapure water and analyzed by ion chromatography. The detection limit depends on the sensitivity of the ion chromatography analysis as well as the volume of air sampled, and is typically below 1 ppb (Brauer et al., 1989), with a collection efficiency of 99.3% (Koutrakis et al., 1988). Another active sampler, developed for a study in Baltimore, MD, used a hollow glass denuder coated with triethanolamine, with SO_2 detection by ion chromatography (Chang et al., 2000). At a sampling rate of 100 mL/minute for 1 hour, the detection limit was 62 ppb, resulting in many of the 1-hour SO_2 samples being below the detection limit; see Section 2.5 for a summary of typical ambient SO_2 concentrations.

Passive badge-type samplers have also been developed to eliminate the need for a powered sampling pump. A common version is manufactured by Ogawa USA, Inc. and consists of a cellulose fiber filter coated with triethanolamine (Ogawa & Co, 2007). SO_2 is detected via ion chromatography with a reported detection limit for a 24-hour sample of 2−6 ppb (Sarnat et al., 2006; Sarnat et al., 2005; Sarnat et al., 2000). Passive badge samplers can also be combined with active particle samplers to create a multipollutant sampler [e.g., Demokritou et al. (2001)]. Passive badges for measuring SO_2 concentrations are not very sensitive to ambient concentration level, temperature, relative humidity, or exposure duration, unlike passive badges for measuring NO_2 (Swaans et al., 2007). The cumulative sampling approach and the relatively high detection limit of the passive badges makes them mainly suitable for monitoring periods of 24 hours or greater, which limits their ability to measure short-term daily fluctuations in personal SO_2 exposures.

3.3.2 Modeling

Models can be used to predict the outdoor concentration of SO_2 across geographic regions or at specific locations of interest where people spend time (e.g., outdoors at homes, schools, workplaces, roadways). The modeled concentration can be used as a surrogate for human exposure to SO_2. Models do not estimate exposures to ambient SO_2 directly, because time-activity patterns and indoor concentrations of ambient SO_2 in various microenvironments are not considered. Approaches described below include

source proximity models (SPM), LUR, inverse distance weighting (IDW) models, dispersion models, CTM, and microenvironmental models. These models can be employed at urban, regional, or national scales to estimate daily, or longer, average ambient SO_2 concentrations as an exposure surrogate. Short-term (e.g., daily) ambient SO_2 concentration estimates are needed for ambient SO_2 exposure surrogates in acute exposure assessments, whereas long-term (e.g., annual) ambient SO_2 concentration estimates can be used for ambient SO_2 exposure surrogates in chronic exposure assessments.

3.3.2.1 Source Proximity Models

SPMs provide a simple method to estimate ambient SO_2 concentration as a surrogate for ambient SO_2 exposure. These models calculate the distance from receptors (e.g., homes, schools) to a source of SO_2 emissions (e.g., industrial facilities). It is assumed that ambient SO_2 concentration is some function of distance from the source. SO_2 emitted from a point source is thought to disperse as a meandering plume, such that average ambient SO_2 concentration decreases with distance from the source (Section 2.6.1). These models do not necessarily account for the effect of stack height to limit ambient SO_2 concentrations in the immediate vicinity of the point source. Burstyn et al. (2008) avoided the stack height issue by modeling ambient SO_2 concentration as a function of the inverse distance within 2- and 50-km buffers of each gas plant and oil well. In another study, proximity to source was treated as a Boolean variable as a surrogate for high and moderate ambient SO_2 exposure (Cambra et al., 2011). Likewise, Liu et al. (2012b) computed relative risk of respiratory disease using ZIP codes with fuel-fired power plants compared with the reference of ZIP codes without fuel-fired power plants. One study specifically examined near-road proximity and ambient SO_2 concentration and found no statistically significant decrease in ambient SO_2 concentration near a highway (McAdam et al., 2011).

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

To improve the accuracy of SPMs in providing a surrogate for exposure, an emission-weighted proximity model (EWPM) was developed that considers the emission rate and duration of each ambient SO_2 point source, in addition to the distance from source. Zou et al. (2009b) evaluated the SPM and EWPM to estimate ambient SO_2

concentrations in Dallas and Ellis counties, TX. Normalized ambient SO_2 concentration estimates based on SPM and EWPM were compared to normalized ambient SO_2 concentration measurements at three monitoring sites and found that EWPM-based ambient SO_2 concentration estimates agreed more closely to the observed ambient SO_2 concentrations than SPM-based ambient SO_2 concentration estimates. Epidemiologic estimates of risk also were in closer agreement between EWPM and AERMOD compared with the comparison of results using SPM and AERMOD (Zou et al., 2011). In addition, surface maps of EWPM- and SPM-predicted ambient SO_2 concentrations across two counties showed that with SPM risk of exposure is usually overestimated in the region of dense emission sources and underestimated where emission sources were sparse (Zou et al., 2009b). As compared to SPM, EWPM more accurately predicted ambient SO_2 concentrations that individuals were exposed to across these regions.

3.3.2.2 Land Use Regression Models

LUR models are used to estimate ambient SO_2 concentration as a surrogate for exposure in some large health studies, because they provide spatial variability in estimates of ambient SO_2 concentration across the geographic area of the study population. A detailed description of LUR models is provided in Chapter 3 of the 2016 ISA for Oxides of Nitrogen (U.S. EPA, 2016e). Briefly, LUR fits a multiple linear regression model of concentration based on local data (e.g., proximity to SO_2 emissions sources, road length, land use, population density) and then applies that model to locations without monitors as an attempt to increase heterogeneity in the spatial resolution of the ambient SO_2 concentration field compared with other methods, such as central site monitoring (Marshall et al., 2008). A structured framework for comparing modeling approaches could occur with reporting of metrics such as spatial scale, averaging time, out-of-sample coefficient of variation (i.e., goodness of fit of the model with data not used to fit it to cross-validate the model), in-sample coefficient of variation (i.e., goodness of fit of the model with data used to fit it), and root mean squared error (RMSE). However, studies in the literature of LUR model results do not consistently report all of these parameters. The discussion of LUR models below includes the metrics provided in specific papers.

Models are typically calibrated using ambient SO_2 concentration data from passive sampler measurements and several local predictor variables. Given that most passive ambient SO_2 concentration measurement methods are not designed for short-term sampling, LUR models are typically based on several days, weeks, or years of data and thus do not account well for short-term temporal variability in the ambient SO_2 concentration estimates. Hence, LUR is commonly used to estimate air pollution exposure in long-term epidemiologic studies. Although LUR is usually employed for

NO_2, it has also been used to study spatial variability in ambient SO_2 concentration in a small number of studies [e.g., Atari et al. (2008)]. Several methodological issues must be considered when interpreting LUR model results. These issues include number of measurement sites used to fit the statistical model, predictor variable selection, and comparison of LUR performance among LUR model formulations and with other models. These issues affect how well the spatial variability of ambient SO_2 concentration in a city is represented by the LUR. For example, in a study incorporating aerosol optical density from satellite measurements and three-dimensional building data with land use variables in predicting variation in SO_2 concentration across space, the LUR model fit improved from adjusted $R^2 = 0.52$ to 0.71 (Gong et al., 2016).

LUR models have been applied to estimate ambient SO_2 concentrations in close proximity to industrial SO_2 sources. Atari et al. (2008) developed an LUR model to predict ambient SO_2 concentrations in Sarnia, Ontario, Canada, an area known as "Chemical Valley" for its high density of chemical industries. Ambient SO_2 concentrations measured by passive badge monitors were used to "train" the model, and the explanatory variables for the LUR model were distance to an industrial zone, location within 1,200 m of industrial areas, and location within 100 m of major roads. Measurements of ambient SO_2 concentration for model training were collected with passive samplers at 37 locations across the city for 2 weeks in the fall of 2005, with an average concentration of 3.4 ppb. The in-sample coefficient of determination was $R^2 = 0.66$. An out-of-sample coefficient of determination was calculated to cross-validate the model. The out-of-sample coefficient ranged from $R^2 = 0.62$ to $R^2 = 0.73$, and the RMSE of the out-of-sample predictions were 0.3 to 1 ppb. The ambient SO_2 concentration validation produced a wider range of errors and lower out-of-sample R^2 compared with LUR simulations for ambient NO_2 concentration; Atari et al. (2008) attributed this moderate validation to a skewed ambient SO_2 concentration distribution compared with the concentration distribution of ambient NO_2, although skewness metrics were not provided.

Spatial variability in ambient SO_2 concentrations offered by LUR has been used to estimate inter-individual variability in exposure by assuming the ambient SO_2 concentration modeled at the study participants' homes matched their exposure. Ambient SO_2 concentrations computed using LUR by Atari et al. (2008) were used by Atari et al. (2009) to correlate modeled ambient SO_2 concentrations with individual and community perceptions of odor, by Oiamo and Luginaah (2013) to study whether males and females are affected differently by ambient SO_2 exposure, and by Oiamo et al. (2011) to investigate the relationship between estimated ambient SO_2 exposure and access to a general practitioner. Kanaroglou et al. (2013) used a spatial autocorrelation LUR model to estimate ambient SO_2 concentrations, in which the spatial autocorrelation component

of the model's residuals was removed. Kanaroglou et al. (2013) applied the spatial autocorrelation LUR model in the vicinity of an industrial area in Hamilton, Ontario, Canada and observed that location and difference between wind direction and direction of the industrial area to the receptor were each statistically significant predictors of ambient SO_2 concentration ($p < 0.001$, RMSE = 1.24).

LUR has also been applied to predict ambient SO_2 concentrations in the vicinity of urban sources. Clougherty et al. (2013) modeled concentrations of ambient SO_2, NO_2, $PM_{2.5}$, and black carbon (BC) across New York City, NY. Ambient SO_2 concentration was predicted by the reference site mean (partial $R^2 = 0.35$), number of oil-burning units (partial $R^2 = 0.36$), and nighttime population within 1 km (partial $R^2 = 0.06$) to give an overall out-of-sample model fit of $R^2 = 0.77$, where R^2 was based on the comparison between raw ambient SO_2 concentrations and model predictions. Traffic covariates were not included in the model. The study authors thought these findings reflected the presence of large combustion boilers in Manhattan and western Bronx, where ambient SO_2 concentrations were predicted to be highest because sulfur content in residential heating fuel is high. Ambient SO_2 concentration was not influenced by vehicle traffic, unlike the other air pollutants studied. Beelen et al. (2007) modeled ambient SO_2, NO_2, NO, and black smoke (BS) concentrations as the sum of regional, urban, and local components. LUR was applied at the urban level to indicate land use (as location in a nonrural, urban, or industrial area) and at the local level to indicate traffic intensity with the combined spatial scale model in-sample $R^2 = 0.56$. The analysis used data from 1999−2000, when diesel fuel contained higher concentrations of sulfur, prior to 2006 and 2007 when the fuel standards promulgated in 2001 (66 FR 5002) reducing sulfur concentrations in diesel fuel took effect for highway vehicles and heavy-duty vehicles, respectively.
The out-of-sample RMSE was 1.6 ppb for the background model and 1.2 ppb for the urban model; RMSE was not reported for the local model. Ambient SO_2 concentrations modeled in the Beelen et al. (2007) study were used as exposure estimates in a longitudinal cohort study of vascular damage among young adults [see Section 5.3.2.5 and Lenters et al. (2010)]. Wheeler et al. (2008) applied LUR for a study of ambient SO_2 concentration to estimate exposure in Windsor, Ontario and found that distance to the Ambassador Bridge, housing density, and SO_2 emission sources from Detroit within 3 km were all significant predictors of ambient SO_2 concentration with in-sample $R^2 = 0.69$ and out-of-sample $R^2 = 0.65$. Wheeler et al. (2008) also evaluated LUR performance for predicting ambient SO_2 concentration across seasons by comparing the LUR results with measurements to estimate air pollutant exposure in Windsor, Ontario. They found that correlation of summer predictions of ambient SO_2 concentrations with those from other seasons was lower, suggesting that photochemistry might not be well represented in the LUR model.

3.3.2.3 Inverse Distance Weighting

IDW, in which ambient SO_2 concentration at a receptor point is calculated as the weighted average of ambient SO_2 concentration measured at monitoring locations, has been used to estimate exposure based on ambient SO_2 concentration surfaces. Several recent studies using IDW have been published. The weighting factor is an inverse function of distance between the receptor and the monitor. For example, Brauer et al. (2008) and MacIntyre et al. (2011) estimated exposure to ambient SO_2 and other industrial pollutants within 10 km of point sources using an IDW sum of ambient SO_2 concentration and the three closest monitors within 50 km for application in epidemiologic models (Clark et al., 2010). Often, the weighting factor is the inverse distance raised to some power, and a higher power is applied to increase the weight on monitors that are closer to the receptor. Rivera-González et al. (2015) applied an inverse-distance-squared weighting and compared the results with a citywide average, use of the nearest monitor, or kriging to develop an ambient SO_2 concentration surface. The results from IDW were correlated with the other three methods (r = 0.88−0.97), and the mean ambient SO_2 concentration estimated with IDW was within 10% of the mean computed with the other methods. However, Neupane et al. (2010) estimated the ambient SO_2 concentration surface using both bicubic spline interpolation and IDW for a study of long-term exposure to air pollutants and risk of hospitalization for pneumonia in Hamilton, Ontario, Canada in a case-control study design. Bicubic spline interpolation produced a lower mean ambient SO_2 concentration and larger IQR compared with IDW; the odds ratio (OR) was higher for the cubic splines model [OR: 0.23, 95% confidence interval (CI): 0.02−0.45] compared with the IDW model (OR: 0.06, 95% CI: −0.06−0.18), probably due to greater variability in the ambient SO_2 concentration data.

3.3.2.4 Dispersion Models

Gaussian dispersion models have been applied to estimate ambient SO_2 concentration as a surrogate for human exposure to SO_2. A detailed description of Gaussian dispersion modeling, along with its strengths and limitations for modeling ambient SO_2 concentrations, can be found in Section 2.6. This section highlights examples of using dispersion models to estimate ambient SO_2 concentration as a surrogate for exposure.

Zou et al. (2009c) developed a hybrid modeling system to estimate source-specific ambient SO_2 concentration across space as a surrogate for population exposure to ambient SO_2 in Dallas County, TX. First, an AERMOD dispersion model was run for three source scenarios (vehicle only, industrial only, and combined vehicle and industrial), and kriging interpolation was applied to the modeling results to produce a

monthly average ambient SO_2 concentration grid map (100 m × 100 m). The population exposure was next estimated by multiplying the ambient SO_2 concentration value and the corresponding population density value for each grid cell (100 m × 100 m) and for the three source classifications. The results showed that monthly population SO_2 exposure concentrations were moderately correlated with simulated ambient SO_2 concentrations from vehicle sources (r = 0.440) and weakly correlated with ambient SO_2 concentrations from industrial sources (r = 0.069); this study used emissions data from the year 2000, before the ultra-low sulfur diesel fuel regulations were enacted.

Lagrangian particle modeling has also been used to estimate ambient SO_X concentration as a surrogate for ambient SO_X exposure from specific sources (Ancona et al., 2015) to study the relationship of long-term exposure to SO_X with mortality for all-causes (Section 5.5.2.2), cardiovascular disease (Section 5.3.2.2), and cancer (Section 5.6.1). The Lagrangian particle model tracks the movement of SO_X as nonreactive parcels (i.e., massless particles), considering SO_X to be a marker of the emission source representing some combination of directly emitted SO_2 and sulfate formed in the atmosphere (Section 2.3). Gariazzo et al. (2004) compared this type of Lagrangian particle model against ambient SO_2 concentration measurements and observed reasonable agreement, although the observations seemed to lag the modeled ambient SO_2 concentration at times. The results suggest that the model would have provided a reasonable estimate of exposure in the Ancona et al. (2015) study, especially given the long-term nature of the study.

3.3.2.5 Chemical Transport Models

Ambient SO_2 concentrations calculated with CTMs, such as the CMAQ model, are sometimes used to estimate human exposure to ambient SO_2 (Section 2.6). For example, Lipfert et al. (2009) estimated ambient SO_2 concentration based on the CMAQ model for use as an exposure surrogate. Annual average ambient SO_2 concentrations were estimated with a 36-km by 36-km grid across the contiguous U.S. The modeled ambient SO_2 concentrations were used as exposure surrogates to determine their association with county-level mortality data for the Washington University-Electric Power Research Institute Veterans Cohort Mortality Study. To assign exposures at the county level, the CMAQ grid that included the largest city within each county was determined, and the associated CMAQ ambient SO_2 concentration was used as the exposure metric for the entire county.

CTMs can be applied in epidemiologic studies of either short- or long-term exposure to ambient SO_2 but are more commonly used in long-term ambient SO_2 exposure studies.

Given observed biases in the CTMs [e.g., U.S. EPA (2008c)], much attention has been given to bias correction of these models for application in exposure assessment. Chen et al. (2014a) evaluated CMAQ v4.7.1 results for several pollutants and found that ambient SO_2 concentration was underpredicted by roughly a factor of two, but this problem was largely ameliorated through bias correction techniques. Improvements to modeling ambient SO_2-related reactions have been corrected in CMAQ v5.0.2, so that ambient SO_2 concentrations used for exposure surrogates from this or later versions would have smaller exposure errors.

One major limitation of CTMs for estimating ambient SO_2 concentrations as exposure surrogates is that the grid resolution, typically between 4 and 36 km, can be much larger than the length scale of the meandering plume upon touch-down. This limitation presents the possibility that ambient SO_2 concentrations can be underestimated along the plume path when localized peaks are averaged over space. Baldasano et al. (2014) recognized this limitation and merged HYSPLIT with a CTM simulation of ambient SO_2 and PM_{10} transport in the vicinity of a refinery. HYSPLIT models dispersion of pollutants, such as ambient SO_2, as particle trajectories; the WRF meteorological model is coupled with the particle trajectory model to account for wind speed, wind direction, and atmospheric turbulence. Ching et al. (2006) nested smaller grids (1, 4, 12 km) within larger grids (36 km) to improve spatial variability of the simulation. Similarly, Karamchandani et al. (2010) coupled a plume-in-grid model with CTM that treats dispersion as a Gaussian process with parameters that are set using micrometeorological conditions. Inclusion of subgrid-scale modeling enables calculation of the ambient SO_2 plume at finer spatial scales so that maximum ambient SO_2 concentration, and potentially maximum exposures, can be estimated by the model suite (Baldasano et al., 2014).

3.3.2.6 Microenvironmental Exposure Models

Microenvironmental exposure models are designed to account for variations in the amount of time people spend in different locations by using time-weighted SO_2 concentrations in each microenvironment (e.g., outdoors; indoors at home, school, workplace; in-vehicle) for the exposure surrogate. Models such as SHEDS and APEX are used occasionally for exposure assessment in epidemiologic studies (Dionisio et al., 2014; Mannshardt et al., 2013; Chang et al., 2012a), and they are also used for the risk assessment performed as part of the NAAQS review process, as was done for the risk and exposure assessment during the last review of the SO_2 NAAQS (U.S. EPA, 2009b).

The fundamental principles of stochastic population exposure models are described in detail in the 2008 NO_X ISA Annex 3.6 (U.S. EPA, 2008a). Briefly, the models combine

ambient concentration data with information on infiltration into enclosed microenvironments, such as buildings and vehicles (see Section 3.4.1.1), to estimate microenvironmental concentrations. The models then use demographic variables such as age and sex to select appropriate activity patterns from a database. For the risk assessment done during the last review of the SO_2 NAAQS, the U.S. EPA used CHAD, which is described in Section 3.4.2.1 and in the 2016 NO_X ISA (U.S. EPA, 2016e). Inhalation rates are determined from the level of effort associated with each activity (e.g., sitting, walking, or running). Inhalation rates and microenvironmental concentrations are combined to estimate dose. Depending on the availability of controlled human exposure data, response functions based either on microenvironmental exposure concentrations or inhaled dose are used to characterize expected health effects. For population-level exposure assessments, exposure models such as SHEDS and APEX estimate the distribution of exposures across the population of interest (U.S. EPA, 2012c; Burke et al., 2001).

To improve the characterization of activity patterns, mobile electronic devices, such as smartphones with embedded GPS receivers and dedicated GPS data loggers, are increasingly used to collect time-location information. However, manual processing of GPS data to determine time spent in different microenvironments is limited due to large (potentially thousands of samples per person per day) and multidimensional (location, speed, time, signal quality) data sets, missing data due to loss of GPS signal reception while inside certain buildings, and difficulty discriminating among certain microenvironments (e.g., wooden structures have no substantial indoor/outdoor differences in satellite signal strength). To address these limitations, automated microenvironmental classification models have been developed (Breen et al., 2014a; Kim et al., 2012; Wu et al., 2011a; Adams et al., 2009; Elgethun et al., 2007). For example, Breen et al. (2014a) recently developed a classification model called MicroTrac to estimate time of day and duration spent in eight microenvironments (indoors and outdoors at home, work, school; inside vehicles; other locations) from GPS data and geocoded building boundaries. MicroTrac estimates were compared with diary data and correctly classified the microenvironment for 99.5% of the daily time spent by the participants. In conjunction with accelerometers, air pollutant monitors, and health monitors, GPS-based time-activity data and related monitors have the potential to reduce error in exposure assessment (NRC, 2012). Although these techniques are promising, researchers to date have not applied them to estimate exposures to SO_2 or to large field studies that could provide activity patterns suitable for inclusion in CHAD.

3.3.3 Choice of Exposure Metrics in Epidemiologic Studies

Epidemiologic studies use a variety of methods to assign a surrogate for ambient SO_2 exposure. Study design, data availability, and research objectives are all important factors when selecting an exposure assessment method. Common methods for assigning an exposure surrogate from monitoring data include using ambient SO_2 concentration measured at a single monitor to represent population exposure and averaging ambient SO_2 concentrations from multiple monitors. Investigators may also use statistical adjustment methods, such as trimming extreme values, to prepare the ambient SO_2 exposure concentration data. Epidemiologic study design influences the relevance and utility of exposure metrics. Table 3-1 summarizes various metrics used in epidemiologic studies of ambient SO_2 exposure, appropriate applications for the metrics, and errors and uncertainties that may be associated with the metrics.

3.4 Exposure Assessment, Error, and Epidemiologic Inference

This section describes exposure assessment issues related to the use of surrogates for ambient SO_2 exposure in epidemiologic studies that may influence or introduce error into the observed health effect estimate.

3.4.1 Relationships between Personal Exposure and Ambient Concentration

Several factors influence the relationship between personal SO_2 exposure and ambient SO_2 concentration. Indoor SO_2 concentrations are highly dependent on air exchange rate (AER) due to the lack of indoor SO_2 sources and the rapid deposition of ambient SO_2 after it penetrates into enclosed microenvironments (Section 3.4.1.1). Generally, indoor SO_2 concentrations are lower than ambient SO_2 concentrations measured outdoors. Because people spend the bulk of their time indoors (Section 3.4.2.1), personal SO_2 exposures are often much lower than ambient SO_2 concentrations. For example, Brown et al. (2009) reported the mean winter personal SO_2 exposure concentrations in Boston to be 1.8 ppb, while the ambient SO_2 concentration was 11.3 ppb. Both personal SO_2 exposure concentration and ambient SO_2 concentration were even lower in summer, with mean values of near zero and 3.6 ppb, respectively. The following sections describe studies evaluating AER, relationships between indoor and outdoor SO_2 concentrations, and personal-ambient relationships for SO_2.

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_2 concentration	Short-term community time-series studies: surrogate for ambient SO_2 exposure of a population within a city	Ambient SO_2 concentration measurements undergo rigorous quality assurance	Measurements of ambient SO_2 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_2 concentrations proximal to the receptors and ambient SO_2 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_2 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_2 concentration using ion chromatography to measure personal SO_2 exposure	Short-term panel epidemiologic studies: SO_2 exposure (e.g., personal or residential samples) within a geographic area	SO_2 concentrations are obtained at the site of the exposed person	High detection limit	High detection limit and potential for nonambient SO_2 exposure sampling may lead to reduced precision
		Long-term epidemiologic studies: SO_2 exposure within a city or among multiple cities			Potential for nonambient SO_2 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.

Exposure Assignment Method	Description	Epidemiologic Application	Strengths	Limitations	Errors and Uncertainties
Passive personal exposure monitors (Section 3.3.1.2)	SO_2 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_2 exposure within a city or among multiple cities	SO_2 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_2 exposure sampling may lead to bias and reduced precision
Source proximity model (Section 3.3.2.1)	Ambient SO_2 concentrations are estimated from distance of receptor from source	Long-term epidemiologic studies: surrogate for ambient SO_2 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_2 concentration at a receptor location is higher or lower than the average ambient SO_2 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_2 concentrations are estimated from distance of receptor to pollution source, emission rate, and duration	Long-term epidemiologic studies: surrogate for ambient SO_2 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_2 concentration at a receptor location is higher or lower than the average ambient SO_2 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_2 concentrations are regressed on local variables (e.g., land use factors), and the resulting model is used to estimate ambient SO_2 concentrations at specific locations	Long-term epidemiologic studies: surrogate for ambient SO_2 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_2 concentrations are interpolated to estimate ambient SO_2 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_2 exposure, usually within a city or geographic region	High spatial resolution, few input data needed	Does not fully capture spatial variability of ambient SO_2 concentration among monitors	Potential for negative bias and reduced precision if ambient SO_2 sources are not captured or overly smoothed
Dispersion modeling (Section 3.3.2.4)	Ambient SO_2 concentrations at specific locations are estimated from emissions, meteorology, and atmospheric physics	Long-term epidemiologic studies: surrogate for ambient SO_2 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_2 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_2 concentrations are estimated from emissions, meteorology, and atmospheric chemistry and physics	Long-term epidemiologic studies: surrogate for ambient SO_2 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_2 emissions sources	Potential for bias and reduced precision when grid cells are too large to capture spatial variability of ambient SO_2 exposures
Microenvironmental model (e.g., APEX, SHEDS) (Section 3.3.2.6)	Estimates distributions of micro-environmental SO_2 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_2 exposures across large populations, accounts for different concentrations in different microenvironments, accounts for location-activity information	Input data from ambient SO_2 concentrations are required, does not estimate exposures for individuals	Potential for bias and reduced precision when the modeled distributions of ambient SO_2 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_2 = sulfur dioxide.

3.4.1.1 Air Exchange Rate

AER, which is the airflow into and out of a building and is represented by *a* in the conceptual model presented in Section 3.2.2, influences the rate of entry of ambient SO_2 and hence personal exposure to SO_2, because people spend an average of 87% of their time indoors (Klepeis et al., 2001). Several factors affect the AER, including the physical driving forces of the airflows (e.g., pressure differences across the building envelope from wind, indoor-outdoor temperature differences, and mechanical ventilation), building characteristics (e.g., local wind sheltering, tightness of the building envelope), and occupant behavior (e.g., opening windows, operating outdoor-vented fans, thermostat temperature setting during heating and cooling seasons). Therefore, substantial spatial and temporal AER variations can occur due to temporal and geographical differences in

weather conditions, building characteristics, and occupant behavior. The resulting spatial-temporal variations in ambient SO_2 exposure may help explain possible differences in epidemiologic associations between ambient SO_2 concentrations and health effects in different U.S. communities (Baxter and Sacks, 2014).

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

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

AER is a critical parameter for estimating indoor SO_2 concentrations, because indoor sources of SO_2 are relatively scarce and SO_2 rapidly reacts with indoor surfaces [see Grontoft and Raychaudhuri (2004) and references cited therein] or oxidizes rapidly via indoor Criegee intermediates [see Section 2.3 for a description of Criegee chemistry or Shallcross et al. (2014) for the role of indoor Criegee intermediates in SO_2 losses]. The main indoor source of SO_2 is combustion of sulfur-containing fuels, such as kerosene, which is generally considered an emergency or supplemental source of heat in the U.S. Kerosene heaters, but not fireplaces, woodstoves, or gas space heaters, caused

elevated SO_2 concentrations indoors in a study conducted in Connecticut and Virginia (Triche et al., 2005). The median indoor SO_2 concentration measured by passive sampler over two weeks in homes using kerosene heat was 6.4 ppb, compared with 0.22 ppb for homes that did not use kerosene heat in the two-week period. This relatively low concentration when the kerosene heater was not in use is consistent with the rapid removal rate of infiltrated ambient SO_2. As discussed in Section 2.3, SO_2 is removed from the atmosphere by both dry and wet deposition to surfaces, represented by k in the conceptual model presented in Section 3.2.2. The deposition rate of SO_2 in apartments in Athens, Greece was found to range from 0.76−4.3 /hour, similar to the rate observed for O_3, but an order of magnitude higher than the deposition rate measured for NO_2 (Halios et al., 2009).

Limited information was identified regarding the penetration factor P (Equation 3-4). López-Aparicio et al. (2011) measured SO_2 concentrations indoors and outdoors at the National Library in Prague, Czech Republic from July 2009 to March 2010 and observed SO_2 penetration values ranging from P = 0.25 to 0.74. Measured outdoor SO_2 concentrations were higher for the cold months of January, February, and March compared with the remainder of the sampling campaign, and penetration was lower during that period (P = 0.25 to 0.48). The literature search only produced this one recent study of SO_2 infiltration.

Vehicle AERs can be substantially higher than residential AERs, leading to rapid infiltration of on-road pollutants. While on-road SO_2 emissions have declined due to reductions in fuel sulfur content (Section 2.2.3), high vehicle AER would increase exposure in areas with high ambient SO_2 concentrations. Many factors affect vehicle AER, including vehicle make and model, vehicle age, driving speed, and fan/recirculation setting on the vehicle ventilation system. The combined effect of these factors result in AERs that vary by more than two orders of magnitude, from less than 1/hour (approximately equivalent to a typical residential AER) to more than 100/hour (Hudda et al., 2011). In a model fit to AER measurements on 59 vehicles driven at three different speeds under recirculation conditions, the most important variables were vehicle age, mileage, and speed, plus an adjustment for manufacturer (Fruin et al., 2011). Fan speed and vehicle shape were not influential variables.

3.4.1.2 Indoor-Outdoor Relationships

A number of studies from the U.S., Canada, Europe, and Asia summarized in the 2008 SO_X ISA (U.S. EPA, 2008d), as well as a few new studies conducted outside the U.S., have characterized the relationship between outdoor and indoor SO_2 concentrations.

Ratios and slopes of the indoor SO_2 concentration versus the SO_2 concentration immediately outside the indoor microenvironment had an extremely wide range in the studies described in the 2008 SO_X ISA, from near zero to near unity. One of the most detailed older studies of SO_2 in a school was able to detect an indoor-outdoor slope of 0.02−0.03, with near-zero intercept and a correlation of 0.79−0.91, while measuring indoor concentrations < 1 ppb, obtained over 10-hour periods when school was in session and 14-hour periods when the school was vacant (Patterson and Eatough, 2000). Studies conducted since the 2008 SO_X ISA have focused on public buildings and show generally similar results to older studies. A historic library in Prague without heating or air conditioning had indoor:outdoor ratios of 0.25−0.74 (mean = 0.49) for monthly average outdoor SO_2 concentrations of 1−7 ppb obtained with passive samplers (López-Aparicio et al., 2011). In Brazil, ratios of average indoor and outdoor SO_2 concentrations from 2-week passive samples were 0.7 and 1.0 for urban and suburban schools, respectively (Godoi et al., 2013).

Several factors could contribute to the differences observed among studies, including building characteristics (e.g., forced ventilation, building age, and building type such as residences or public buildings), behaviors affecting air exchange rates such as opening windows, indoor deposition of SO_2, and analytical capabilities. When reported, correlations between indoor and outdoor ambient SO_2 concentrations were relatively high (>0.75), suggesting that variations in outdoor ambient SO_2 concentration are driving indoor SO_2 concentrations. These high correlations were observed across seasons and geographic locations. This is consistent with the relative lack of indoor sources of SO_2 (Section 3.4.1.1). For other criteria pollutants, nonambient sources can be an important contributor to total personal exposure, but personal SO_2 exposure is expected to be dominated by ambient SO_2 in outdoor microenvironments and in enclosed microenvironments with high air exchange rates (e.g., buildings with open windows and vehicles).

3.4.1.3 Personal-Ambient Relationships

As discussed in the 2008 SO_X ISA (U.S. EPA, 2008d), personal monitoring studies for SO_2 exposure assessment have frequently found that most SO_2 exposure concentrations are below the detection limit of the personal samplers used in the study. Several studies using passive samplers (Section 3.3.1.2) found that 95% or more of the personal SO_2 exposure concentrations were less than the field detection limit of 2−6 ppb for 24-h avg samples (Sarnat et al., 2006; Sarnat et al., 2005; Sarnat et al., 2001; Sarnat et al., 2000). Thus, these data are not suitable for evaluating the relationship between personal exposure and ambient concentration for SO_2.

A study in Boston using a different type of sampler, a personal annular denuder (Section 3.3.1.2) with a detection limit of 0.19 ppb, found that the slope between 24-hour personal SO_2 exposure concentration and ambient SO_2 concentration was 0.13, with a standard error of 0.02 and zero intercept (Brauer et al., 1989). The 2008 SO_X ISA reported slopes of 0.03−0.13. Assuming that there are no nonambient sources of SO_2, the slope can be considered an estimate of α. The R^2 value was 0.43 (r = 0.66) in this analysis, which excluded values below the detection limit, indicating that personal SO_2 exposure concentration was moderately correlated with ambient SO_2 concentration.

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

Ambient SO_2 concentrations measured at central monitoring sites are commonly used for exposure surrogates in epidemiologic studies. As noted in Section 3.3.1.1, use of a central site SO_2 monitor to capture a surrogate for true, likely unobserved ambient SO_2 exposure may lead to exposure error. Factors that may influence this type of error include human activity patterns, spatial and temporal variation in ambient SO_2 concentration, and indoor exposure to ambient SO_2 (Brown et al., 2009; Zeger et al., 2000). Additionally, uncertainty in the metric used to represent exposure is a source of exposure error. This type of error may be influenced by method detection limit, accuracy, and precision of the instrument. These factors are discussed in the following section.

3.4.2.1 Activity Patterns

The activity pattern of individuals is an important determinant of their exposure. Variation in SO_2 exposure concentrations among microenvironments means that the amount of time spent in each location will influence an individual's exposure to ambient SO_2. The effect of activity pattern on exposure is explicitly accounted for in Equation 3-3 by the fraction of time spent in different microenvironments. As discussed in the 2008 SO_X ISA (U.S. EPA, 2008d), although activity patterns vary both among and within individuals, resulting in corresponding variations in exposure across a population and over time, people generally spend more than 80% of their time indoors (Spalt et al., 2015; Klepeis et al., 2001).

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

outdoors, while the school age population spent the most time outdoors. NHAPS respondents aged 65 years and over spent somewhat more time outdoors than adults aged 18−64 years, with a greater fraction of time spent outdoors at a residence. Children aged 0−4 years also spent most of their outdoor time in a residential outdoor location. On average, the fraction of time spent outdoors by school age respondents was 2.62 percentage points higher than working respondents, corresponding to approximately 38 minutes more time outdoors per day. Moreover, in a survey comparing children (mostly less than age 8 years), their parents who were mostly under age 55 years, and adults older than age 55 years, a larger proportion of children reported spending over 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).

Longitudinal activity pattern information is also an important determinant of exposure, as different people may exhibit different patterns of time spent outdoors over time due to race/ethnicity, age, sex, employment, and lifestyle-dependent factors. Spalt et al. (2015) analyzed the relationship between time-activity patterns and demographic patterns for the MESA Air cohort. They found that time spent indoors was best predicted by employment status, and participants of Chinese ethnicity were more likely to spend time indoors compared with white, black, or Hispanic study participants. These differences may manifest as higher mean SO_2 exposures or more frequent high-exposure episodes for some individuals. The extent to which longitudinal variability in individuals contributes to the population variability in activity and location can be quantified by the ratio of between-person variance to total variance in time spent in different locations and activities [the intraclass correlation coefficient (ICC)]. Xue et al. (2004) quantified ICC values in time-activity data collected by Harvard University for 160 children aged 7−12 years in Southern California (Geyh et al., 2000). For time spent outdoors, the ICC was approximately 0.15, indicating that 15% of the variance in outdoor time was due to

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

Several methods are available for sampling diary information, and the method chosen can affect estimated personal SO_2 exposures and related exposure errors. Che et al. (2014) evaluated how diary sampling methods influenced estimates of children's exposure (in this case, to ambient $PM_{2.5}$). Random resampling, diversity and autocorrelation, and Markov-chain cluster methods of diary sampling were tested. The three sampling methods provided similar results for total ambient exposure, outdoor ambient exposure, and ambient exposure at homes and indoor locations not including home, school, or vehicles.

The U.S. EPA's National Exposure Research Laboratory has consolidated many of the most important human activity databases into one comprehensive database called the Consolidated Human Activity Database (CHAD). The current version of CHAD contains data from 22 human activity pattern studies (including NHAPS), which were conducted between 1982 and 2010 and evaluated to obtain over 54,000 person-days of 24-hour human activities in CHAD (Isaacs, 2014; McCurdy et al., 2000). Five studies conducted between 1997 and 2010 comprising over 30,000 person-days have been added to CHAD since the previous SO_X ISA (University of Michigan, 2016; Isaacs et al., 2013; Wu et al., 2012; Hertz-Picciotto et al., 2010; Knowledge Networks, 2009; Williams et al., 2009). The surveys include probability-based recall studies conducted by U.S. EPA and the California Air Resources Board, as well as real-time diary studies, telephone interviews, and internet-based surveys conducted nationally and in individual U.S. metropolitan areas using both probability-based and volunteer subject panels. All ages of both sexes are represented in CHAD. The data for each subject consist of 1 or more days of sequential activities, in which each activity is defined by start time, duration, activity type, and microenvironmental classification (i.e., location). Activities vary from 1 minute to 1 hour in duration, with longer activities being subdivided into clock-hour durations to facilitate exposure modeling. CHAD also provides information on the level of exertion associated with each activity, which can be used by exposure models, including the APEX model, to estimate ventilation rate and pollutant dose (Section 3.3.2.6).

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

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

3.4.2.2 Spatial Variability

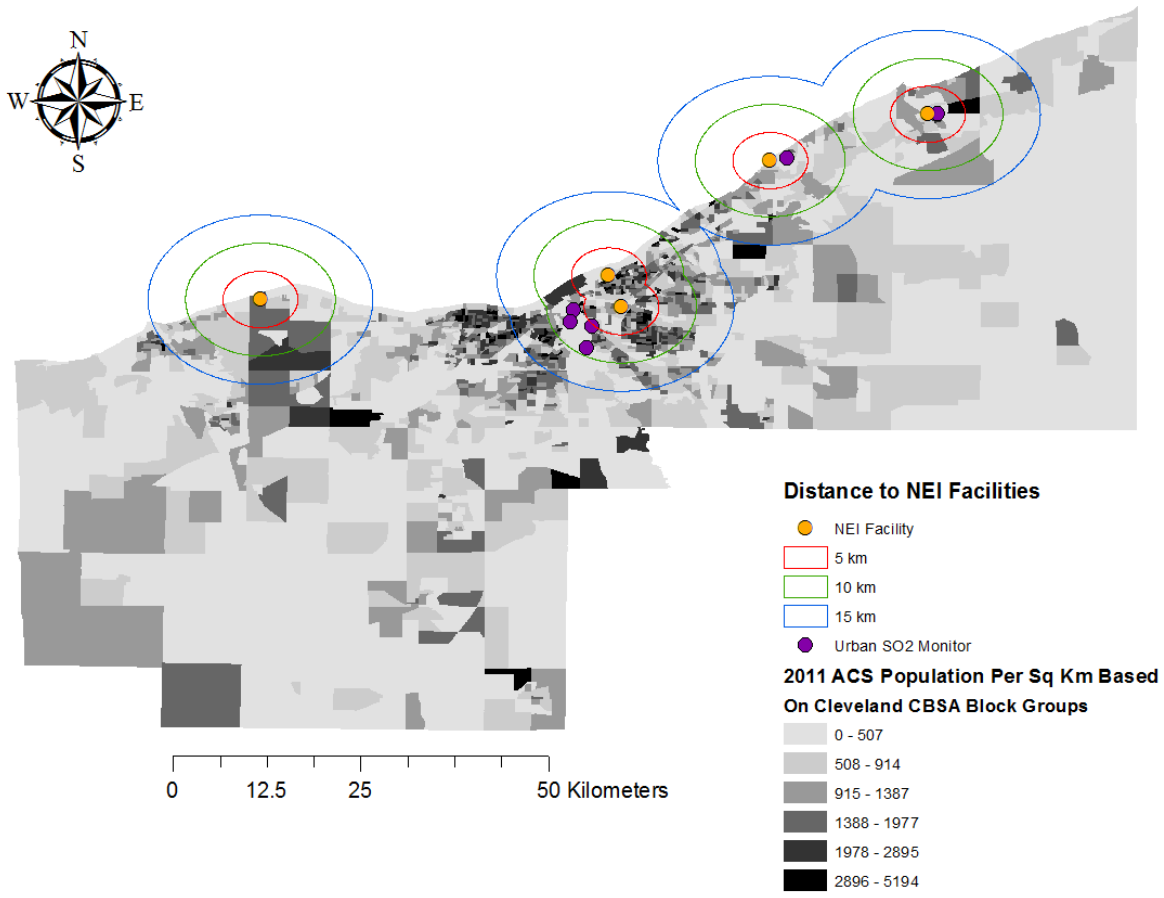
Spatial variability in ambient SO_2 concentrations can contribute to exposure error in epidemiologic studies, whether the studies rely on central site monitor data or model output as a surrogate for exposure concentration. Low correlations between the monitor used to measure concentration as an exposure surrogate and the true exposure concentrations at the locations of the study population contribute to exposure error in time-series studies Goldman et al. (2010).

The 2008 SO_X ISA (U.S. EPA, 2008d) discussed spatial variability in ambient SO_2 concentrations and the impact of this variability on effect estimates from epidemiologic studies. Inter-monitor correlations within urban areas ranged from very low to very high values, suggesting that ambient SO_2 concentrations at some monitors may not be highly correlated with the community average SO_2 exposure concentration. Of particular concern for SO_2 is the predominance of point sources, resulting in an uneven distribution of ambient SO_2 concentrations across an urban area. Factors contributing to differences among monitors include the presence of point sources, proximity to point sources, terrain features, and uncertainty regarding the measurement of low ambient SO_2 concentrations. The 2008 SO_X ISA (U.S. EPA, 2008d) concluded that low correlation between a specific monitor and the community average ambient SO_2 exposure concentration will tend to bias an effect estimate toward the null.

Because ambient SO_2 concentrations can have high spatial variability, average SO_2 exposure concentration estimates may have less error for populations living close to a monitor. Figure 3-1 and Figure 3-2 illustrate proximity of populations and SO_2 monitors

to multiple ambient SO_2 sources in the Cleveland and Pittsburgh CBSAs, respectively (discussed in Chapter 2). These CBSAs were chosen for further discussion here, because they have both high population density and numerous sources above 2,000 tpy. Figure 3-1 shows the location of central site SO_2 monitors and sources with respect to population density for the Cleveland, OH CBSA. Four of the monitors are centrally located in the urban area, and are also within 10 km of SO_2 sources, while two other monitors are located much closer to point sources (<5 km). While some densely populated areas are near central site SO_2 monitors, some of the highest density census block groups are located more than 10−15 km from central site monitors despite proximity to the sources. Table 3-3 indicates that approximately one-third of the population in various age groups lives more than 15 km from a central site SO_2 monitor. For the Pittsburgh CBSA (Figure 3-2), only two of the monitors are located near sources, with the other monitors distributed among population centers and less densely populated areas. Here, approximately 40% of the population lives more than 15 km from a central site SO_2 monitor (Table 3-4). Such variability in the proximity of populations to central site monitors suggests that some portions of an urban area may be subject to increased exposure error. While only minor differences were noted among age groups in the portion of the population living at specific distances from monitors, the potential exists for exposure error to differ among other potentially at-risk groups due to monitor proximity.

Several recent studies have evaluated the impact of spatial variability in ambient SO_2 concentration on epidemiologic effect estimates. Strickland et al. (2011) reported a relatively low chi-squared statistic for ambient 1-hour SO_2 exposure concentration (from a central site monitor, unweighted average across monitors, and population-weighted average) compared with other primary and secondary criteria pollutants in Atlanta, GA. The authors attributed this poor fit to spatial heterogeneity in ambient SO_2 exposure concentrations used as exposure surrogates and the inability of a central site monitor to capture ambient SO_2 plume touch-downs in other parts of the city. The chi-squared statistic moderately increased when average ambient SO_2 exposure concentrations (both population-weighted and unweighted) from monitors across the city were used. Effect estimates were higher for the monitor average metrics than for the central site monitor, and this difference was magnified when effect estimates were based on a standardized increment rather than the IQR. Because the IQR of the data covered the range of values observed across the monitors in Atlanta for the Strickland et al. (2011) study, spatial variability was partially accounted for in the IQR. The different exposure assignment 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.

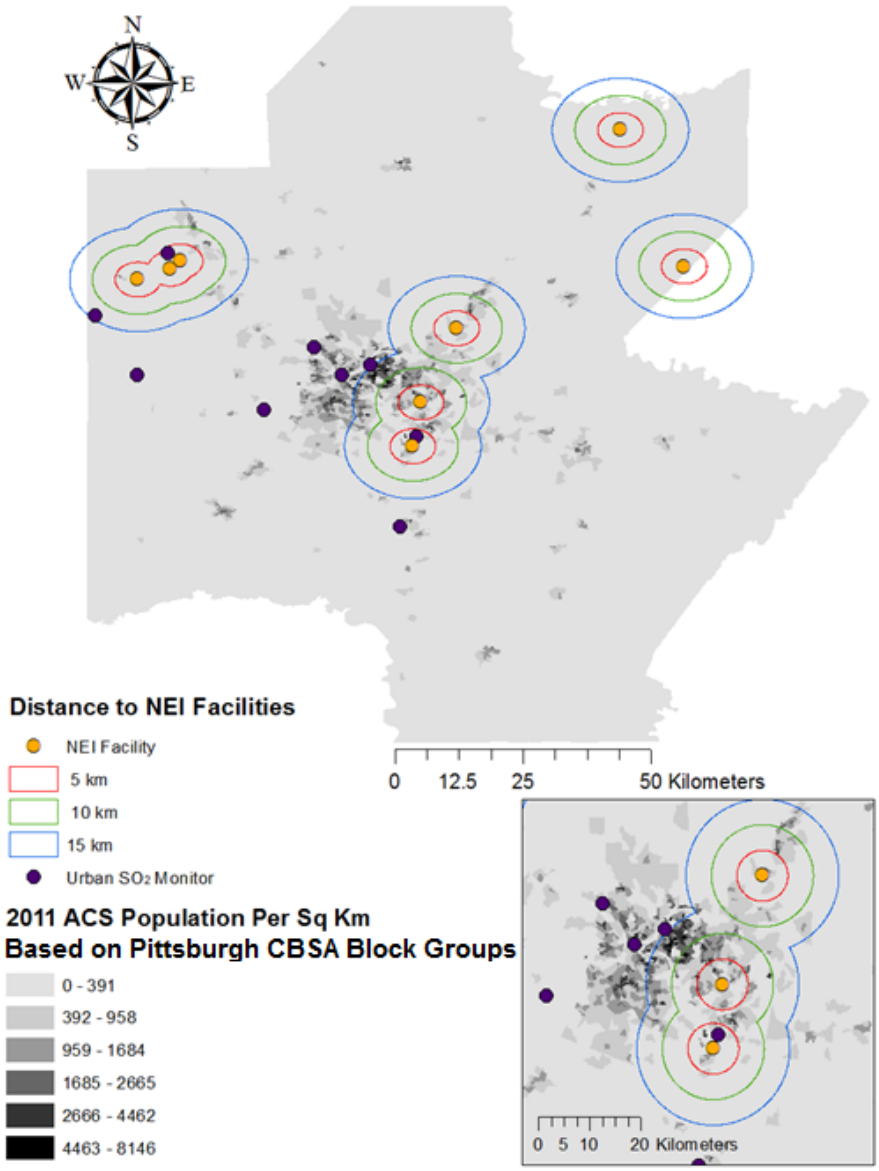
Figure 3-1 Map of the Cleveland, OH core-based statistical area including National Emissions Inventory facility locations, urban sulfur dioxide monitor locations, and distance to each facility with respect to core-based statistical area block group population density estimates for 2011. National Emissions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

1

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.

Age Group	Total Population	Within 1 km	Within 5 km	Within 10 km	Within 15 km
Total	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).



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).

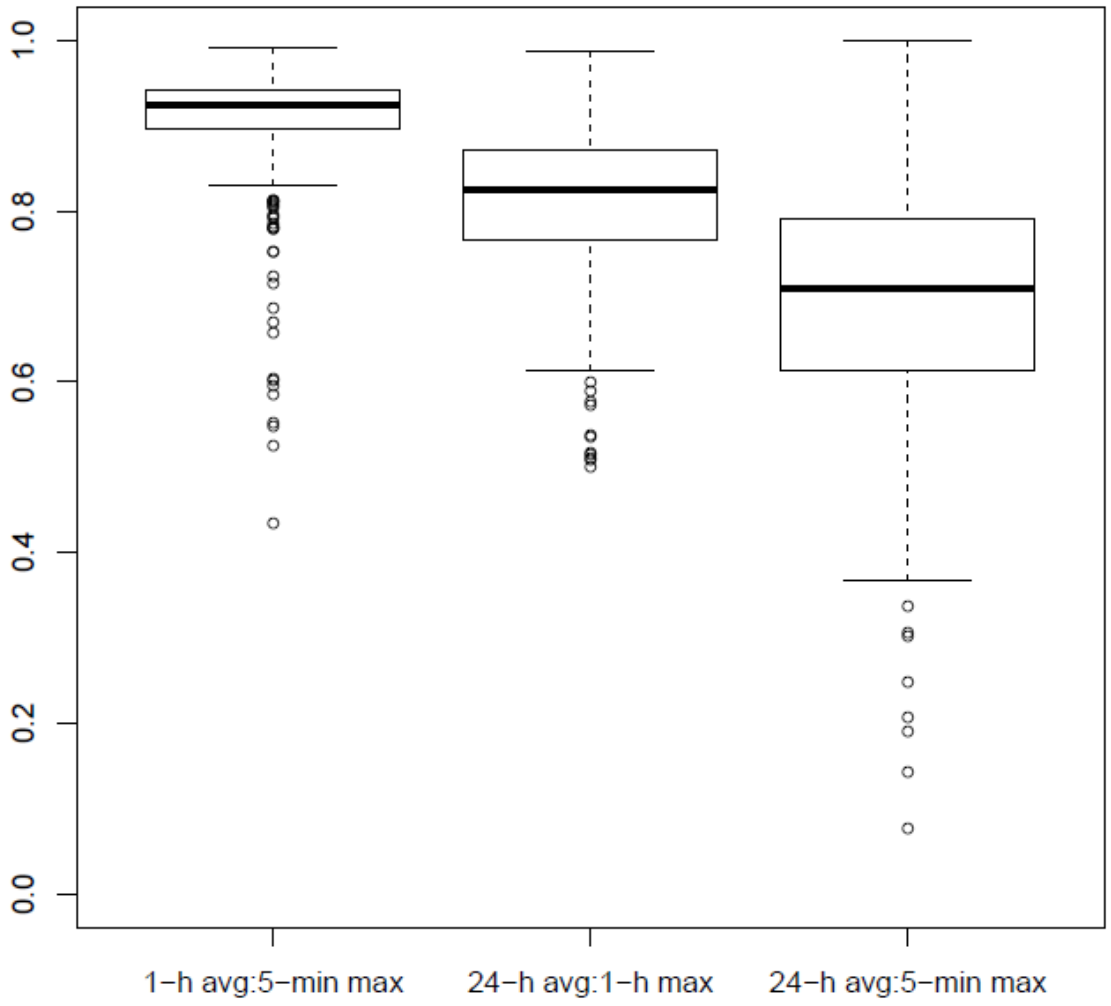
High spatial and temporal variability in ambient SO_2 concentration leading to a null-biased effect estimate was also observed in Atlanta by Goldman et al. (2010) when using 1-h daily max SO_2 concentration as an exposure surrogate. In this study, the authors used a semivariance analysis incorporating both spatial and temporal variability to show that secondary pollutants such as $PM_{2.5}$ and O_3 have lower exposure error (where ambient concentration is a surrogate for exposure) than primary pollutants such as CO and SO_2, for which concentrations tend to have higher spatial variability than those of secondary pollutants. Goldman et al. (2010) simulated exposure error as the difference between concentration measured at the central site monitor and the concentration estimated at a receptor's location. The study authors computed a semivariance term over distance to the central site monitor to concentration at a distance from the monitor. The estimated error for SO_2 was then added to a base case scenario, in which the authors assumed that the central site monitor would produce an accurate exposure. Both the central site monitor estimate and the estimate at the receptor location were used in epidemiologic models to estimate the risk ratio for cardiovascular emergency department visits. The authors estimated that the risk ratio was biased towards the null by approximately 60% when estimating exposure using the central site monitor in lieu of estimating exposure at the receptors' locations. In a related study, Goldman et al. (2012) used different methods to obtain the surrogate for exposure: central site monitor, unweighted average across monitors, population-weighted average across monitors, and area-weighted average across monitors. The bias decreased for 1-h daily max SO_2 when using unweighted, population-weighted, and area-weighted averages of concentrations from multiple monitors for the exposure estimate compared with using concentration from a central site

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 associations between ambient SO_2 concentrations (used as exposure surrogates) and birth outcomes when the analysis was restricted to mothers matched with an ambient SO_2 monitor within 3−5 km of their residence, suggesting bias towards the null remained in the spatial averages used in the base case (Section 5.4).

3.4.2.3 Temporal Variability

The influence of plume dynamics on human exposures is important for considering results of time-series studies of ambient SO_2 exposure. As described in Section 2.5.4, peak concentrations within the ambient SO_2 plume can exceed concentrations averaged over an hour by up to a factor of five; for the observations made in this assessment, the peak was observed to exceed the mean by up to a factor of 5.5. Hence, SO_2 central site monitoring with averaging times of 1 hour or 1 day, commonly used in time-series epidemiologic studies as an exposure metric (Chapter 5), may fail to characterize the variability and peak SO_2 exposure concentrations associated with a meandering plume, resulting in exposure error. Moreover, controlled human exposure studies have demonstrated health effects at 5-minute time scales (Chapter 5). The longer averaging times used in epidemiologic studies may be misaligned with the critical time window of the health effect corresponding to peak SO_2 exposure.

Most of the community time-series epidemiologic studies on the health effects of ambient SO_2 exposure described in Chapter 5 use 24-h avg concentration as a surrogate for exposure. Correlations among different temporal aggregations (1-h avg vs. 5-minute hourly max, 24-h avg vs. 1-h daily max, and 24-h avg vs. 5-minute daily max) were computed from the AQS data presented in Section 2.5.4 to glean an indication of how well the 24-h avg represents the 1-h daily max and 5-minute daily max measures that correspond to peak SO_2 plume exposure (Figure 3-3). Approximately 75% of correlations between 1-h avg and 5-minute hourly max were above 0.9. Correlations between 24-h avg and 1-h daily max were slightly lower, with roughly 75% of the data having correlations above 0.75. A larger range of data was observed for the correlations between 24-h avg and 5-minute daily max, with 75% of the data having correlations above 0.60 and more than 50% of the data having correlations above 0.70. These moderate-high correlations suggest that 24-h avg data used in many time-series epidemiologic studies capture the peak exposure reasonably well, but exceptions may be found for specific sites, as suggested by the lower outliers ($r < 0.35$) and lower whisker ($r < 0.6$) of the 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.

A study in Canada suggests that ambient SO_2 concentration measured over a single year can represent ambient SO_2 exposure concentration over a multidecade period. The authors compared measurement methods used to represent long-term SO_2 exposure concentration and found that the annual average ambient SO_2 exposure concentration in the census tract of a subject's residence during 1980 and 1994 was well correlated (Pearson R = 0.83 and 0.85 for all subjects, respectively) with an ambient SO_2 exposure

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

3.4.2.4 Method Detection Limit, Instrument Accuracy, and Instrument Precision

Personal SO_2 exposure measurements with ambient SO_2 concentration typically have correlations of $0.4 < r < 0.9$ when personal SO_2 exposure measurements are above the MDL. However, although the magnitude of personal SO_2 exposure measurements is often much lower than the magnitude of ambient SO_2 concentrations [Section 3.4.1.3; U.S. EPA (2008d)]. Moderate to high correlation indicates that using ambient concentration as a surrogate for personal exposure captures the variability needed for epidemiologic studies, particularly for time-series and panel studies. Low personal-ambient correlations reported in the literature are strongly influenced by low personal exposures relative to the detection limits of personal samplers. When this happens, personal samplers are unable to provide a signal to correlate with variations in ambient concentration. Low correlations ($r < 0.4$) in situations with a high proportion of samples below the detection limit should not be interpreted as evidence for the lack of a relationship between personal exposure and ambient SO_2 concentrations. Instead, a low personal sample value likely represents a true low exposure and thus appropriately leads to a low personal:ambient ratio. Low personal:ambient ratios may be due to low penetration and high deposition of SO_2 in indoor microenvironments where people spend most of their time. In a study of personal:ambient exposure ratios by Brown et al. (2009), the authors cited personal SO_2 samples below MDL and extremely low SO_2 levels to rationalize not pursuing further analysis.

Instrument error occurs when the measured SO_2 concentrations are subject to interferences that cause biases or noise leading to error in estimating exposure. Ambient SO_2 concentrations measured by FRM or FEM are subject to positive bias from the detection of interfering compounds. See Section 2.4.1.2 for details on errors that affect FRMs and FEMs used for central site monitoring. Inter-monitor comparison is often used to estimate instrument precision. Goldman et al. (2010) used a simulation to investigate the influence of instrument precision error at locations where ambient SO_2 central site

monitors were collocated. Instrument precision error increased with increasing ambient concentration for the central site monitors. When instrument error and ambient SO_2 concentration were correlated, error was larger in locations with more prevalent or stronger sources or at times when SO_2 emissions were higher for a given location. For example, the magnitude of the instrument error was expected to be largest at times of day when SO_2 emissions were highest, such as during peak energy usage times. Instrument error was also observed to exhibit some autocorrelation at 1- and 2-day lags in the Goldman et al. (2010) simulation. Hence, the diurnal variability in relative SO_2 instrument error does not change substantially from day to day. For epidemiologic studies of short-term SO_2 exposure that use central site-monitored ambient SO_2 concentration as a surrogate for exposure, instrument error would not be expected to influence the exposure surrogate on a daily basis. When comparing health effect estimates among cities for an epidemiologic study of long-term SO_2 exposure, differences in instrument error among cities could lead to biased exposure surrogates, given the reliance on differences in magnitude of the exposure surrogate to study spatial contrasts. Section 3.4.4 describes the influence of instrument error and high MDL on exposure error and health effect estimates for community time-series (Section 3.4.4.1), long-term average (Section 3.4.4.2), and panel (Section 3.4.4.3) epidemiologic studies.

3.4.3 Copollutant Relationships

Simulations by Zeger et al. (2000) indicate that unaccounted correlation among exposure concentrations or exposure errors for copollutants may lead to bias and uncertainty in the health effect estimates in epidemiologic studies. Correlation among copollutant exposure concentrations may amplify the health effect estimates. In some cases, this could promote a false conclusion of an association between a health effect and the copollutant exposure concentration even if no relationship between the health effect and copollutant exposure actually exists. Correlation of the errors in measuring copollutant concentrations may cause bias in the health effect estimate, especially when one is measured with more error than the other (Zeger et al., 2000). Confounding is described in the Preamble to the ISAs (U.S. EPA, 2015b). Briefly, confounding occurs when the copollutant exposure concentrations are correlated with those of the pollutant of interest and the health effect. Confounding can cause misleading results for estimating the health effect of SO_2 if the copollutant is not accounted for (Rothman and Greenland, 1998). This differs from effect modification, where the health effect estimate for SO_2 is conditional upon the copollutant exposure concentration via interaction of the SO_2 and copollutant exposures.

To assess the independent health effects of ambient SO_2 exposure in an epidemiologic study, it is necessary to identify (Bateson et al., 2007) (1) measurement error for all

copollutants; (2) which copollutants (e.g., NO_2, $PM_{2.5}$, UFP, BC) are potential confounders of the health effect-SO_2 relationship so that their correlation and collinearity with SO_2 can be tested and, if needed, accounted for in the epidemiologic model; (3) the time period over which correlations might exist so that potential confounders are considered appropriately for the time period relevant for the epidemiologic study design (e.g., pollutants or other factors that are correlated over the long term might not be important for a short-term exposure epidemiologic study); and (4) the spatial correlation structure across multiple pollutants, if the epidemiologic study design is for long-term exposure Paciorek (2010). Additionally, confounding can also vary by the health endpoint studied.

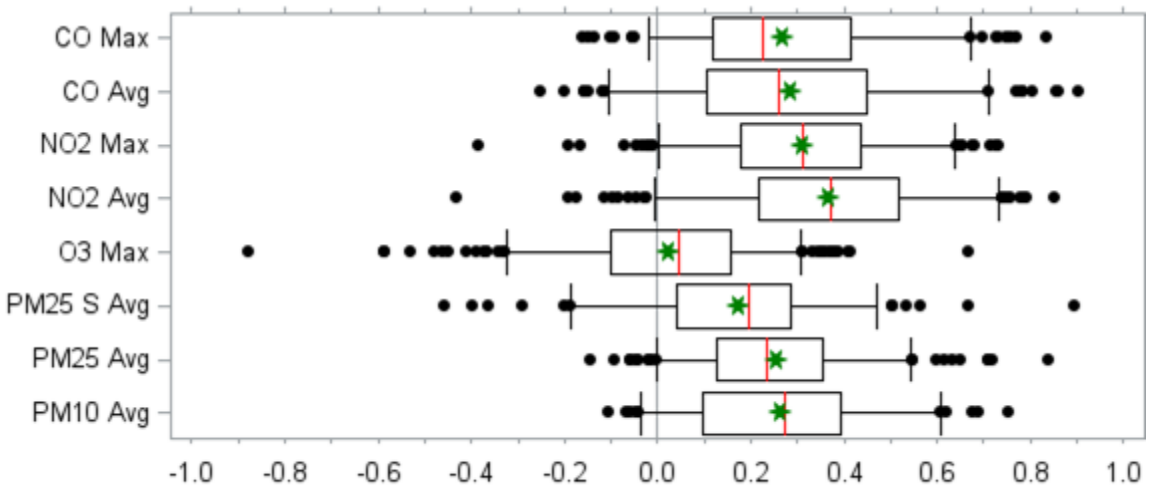
When SO_2 and a copollutant are correlated, copollutant epidemiologic models may be used to adjust the SO_2 effect estimate for potential confounding by the copollutant (Tolbert et al., 2007). Two-pollutant models can help identify which is the better predictor of the effect, particularly if the etiologically linked pollutant is measured with more error than the other pollutant (Zeger et al., 2000). However, collinearity potentially affects the epidemiologic model's effect estimate when highly correlated pollutants are modeled simultaneously, and differences in the spatial distribution of ambient SO_2 concentration and the copollutants' ambient concentrations may also complicate model interpretation [Section 5.1.2.1 and Gryparis et al. (2007)]. Because ambient SO_2 exhibits a relatively high degree of exposure error compared with other criteria pollutants [e.g., Section 3.4.4.1;Goldman et al. (2010)], two-pollutant models in which the SO_2 effect estimate remains robust may provide additional support for a health effect to be associated with SO_2 exposure [e.g., Ito et al. (2007)].

This section considers temporal copollutant correlations and how relationships among copollutants may change in space using AQS data and data reported in the epidemiologic literature (Chapter 5). Temporal copollutant correlations are computed from the time series of ambient concentrations for two copollutants measured with collocated AQS monitors. Spatial relationships are evaluated by comparing within-pollutant variation across space for different pollutants. The following sections review coexposures that can potentially confound the relationship between a health effect and ambient SO_2 exposure over different temporal and spatial resolutions.

3.4.3.1 Temporal Relationships among Ambient Sulfur Dioxide and Copollutant Exposures

Short-Term Temporal Correlations

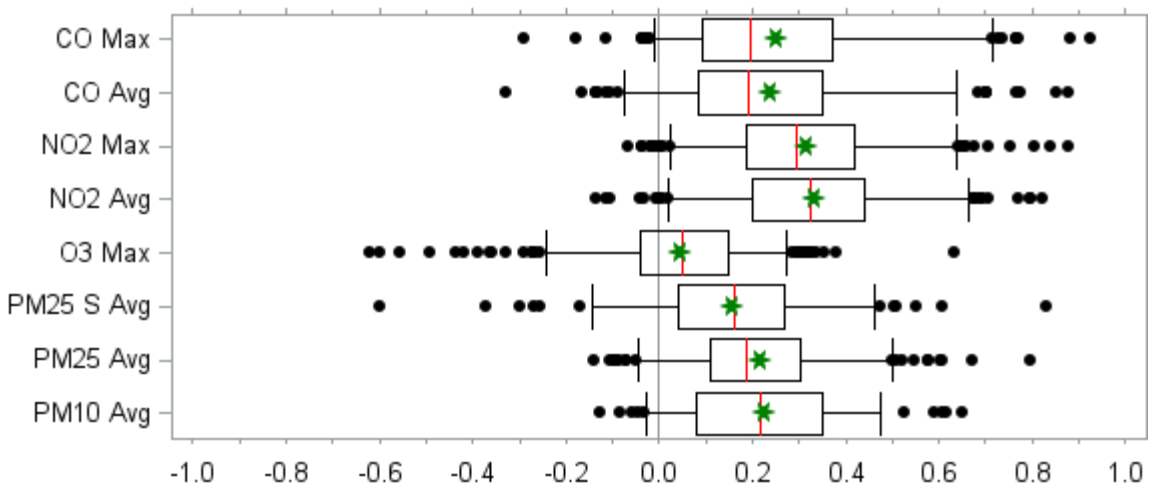
Short-term copollutant correlations were studied using collocated air quality data reported within the U.S. EPA AQS repository system during 2013−2015. 438 sites met the 75% data completeness criteria presented in Section 2.5.1. Daily air quality metrics representing either 1-h daily max or 24-h avg ambient SO_2 concentration values were used. Pearson correlations were used to evaluate temporal correlations among ambient SO_2 concentrations and NAAQS copollutant concentrations. In addition, correlations between ambient SO_2 and $PM_{2.5}$-sulfur were examined because $PM_{2.5}$-sulfur serves as a surrogate for SO_2 oxidation products (i.e., sulfate) and may have confounding effects on health outcomes associated with ambient SO_2 exposure. Figure 3-4 and Figure 3-5 display the distribution of correlations between NAAQS copollutants and SO_2 daily metrics (24-h avg, 1-h daily max) for all data combined, and Figure 3-6 and Figure 3-7 display those copollutant correlations broken down by season. Because epidemiologic studies may use either daily average or daily maximum metrics, correlations are presented for both metrics, when available. For CO and NO_2, 1-h daily max concentrations are used, while for O_3, 8-h daily max concentrations are considered.



CO = carbon monoxide; NO_2 = nitrogen dioxide; O_3 = ozone; PM_{25} = particulate matter with a nominal aerodynamic diameter less than or equal to 2.5 µm; PM_{10} = 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)

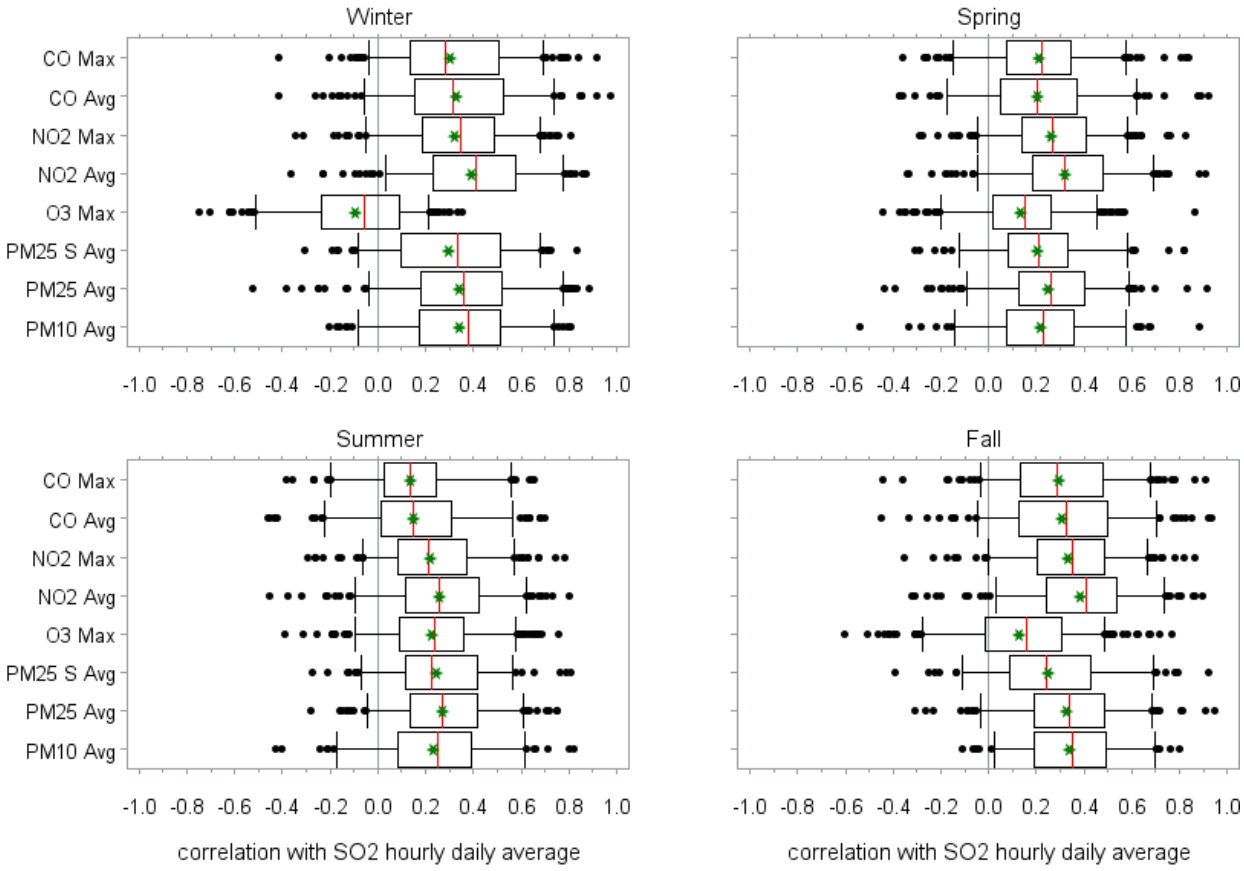
Figure 3-4 Distribution of Pearson correlation coefficients for comparison of 24-h avg sulfur dioxide concentration from the year-round data set with collocated National Ambient Air Quality Standards pollutants (and sulfur in $PM_{2.5}$) from Air Quality System during 2013−2015.



CO = carbon monoxide; NO_2 = nitrogen dioxide; O_3 = ozone; PM_{25} = particulate matter with a nominal aerodynamic diameter less than or equal to 2.5 µm; PM_{10} = 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)

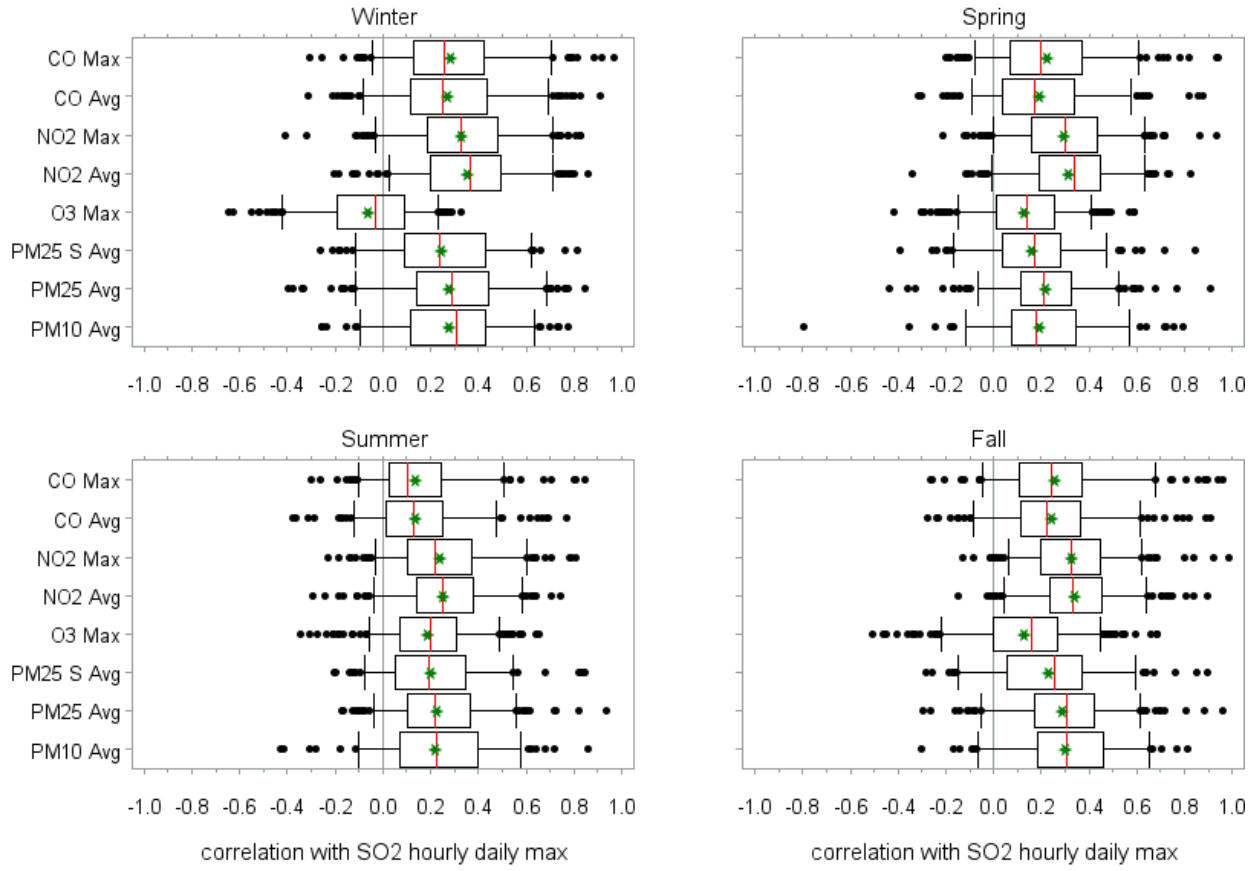
Figure 3-5 Distribution of Pearson correlation coefficients for comparison of daily 1-h max sulfur dioxide concentration from the year-round data set with collocated National Ambient Air Quality Standards pollutants (and sulfur in $PM_{2.5}$) from Air Quality System during 2013−2015.



CO = carbon monoxide; NO_2 = nitrogen dioxide; O_3 = ozone; PM_{25} = particulate matter with a nominal aerodynamic diameter less than or equal to 2.5 µm; PM_{10} = particulate matter with a nominal aerodynamic diameter less than or equal to 10 µm; S = sulfur; SO_2 = 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 $PM_{2.5}$) from Air Quality System during 2013−2015.



CO = carbon monoxide; NO_2 = nitrogen dioxide; O_3 = ozone; PM_{25} = particulate matter with a nominal aerodynamic diameter less than or equal to 2.5 µm; PM_{10} = particulate matter with a nominal aerodynamic diameter less than or equal to 10 µm; S = sulfur; SO_2 = 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 $PM_{2.5}$) from Air Quality System during 2013−2015.

While 24-h avg ambient SO_2 concentration exhibits a wide range of correlations with NAAQS copollutants, median correlations are all below 0.4 (Figure 3-4). The lowest correlations are observed between ambient SO_2 concentration and ambient O_3 concentration, with median correlations below 0.1. Slightly higher correlations are observed between ambient SO_2 concentration and other primary NAAQS pollutant concentrations (NO_2 and CO), with median correlations between 0.3 and 0.4. Common fuel combustion sources may be responsible for these correlations (Section 2.2). Lower correlations with $PM_{2.5}$ sulfur than $PM_{2.5}$ mass may reflect the secondary formation of

sulfate by oxidation of SO_2, while $PM_{2.5}$ mass also has a primary component. Correlations close to 1 or below 0 are sometimes observed but only occur at a few outlier monitoring sites. Comparatively, copollutant correlations of daily 1-h max ambient SO_2 in Figure 3-5 are also slightly lower than the copollutant correlations based on ambient SO_2 24-h avg values in Figure 3-4. The medians of correlations between daily 1-h max ambient SO_2 concentrations and other NAAQS pollutants are below 0.3, with the exception of NO_2, which exhibits median correlations slightly above 0.3. These results indicate that for short-term epidemiologic studies, the minority of sites with stronger correlations may introduce a greater degree of confounding into those epidemiologic results. It is notable that the nature of correlations between SO_2 and copollutants is changing given rulemaking on use of ultra-low sulfur diesel fuel that went into effect in 2006 (66 FR 5002). Some of the epidemiologic studies cited in Chapter 5 included data obtained prior to 2006 and 2007, when the new sulfur standards took effect for highway vehicles and heavy-duty vehicles, respectively. This change may have contributed to the wider variation observed in correlation between ambient SO_2 and copollutant concentrations. Note that potential for confounding also varies by health endpoint.

Correlations between ambient SO_2 and NAAQS copollutant concentrations demonstrate very little variability across seasons (Figure 3-6 and Figure 3-7). All median and average copollutant correlations are below 0.4 across every season. The only substantial seasonal difference in correlations between ambient SO_2 and copollutant concentrations occurs during the winter, when ambient SO_2 concentration exhibits lower negative correlations with ambient O_3 concentration (median winter correlations = −0.1). SO_2-O_3 correlations are generally low year-round, potentially because the regional nature of O_3 formation contrasts with the local nature of SO_2 plumes from point sources. In winter, the low correlations could be directly linked to relatively low ambient O_3 concentrations during this time of year due to less photochemical O_3 production and SO_2 oxidation.

Overall, daily and hourly ambient SO_2 concentrations generally exhibit median correlations around 0.2−0.4 with respect to other collocated NAAQS copollutants at AQS monitoring sites. However, given that a small subset of sites report relatively higher copollutant correlations, confounding may need to be considered on a study-by-study basis, preferably with correlations reported in the individual studies. High copollutant correlations in the national distribution could be due either to consistently low concentrations for both SO_2 and the copollutant or to consistent fluctuations in concentrations of both pollutants due to source behavior and meteorology.

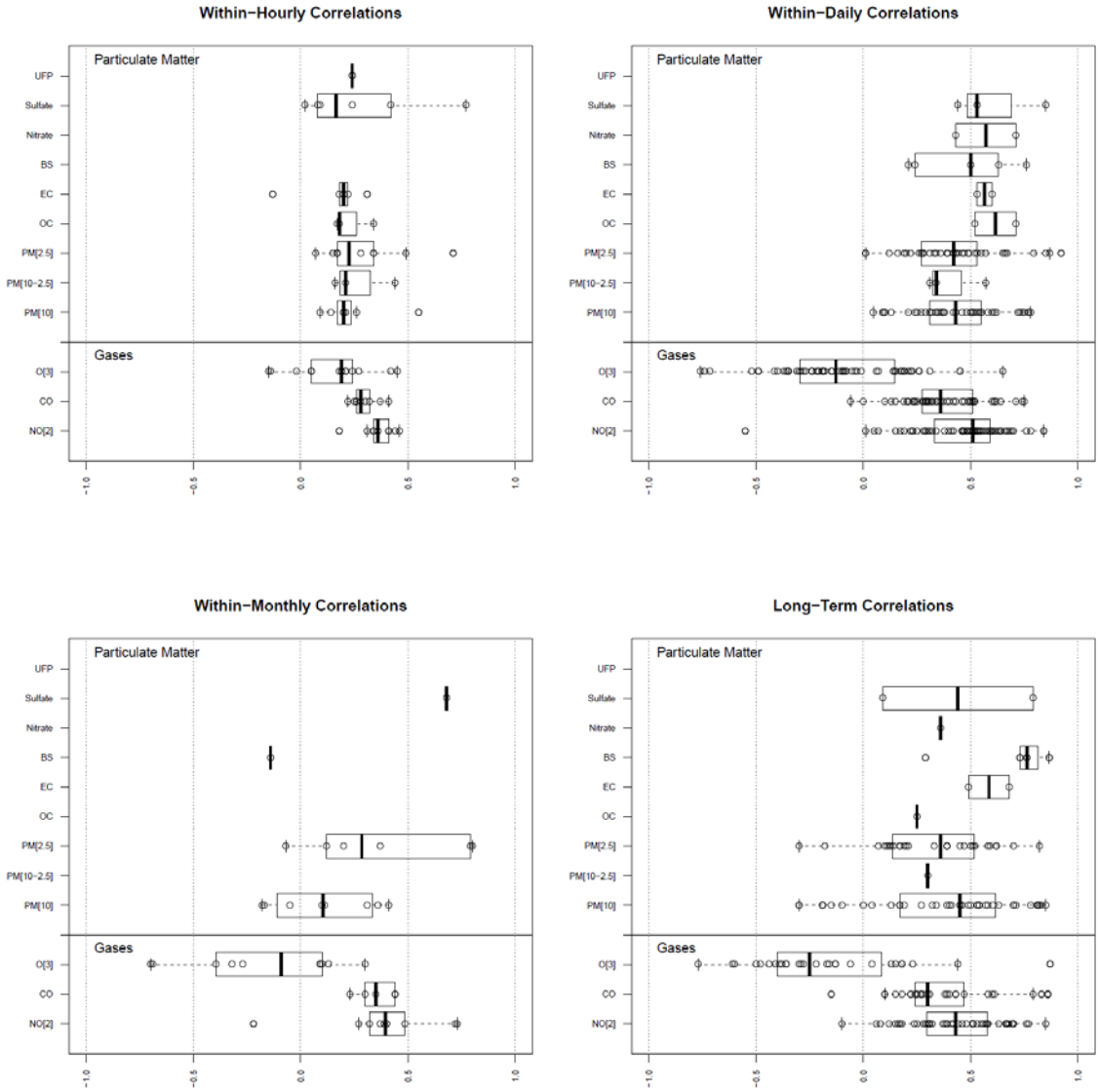
Exposure studies have also examined correlations between ambient SO_2 concentration and ambient or personal copollutant exposure concentrations, generally reporting low or moderate correlations. For SO_2, within-hourly concentrations have median correlations

around 0.2 for most PM of different cut-points and species. For gases, median correlations of within-hourly data were lower for O_3 than for CO and NO_2, respectively, but median correlations did not surpass 0.4. Correlations were mostly positive for all but O_3, which exhibits both negative and positive correlations. See Figure 3-8 and references cited therein for copollutant correlation data reported in the literature (Liu et al. (2016); Mendola et al. (2016a); Michikawa et al. (2016); Neophytou et al. (2016); Smith et al. (2016); Wallace et al. (2016); Ancona et al. (2015); Assibey-Mensah et al. (2015); Bentayeb et al. (2015); Byers et al. (2015); Deng et al. (2015a); Dibben and Clemens (2015); Huang et al. (2015a); Hwang et al. (2015b); Ierodiakonou et al. (2015); Michikawa et al. (2015); Qian et al. (2015); Radwan et al. (2015); Ware et al. (2015); Yorifuji et al. (2015b); Zhu et al. (2015); Chen et al. (2014b); Gorai et al. (2014); Lin et al. (2014); Liu et al. (2014a); Winquist et al. (2014); Xu et al. (2014); Altuğ et al. (2013); Carey et al. (2013); Clougherty et al. (2013); Dong et al. (2013a); Faiz et al. (2013); Greenwald et al. (2013); Mehta et al. (2013); Qiu et al. (2013b); Slama et al. (2013); Son et al. (2013); Zheng et al. (2013); Costa Nascimento et al. (2012); Ebisu and Bell (2012); Faiz et al. (2012); HEI (2012); Le et al. (2012); Lee et al. (2012); Portnov et al. (2012); Tsai et al. (2012); Turin et al. (2012); Bhaskaran et al. (2011); Darrow et al. (2011); Hwang et al. (2011); Ito et al. (2011); Lee et al. (2011b); Li et al. (2011); Liao et al. (2011); Peel et al. (2011); Samoli et al. (2011); Zhao et al. (2011); Akinbami et al. (2010); Chen et al. (2010b); Hsieh et al. (2010); Pan et al. (2010); Penard-Morand et al. (2010); Arbex et al. (2009); Arnedo-Pena et al. (2009); Cheng et al. (2009); Darrow et al. (2009); Forbes et al. (2009c); Guo et al. (2009); Lipfert et al. (2009); Rich et al. (2009); Sahsuvaroglu et al. (2009); Stieb et al. (2009); Strickland et al. (2009); Dales et al. (2008); Hwang and Jaakkola (2008); Jalaludin et al. (2008); Ségala et al. (2008); Woodruff et al. (2008); Ko et al. (2007a); Liu et al. (2007); Tolbert et al. (2007); ATSDR (2006); Ballester et al. (2006); Cendon et al. (2006); Fung et al. (2006); Jalaludin et al. (2006); Leem et al. (2006); Lipfert et al. (2006a); Filleul et al. (2005); Llorca et al. (2005); Peel et al. (2005); Sagiv et al. (2005); Wilson et al. (2005); Metzger et al. (2004); Jaffe et al. (2003); Lee et al. (2003); Liu et al. (2003); Sheppard (2003); Yang et al. (2003b); Yang et al. (2003a); Anderson et al. (2001); Ballester et al. (2001); Ha et al. (2001); Krewski et al. (2000); Lipfert et al. (2000b); Abbey et al. (1999); Sheppard et al. (1999); Pereira et al. (1998); Burnett et al. (1997); Schwartz (1997)).

More data were available for within-daily correlations of SO_2 and copollutant exposure concentrations. Median correlation around 0.5 were observed for SO_4^{2-}, NO_3^-, black smoke (BS), and organic carbon (OC) $PM_{2.5}$ species, PM_{10}, and NO_2 for that time scale. Median correlation was around 0.3 for $PM_{10-2.5}$, around 0.4 for CO and $PM_{2.5}$, and around −0.2 for O_3. Both data availability and inter-site variability were much greater for the gases, $PM_{2.5}$, and PM_{10} compared with the individual $PM_{2.5}$ species or $PM_{10-2.5}$. Where data were available, a large degree of scatter was evident in the data. In studies where

within-daily correlations of SO_2 exposure concentrations with NO_2 and CO exposure concentrations were observed to be high, it is possible the data were collected before the rulemaking to reduce sulfur content in diesel fuel went into effect in 2006 (66 FR 5002) or when coal was in greater use in energy generation (Section 2.2). The minority of sites with stronger correlations may introduce a greater degree of confounding into the epidemiologic results. For this reason, copollutant correlations need to be reported in individual epidemiological studies to assess if confounding is a possibility.

Data for correlations between ambient SO_2 concentrations and personal copollutant exposures were reported in the 2008 SO_X ISA (U.S. EPA, 2008d), and no studies have been produced to substantiate or revise the observations reported at that time. Between-subject correlations of daily ambient SO_2 concentration with personal $PM_{2.5}$ exposures were found to vary widely with positive and negative correlations in the Sarnat et al. (2005) and Sarnat et al. (2001) studies. In the (Sarnat et al., 2005) study, 95−97% of the SO_2 data were below the MDL, indicating high uncertainty. This evidence suggests that correlations between personal copollutant exposures and ambient SO_2 concentration vary among individuals, and thus the potential for copollutant confounding cannot be ruled out.

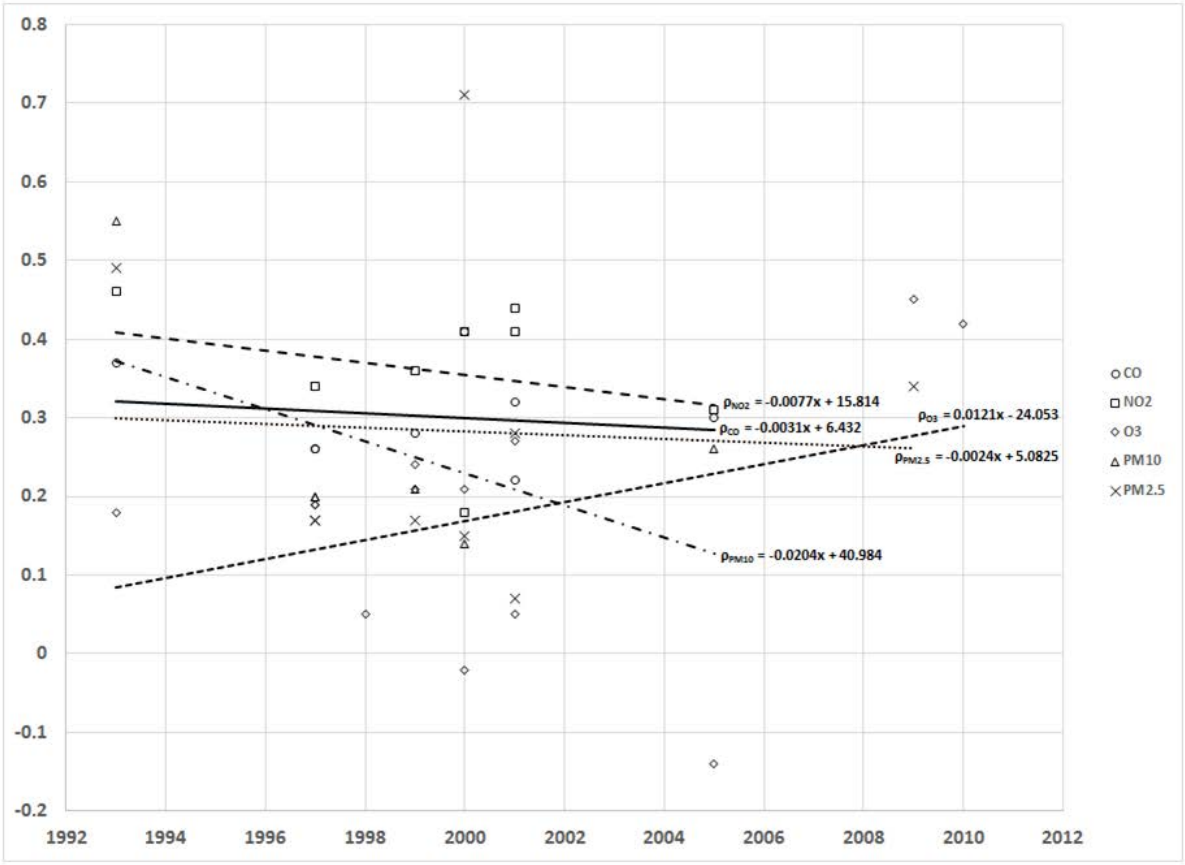


BS = black smoke; CO = carbon monoxide; EC = elemental carbon; LUR = land use regression; NO[2] = nitrogen dioxide; O[3] = ozone; OC = organic carbon; PM[2.5] = in general terms, particulate matter with a nominal aerodynamic diameter less than or equal to 2.5 µm, a measure of fine particles; PM[10] = 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[10−2.5] = 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_{10}; SO[2] = 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_2.

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

Data from the studies cited in Figure 3-8 suggest that the correlations between exposure concentrations of SO_2 and copollutants have changed over time for some cases (Figure 3-9). On average, copollutant correlations using 1-hour data have declined in magnitude over the last two decades for CO, NO_2, PM_{10}, and $PM_{2.5}$, albeit with a lot of scatter in these relationships reflected in the mostly low correlation values. These trends may be related to the adoption of alternatives to coal in energy generation (Section 2.2). Most of the studies presented were performed during periods that precede 2006, when the ultra-low sulfur diesel rule went into effect (66 FR 5002). The amount of SO_2 co-emitted with CO and NO_X during combustion processes has since been greatly reduced. Hence, copollutant confounding is less probable for newer studies of the health effects of SO_2 exposure compared with older studies. At the same time, scatter in the copollutant correlation trends suggests that copollutant correlations need to be checked for individual epidemiological studies to assess if confounding is a possibility.



CO = carbon monoxide; NO2 = nitrogen dioxide; O3 = ozone; PM2.5 = particulate matter with a nominal aerodynamic diameter less than or equal to 2.5 µm; PM10 = 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

Long-term epidemiologic studies that have reported copollutant correlations are also displayed in Figure 3-8 and references cited therein for within-monthly and longer term correlations. Data were limited for many of the $PM_{2.5}$ components. For exposure concentrations of $PM_{2.5}$, PM_{10}, O_3, CO, and NO_2, a wide range of correlations has been reported. Median correlation was lower for $PM_{2.5}$ exposure concentration (r = 0.2) compared with that of PM_{10} (r = 0.4), CO (r = 0.3), and NO_2 (r = 0.3). Median correlation was negative (r = −0.3) for O_3 exposure concentration. For correlations between exposure concentrations of SO_2 and $PM_{2.5}$, most of the data were clustered around the median,

while variability in the correlations was larger for the other copollutants. As for short-term copollutant relationships, no clear conclusion can be drawn regarding the potential for confounding of long-term SO_2 epidemiologic estimates by copollutants. Wide variability in copollutant correlations with the highest correlations around 0.7−0.8 for $PM_{2.5}$, PM_{10}, CO, and NO_2 suggests that confounding may need to be considered on a study-by-study basis.

3.4.3.2 Spatial Relationships among Ambient Sulfur Dioxide and Copollutants

Spatial confounding can potentially influence health effect estimates in epidemiologic studies of long-term SO_2 exposure. Paciorek (2010) performed simulations to test the effect of spatial confounding on health effect estimates in long-term exposure epidemiologic studies. He identified unmeasured spatial confounding as a key driver in biasing health effect estimates in a spatial regression. The study author maintained that bias can be reduced when variation in the exposure metric occurs at a smaller spatial scale than that of the unmeasured confounder.

3.4.4 Implications for Epidemiologic Studies of Different Designs

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

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

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

A longitudinal cohort epidemiologic study, such as the American Cancer Society (ACS) cohort study, typically involves hundreds or thousands of subjects followed over several years or decades [e.g., Jerrett et al. (2009)]. Concentrations are generally aggregated over time and by community to estimate exposures. The importance of exposure error varies with study design and is dependent on the spatial and temporal aspects of the design. Factors that could influence exposure estimates include topography of the natural and built environment, meteorology, instrument errors, use of ambient SO_2 concentration as a surrogate for exposure to ambient SO_2, and the presence of SO_2 in a mixture of pollutants. The following sections will consider various sources of error and how they affect the interpretation of results from epidemiologic studies of different designs.

3.4.4.1 Community Time-Series Studies

In most short-term exposure epidemiologic studies of the health effects of SO_2, the health effect endpoint is modeled as a function of ambient exposure, E_a, which is defined as the product of C_a, and α, a term encompassing time-weighted averaging and infiltration of SO_2 (Section 3.2.2). Community time-series epidemiologic studies capturing the exposures and health outcomes of a large cohort frequently use the ambient concentration at a central site monitor ($C_{a,csm}$) as a surrogate for E_a in an epidemiologic model (Wilson et al., 2000). At times, an average of central site-monitored concentrations is used for the E_a surrogate. For studies involving thousands of participants, it is not feasible to measure personal exposure concentrations or time-activity patterns. Moreover, for community time-series epidemiology studies of short-term exposure, the temporal variability in ambient SO_2 concentration is of primary importance to relate to variability in the health effect estimate (Zeger et al., 2000). $C_{a,csm}$ can be an acceptable surrogate if the central site monitor captures the temporal variability of the true air pollutant exposure. Spatial variability in ambient SO_2 concentrations across the study area could attenuate an epidemiologic health effect estimate if the exposures are not correlated in time with $C_{a,csm}$ when central site monitoring is used to represent exposure in the epidemiologic model. If exposure assessment methods that more accurately capture spatial variability in the concentration distribution over a study area are employed, then the confidence intervals around the health effect estimate may decrease. $C_{a,csm}$ may be an acceptable surrogate for E_a if the concentration time series at the central site monitor is correlated in time with the exposures.

In a time-series study of ED visits for cardiovascular disease, Goldman et al. (2011) simulated the effect of classical and Berkson errors due to spatiotemporal variability among ambient or outdoor (i.e., a noncentral site monitor situated outside the home) air pollutant concentrations over a large urban area. For 1-h daily max SO_2, the relative risk

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

Recent studies have explored the effect of spatial exposure error on health effect estimates to test the appropriateness of using central site monitoring for time-series studies. Goldman et al. (2010) simulated spatial exposure error based on a semivariogram function across monitor sites with and without temporal autocorrelation at 1- and 2-day lags to analyze the influence of spatiotemporal variability among ambient concentrations over a large urban area on a time-series study of ED visits for cardiovascular disease. A random term was calculated through Monte Carlo simulations based on the data distribution from the semivariogram, which estimated the change in spatial variability in exposure concentration with distance from the monitoring site. The average of the calculated random term was added to an ambient central site monitoring SO_2 concentration time series (considered in this study to be the base case) to estimate SO_2 population exposure concentration subject to spatial error. For the analysis with temporal autocorrelation considered, RR per ppm for 1-h daily max SO_2 dropped slightly to 1.0045 (95% CI: 1.0023, 1.0065) when it was compared with the central site monitor RR per ppm = 1.0139 (for all air pollutants).[1] When temporal autocorrelation was not considered, RR per ppm dropped very slightly to 1.0042 for 1-h daily max SO_2. The results of Goldman et al. (2010) suggest that spatial exposure error from the use of ambient central site SO_2 concentration monitoring data results in biasing the health effect estimate towards the null, but the magnitude of the change in effect was small.

In another simulation study analyzing the influence of spatiotemporal variability among ambient concentrations over a large urban area on health effect estimates, Goldman et al. (2012) evaluated the effect of different types of spatial averaging on bias in the health effect risk ratio and the effect of correlation between measured and reference ambient concentrations of SO_2 and other air pollutants. Ambient concentrations were simulated at alternate monitoring locations using the geostatistical approach described above (Goldman et al., 2010) for the 20-county Atlanta metropolitan area for comparison with ambient concentration measurements obtained directly from monitors at those sites. Geostatistical-simulated ambient exposure concentrations were designated as the reference in this study, and other exposure assessment methods were assumed to have some error. Five different exposure assessment approaches were tested: (1) using a single central site monitor, (2) averaging the simulated exposures across all monitoring sites,

[1] Note that 95% CIs were not reported for the central site monitor RR or for the cases where temporal autocorrelation was not considered.

(3) performing a population-weighted average across all monitoring sites, (4) performing an area-weighted average across all monitoring sites, and (5) performing population-weighted averaging of the geostatistical simulation. Goldman et al. (2012) observed that the exposure error was somewhat correlated with both the measured exposure concentration and the reference ambient concentrations, reflecting both Berkson and classical error components. For the central site monitor, the exposure errors were somewhat inversely correlated with the exposure concentration reference value but had relatively higher positive correlation with the measured ambient concentration. For the other exposure estimation methods, the exposure errors were inversely correlated with the reference exposure concentration, while having positive but lower magnitude correlation with the measured ambient concentration. Additionally, the exposure bias, given by the ratio of the exposure error to the measured value, was much higher in magnitude at the central site monitor than for the spatial averaging techniques for SO_2. Hence, compared with other exposure assessment methods, the health effect estimate would likely have greater bias towards the null with reduced precision when a central site monitor is used to measure ambient SO_2 concentration as a surrogate for exposure. However, exposure error is likely to cause some bias and imprecision for other exposure surrogate methods as well.

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

Section 3.4.2.4 describes the influence of high MDL on the relationship between measured ambient SO_2 concentrations and personal SO_2 exposures. When measurements are above MDL, then the amount of correlation between personal SO_2 exposure and ambient SO_2 concentrations determines the extent of bias in a time-series study. If the reported values of personal exposure measurements are below MDL, correlation between personal SO_2 exposure measurements and ambient SO_2 concentrations will likely be low due to random noise in the signal. To the extent that true correlations are less than one, epidemiologic effect estimates based on ambient concentration will be biased toward the null, based on simulations by Zeger et al. (2000). Time-series epidemiologic studies employing data below MDL may demonstrate attenuated effect, but this scenario cannot be used to reject the hypothesis of a health effect.

Section 3.4.2.4 also describes the influence of instrument accuracy and precision on the relationship between ambient SO_2 concentrations and personal SO_2 exposures. Exposure measurement error related to instrument precision has a smaller influence on health effect estimates in time-series studies compared with error related to spatial gradients in the ambient SO_2 concentration because instrument precision would not be expected to modify the ability of the instruments to respond to changes in ambient concentration over time. Goldman et al. (2010) investigated the influence of instrument error on health effect estimates in a time-series epidemiology study by studying differences in exposure concentration estimates and health effect estimates obtained using collocated monitors. In this study, a random error term based on observations from collocated monitors was added to a central site monitor's ambient concentration time series to simulate population estimates for ambient air concentrations subject to instrument precision error in 1,000 Monte Carlo simulations. Very small changes in the risk ratios were observed for 1-h daily max SO_2 ambient concentrations. For 1-h daily max SO_2 ambient concentration, the RR per ppm of SO_2 ambient concentration with simulated instrument precision error was 1.0132 compared with RR per ppm = 1.0139 for the central site monitor. The amount of bias in the health effect estimate related to instrument precision was very small.

As described in Section 3.4.1 nonambient sources of SO_2 are rare. Even in microenvironments where nonambient SO_2 exposure is substantial, such as in a room with a kerosene heater, such nonambient exposure concentrations are unlikely to be temporally correlated with ambient SO_2 exposure concentrations (Wilson and Suh, 1997), and therefore would not affect epidemiologic associations between ambient SO_2 exposure concentrations and a health effect in a time-series study. Sheppard et al. (2005) concluded that nonambient exposure does not influence the health outcome effect estimate if ambient and nonambient exposure concentrations are independent. Personal exposure to ambient SO_2 is some fraction of the ambient concentration. Therefore, effect estimates based on personal SO_2 exposure rather than ambient SO_2 concentration will be positively

biased in proportion to the ratio of ambient SO_2 concentration to ambient SO_2 exposure concentration. Daily fluctuations in this ratio can widen the confidence intervals in the ambient SO_2 concentration effect estimate beyond the nominal coverage of the confidence intervals obtained using the true exposure. Uncorrelated nonambient exposure concentration will not bias the effect estimate but may also widen the confidence intervals (Sheppard et al., 2005; Wilson and Suh, 1997).

3.4.4.2 Long-Term Cohort Studies

For cohort epidemiologic studies of long-term human exposure to SO_2, where the spatial difference in the magnitude of the ambient SO_2 exposure is often of most interest and if $C_{a,csm}$ is used as a surrogate for E_a, then α can be considered to encompass the exposure measurement error related to uncertainties in the time-activity data and air exchange rate. Spatial variability in ambient SO_2 exposure concentrations across the study area could lead to bias in the health effect estimate if $C_{a,csm}$ is not representative of E_a. This could occur, for example, if the study participants were clustered in a location where their SO_2 exposure concentration is higher or lower than the exposure concentration estimated at a modeled or measurement site. $C_{a,csm}$ may be an acceptable surrogate for E_a if the central site monitor is located close to the study participants and the ambient SO_2 source (e.g., near the plume touch-down of a power plant) and spatial variability of the ambient SO_2 concentration across the study area where the study participants are located is minimal in the vicinity of each sample group.

For long-term epidemiologic studies, the lack of personal exposure data means that investigators must rely on central site monitoring data or model estimates. Concentration data may be used directly, averaged across counties or other geographic areas, or used to construct geospatial or regression models to assign exposure concentrations to unmonitored locations. The number of long-term studies of SO_2 exposure that permit evaluation of the relationship between long-term average SO_2 concentrations and personal or population exposures is limited, and the value of short-term exposure concentration data for evaluating long-term exposure concentration relationships is uncertain. If the longer averaging time (annual vs. daily or hourly) smoothes out short-term fluctuations, long-term concentrations may be well correlated with long-term exposure concentrations that can be employed in long-term epidemiologic studies. For example, Guay et al. (2011) observed high correlation between single-year/single-location SO_2 concentrations used for an exposure surrogate with concentrations averaged over a 22-year period when the annual SO_2 concentrations were assigned based on the study participants' census subdivision. However, lower correlation between long-term exposure and ambient concentration could occur if important

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

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

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

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

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

Instrumentation bias could be expected to influence health effect estimates from epidemiologic studies of long-term SO_2 exposures in some situations. Section 2.4.1 describes how the presence of copollutants can cause ambient SO_2 concentrations measured using central site monitors to be overestimated and how high relative humidity can cause ambient SO_2 concentration measurements to be underestimated. Relative humidity would not be expected to vary greatly within a city. However, local ambient copollutant concentrations may be spatially variable such that failure to account for differences in measurement errors could lead to some differential bias in health effect estimates across a city related to instrument error. Because climate and ambient sources are more likely to differ among cities, instrumentation error could have a larger influence on the comparison of health effect estimates among cities when central site monitors are used to estimate exposure concentrations.

3.4.4.3 Panel Studies

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

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

Section 3.4.2.4 describes the influence of high MDL on the relationship between measured ambient SO_2 concentrations and personal exposures for ambient SO_2. Personal exposure measurements below MDL will likely cause the correlation between personal exposure measurements and ambient SO_2 concentrations to be low due to random noise in the signal. Noise in the exposure signal would add noise to the health effect estimate in a panel epidemiologic study as well. Below MDL measurements would be unlikely to bias the effect estimate, however, because the magnitude of exposure would be low whether measured with a high-precision or low-precision device.

It is also possible that the ratio of personal SO_2 exposure to ambient SO_2 concentration in panel studies is low due to the compound's low penetration and high reactivity. This results in attenuation of the magnitude of the exposure concentration-based effect estimate relative to the ambient concentration-based effect estimate (see Equation 3-6). However, if the ratio is approximately constant over time, the strength of the statistical association would be similar for ambient concentration- and exposure concentration-based effect estimates (Sheppard, 2005; Sheppard et al., 2005).

3.5 Summary and Conclusions

The 2008 SO_X ISA (U.S. EPA, 2008d) evaluated studies of ambient SO_2 concentrations and exposures in multiple microenvironments, discussed methods for estimating personal and population exposure concentrations via monitoring and modeling, analyzed relationships between personal exposure and ambient concentrations, and discussed the implications of using ambient SO_2 concentrations as estimates of exposure concentration in epidemiologic studies. Key findings were that indoor SO_2 concentrations and personal SO_2 exposure concentrations tended to be below the detection limit of personal SO_2 samplers for averaging times of 24 hours or less, making it difficult to evaluate the relationship between ambient SO_2 concentrations and indoor or personal SO_2 exposure concentrations. However, in studies with the bulk of personal samples above the detection limit, personal measurements of SO_2 exposure were moderately correlated with ambient SO_2 concentrations. Regarding the influence of exposure concentration estimates on epidemiologic study results, high spatial variability of ambient SO_2 concentrations across an urban area results in highly variable correlations among urban SO_2 monitors.

Low correlations between individual monitored ambient SO_2 concentrations and the community average ambient SO_2 concentration tend to bias effect estimates toward the null, while variations in individual personal-ambient relationships across a community will tend to widen confidence intervals around the effect estimates compared with the nominal coverage that would be obtained if the true exposure were used in the epidemiologic model. All of these findings are supported by the recent evidence available since the previous ISA.

In the current ISA, increased focus has been placed on the use of exposure surrogates in epidemiologic studies. Multiple techniques can be used to assign SO_2 exposure concentrations for epidemiologic studies, including the use of central site monitor ambient SO_2 concentrations, personal SO_2 monitors, and various types of models. Each has strengths and limitations, as summarized in Table 3-1. Central site monitors provide a continuous record of ambient SO_2 concentrations over many years, but they do not fully capture the relatively high spatial variability in ambient SO_2 concentration across an urban area, which tends to attenuate health effect estimates in time-series epidemiologic studies. For long-term studies, bias may occur in either direction depending on whether the monitor is over- or underestimating ambient SO_2 exposure concentration for the population of interest. In all study types, use of central site monitor ambient SO_2 concentrations in lieu of the true SO_2 exposures is expected to widen confidence intervals beyond the nominal coverage of the confidence intervals that would be obtained if the true exposure were used. Personal SO_2 monitors directly measure exposure, but low ambient SO_2 concentrations often result in a substantial fraction of the samples falling below the MDL for averaging times of 24 hours or less. Personal monitors also provide a relatively limited data set, making them more suitable for panel epidemiologic studies.

Computational models can be used to develop exposure concentration surrogates for individuals and large populations when personal exposure measurements are unavailable. Modeling approaches may include SPMs, LUR models, IDW, dispersion models, and CTMs. Strengths and limitations of each method are discussed in Table 3-1. Briefly, SPMs, LUR, and IDW do not take into account atmospheric chemistry and physics. SPMs require only distances between SO_2 sources and receptors for input. EWPM also require emission rates. IDW is a weighted average of ambient SO_2 concentrations measured at several monitors. Other spatial interpolation techniques, such as kriging, also require ambient SO_2 concentrations from several monitors and apply more complex mathematical functions to interpolate among monitors. LUR regresses measured ambient SO_2 concentrations on local variables and then uses the resulting model to predict ambient SO_2 concentrations across a study area or at the locations of specific receptors. As such, LUR enables higher spatial resolution of predicted ambient SO_2 concentrations and requires more detailed input data compared with IDW and LUR. Mechanistic

models, such as dispersion models and CTMs, simulate the transport and dispersion of ambient SO_2, and in the case of CTMs, the atmospheric chemistry. The strength of mechanistic models is increased accuracy of the ambient SO_2 concentration field over time and space. However, they are much more computationally intensive. Microenvironmental models require personal sensor data for input and are resource intensive. The strength of these models is that they account for time the exposed population spend in different microenvironments. With the exception of microenvironmental models, these methods tend to be used in epidemiologic studies of long-term ambient SO_2 exposure. Depending on the modeling approach, there is the potential for bias and reduced precision due to model misspecification, missing sources, smoothing of concentration gradients, and complex topography. Evaluation of model results helps demonstrate the suitability of that approach for particular applications.

The current ISA also reviews the newly available literature regarding indoor and personal exposures to SO_2. New studies of the relationship between indoor and outdoor SO_2 concentrations have focused on public buildings and are consistent with previous studies showing that indoor:outdoor ratios and slopes cover an extremely wide range, from near zero to near one. Differences in results among studies are due to the lack of indoor sources of SO_2, indoor deposition of ambient SO_2, building characteristics (e.g., forced ventilation, building age, and building type such as residences or public buildings), personal activities, and analytical approaches. When reported, correlations between indoor and outdoor SO_2 concentrations were relatively high (>0.75), suggesting that variations in outdoor SO_2 concentrations are driving indoor SO_2 concentrations. Several studies of personal-ambient SO_2 relationships available at the time of the previous ISA showed a large fraction of samples below the MDL, making them unsuitable for determining personal-ambient correlations. In a study with all personal samples above the MDL, personal exposure was moderately correlated with ambient concentration.

Additional factors that could contribute to error in estimating exposure to ambient SO_2 include time-location-activity patterns, spatial and temporal variability in SO_2 concentrations, and proximity of populations to central site monitors and sources. Activity patterns vary both among and within individuals, resulting in corresponding variations in exposure across a population and over time. Ambient SO_2 concentrations among different microenvironments and the amount of time spent in each location will jointly influence an individual's exposure to ambient SO_2 (see Equation 3-3). Time spent in different locations has also been found to vary by age, with younger and older age groups spending a greater percentage of time outdoors than adults of typical working age (18−64 years). These variations in activity pattern contribute to differences in exposure and introduce error into population-averaged SO_2 exposure estimates.

Spatial and temporal variability in ambient SO_2 concentrations can contribute to exposure error in epidemiologic studies, whether the study relies on central site monitor data or concentration modeling for exposure assessment. Ambient SO_2 concentrations have low to moderate spatial correlations between ambient monitors across urban geographic scales; thus, using ambient SO_2 concentration data measured at central site monitors as exposure surrogates in epidemiologic studies introduces exposure error into the resulting health effect estimate. Spatial variability in the magnitude of ambient SO_2 concentrations can affect cross-sectional and large-scale cohort studies by undermining the assumption that intra-urban ambient SO_2 exposure differences across space are less important than inter-urban differences. This issue may be less important for time-series studies, which rely on day-to-day temporal variability in ambient SO_2 exposure concentrations to evaluate health effects.

Proximity of populations to ambient SO_2 monitors may influence how well human exposure to ambient SO_2 is represented by measurements at the monitors, although factors other than distance also play an important role. While many ambient SO_2 monitors are located near dense population centers, other monitors are located near sources and may not fully represent ambient SO_2 concentrations experienced by populations in epidemiologic studies. Use of these near-source monitors introduces exposure error into health effect estimates, and this error may be mitigated by using average ambient SO_2 concentrations across multiple monitors in an urban area.

Exposure to copollutants may result in confounding of health effect estimates. For ambient SO_2, daily concentrations generally exhibit low to moderate correlations with daily NAAQS copollutant concentrations at collocated monitors (Figure 3-4). However, a wide range of copollutant correlations is observed at different monitoring sites, from moderately negative to moderately positive. In studies where daily correlations of ambient SO_2 concentrations with ambient NO_2 and CO concentrations were observed to be high, it is possible the data were collected before rulemaking to reduce sulfur content in diesel fuel went into effect in 2006 (66 FR 5002). Sites with stronger correlations may introduce a greater degree of confounding into epidemiologic results, depending on the relationship between the copollutants and the health effect of interest. A similar impact is expected for epidemiologic studies of long-term ambient SO_2 exposure, because a wide range of copollutant correlations have also been reported over time periods of months to years.

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

design, especially regarding the study's spatial and temporal aspects. For example, in time-series and panel studies, low personal-ambient correlations tend to bias the effect estimate toward the null, while spatial variation in personal-ambient correlations across an urban area contributes to widening of the confidence interval around the effect estimate compared with the nominal confidence interval. For long-term studies, bias of the health effect estimate may occur in either direction depending on whether the monitor is over- or underestimating true ambient SO_2 exposure for the population of interest. In all study types, use of central site monitors in lieu of the true ambient SO_2 exposure is expected to decrease precision of the health effect estimate because spatial variation in personal-ambient correlations across an urban area contributes to widening of the confidence interval around the effect estimate compared with the nominal coverage of the confidence intervals obtained if the true ambient SO_2 exposure were used. Choice of exposure estimation method also influences the impact of exposure error on epidemiologic study results. Central site monitors offer a convenient source of time-series data. However, because they are in a fixed location, ambient SO_2 concentration measurements obtained from a central site monitor do not account for the effects of spatial variation in ambient SO_2 concentration, ambient and nonambient concentration differences, and varying activity patterns on personal exposure to ambient SO_2. Personal exposure measurements, such as those made in panel epidemiologic studies, provide specific exposure estimates that may more accurately reflect spatial and temporal variability, but sample size is often small and only a limited set of health outcomes can be studied. Modeled ambient SO_2 concentration or exposure concentration estimates offer alternatives or supplementation to measurements, with the advantage of estimating ambient SO_2 exposure concentrations over a wide range of scales, populations, and scenarios, particularly for locations lacking monitoring data. Model estimates are most useful when compared to an independent set of measured ambient SO_2 concentrations or exposure concentrations. The various sources of exposure error and their potential impact are considered in the evaluation of epidemiologic study results in this ISA.

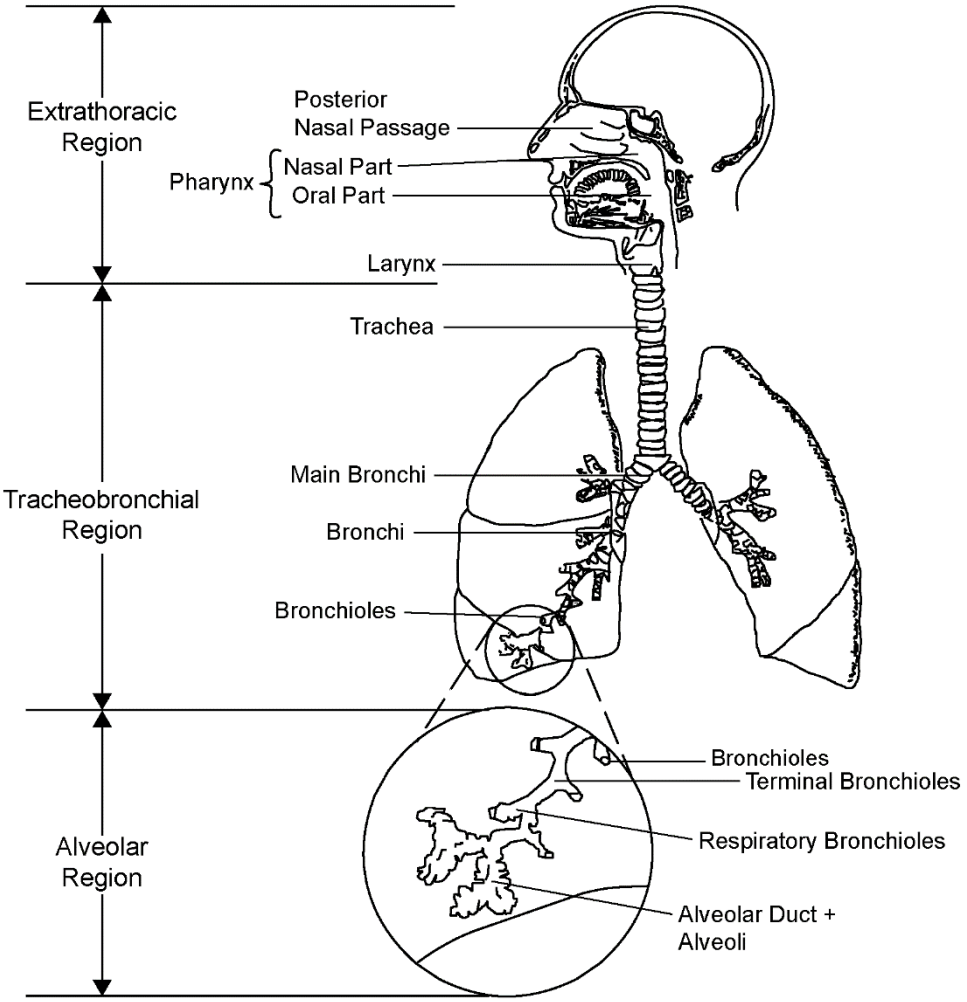
Chapter 4 Dosimetry and Mode of Action

4.1 Introduction

Chapter 4 begins by providing background information on the structure and function of the respiratory tract (Section 4.1.1) and breathing rates and habits (Section 4.1.2). The subsequent discussion of dosimetry of inhaled SO_2 (Section 4.2) considers the chemical properties of SO_2 and the processes of absorption, distribution, metabolism, and elimination, as well as sources and levels of exogenous and endogenous sulfite. The biological pathways that potentially underlie health effects are described in "Modes of Action of Inhaled Sulfur Dioxide" (Section 4.3). This section includes a description of processes by which inhaled SO_2 initiates a cascade of molecular and cellular responses and the organ-level responses that follow. Together, these sections provide the foundation for understanding how exposure to inhaled SO_2 may lead to health effects. This understanding may provide biological plausibility for effects observed in the epidemiologic studies.

4.1.1 Structure and Function of the Respiratory Tract

The basic structure of the human respiratory tract is illustrated in Figure 4–1. In the literature, the terms extrathoracic (ET) region and upper airways or upper respiratory tract are used synonymously. The terms lower airways and lower respiratory tract are used to refer to the intrathoracic airways [i.e., the combination of the tracheobronchial (TB) region, which includes the conducting airways and the alveolar region, the 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

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

from those tables. Except for the oldest age range, ventilation rates (volume/time) 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[a]	20.6	41.4

[a]No value for ≥81 provided, substituted 71 to <81 value.

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

Another way to consider differences in ventilation rates between adults and children is to normalize to body weight. This metric is relevant especially for SO_2 absorbed in the nasal airways and the fraction of absorbed SO_2 that distributes systemically (see Section 4.2.3). Normalized to body mass, median daily ventilation rates (m^3/kg-day) decrease over the course of life (Brochu et al., 2011). This decrease in ventilation relative to body mass is rapid and nearly linear from infancy through early adulthood. Relative to normal-weight male and female adults (25−45 years of age; 0.271 m^3/kg-day), ventilation rates

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

The metric for effects on the bronchi and differences between children and adults in bronchial effects of SO_2 is likely to be SO_2 absorbed dose per bronchial surface area (see Section 4.2.2). Ventilation per tracheobronchial surface area is also used to approximate absorbed dose per bronchial surface area for interspecies extrapolation [see Appendix A of U.S. EPA (2009c)].

4.1.2.2 Breathing Habit

As humans, we breathe oronasally (i.e., through both our nose and mouth). In general, we breathe through our nose when at rest and increasingly through the mouth with increasing activity level. Few people breathe purely through their mouth. In contrast to the oronasal breathing of humans, rodents are obligate nasal breathers. Described in Section 4.2.2, the nasal passages more efficiently remove SO_2 from inhaled air than the oral passage. As the fraction of inhaled air passing through the mouth increases so too does the amount of inhaled SO_2 reaching the tracheobronchial airways where SO_2 may cause bronchoconstriction. Thus, route of breathing (namely, the fraction of inhaled air passing through the mouth) is a critical determinate of dose to the lower airways and the potential respiratory effects of SO_2. This section describes how route of breathing, also referred to as "respiratory mode" or "breathing habit" in the literature, is affected by age, sex, obesity, activity level, and upper respiratory tract anomalies.

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

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

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

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

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

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

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

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

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

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

4.2 Dosimetry of Inhaled Sulfur Dioxide

This section provides a brief overview of SO_2 dosimetry and updates information provided in the 2008 ISA for Sulfur Oxides (U.S. EPA, 2008d). Dosimetry of SO_2 refers to the measurement or estimation of the amount of SO_2 and its reaction products reaching and/or persisting at specific sites within the respiratory tract or systemically after exposure. One principal effect of inhaled SO_2 is to stimulate bronchial epithelial irritant receptors and initiate a reflexive contraction of smooth muscles in the bronchial airways. Health effects may be due to the inhaled SO_2 or its chemical reaction products. Complete identification of the causative agents and their integration into SO_2 dosimetry is a complex issue that has not been thoroughly evaluated. The major factors affecting the transport and fate of gases and aerosols in the respiratory tract are the morphology of the respiratory tract; the physiochemical properties of the epithelial lining fluid (ELF); respiratory functional parameters, such as tidal volume, flow rate, and route of breathing; physicochemical properties of the gas; and the physical processes that govern gas transport. Few studies have investigated SO_2 dosimetry since the 1982 AQCD for Particulate Matter and Sulfur Oxides (U.S. EPA, 1982a) and the 1986 Second Addendum (U.S. EPA, 1986b).

The following sections will address the chemistry, and the processes of absorption, distribution, metabolism, and elimination that pertain to the dosimetry of inhaled SO_2. Studies investigating the dosimetry of SO_2 generally are for concentrations of SO_2 that are higher than those present in ambient air. However, these studies are included here because they provide the foundation for understanding SO_2 toxicokinetics and toxicodynamics. The discussion of dosimetry will conclude with a consideration of other sources of SO_2-derived products in the body.

4.2.1 Chemistry

Physicochemical properties of SO_2 most relevant to respiratory tract uptake include its solubility in the ELF and its chemical transformations and reactions that occur there. Henry's law relates the gas-phase and liquid-phase interfacial concentrations at equilibrium and is a function of temperature and pressure. The Henry's law constant, defined as the ratio of partial pressure or concentration of SO_2 in the gas phase to SO_2 dissolved in the liquid phase, is an inverse measure of solubility. Although the solubility

of most gases in the ELF is not known, the Henry's law constant is known for many gases in water, and for SO_2, it is 0.047 $(mol/L)_{air}$ per $(mol/L)_{water}$ at 37°C and 1 atmosphere (Hales and Sutter, 1973). For comparison, Henry's law constant for O_3 is 6.4 $(mol/L)_{air}$ per $(mol/L)_{water}$ under the same conditions (Kimbell and Miller, 1999). Thus, SO_2 is nearly 140-times more soluble than O_3 in water. In general, the more soluble a gas is in biological fluids, the more rapid, and proximal its absorption will be in the respiratory tract. In addition to the Henry's law constant, it is also necessary to consider the transport of SO_2 from the lumen to the ELF of the tracheobronchial airways (see Section 4.2.2). When the partial pressure of SO_2 on mucosal surfaces exceeds that of the gas phase, such as during expiration, some desorption of SO_2 from the ELF may be expected (see Section 4.2.5).

Once SO_2 contacts the fluids lining the airways, it dissolves into the aqueous compartment and rapidly hydrates to form H_2SO_3, which forms hydrogen (H^+) ions, bisulfite HSO_3^- anions, and sulfite (SO_3^{2-}) anions (Gunnison et al., 1987a; Gunnison, 1981).

$$SO_2 + H_2O \rightleftharpoons H_2SO_3 \underset{+H^+}{\overset{-H^+}{\rightleftharpoons}} HSO_3^- \underset{+H^+}{\overset{-H^+}{\rightleftharpoons}} SO_3^{2-}$$

Equation 4-1

The prevalence of these sulfur species in solution is determined primarily by pH and, to a lesser extent, by temperature and ionic strength. In the human respiratory tract (pH of 7.4 and 37°C), dissolved SO_2 exists as a mixture exclusively of bisulfite and sulfite with the latter predominating (Gunnison, 1981). Subsequent reactions of bisulfite and sulfite such as sulfitolysis, enzymatic detoxification, and auto-oxidation are described below.

4.2.2 Absorption

Because SO_2 is highly soluble in water, it is expected to be almost completely absorbed in the nasal passages of both humans and laboratory animals under resting conditions. The dosimetry of SO_2 can be contrasted with the lower solubility gas, O_3, for which the predicted tissue doses (O_3 flux to liquid-tissue interface) are very low in the trachea and increase to a maximum in the terminal bronchioles or first airway generation in the pulmonary region [see Chapter 5 of U.S. EPA (2013c)]. The mass transfer (cm/s) of SO_2 from the air-phase to the ELF is proportion to the Sherwood number (dimensionless) and diffusion coefficient of SO_2 in air (0.23 cm^2/s) and inversely proportion to the diameter (cm) of an airway [see Equation 10 of Asgharian et al. (2011)]. The Sherwood number for various breathing patters from infants to young adults may be calculated using

Equation 13 of Asgharian et al. (2011) in combination with age specific airway morphology from Phalen et al. (1985). For 50th-percentile ventilation rates from Brochu et al. (2011), the mass transfer rates of SO_2 in the trachea and bronchi of infants (4-months) are about 1.8-times greater than in young adults (18 years). By 8.5 years of age, the mass transfer rate is only about 1.2-times greater than in young adults.

Melville (1970) measured the absorption of SO_2 [1.5 to 3.4 parts per million (ppm)] during nasal and oral breathing in 12 healthy volunteers. Total respiratory tract absorption of SO_2 (expressed as a percentage of the amount inhaled) was significantly greater ($p < 0.01$) during nasal than oral breathing (85 vs. 70%, respectively) and was independent of the inspired concentration. Respired flows were not reported. Andersen et al. (1974) measured the nasal absorption of SO_2 (25.5 ppm) in seven volunteers at an average inspired flow of 23 L/minute [i.e., eucapnic hyperpnea (presumably to simulate light exertion)]. These investigators reported that the oropharyngeal SO_2 concentration was below their limit of detection (0.25 ppm), implying that at least 99% of SO_2 was absorbed in the nose of subjects during inspiration. Speizer and Frank (1966) also measured the absorption of SO_2 (16.1 ppm) in seven healthy subjects at an average ventilation of 8.5 L/minute (i.e., at rest). They reported that 14% of the inhaled SO_2 was absorbed within the first 2 cm into the nose. The concentration of SO_2 reaching the pharynx was below the limit of detection, suggesting that at least 99% was absorbed during inspiration.

Frank et al. (1969) and Brain (1970) investigated the oral and nasal absorption of SO_2 in the surgically isolated upper respiratory tract of anesthetized dogs. Radiolabeled SO_2 ($^{35}SO_2$) at concentrations of 1, 10, 25, or 50 ppm was passed separately through the nose and mouth at steady flows of 3.5 and 35 L/minute for 5 minutes by Brain (1970). The nasal absorption of SO_2 (1 ppm) was effectively 100% at 3.5 L/minute and 96.8% at 35 L/minute. A negligible effect of SO_2 concentration was observed with nasal absorption increasing from 99.9% at 1 ppm to 99.99% at 10 ppm and 99.999% at 50 ppm. The oral absorption of SO_2 (1 ppm) was 99.56% at 3.5 L/minute, but only 34% at 35 L/minute. There was a slight decrease in oral SO_2 absorption from 99.56 to 96.3% when the concentration was increased from 1 to 10 ppm at 3.5 L/minute, whereas nasal absorption was unaffected by changes in concentration (1−50 ppm). In an earlier experiment, Frank et al. (1967) showed that nasal absorption of 2.2 ppm $^{35}SO_2$ at 3.5 L/minute was 100% throughout the first 20 minutes of exposure. On average, there was a small reduction in $^{35}SO_2$ absorption to 94% approaching 30 minutes of exposure. Frank et al. (1969) noted that the aperture of the mouth may vary considerably, and that this variation may affect SO_2 uptake in the mouth. Although there was a minor effect of inhaled concentration on SO_2 absorption, the route of breathing and rate of flow were the main factors affecting the magnitude of SO_2 absorption in the upper airways of dogs.

Modeling shows that virtually all SO_2 reaching the lower airways in young adults, as well as in dogs and rats, is absorbed in the bronchi and does not penetrate into the bronchioles or alveolar region (Tsujino et al., 2005). Considering the effect of age on SO_2 dose to the airways of humans, dose as ventilation per bronchial surface area can be estimated using bronchial morphology from Phalen et al. (1985) and 50th-percentile ventilation rates from Brochu et al. (2011). This approximation shows a gradual reduction in bronchial surface dose with decreasing age from young adults to infants. Using this approximation, an infant (4-months) would have approximately 80% of the bronchial surface dose of a young adult (18-years). However, as described in Section 4.1.2.2, children breathe more through the mouth than adults, which is associated with greater SO_2 penetration to the lower respiratory tract. In addition, as described above, mass transfer rates of SO_2 from the lumen to the ELF in the trachea and bronchi increase with decreasing age. Based on these observations, it is expected that SO_2 penetrating through the upper airways is rapidly removed in the trachea and first several generations of bronchi and this may result in somewhat greater airway surface doses of SO_2 of children than adults in proximal bronchi.

In summary, inhaled SO_2 is readily absorbed in the upper airways of both humans and laboratory animals. During nasal breathing, the majority of available data suggests 95% or greater SO_2 absorption occurs in the nasal passages, even under ventilation levels comparable to exercise. Somewhat less SO_2 is absorbed in the oral passage than in the nasal passages. The difference in SO_2 absorption between the mouth and the nose is highly dependent on respired flow rates. With an increase in flow from 3.5 to 35 L/minute, nasal absorption is relatively unaffected, whereas oral absorption is reduced from 100 to 34%. Inhaled SO_2 concentration has a negligible effect of nasal absorption, where oral absorption may decrease slightly with increasing concentration from 1 ppm to 10 ppm SO_2. Thus, the rate and route of breathing have a great effect on the magnitude of SO_2 absorption in the upper airways and on the penetration of SO_2 to the lower airways. Overall, the available data clearly show a pattern of SO_2 absorption that shifts from the upper airways to the tracheobronchial airways in conjunction with a shift from nasal to oronasal breathing and associated increased ventilatory rates in exercising humans. Due to their increased amount of oral breathing, children (particularly boys and the obese) and individuals with allergies or upper airway infections may be expected to have greater SO_2 penetration into the lower respiratory tract than healthy adults (see Section 4.1.2). Children may also be expected to have a greater intake dose of SO_2 per body mass than adults due to their ventilation rates (see Section 4.1.2).

4.2.3 Distribution

Once inhaled, SO_2 is absorbed in the respiratory tract and SO_2-derived products are widely distributed throughout the body, as was demonstrated in early studies using radiolabeled $^{35}SO_2$. Although rapid extrapulmonary distribution of SO_2-derived products occurs, the highest tissue concentrations of the ^{35}S retained in the body at any given time are found primarily in the respiratory tract (upper and lower) and may be detected there for up to a week following inhalation (Balchum et al., 1960, 1959). Frank et al. (1967) observed ^{35}S in the blood and urine of dogs within 5 minutes, the first time point, after starting 22 ppm $^{35}SO_2$ exposures of the surgically isolated nasal airways. At the end of 30−60-minute exposures, the authors estimated that 5−18% of the administered ^{35}S was in the blood. Balchum et al. (1959) investigated the tissue distribution of ^{35}S in dogs exposed for 20−40 minutes to $^{35}SO_2$ ranging in concentration from 1.1 to 141 ppm via tracheostomy or by nose/mouth breathing. At approximately 1-hour post-exposure, regardless of the exposure route or the $^{35}SO_2$ exposure concentration, about 6% of the retained ^{35}S was found in the liver, with lesser amounts found in the heart, spleen, kidney, brain, and other tissues. However, the percent of retained ^{35}S was, on average, 13-times greater in the trachea and lungs of the tracheostomized group than in the nose/mouth breathing group, demonstrating the protection of the lower respiratory tract provided by SO_2 removal in the upper airways. Comparison of dogs retaining similar total amounts of ^{35}S (i.e., controlling for retained dose), showed that the blood concentrations of ^{35}S were higher in the tracheostomized dogs than in the nose/mouth breathing dogs. Given very high ^{35}S concentrations in the tongues of the nose/mouth breathing dogs and that blood concentrations had not decreased in two-thirds of these dogs by 1-hour post-exposure, the authors postulated that a substantial portion of the $^{35}SO_2$ products may have been retained within the upper airways with only slow absorption into the blood. Studies in rabbits and rats also show that there can be an accumulation and retention of SO_2-derived products within proximal regions of the respiratory tract (discussed below).

The distribution and clearance of inhaled SO_2 from the respiratory tract may involve several intermediate chemical reactions and transformations. In particular, hydrated SO_2 transforms to sulfite/bisulfite at physiologic pH. Sulfite can diffuse across cell membranes, and bisulfite can react with disulfide bonds (R_1-S-S-R_2) to form thiols (R_1-SH) and S-sulfonates (R_2-S-SO_3^-) by a process termed sulfitolysis (Gunnison and Benton, 1971). Because disulfide bonds are important determinants of protein structure and function in biological systems, breaking such bonds may have important biologic effects. Secreted airway mucins contain many disulfide bonds, and breaking these bonds might alter their function and thereby alter mucociliary clearance.

Studies in rabbits and rats found measurable levels of sulfite and S-sulfonates in the upper respiratory tract following inhalation of 10−30 ppm SO_2. Levels of sulfite and S-sulfonates were increased in tracheal washings of rabbits exposed to 10 ppm SO_2 for up to 72 hours (Gunnison et al., 1981). This implies reaction of sulfite with disulfide groups in mucus proteins in the ELF. In addition, tracheal tissue contained elevated levels of S-sulfonates, implicating reaction of sulfite with disulfide groups in tissue proteins. Bronchial tissue from rats had increased levels of sulfites and S-sulfonates when higher concentrations (30 ppm) of SO_2 were employed (Gunnison et al., 1987b). Under these conditions, no S-sulfonates were found in lung parenchyma, and neither sulfites nor S-sulfonates were found in the plasma. The lack of sulfites and S-sulfonates in the plasma of rats may have been due to their high levels of sulfite oxidase and rapid metabolism of sulfite (see Section 4.2.4). Consistent with ^{35}S rapidly appearing in the blood of $^{35}SO_2$-exposed dogs, S-sulfonates were found in plasma of rabbits following 10 ppm SO_2 exposure, providing evidence for absorption of sulfite into the blood of rabbits (Gunnison et al., 1981; Gunnison and Palmes, 1973). Studies with ex vivo plasma suggested that disulfide bonds in albumin and fibronectin are reactive with sulfite (Gregory and Gunnison, 1984).

Exposure of humans to SO_2 also resulted in measurable S-sulfonates in plasma (Gunnison and Palmes, 1974). In this study, humans were exposed continuously to 0.3−6 ppm SO_2 for up to 120 hours and plasma levels of S-sulfonates were positively correlated with concentrations of SO_2 inhaled. The regression line for this relationship had a correlation coefficient of 0.61 and the slope was 1.1 nmol/mL of plasma S-sulfonate for each 1-ppm increment in SO_2 concentration. Recently, a subacute study measured sulfite plus S-sulfonate content of the lung, liver, and brain of mice exposed to 5, 10, or 20 ppm SO_2, 4 hours/day for 7 days (Meng et al., 2005a). A concentration-dependent increase in sulfite and S-sulfonate levels was observed. Thus, in humans and mice, the amount of SO_2-derived species in blood and other tissues increases with the concentration in inhaled air. It should also be noted that measurable amounts of sulfite/S-sulfonate were found in tissues of humans and mice inhaling filtered air instead of SO_2 (Meng et al., 2005a; Gunnison and Palmes, 1974). Besides inhaled SO_2, sulfite is derived from other exogenous, as well as endogenous sources (see Section 4.2.6).

Inhaled SO_2 need not reach the lower airways for SO_2-derived species to be found in the blood. During the 5 full day of SO_2 exposure in the Gunnison and Palmes (1974) study, volunteers were likely at rest or sleeping for much of their exposures. Given that ventilation rates would be relatively low and breathing would be largely nasal (see Section 4.1.2), most inhaled SO_2 would likely be absorbed in the extrathoracic airways (see Section 4.2.2). A number of studies also exposed the surgically isolated upper airways of dogs to $^{35}SO_2$ and observed ^{35}S to rapidly appear in the blood and for the

concentration in blood to continually increase during exposure (e.g., Yokoyama et al., 1971; Frank et al., 1967). Frank et al. (1969) proposed the majority of SO_2-derived products found in the blood originated from SO_2 absorbed in the upper airways.

In summary, inhaled SO_2 is readily dissolved in the ELF where it exists as a mixture of bisulfite and sulfite with the latter predominating. Bisulfite reacts with disulfide groups forming S-sulfonates; sulfite can diffuse across cell membranes and reach the circulation. Following absorption in the respiratory tract, SO_2-derived products (e.g., sulfite and/or S-sulfonates) are widely distributed throughout the body and have been observed in the blood and urine within 5 minutes of starting an SO_2 exposure of surgically isolated nasal airways. Measurable levels of S-sulfonates have been observed in plasma following inhalation of SO_2 in humans, dogs, mice, and rabbits. Perhaps due to higher levels of hepatic sulfite oxidase relative to other species, sulfites, and S-sulfonates are not found in the plasma of rats. Although the majority of SO_2-derived products remain in the respiratory tract following exposure, extrapulmonary SO_2-derived products are found in the liver, with lesser amounts found in the heart, spleen, kidney, brain, and other tissues. The amount of SO_2-derived species in blood and other tissues increases with the concentration of SO_2 in inhaled air, while the distribution within the body is generally unaffected. A substantial portion of SO_2-derived products appear to be retained within the upper airways, particularly during nasal breathing, with only slow absorption into the blood.

4.2.4 Metabolism

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

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

Sulfite oxidase activity is highly variable among species. Liver sulfite oxidase activity in the rat is 10−20 times that in humans. Rapid metabolism of circulating sulfite to sulfate may explain the lack of sulfite/S-sulfonates found in blood of rats exposed by inhalation to 30 ppm SO_2, whereas these products were found in other species (Gunnison et al., 1987a). In sulfite oxidase-deficient rats, plasma sulfite levels increase with the severity of the deficiency (Gunnison et al., 1987b).

Gunnison and Benton (1971) also identified S-sulfonate in blood as a reaction product of inhaled SO_2. S-sulfonates, which are produced by the reaction of bisulfite with disulfide bonds, may be metabolized back to disulfides. Although the enzymatic pathways and cofactors are not clearly established for this repair process, it requires reducing equivalents, and thus, has a metabolic cost.

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

4.2.5 Elimination

Mechanisms involved in elimination include both desorption of SO_2 from the respiratory tract and the clearance of reaction products from the body.

When the partial pressure of SO_2 on mucosal surfaces exceeds that of the gas phase, such as during expiration, some desorption of SO_2 from respiratory tract lining fluids may be expected. Speizer and Frank (1966) found that on expiration, 12% of the SO_2 absorbed during inspiration was desorbed into the expired air. During the first 15 minutes after the 25- to 30-minute SO_2 exposure, another 3% was desorbed. In total, 15% of the amount of originally inspired and absorbed SO_2 was desorbed from the nasal mucosa. Frank et al. (1969) reported that up to 18% of the SO_2 was desorbed within ~10 minutes after exposure.

SO_2 that does not desorb is transformed to bisulfite/sulfite (Section 4.2.1). Because the lung tissue has a low activity of sulfite oxidase, diffusion into the circulation may be a more important route of sulfite clearance from the lung than enzyme-catalyzed transformation to sulfates. Within a period of minutes after starting $^{35}SO_2$ inhalation exposures, ^{35}S was observed in the blood and urine of dogs and distributed about the body (Frank et al., 1967; Balchum et al., 1959). At the end of 30−60-minute exposures, 5−18% of the administered ^{35}S was in the blood, and 1−6% had been excreted in the urine by 3 hours post-exposure (Yokoyama et al., 1971; Frank et al., 1967). The rate of urinary excretion was proportional to the blood concentration, and 92% of the urinary ^{35}S was in the form of sulfate (Yokoyama et al., 1971). In contrast, S-sulfonates formed in the circulation were reported to have a clearance half-time of 3.2 days (Gunnison and Palmes, 1973).

In summary, when the partial pressure of SO_2 on mucosal surfaces exceeds that of the gas phase, such as during expiration or following exposure, some desorption of SO_2 from the respiratory tract lining fluids may be expected. SO_2 that does not desorb is transformed to bisulfite/sulfite. Given the low activity of sulfite oxidase in the respiratory tract, sulfite is more likely to diffuse into the circulation or react with tissue constituents than be metabolized to sulfate. Circulating sulfite may subsequently react with constituents of the blood to form S-sulfonates or other species. It may appear in other organs, particularly the liver (Section 4.2.3), where it is efficiently metabolized to sulfate (Section 4.2.4). Urinary excretion of sulfate is rapid and proportional to the concentration of SO_2 products in the blood. S-sulfonates are cleared more slowly from the circulation with a clearance half-time of days. The portion of SO_2-derived products that are retained within the respiratory tract are only slowly absorbed into the blood (Section 4.2.3).

4.2.6 Sources and Levels of Exogenous and Endogenous Sulfite

The primary endogenous contribution of sulfite is from the catabolism of sulfur-containing amino acids (namely, cysteine and methionine). Sulfite may subsequently be metabolized to sulfate in a reaction catalyzed by sulfite oxidase in most tissues, but especially in the liver (Section 4.2.4). Mean daily sulfate produced following ingestion of cysteine and methionine in the U.S. increases from 70 mg/kg-day in infants (2−6 months) to 100 mg/kg-day in young children (1−3 years) and then decreases to 30 and 40 mg/kg-day in adult (19−50 years) females and males, respectively (IOM, 2005). To facilitate comparison with exogenous sources, a mole of SO_2 can produce a mole of sulfate, but the SO_2 mass is only two-thirds of the sulfate mass.

Sulfite is also added to foods because it has antioxidant and antimicrobial properties (Vandevijvere et al., 2010; Gunnison, 1981). In a study considering actual food consumption of Belgian adults and measured sulfite levels in food, Vandevijvere et al. (2010) observed a wide distribution in exogenous sulfite from ingestion. Expressed in terms of SO_2 equivalents, rates of exogenous sulfite ingestion may be described by a log-normal distribution with a median intake of 0.14 SO_2 mg/kg-day and a geometric standard deviation of 2.15. Individuals at the 5th and 95th percentiles of this distribution are estimated to consume 0.04 and 0.49 SO_2 mg/kg-day. In a comparison of theoretical food-consumption data with maximum permissible SO_2/sulfites to foods, the Belgian adults in the Vandevijvere et al. (2010) study had a similar potential sulfite intake to U.S. adults. The estimated intake for children could be in the range of that for adults or less due to the likely minimal consumption of sulfite sources such as wine. Endogenous sulfite from catabolism of ingested sulfur-containing amino acids far exceeds exogenous sulfite from ingestion of food additives [by 140 and 180 times in adult (19−50 years) females and males, respectively, and by 500 times or more in young children (1−3 years)].

Exogenous sulfite may also be derived from SO_2 inhalation. For the purposes of comparisons herein, all inhaled SO_2 is assumed to contribute to systemic sulfite levels. In reality, as discussed in Section 4.2.3, the majority of SO_2-derived products from SO_2 inhalation are retained in the respiratory tract and may be detected there for up to a week following inhalation. The potential contribution of inhaled SO_2 to systemic sulfite levels varies with age, activity level, and SO_2 concentration. Using median and 97.5th percentile daily ventilation rates from Brochu et al. (2011), adults (25−45 years of age) are estimated to receive 0.004 and 0.006 mg SO_2 per kg body mass, respectively, from a full day exposure to 5 parts per billion (ppb) SO_2. As an upper-bound estimate for ambient exposure in most locations, a full-day exposure to 75 ppb SO_2 (the level of the current National Ambient Air Quality Standard for SO_2) would result in 0.053 SO_2 mg/kg-day and 0.085 SO_2 mg/kg-day for adults having median and 97.5th percentile ventilation rates, respectively. The estimated daily SO_2 intake (mg/kg-day) would be roughly 1.5 times greater in children (7−10 years of age) and doubled in infants (0.22−0.5 years of age) due to the greater ventilation rate per body mass of children compared to adults (25−45 years of age). Even upper-bound sulfite levels from inhalation (75 ppb SO_2, 24 hours, 97.5th percentile ventilation) are far less than those derived from catabolism of sulfur-containing amino acids, by 230 to 300 times in adults (25−45 years) and nearly 500 times in young children (1−3 years).

Comparison of sulfite derived from SO_2 inhalation with that from ingestion of food additives is more complicated. In adults (25−45 years), sulfite intake (mg/kg-day) from inhalation (75 ppb SO_2, 24 hours, 97.5th percentile ventilation) is 1.6 times lower than

median sulfite intake from ingestion of food additives. In children (<10 years), assuming similar levels of sulfite intake as adults, sulfite intake from inhalation (75 ppb SO_2, 24 hours, 97.5th percentile ventilation) is approximately the same as median sulfite intake from ingestion of food additives. However, ingested sulfite absorbed into the blood goes directly to the liver where much of it will be metabolized into sulfate. The majority of sulfite derived from inhalation that enters the blood is rapidly distributed [as either sulfite or S-sulfonate (Yokoyama et al., 1971; Balchum et al., 1959)] about the body with around a quarter of total blood flow going to the liver (ICRP, 2002) where there is a high activity of sulfite oxidase compared to other tissues. For lower exposure concentrations and durations than considered above, sulfite (and/or S-sulfonate) levels in the blood following SO_2 inhalation could exceed those from ingestion of food additives, particularly in children.

In summary, exogenous sources contribute hundreds of times lower amounts of sulfite than the catabolism of sulfur-containing amino acids, when averaged across the entire body. Sulfite and sulfate derived from the catabolism of sulfur-containing amino acids are distributed broadly and do not accumulate in respiratory tract tissues. Following ingestion of sulfite-containing food additives, sulfite enters the circulation and is subject to first pass clearance in the liver where it is metabolized to sulfate. Following inhalation, a substantial portion of SO_2-derived products accumulate and are retained within the respiratory tract; SO_2-derived products that enter the circulation are rapidly distributed throughout the body, appear primarily in the liver, and are excreted via the urine (Section 4.2.5).

4.3 Mode of Action of Inhaled Sulfur Dioxide

This section describes the biological pathways that potentially underlie health effects resulting from short-term and long-term exposure to SO_2. Extensive research carried out over several decades in humans and in laboratory animals has yielded much information about these pathways. This section is not intended to be a comprehensive overview, but rather, it updates the basic concepts derived from the SO_2 literature presented in the AQCD (U.S. EPA, 1982a) and the 2008 ISA for Sulfur Oxides (U.S. EPA, 2008d) and introduces the recent relevant literature. While this section highlights findings of studies published since the 2008 SO_X ISA (U.S. EPA, 2008d), earlier studies that represent the current state of the science are also discussed. Studies conducted at more environmentally relevant concentrations of SO_2 (i.e., ≤2 ppm, see Section 1.2) are of greater interest because biological pathways responsible for effects at higher concentrations may not be identical to those occurring at lower concentrations. Some studies at higher concentrations are included if they were early demonstrations of key biological pathways

or if they are recent demonstrations of potentially important new pathways. This information will be used to develop a mode of action framework for inhaled SO_2 that serves as a guide to interpreting health effects evidence presented in Chapter 5.

Mode of action refers to a sequence of key events, endpoints, and outcomes that result in a given toxic effect (U.S. EPA, 2005a). Elucidation of mechanism of action provides a more detailed understanding of key events, usually at the molecular level (U.S. EPA, 2005a). The framework developed in this chapter will include some mechanistic information on initiating events at the molecular level, but will mainly focus on the effects of SO_2 at the cellular, tissue, and organism level.

SO_2 is a highly reactive antioxidant gas. At physiologic pH, its hydrated forms include sulfurous acid, bisulfite, and sulfite, with the latter species predominating. Sulfite is a strong nucleophilic anion that readily reacts with nucleic acids, proteins, lipids, and other classes of biomolecules. It participates in many important types of reactions including sulfonation (sulfitolysis) and autoxidation with the generation of free radicals. This latter reaction may be responsible for the induction of oxidative stress that occurs as a result of exposure to SO_2.

As described in Section 4.2, SO_2 is a water-soluble gas that is absorbed almost entirely in the upper respiratory tract. However, under conditions of mouth breathing and exercise, some SO_2 may penetrate to the tracheobronchial region. The main effects of SO_2 inhalation are seen at the sites of absorption (i.e., the respiratory tract) and include (1) activation of sensory nerves in the respiratory tract resulting in neural reflex responses, (2) injury to airway mucosa, and (3) increased airway hyperreactivity and allergic inflammation. Effects outside the respiratory tract may occur at very high concentrations of inhaled SO_2. Biologic pathways involved in mediating these responses to inhaled SO_2 will be discussed below. In addition, a brief synopsis of pathways involved in mediating the effects of endogenous SO_2/sulfite will be presented. This section will conclude with the development of a mode of action framework.

4.3.1 Activation of Sensory Nerves in the Respiratory Tract

SO_2 is classified as a sensory (or nasal) irritant in mice, guinea pigs, rats, and humans (Alarie, 1973). As such, it may stimulate trigeminal nerve endings when inhaled by the nose, which results in an inhibition of respiration. It may also stimulate trigeminal nerves in the larynx, which results in coughing, and in the cornea, which induces tearing. Other reflexes stimulated by trigeminal nerve endings include decreased heart rate, peripheral vasoconstriction, closure of the glottis, closure of the nares, and increased nasal flow resistance. These responses are variable among species. Increased nasal flow resistance

has been demonstrated in humans breathing SO_2 gas through the nose. Furthermore, desensitization of the respiratory rate response occurs with repeated exposure. Most sensory (or nasal) irritants, including SO_2, also cause bronchoconstriction, but at concentrations higher than those stimulating nerve endings in the nose.

SO_2 is also classified as a pulmonary (or bronchial) irritant that evokes reflex reactions through effects on pulmonary nerve endings (Alarie, 1973). These reactions usually include an increase in respiratory rate accompanied by a decrease in tidal volume, sometimes preceded by coughing and brief apnea, and sometimes accompanied by bronchoconstriction. These responses have been observed in guinea pigs and cats breathing via a tracheal cannula, which bypasses the nose. In the cat, SO_2 exposure increased the activity of vagal afferent fibers by either stimulating or sensitizing tracheobronchial receptors on the nerve endings. SO_2 also increased airway resistance in guinea pigs and humans breathing through the nose, mouth, and/or tracheal cannula. Increased airway resistance may occur via a variety of mechanisms including accumulation of secretions, inflammatory changes of the airway walls, collapsing airways, and constrictions of the central and peripheral airways. Constriction may be due to direct action on the smooth muscle, axonal reflexes, vagal nerve stimulation, and release of mediators such as histamine.

Continuous or repeated exposure to inhaled SO_2 has a different pattern of responses in different species (Alarie, 1973). In guinea pigs, the increase in airway resistance rose to a plateau upon exposure and decreased to baseline with cessation of exposure. In humans and dogs, resistance increased with exposure but decreased after 10 minutes (humans) or 3 minutes (dogs) despite the continuous presence of the gas. Studies in adults with asthma demonstrated a different pattern. When exposure to SO_2 occurred during a 30-minute period with continuous exercise, the response to SO_2 developed rapidly and was maintained throughout the 30-minute exposure (Kehrl et al., 1987; Linn et al., 1987; Linn et al., 1984c). Sequential exposures in nonasthmatic human subjects and in cats resulted in a decreased response to SO_2 in the second exposure compared with the first, indicative of desensitization.

Early experiments demonstrated that SO_2-induced reflexes were mediated by cholinergic parasympathetic pathways involving the vagus nerve and inhibited by atropine (Grunstein et al., 1977; Nadel et al., 1965a, b). Bronchoconstriction was found to involve smooth muscle contraction because β-adrenergic agonists such as isoproterenol reversed the effects. Rapid shallow breathing was observed in SO_2-exposed tracheotomized cats (bypassing the nose). Histamine was proposed to play a role in SO_2-induced bronchoconstriction (U.S. EPA, 1982a), but this hypothesis remains unconfirmed. Hydrogen ions, sulfurous acid, sulfite, and bisulfite are all putative mediators of the

reflex responses (Gunnison et al., 1987a). In particular, sulfite-mediated sulfitolysis of disulfides present in receptor proteins on sensory nerve fibers has been postulated because S-sulfonate formation may potentially disrupt protein structure or function (Alarie, 1973).

More recent experiments in animal models conducted since 1982 have demonstrated that both cholinergic and noncholinergic mechanisms may be involved in SO_2-induced effects. In two studies using bilateral vagotomy, vagal afferents were found to mediate the immediate ventilatory responses to SO_2 (Wang et al., 1996), but not the prolonged bronchoconstrictor response (Barthelemy et al., 1988). Other studies showed that atropine failed to block SO_2-induced bronchoconstriction, and that a local axon reflex resulting in C-fiber secretion of neuropeptides (i.e., neurogenic inflammation) was responsible for the effect (Hajj et al., 1996; Atzori et al., 1992). Neurogenic inflammation has been shown to play a key role in animal models of airway inflammatory disease (Groneberg et al., 2004). Furthermore, in isolated perfused and ventilated guinea pig lungs, bronchoconstriction to SO_2 was biphasic. The initial phase was mediated by a local axon reflex involving the release of the neuropeptide calcitonin gene-related peptide from sensory nerves, while the later phase involved other mechanisms (Bannenberg et al., 1994).

In humans, the mechanisms responsible for SO_2-induced bronchoconstriction are not entirely understood. In nonasthmatic subjects, near complete attenuation of bronchoconstriction has been demonstrated using the anticholinergic agents atropine and ipratropium bromide (Yildirim et al., 2005; Snashall and Baldwin, 1982; Tan et al., 1982). However, in asthmatic subjects, these same anticholinergic agents (Field et al., 1996; Myers et al., 1986a), as well as short- and long-acting β2-adrenergic agonists (Gong et al., 1996; Linn et al., 1988), theophylline (Koenig et al., 1992), cromolyn sodium (Myers et al., 1986a), neodocromil sodium (Bigby and Boushey, 1993), and leukotriene receptor antagonists (Gong et al., 2001; Lazarus et al., 1997) only partially blocked SO_2-induced bronchoconstriction. That none of these therapies have been shown to completely attenuate the effects of SO_2 implies the involvement of both parasympathetic pathways and inflammatory mediators in asthmatic individuals. Strong evidence of this was borne out in a study by Myers et al. (1986a) in which asthmatic adults were exposed to SO_2 following pretreatment with cromolyn sodium (a mast cell stabilizer), atropine (a muscarinic receptor antagonist), and the two medications together. While both treatments individually provided some protection against the bronchoconstrictive effects of SO_2, there was a much stronger and statistically significant effect following concurrent administration of the two medications. Besides mast cell stabilization, cromolyn sodium may also reduce the activity of lung irritant receptors

(Harries et al., 1981), providing an alternative mechanism for the reduction in SO_2-induced bronchoconstriction observed.

It has been proposed that inflammation contributes to the enhanced sensitivity to SO_2 seen in asthmatic human subjects by altering autonomic responses (Tunnicliffe et al., 2001), enhancing mediator release (Tan et al., 1982), and/or sensitizing C-fibers and rapidly adapting receptors (Lee and Widdicombe, 2001). Whether local axon reflexes also play a role in SO_2-induced bronchoconstriction in asthmatic individuals is not known (Groneberg et al., 2004; Widdicombe, 2003; Lee and Widdicombe, 2001). However, differences in respiratory tract innervation between rodents and humans suggest that C-fiber-mediated neurogenic inflammation may be unimportant in humans (Groneberg et al., 2004; Widdicombe, 2003; Widdicombe and Lee, 2001). Furthermore, enhanced sensitivity to SO_2 in asthmatic individuals may be related to genetic polymorphisms of inflammatory mediators, such as TNF-α (Winterton et al., 2001).

Studies in vitro provide support for SO_2 exposure-mediated effects that involve inflammatory cells. It is known that sulfite exposure of cultured rat basophil leukemia cells, a mast cell analog, causes immunoglobulin E (IgE)-independent degranulation, release of histamine, serotonin and other mediators, and intracellular production of reactive oxygen species (Collaco et al., 2006). In addition, peroxidases, such as neutrophil myeloperoxidase, oxidize bisulfite anion to several radical species that in turn attack proteins (Ranguelova et al., 2013; Ranguelova et al., 2012). This represents a potentially important new toxicological pathway for sulfite, especially in the presence of neutrophilic and/or eosinophilic inflammation.

Irritant responses are indicative of a chemical's ability to damage the respiratory tract (Alarie and Luo, 1986; Alarie, 1981). In the case of sensory irritation, there is a characteristic decrease in respiratory rate, which is often used to set health-protective standards for occupational exposures. Chemicals that are pulmonary irritants often lead to rapid shallow breathing. They typically induce pulmonary edema or congestion if inhaled for a long enough period of time. Some chemicals are both sensory and pulmonary irritants and pulmonary irritation may occur at concentrations below which sensory irritation occurs. In the case of SO_2, a concentration-dependent hierarchy of effects has been noted in humans (Kane et al., 1979). Lethal or extremely severe injury to the respiratory tract has been reported at and above 190 ppm. Intolerable sensory irritation and respiratory tract injury that may occur with extended exposure has been associated with 10−15-minute exposures to 30−100 ppm SO_2, and tolerable sensory irritation has been associated with 10-minute exposures to 5−11.5 ppm SO_2. Minimal sensory irritation has been associated with exposures at and below 1 ppm. Increased airway resistance, likely due to pulmonary irritation and reflex bronchoconstriction, has been observed at

5 ppm in adults without asthma at rest and at 1 ppm SO_2 in adults without asthma while exercising (Arts et al., 2006). However, lung function changes have been observed at concentrations of SO_2 lower than 1 ppm in exercising adults with asthma. Thus, pulmonary irritation may occur at levels of SO_2 below those that cause sensory irritation, especially in exercising adults with asthma.

In summary, SO_2 acts as both a sensory and a pulmonary irritant through activation of sensory nerves in the respiratory tract resulting in neural reflex responses. This occurs in a variety of species, including humans. Pulmonary irritant responses due to SO_2 exposure result in reflex bronchoconstriction, especially in adults with asthma. Both cholinergic parasympathetic pathways involving the vagus nerve and inflammation contribute to reflex bronchoconstriction in asthmatic individuals.

4.3.2 Injury to Airway Mucosa

A common feature of irritant gases, including SO_2, is the capacity to injure airway mucosa, resulting in decreased epithelial barrier function, inflammation, and compromised ciliary function (Carson et al., 2013). Despite being the initial site of SO_2 absorption and having low activity of sulfite oxidase, the respiratory tract of healthy humans is thought to be capable of detoxifying 5 ppm inhaled SO_2 (Gunnison et al., 1987a). In fact, exposure to 0.5−2 ppm SO_2 for 4 hours did not result in any measurable changes in biomarkers of oxidative stress or inflammation in exhaled breath condensate (EBC) or nasal lavage fluid (NALF) from healthy adults subjected to two periods of moderate exercise (Raulf-Heimsoth et al., 2010). In addition, no changes in nasal lining fluid ascorbic acid or uric acid levels were observed following 1-hour exposure of adults with asthma to 0.2 ppm SO_2 (Tunnicliffe et al., 2003).

However, respiratory tract injury has been observed in humans exposed for extended periods to SO_2 concentrations of 30 ppm and greater. In animal models, airway injury and histopathological changes, such as mucous cell metaplasia and intramural fibrosis, have generally been observed following chronic exposure to SO_2 concentrations of 10 ppm and higher (U.S. EPA, 2008d). Rats exposed to 20 ppm SO_2 for several weeks exhibit fibrotic remodeling of airway epithelium and mucus hypersecretion, key features of COPD and chronic asthma in humans (Wagner et al., 2006). Inflammatory changes have been noted in some animal models following subacute exposure to 5−100 ppm SO_2 (U.S. EPA, 2008d). However, adults with asthma and animal models of allergic airway disease exhibit greater sensitivity to SO_2 (see below). Impaired mucociliary clearance has also been demonstrated at high concentrations of SO_2. In humans, nasal mucus flow was decreased during a 5-hour exposure to 5 and 25 ppm SO_2 (Gunnison et al., 1981).

Impaired mucus flow in the trachea has been observed in rats exposed subacutely to 11.4 ppm SO_2 and in dogs exposed chronically to 1 ppm SO_2 (Gunnison et al., 1981; Hirsch et al., 1975). Whether these effects were due to compromised ciliary function or altered properties of the mucus due to sulfite-mediated sulfitolysis of disulfide bonds in mucus was not investigated.

Recent studies provide additional insight. An ultrastructural examination of nasal biopsy tissue by freeze fracture microscopy was conducted in humans exposed to 0.75 ppm SO_2 for 2 h (Carson et al., 2013). Evidence of fragmentation of the tight junctional complex and polymorphonuclear infiltrate was reported although no effects on ciliary membranes were observed. These subtle responses suggest a slight decrease in barrier function due to acute SO_2 exposure at this level. Furthermore, a subacute exposure of rats to 2.67 ppm SO_2 (6 hours/day, 7 days) resulted in altered lung mRNA levels for inducible nitric oxide synthase (involved in inflammation) and for bax (or B-cell lymphoma 2-like protein 4; involved in regulating apoptosis) (Sang et al., 2010). In this study, gene expression changes were also found in the heart and they were more pronounced than in the lung. These results suggest that, despite low sulfite oxidase activity, the respiratory tract may be more resistant than the heart to the effects of inhaled SO_2.

In summary, exposure to SO_2 results in injury to airway mucosa, especially at higher concentrations and following extended periods of exposure. There is little evidence of injury or inflammation in response to acute exposures to concentrations of 2 ppm SO_2 or less in human subjects. However, one new study found subtle histopathological changes at the ultrastructural level following a 2-hour exposure to 0.75 ppm SO_2. New evidence also suggests subtle changes in the lung related to inflammation and apoptosis in rats exposed over several days to 2.67 ppm SO_2.

4.3.3 Modulation of Airway Responsiveness and Allergic Inflammation

Asthma is a chronic inflammatory disease of the airways that is characterized by increased airway responsiveness [i.e., airway hyperresponsiveness (AHR)] and variable airflow obstruction. Respiratory irritants, including SO_2, are thought to be a major cause of occupational asthma (Baur et al., 2012; Andersson et al., 2006). Both peak high-level exposures and low-level persistent exposures have been associated with the development of irritant-induced asthma.

Studies in several different animal species have shown that a single exposure to SO_2 at a concentration of 10 ppm or less failed to induce AHR following a challenge agent (U.S. EPA, 2008d). However, in an animal model of allergic airway disease, SO_2 exposure enhanced airway responsiveness. In this study, sheep previously sensitized and

challenged with *Ascaris suum* extract were exposed to 5 ppm SO_2 for 4 hours (Abraham et al., 1981). Airway responsiveness to carbachol was increased at 24 hours, but not immediately, after SO_2 exposure. This response was not observed in sheep that had not been sensitized and challenged with *Ascaris suum* extract. The mechanism underlying the SO_2-induced AHR was not investigated in this study. However, the AHR response could have resulted from sensitization of vagal irritant receptors, greater sensitivity of smooth muscle to bronchoconstriction agents, or enhanced concentrations of bronchoconstriction agents reaching the receptors or bronchial smooth muscle. The delayed nature of the response points to a possible role of inflammation in mediating AHR.

Two controlled human exposure studies in adults with asthma provide further evidence of AHR to an allergen when exposure to SO_2 was in combination with NO_2. In one of these studies, exposure to 0.2 ppm SO_2 or 0.4 ppm NO_2 alone did not affect airway responsiveness to house dust mite allergen immediately after a 6-hour exposure at rest (Devalia et al., 1994). However, following exposure to the two pollutants in combination, subjects demonstrated an increase response to the inhaled allergen. Rusznak et al. (1996) confirmed these results in a similar study and found that AHR to dust mites persisted up to 48 post-exposure. These results provide further evidence that SO_2 may elicit effects beyond the short time period typically associated with this pollutant.

Several other studies have examined the effects of SO_2 exposure on allergic inflammation. One of these was a controlled human exposure study of adults with asthma. Subjects were exposed for 10 minutes to 0.75 ppm SO_2 while exercising at a moderate level (Gong et al., 2001). In addition to changes in lung function and symptoms, there was a statistically significant increase in eosinophil count in induced sputum 2 hours post-exposure. Pretreatment with a leukotriene receptor antagonist dampened these responses, implicating a role for leukotrienes in mediating SO_2 exposure-induced effects.

The other studies investigated the effects of repeated exposure to SO_2 on inflammatory and immune responses in an animal model of allergic airways disease. Li et al. (2007) demonstrated that in ovalbumin-sensitized rats, exposure to 2 ppm SO_2 for 1 hour followed by challenge with ovalbumin each day for 7 days resulted in an increased number of inflammatory cells in bronchoalveolar lavage fluid (BALF) and an enhanced histopathological response compared with rats treated with SO_2 or ovalbumin alone. Similarly, intercellular adhesion molecule 1 (ICAM-1), a protein involved in regulating inflammation, and mucin 5AC glycoprotein (MUC5AC), a mucin protein, were upregulated in lungs and trachea to a greater extent in rats treated both with SO_2 and ovalbumin. A follow up study involving the same exposure regimen (2 ppm SO_2 for 1 hour) in the same allergic animal model (rats sensitized and challenged with

ovalbumin) also found that repeated SO_2 exposure enhanced inflammatory and allergic responses to ovalbumin (Li et al., 2014). Numbers of eosinophils, lymphocytes, and macrophages were greater in the BALF of SO_2-exposed and ovalbumin-treated animals than in animals treated only with ovalbumin. In addition, SO_2 exposure enhanced upregulation and activation of nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB), a transcription factor involved in inflammation, and upregulation of the cytokines interleukin-6 (IL-6) and interleukin-4 (IL-4) in lung tissue. Furthermore, BALF levels of IL-6 and IL-4 were increased to a greater extent in SO_2-exposed and ovalbumin-treated animals compared with ovalbumin treatment alone. These results indicate that repeated SO_2 exposure enhanced activation of the NFκB inflammatory pathway and upregulation of inflammatory cytokines in ovalbumin-treated animals. Furthermore, SO_2 exposure enhanced the effects of ovalbumin on levels of interferon gamma (IFN-γ) (decreased) and IL-4 (increased) in BALF and on IgE levels in serum (increased). Because levels of IL-4 are often indicative of T helper 2 (Th2) status and levels of IFN-γ are indicative of a T helper 1 (Th1) status, these results suggest a shift in Th1/Th2 balance away from Th2 in rats made allergic to ovalbumin, an effect that was exacerbated by SO_2 exposure. These Th2-related changes are consistent with the observed increases in serum IgE and BALF eosinophils in ovalbumin-treated animals, effects that were also enhanced by SO_2 exposure. Taken together, these results indicate that repeated exposure to SO_2 exacerbated inflammatory and allergic responses in this animal model. It should be noted, however, that group 2 innate lymphoid cells can mediate Type 2 immunity, as has been described for O_3-mediated responses in mice (Ong et al., 2016). Whether group 2 innate lymphoid cells mediate effects of inhalation of SO_2, which like O_3 is an irritant gas, is unexplored.

Two other follow-up studies by the same laboratory examined the effects of inhaled SO_2 on the asthma-related genes encoding epidermal growth factor (EGF), epidermal growth factor receptor (EGFR), and cyclooxygenase-2 (COX-2), and on apoptosis-related genes and proteins in this same model based on sensitization with ovalbumin (Xie et al., 2009; Li et al., 2008). While EGF and EGFR are related to mucus production and airway remodeling, COX-2 is related to apoptosis and may play a role in regulating airway inflammation. SO_2 exposure enhanced the effects of ovalbumin in this model, resulting in greater increases in mRNA and protein levels of EGF, EGFR and COX-2 in the trachea compared with ovalbumin treatment alone. SO_2 exposure enhanced other effects of ovalbumin in this model, resulting in a greater decline in mRNA and protein levels of tumor protein p53 (p53) and bax and a greater increase in mRNA and protein levels of B-cell lymphoma 2 (bcl-2) in the lungs compared with ovalbumin challenge alone. The increased ratio of bcl-2:bax, an indicator of susceptibility to apoptosis, observed following ovalbumin challenge, was similarly enhanced by SO_2. Thus, repeated exposure

to SO_2 may impact numerous processes involved in inflammation and/or airway remodeling in allergic airways disease.

The effects of repeated SO_2 exposure on the development of an allergic phenotype and altered physiologic responses in naive animals was examined in two studies in which SO_2 exposure preceded allergen sensitization. Repeated exposure of guinea pigs to SO_2 promoted allergic sensitization and subsequently enhanced allergen-induced bronchial obstruction, as reported by U.S. EPA (2008d). Riedel et al. (1988) examined the effect of SO_2 exposure on local bronchial sensitization to inhaled antigen. Guinea pigs were exposed by inhalation to 0.1, 4.3, and 16.6 ppm SO_2 for 8 hours/day for 5 days. During the last 3 days, SO_2 exposure was followed by exposure to nebulized ovalbumin for 45 minutes. Following bronchial provocation with inhaled ovalbumin (0.1%) 1 week later, bronchial obstruction was measured by examining the respiratory loop obtained by whole-body plethysmography. In addition, specific antibodies against ovalbumin were measured in serum and BALF. Results showed significantly higher bronchial obstruction in animals exposed to SO_2 (at all concentration levels) and ovalbumin, compared with animals exposed only to ovalbumin. In addition, significant increases in anti-ovalbumin immunoglobulin G (IgG) antibodies were detected in BALF lavage fluid of animals exposed to 0.1, 4.3, and 16.6 ppm SO_2 and in serum from animals exposed to 4.3 and 16.6 ppm SO_2 compared with controls exposed only to ovalbumin. These results demonstrate that repeated exposure to SO_2 enhanced allergic sensitization in the guinea pig at a concentration as low as 0.1 ppm. In a second study, guinea pigs were exposed to 0.1 ppm SO_2 for 5 hours/day for 5 days and sensitized with 0.1% ovalbumin aerosols for 45 minutes on Days 4 to 5 (Park et al., 2001). One week later, animals were subjected to bronchial challenge with 0.1% ovalbumin and lung function was evaluated 24 hours later by whole-body plethysmography. Results demonstrated a significant increase in enhanced pause, a measure of airway obstruction, in animals exposed to SO_2 and ovalbumin but not in animals treated with ovalbumin or SO_2 alone. Results also demonstrated increased numbers of eosinophils in lavage fluid and an infiltration of inflammatory cells, bronchiolar epithelial cell damage, and plugging of the airway lumen with mucus and cells in the bronchial tissues of animals treated with both SO_2 and ovalbumin, but not in animals treated with ovalbumin or SO_2 alone. These experiments indicate that repeated exposure to near ambient levels of SO_2 plays a role in allergic sensitization and also exacerbates allergic inflammatory responses in the guinea pig. Furthermore, increases in bronchial obstruction observed in both studies suggest that repeated SO_2 exposure increased airway responsiveness.

Longer term exposure of naive newborn rats to SO_2 (2 ppm, 4 hours/day for 28 days) resulted in altered cytokine levels that suggest a shift in Th1/Th2 balance away from Th2 (Song et al., 2012). Th2 polarization is one of the steps involved in allergic sensitization.

It should be noted, however, that group 2 innate lymphoid cells can mediate Type 2 immunity, as has been described for O_3-mediated responses in mice (Ong et al., 2016). Whether group 2 innate lymphoid cells mediate effects of inhalation of SO_2, which like O_3 is an irritant gas, is unexplored. In naive animals exposed to SO_2, levels of IL-4, which is indicative of a Th2 response, were increased and levels of IFN-γ, indicative of a Th1 response, were decreased in BALF. In ovalbumin-sensitized newborn rats, SO_2 exposure resulted in a greater enhancement of lavage fluid IL-4 and an increase in serum IL-4 levels compared with ovalbumin-sensitization alone. In addition, SO_2 exposure led to AHR and airway remodeling, as indicated by increased content of airway smooth muscle, in the ovalbumin-sensitized animals. Stiffness and contractility of airway smooth muscle was assessed in vitro using cells from experimentally treated animals. In allergic rats, both stiffness and contractility were increased as a result of SO_2 exposure, suggesting an effect on the biomechanics of airway smooth muscle. This study provides evidence for allergic sensitization by SO_2 in naive newborn rats and for enhanced allergic inflammation, AHR, and airway remodeling in SO_2-exposed allergic newborn rats.

Supportive evidence that SO_2 may promote allergic sensitization is provided by a study in mice that were first treated with sodium sulfite and then sensitized and challenged with house dust mite allergen (Lin et al., 2011a). Sulfite is formed in ELF following inhalation of SO_2 (Section 4.2.1). Repeated intranasal treatment with 10 µL of a 5-mM solution of sodium sulfite aggravated inflammation (measured by histopathology) and allergic sensitization in this model. Specific IgE levels were higher in sulfite-treated and allergen-challenged animals compared with either sulfite treatment or allergen challenge alone. Specific IgG2α levels, indicative of a Th1 response, were decreased as a result of sulfite treatment in house dust mite-challenged mice. In addition, interleukin-5 (IL-5) levels, indicative of a Th2 response, and the ratio of Il-5:IFN-γ, a marker of Th2 polarization, were higher in lung tissue from sulfite-treated and allergen-challenged mice compared with either sulfite treatment or allergen challenge alone.

Mixtures of SO_2 and other criteria pollutants have also been shown to modulate airway responsiveness and/or allergic inflammation. As discussed above, AHR to house dust mite allergen occurred in human subjects with mild allergy and asthma immediately following 6 hours of concurrent exposure to 0.2 ppm SO_2 and 0.4 ppm NO_2, but not to either pollutant alone (Rusznak et al., 1996; Devalia et al., 1994). This effect persisted for 48 hours. Recently, the effects of simulated downwind coal combustion emissions (SDCCE) on allergic airway responses was investigated in mice (Barrett et al., 2011). Mice were sensitized and challenged with ovalbumin and exposed for 6 hours/day for 3 days to several concentrations of SDCCE with and without a particle filter. SDCCE exposure was followed by another challenge with ovalbumin in some animals. Results demonstrated that both the particulate and the gaseous phases of SDCCE exacerbated

allergic airways responses. Airway responsiveness (measured by the forced oscillation technique) was enhanced by the gaseous phase of SDCCE in mice that were challenged with ovalbumin after SDCCE exposure. Concentration of SO_2 in the highest exposure was 0.2 ppm. Other gases present in this exposure were NO_2 (0.29 ppm), NO (0.59 ppm), and carbon monoxide (0.02 ppm). Results of this study are consistent with SO_2 playing a role in exacerbating AHR and allergic responses, although the other mixture components may have contributed to the observed effects.

In summary, a growing body of evidence supports a role for SO_2 in exacerbating AHR and/or allergic inflammation in animal models of allergic airway disease, as well as in asthmatic individuals. In addition, repeated or prolonged exposure to SO_2 promotes allergic sensitization in naive newborn animals. Furthermore, one study in newborn allergic rats suggests that airway remodeling may contribute to AHR following prolonged exposure to SO_2.

4.3.4 Induction of Systemic Effects

As described in the 2008 SO_X ISA (U.S. EPA, 2008d), two controlled human exposure studies reported that acute exposure to 0.2 ppm SO_2 resulted in changes in heart rate variability in healthy adults and in asthmatic adults (Routledge et al., 2006; Tunnicliffe et al., 2001). More recently, altered parasympathetic regulation of heart rate was reported in rats exposed to 5 ppm SO_2 during the peri-natal and post-natal period (Woerman and Mendelowitz, 2013a, b). Whether these responses were due to activation of sensory nerves in the respiratory tract resulting in a neural reflex response and altered autonomic function or some other mechanism is not known.

Numerous studies over several decades have reported other extrapulmonary effects of inhaled SO_2 (U.S. EPA, 2008d). Most of these occur at concentrations far higher than those measured in ambient air. As discussed in Section 4.2.3, studies in mice and humans demonstrating the presence of sulfite and S-sulfonates in blood and tissues outside of the respiratory tract point to the likely role of circulating sulfite in mediating these responses. A subacute study measured sulfite plus S-sulfonate content of the lung, liver, and brain of mice exposed to 5, 10, or 20 ppm SO_2 for 4 hours/day for 7 days (Meng et al., 2005a) and found a concentration-dependent increase. Similarly, exposure of human subjects to 0.3−6 ppm SO_2 for up to 120 hours resulted in the appearance in the plasma of sulfite plus S-sulfonates (Gunnison and Palmes, 1974). The relationship between sulfite/sulfonate concentration and chamber SO_2 concentration was linear (regression coefficient of 0.61) with a slope of 1.1 nmol/mL of plasma S-sulfonate for each 1-ppm increment in SO_2 concentration. These results indicate that prolonged (i.e., hours to days)

exposure to as low as 0.3 ppm SO_2 results in measurable amounts of circulating sulfite in humans. The relationship between circulating sulfite/S-sulfonate and extrapulmonary effects of inhaled SO_2 has not yet been explored in human subjects.

Because the activity of sulfite oxidase is variable among species, the degree of sensitivity to SO_2-mediated effects is likely to be variable among species. For example, sulfite oxidase in rats is 10−20 times greater than in humans and 3−5 times greater than in rabbits or rhesus monkeys (Gunnison et al., 1987a; Gunnison, 1981). Thus, the toxicity of SO_2 may be less in rats due to more rapid metabolism of sulfite to sulfate.

Systemic effects are likely due to oxidative stress, possibly from sulfite autoxidation. Alternatively, sulfite-mediated S-sulfonate formation may disrupt protein function, and metabolic reduction of S-sulfonates may alter reduction-oxidation (redox) status. Moreover, sulfite may serve as a substrate for peroxidases, such as myeloperoxidase and eosinophil peroxidase, to produce free radicals, as has been demonstrated in neutrophils and eosinophils (Ranguelova et al., 2013; Ranguelova et al., 2012; Ranguelova et al., 2010). These sulfur-based free radical species may then initiate protein or lipid oxidation.

Baskurt (1988) found that exposure of rats to 0.87 ppm SO_2 for 24 hours resulted in increased hematocrit, sulfhemoglobin, and osmotic fragility, as well as decreased whole blood and packed cell viscosities. These results indicate a systemic effect of inhaled SO_2 and are consistent with an oxidative injury to red blood cells. Other studies have reported lipid peroxidation in erythrocytes and tissues of animals exposed to SO_2 (Qin et al., 2012; Ziemann et al., 2010; Haider et al., 1982). Supplementation with ascorbate and α-tocopherol decreased SO_2-induced lipid peroxidation in erythrocytes (Etlik et al., 1995). Additionally, recent studies report mitochondrial changes in the hearts and brains of rats exposed to 1.34 ppm (4 hours/day) SO_2 for several weeks (Qin et al., 2016; Qin et al., 2012). Demonstration of mitochondrial biogenesis in rat brain suggests that SO_2 exposure induces an adaptive response to oxidative stress (Qin et al., 2012). Changes in cardiac function were observed at higher concentrations (2.7 ppm SO_2); however pretreatment with antioxidants blocked this effect (Qin et al., 2016).Other recent studies report altered markers of brain inflammation and synaptic plasticity following several weeks to months of exposure to 1.34 ppm (4 hours/day) SO_2 (Yao et al., 2015; Yao et al., 2014). Further studies are required to confirm that inhalation exposures of SO_2 at or near ambient levels increase blood sulfite levels sufficiently for oxidative injury to occur in blood cells or other tissues.

In summary, exposure to SO_2 may result in effects outside the respiratory tract via activation of sensory nerves in the respiratory tract resulting in a neural reflex response or mediated by circulating sulfite. A few studies employing concentrations of 2 ppm SO_2 or less have demonstrated effects that are consistent with sulfite-mediated redox stress, such

as increased sulfhemoglobin in red blood cells and lipid peroxidation in the brain. Recent studies also suggest possible inflammation and other effects in tissues distal to the absorption site following several weeks to months of exposure to 1.34 ppm SO_2.

4.3.5 Role of Endogenous Sulfur Dioxide/Sulfite

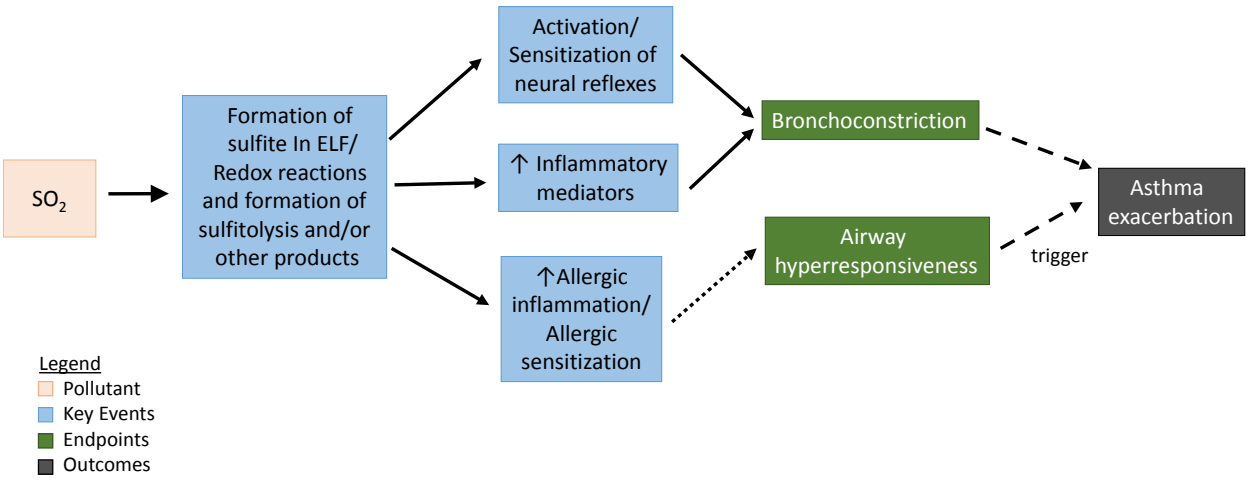
Endogenous SO_2/sulfite is a product of normal metabolism of sulfur-containing amino acids (e.g., cysteine and methionine) (Liu et al., 2010). While SO_2 gas is measured in the head space gas of preparations of various tissues or bodily fluids (Balazy et al., 2003), sulfite/bisulfite is measured in soluble fractions. The distribution of SO_2 and enzymes responsible for SO_2 generation has been reported in tissues of the rat (Luo et al., 2011). Chemical transformations between bisulfite/sulfite/SO_2 and the gasotransmitter H_2S also occur. H_2S is similarly derived from sulfur-containing amino acids. Evidence has accumulated that endogenous H_2S acts as a biological signaling molecule (Filipovic et al., 2012) and plays important roles in the cardiovascular (Coletta et al., 2012) and other systems. Recent studies suggest that endogenous SO_2 may also be a gasotransmitter (Liu et al., 2010). Like the other gasotransmitters NO and CO, SO_2 at physiologic levels may activate guanylyl cyclase to generate cyclic guanosine monophosphate (cGMP), which mediates effects through cGMP-dependent kinases (Li et al., 2009). However, SO_2 may also act through non-cGMP-dependent pathways. Experimental studies in animal models and in vitro systems demonstrate a myriad of effects of exogenous SO_2 on the cardiovascular system, including vasorelaxation, negative inotropic effects on cardiac function, anti-inflammatory and antioxidant effects in pulmonary hypertension, and decreased blood pressure (BP) and vascular remodeling in hypertensive animals, and cytoprotective(Liu et al., 2010). Effects were in many cases concentration dependent. In vivo studies generally were conducted using 5 ppm and higher concentrations of SO_2 (or sulfite/bisulfite) (Liu et al., 2010). In summary, endogenous SO_2 is a newly recognized gasotransmitter that may play important roles in cardiovascular and other systems.

4.3.6 Mode of Action Framework

This section describes the key events, endpoints, and outcomes that comprise the modes of action of inhaled SO_2. Here, key events are subclinical effects, endpoints are effects that are generally measured in the clinic, and outcomes are health effects at the organism level. Biological pathways discussed above that may contribute to health effects resulting from short-term and long-term exposures to SO_2 (Chapter 5) are summarized as a part of

this analysis. These proposed modes of action are based on the available evidence and may not reflect all of the pathophysiology underlying health effects.

Figure 4–2 depicts the mode of action for respiratory effects due to short-term exposure to SO_2.



ELF = epithelial lining fluid; redox = reduction-oxidation; SO_2 = 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.

A characteristic feature of individuals with asthma is an increased propensity of their airways to narrow in response to bronchoconstrictive stimuli relative to nonatopic individuals without asthma. This characteristic is termed airway hyperresponsiveness (AHR). Different kinds of stimuli can elicit bronchoconstriction, but in general they act on airway smooth muscle receptors (direct stimuli, e.g., methacholine) or act via the release of inflammatory mediators (indirect stimuli, e.g., allergens) (O'Byrne et al., 2009). SO_2 is a nonspecific bronchoconstrictive stimuli that is not easily classified as a direct or indirect stimuli, as was discussed in Section 4.3.1.

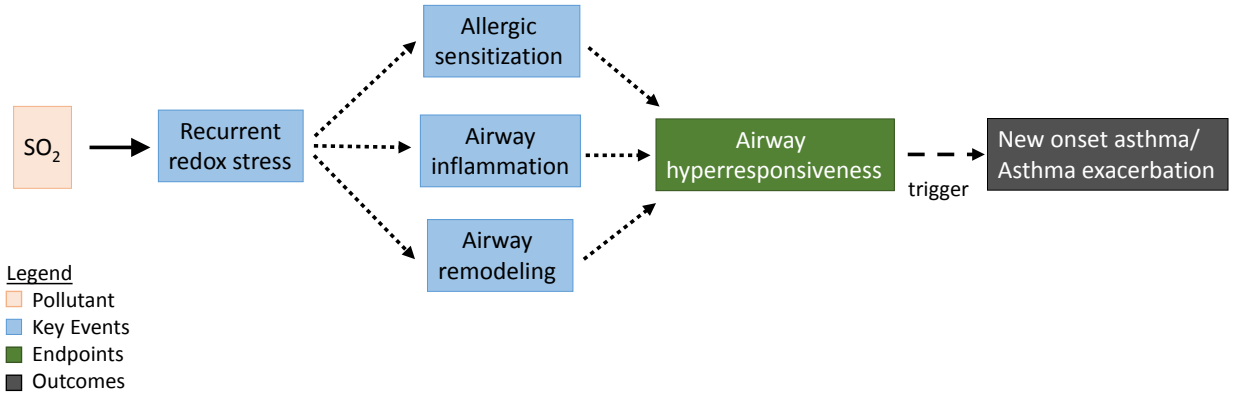
Because inhalation of SO_2 results in chemical reactions in the ELF, the initiating event in the development of respiratory effects is the formation of sulfite, sulfitolysis products, and/or other products. Both sulfite and S-sulfonates have been measured in tracheal and bronchial tissue as well as in tracheal washings of experimental animals exposed to SO_2. Reactive products formed as a result of SO_2 inhalation are responsible for a variety of downstream key events, which may include activation or sensitization of sensory nerves in the respiratory tract resulting in neural reflex responses, release of inflammatory mediators, and modulation of allergic inflammation or sensitization. These key events may collectively lead to several endpoints, including bronchoconstriction and AHR. Bronchoconstriction is characteristic of an asthma attack. However, individuals who are not asthmatic may also experience bronchoconstriction in response to SO_2 inhalation; generally, this occurs at higher concentrations than in an individual who is asthmatic (>1 ppm). Additionally, SO_2 exposure may increase airway responsiveness to subsequent exposures of other stimuli such as allergens or methacholine. These pathways may be linked to the epidemiologic outcome of asthma exacerbation.

The strongest evidence for this mode of action comes from controlled human exposure studies. SO_2 exposure resulted in increased airway resistance due to bronchoconstriction in healthy adults and in adults with asthma. In adults without asthma, this response occurred primarily as a result of activation of sensory nerves in the respiratory tract resulting in neural reflex responses mediated by cholinergic parasympathetic pathways involving the vagus nerve. However, in adults with asthma, evidence indicates that the response is only partially due to vagal pathways and that inflammatory mediators such as histamine and leukotrienes also play an important role. Activation of sensory nerves in the respiratory tract, which result in neural reflex responses, has been studied in humans exposed to occupationally relevant concentrations of SO_2 (up to 2 ppm). Responses measured in these studies include increased respiratory rate and decreased tidal volume, which involve the vagus nerve, and increased nasal air-flow resistance, which involves the trigeminal nerve. These responses are not a part of the mode of action described here, but are mentioned because they are known irritant effects of SO_2. Studies in experimental animals demonstrate that SO_2 exposure activates reflexes that are mediated by cholinergic parasympathetic pathways involving the vagus nerve. However, noncholinergic mechanisms may also play a role because some studies demonstrate that a local axon reflex resulting in C-fiber secretion of neuropeptides (i.e., neurogenic inflammation) is responsible for the effects of SO_2.

Evidence demonstrates that SO_2 exposure modulates allergic inflammatory responses. Enhancement of allergic inflammation was observed in adults with asthma who were exposed for 10 minutes to 0.75 ppm SO_2 (i.e., leukotriene-mediated increases in numbers of sputum eosinophils). In an animal model of allergic airway disease, repeated exposure

to 2 ppm SO_2 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_2 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_2 (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_2 exposure to asthma exacerbation.

Figure 4–3 depicts the mode of action for respiratory effects due to long-term exposure to SO_2.



redox = reduction-oxidation; SO_2 = 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.

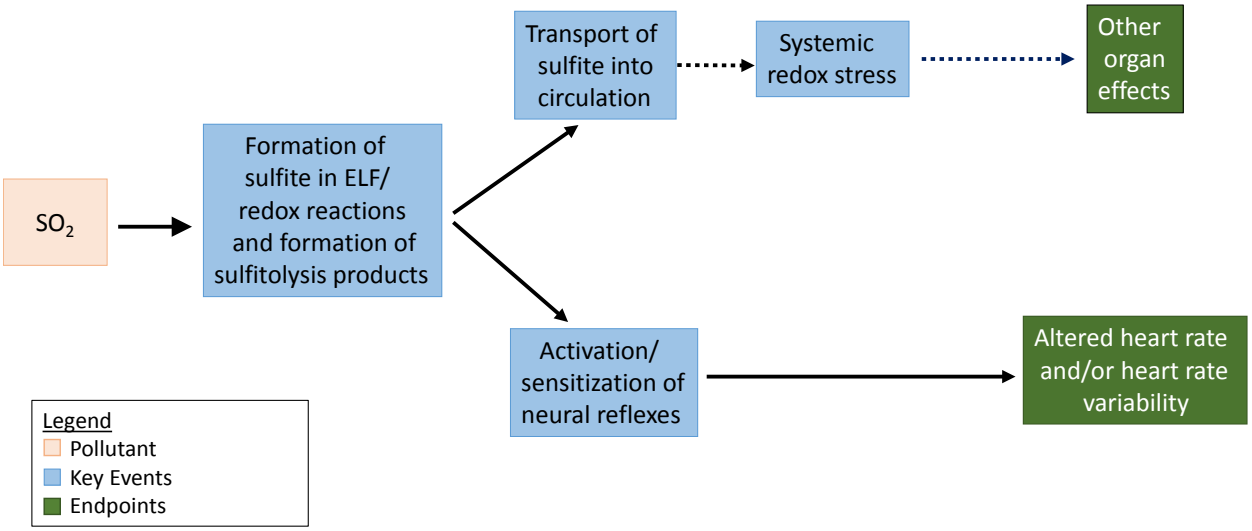
Source: National Center for Environmental Assessment.

Figure 4-3 Summary of evidence for the mode of action linking long-term exposure to sulfur dioxide and respiratory effects.

The initiating event in the development of respiratory effects due to long-term SO_2 exposure is the recurrent or prolonged redox stress due to the formation of reactive products in the ELF. This is the driving factor for the potential downstream key events, airway inflammation, allergic sensitization, and airway remodeling that may lead to the endpoint AHR. Airway inflammation, airway remodeling, and AHR are characteristic of asthma. The resulting outcome may be new asthma onset, which presents as an asthma exacerbation that leads to physician-diagnosed asthma.

Evidence for this mode of action comes from studies in both naive and allergic experimental animals. Exposure of naive newborn animals to SO_2 (2 ppm) for several weeks resulted in hyperemia in lung parenchyma, inflammation in the airways, and Th2 polarization (or group 2 innate lymphoid cell-mediated Type 2 immunity), the latter of which is a key step involved in allergic sensitization. Support is also provided by short-term studies in naive animals in which repeated exposure to SO_2 (2 ppm) over several days led to pathologic changes, including inflammatory cell influx. Th2 polarization (or other Type 2 immune responses) and airway inflammation may set the stage for AHR. In addition, short-term SO_2 exposure (0.1 ppm) promoted allergic sensitization and enhanced other allergic inflammatory responses and AHR when animals were subsequently sensitized with an allergen. Further, repeated exposure of allergic newborn animals to SO_2 (2 ppm) over several weeks enhanced allergic responses and resulted in morphologic responses indicative of airway remodeling and in AHR. Thus, repeated exposure to SO_2 in naive animals may lead to the development of allergic airway disease, which shares many features with asthma. Furthermore, repeated exposure of allergic animals to SO_2 may promote airway remodeling and AHR. The development of AHR may link long-term exposure to SO_2 to the epidemiologic outcome of new onset asthma.

Figure 4–4 depicts the mode of action for extrapulmonary effects due to short-term or long-term exposure to SO_2.



ELF = epithelial lining fluid; redox = reduction-oxidation; SO_2 = 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.

Although SO_2 inhalation results in extrapulmonary effects, there is uncertainty regarding the mode of action underlying these responses. Evidence from controlled human exposure studies (0.2 ppm, 1 hour) points to SO_2 exposure-induced activation/sensitization of neural reflex responses as a key event leading to the endpoint of altered heart rate or heart rate variability. Evidence also points to transport of sulfite into the circulation. Controlled human exposure and experimental animal studies have demonstrated the presence of sulfite and S-sulfonates in plasma, liver, or brain following SO_2 exposure. This occurred at a concentration as low as 0.3 ppm SO_2 in humans exposed for up to 120 hours. Sulfite is highly reactive and may be responsible for redox stress (possibly through auto-oxidation or peroxidase-mediated reactions to produce free radicals) in the circulation and extrapulmonary tissues. However, this is likely to occur only at very high concentrations or during prolonged exposures because circulating sulfite is efficiently metabolized to sulfate in a reaction catalyzed by hepatic sulfite oxidase.

Besides inhalation of SO_2, the ingestion of food additives and the catabolism of sulfur-containing amino acids also contribute to levels of sulfite in the body (Section 4.3.5). In humans, the amount of sulfite derived from inhaled SO_2 (assuming

100% absorption, 75 ppb and 24-hour exposure) is comparable to that derived from the expected daily consumption of food additives. The amount of sulfite derived from the breakdown of endogenous sulfur-containing amino acids is far greater. Sulfite derived from inhaled SO_2, unlike that derived from food additives, enters the circulation without first passing through the liver, which efficiently metabolizes sulfite to sulfate. Thus, the potential exists for inhaled SO_2 to have a greater impact on circulating sulfite levels than sulfite derived from food additives. While the amount of sulfite derived from the breakdown of endogenous sulfur-containing amino acids is far greater, its metabolic pathways and impact on circulating sulfite levels are not clear. Thus, the potential exists for prolonged exposure to high concentrations of inhaled ambient SO_2 to result in extrapulmonary effects due to circulating sulfite.

In summary, this section provides a foundation for understanding how exposure to the gaseous air pollutant SO_2 may lead to health effects. This encompasses the many steps between uptake into the respiratory tract and biological responses that ensue.
The reaction of inhaled SO_2 with components of the ELF initiates a cascade of events occurring at the cellular, organ, and organism level. Biological responses discussed in this section were organized in a mode of action framework that serves as a guide to interpreting health effects evidence presented in Chapter 5.

Chapter 5 Integrated Health Effects of Exposure to Sulfur Oxides

5.1 Introduction

5.1.1 Scope of the Chapter

While the term "sulfur oxides" refers to multiple gaseous oxidized sulfur compounds (e.g., SO_2, SO_3), this chapter focuses on evaluating the health effects associated with exposure to SO_2. As discussed in Section 2.1, the presence of sulfur oxide species other than SO_2 in the atmosphere has not been demonstrated, and the available health evidence examines SO_2. The health effects of particulate sulfur-containing compounds (e.g., sulfate) are considered in the current review of the NAAQS for PM and were evaluated in the 2009 ISA for PM (U.S. EPA, 2009a) (see Section 1.1).

This chapter evaluates the epidemiologic, controlled human exposure, and animal toxicological evidence of SO_2-related respiratory (Section 5.2), cardiovascular (Section 5.3), reproductive and developmental (Section 5.4, total mortality (Section 5.5), and cancer (Section 5.6) effects. Evidence from epidemiologic and animal toxicological studies of other SO_2-related effects are included in Supplemental Tables 5S-1 (U.S. EPA, 2016l) and 5S-2 (U.S. EPA, 2015e). Sections for respiratory, cardiovascular, and mortality effects are divided into subsections describing the evidence for short- (i.e., 1 month or less) and long-term (i.e., more than 1 month) exposures. The evidence for reproductive and developmental and cancer effects is considered within one long-term exposure section, with time-windows of exposure addressed as appropriate. Causal conclusions are determined for both short- and long-term exposures by evaluating the evidence for each health effect and exposure category independently, using the causal framework [described in the Preamble to the ISAs (U.S. EPA, 2015b)].

Each chapter section begins with a summary of the conclusions from the 2008 ISA for Sulfur Oxides, followed by an evaluation of recent studies (i.e., those published since the completion of the 2008 ISA for Sulfur Oxides) that build upon evidence from previous reviews. Within each of the sections focusing on morbidity outcomes (e.g., respiratory morbidity, cardiovascular morbidity), the evidence is organized into more refined outcome groupings (e.g., asthma exacerbation, myocardial infarction) that comprise a continuum of subclinical to clinical effects. The discussion of specific health outcomes is then organized by scientific discipline (i.e., epidemiology, controlled human exposure, toxicology). This structure helps in evaluating coherence and biological plausibility of the

effects observed in association with exposure to SO_2 and promotes the transparent characterization of the weight of evidence in drawing the causal conclusions found at the end of each section (e.g., see Section 5.2.1.9). Causal determinations for total mortality are based on the evidence for nonaccidental causes of mortality and informed by the extent to which evidence for the spectrum of cardiovascular and respiratory effects provides biological plausibility for SO_2-related total mortality. Findings for cause-specific mortality inform multiple causal determinations. For example, studies of respiratory and cardiovascular mortality are used to assess the continuum of effects and inform the causal determinations for respiratory and cardiovascular morbidity. As described in Section 1.2, judgments regarding causality are made by evaluating the evidence over the full range of exposures in animal toxicological, controlled human exposure, and epidemiologic studies defined in this ISA to be relevant to ambient exposure (i.e., ≤2,000 ppb).

5.1.2 Evidence Evaluation and Integration to Form Causal Determinations

5.1.2.1 Evaluation of Individual Studies

As described in the Preamble to the ISAs (U.S. EPA, 2015b) (Section 5.a), causal determinations were informed by integrating evidence across scientific disciplines (e.g., exposure, animal toxicology, epidemiology) and related outcomes, as well as by judgments on the strength of inference from individual studies. These judgments were based on evaluating strengths, as well as various sources of bias and uncertainty related to study design, study population characterization, exposure assessment, outcome assessment, consideration of confounding, statistical methodology, and other factors. This evaluation was applied to controlled human exposure, animal toxicological, and epidemiologic studies included in this ISA, comprising studies from previous assessments as well as those studies published since the 2008 ISA for Sulfur Oxides. Aspects comprising the major considerations in the individual study evaluation are described in the Annex for Chapter 5 of this ISA and are consistent with current best practices employed in other approaches for reporting or evaluating health science data.[1] Additionally, these aspects are compatible with published U.S. EPA guidelines related to

[1] 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), ToxRTool (Klimisch et al., 1997), STROBE guidelines (von Elm et al., 2007), Animals in Research: Reporting In Vivo Experiments guidelines (Kilkenny et al., 2010).

cancer, neurotoxicity, reproductive toxicity, and developmental toxicity (U.S. EPA, 2005a, 1998, 1996a, 1991).

The aspects described in the Annex for Chapter 5 were used as a guideline rather than a checklist or criteria to define the quality of a study. The presence or absence of a particular feature did not necessarily define a less informative study or preclude a study from consideration in the ISA. Further, these aspects were not criteria for a particular determination of causality in the five-level hierarchy. As described in the Preamble to the ISAs (U.S. EPA, 2015b), causal determinations were based on judgments of the overall strengths and limitations of the collective body of available studies and the coherence of evidence across scientific disciplines and related outcomes. Where possible, considerations such as exposure assessment and confounding (i.e., bias due to a relationship with the outcome and correlation with exposures to SO_2), were framed to be specific to sulfur oxides. Thus, judgments of the strength of inference from a study can vary depending on the specific pollutant being assessed.

Evaluation of the extent to which the science informs the understanding of uncertainties related to the independent effect of sulfur oxides is of particular relevance in the review process. Because examination of copollutant confounding is based largely on copollutant models, the inherent limitations of such models are considered in drawing inferences about independent associations for SO_2. For example, collinearity potentially affects model performance when highly correlated pollutants are modeled simultaneously, and inference can also be limited if differences in the spatial distributions of SO_2 and the copollutant do not satisfy the assumptions of equal measurement error or constant correlations for SO_2 and the copollutant (Section 3.4.3). Correlations of short-term SO_2 concentrations with other NAAQS pollutants are generally low to moderate, but may vary by location (Section 3.5). Thus, the interpretation of copollutant model results reported in epidemiologic studies depends on a variety of factors, which are discussed throughout the chapter, generally in the context of a specific study and/or health endpoint.

5.1.2.2 Integration of Scientific Evidence

Causal determinations are made by considering the strength of inference from individual studies and on integrating multiple lines of evidence. As detailed in the Preamble to the ISAs (U.S. EPA, 2015b), evidence integration involved evaluating the consistency and coherence of findings within and across disciplines, as well as within and across related outcomes. Cross-disciplinary integration often addresses uncertainties within a particular discipline. Controlled human exposure and animal toxicological studies can provide

direct evidence for health effects related to SO_2 exposures. Coherence of experimental evidence with epidemiologic findings can advance our understanding about whether epidemiologic associations with health outcomes plausibly reflect an independent effect of ambient SO_2 exposure. For example, the coherence of effects observed in epidemiologic studies with human clinical studies demonstrating direct effects of SO_2 on lung function (Section 5.2.1.2), is drawn upon to reduce uncertainties in epidemiologic studies. Thus, the integration of evidence across a spectrum of related outcomes and across disciplines was used to clarify the understanding of uncertainties for a particular outcome or discipline due to chance, publication bias, selection bias, and confounding by copollutant exposures or other factors.

The integration of the scientific evidence is facilitated through the presentation of data from multiple studies within and across disciplines. To increase comparability of results across epidemiologic studies, the ISA presents effect estimates for associations with health outcomes scaled to the same increment of SO_2 concentration.[1] The increments for standardization vary by averaging time. For 24-h avg, effect estimates were scaled to a 10-ppb increase for SO_2. For 1-h daily max, effect estimates were scaled to a 40-ppb increase for SO_2. Effect estimates for long-term exposures to SO_2 (i.e., annual or multiyear averages) were scaled to a 5-ppb increase. Units of dose in toxicological studies are typically presented in ppm; however, when toxicological data are summarized in the context of epidemiologic findings, units are converted to ppb for comparability.

5.1.3 Summary

The subsequent sections review and synthesize the evidence of SO_2-related health effects from multiple disciplines (e.g., exposure, animal toxicology, and epidemiology). Information on dosimetry and modes of action (Chapter 4) provides the foundation for understanding how exposure to inhaled SO_2 may lead to health effects, providing biological plausibility for effects observed in the health studies. The science related to sources, emissions, and atmospheric concentrations (Chapter 2), as well as the potential for human exposure to ambient sulfur oxides (Chapter 3), also informs the interpretation of the health effects evidence. Integrative "Summary and Causal Determination" sections for short- and long-term exposures follow the discussion of the evidence for each health outcome category. These integrative summary sections include assessments of the strength of inference from studies comprising the evidence base and integrate multiple

[1] Versus reported effect estimates that are scaled to variable changes in concentration such as IQR for the study period or an arbitrary unit.

lines of evidence to characterize relationships between sulfur oxides and various health effects.

5.2 Respiratory Effects

5.2.1 Short-Term Exposure

5.2.1.1 Introduction

The 2008 ISA for Sulfur Oxides (U.S. EPA, 2008d) concluded that there is a causal relationship between respiratory effects and short-term exposure to SO_2. The rationale for this causal determination was heavily based on evidence from multiple, high-quality controlled human exposure studies demonstrating decreased lung function and increased respiratory symptoms following SO_2 exposures of 5−10 minutes in exercising adults with asthma.

There was also epidemiologic evidence indicating associations between short-term increases in ambient SO_2 concentration and respiratory effects in populations living in locations with ambient concentrations below the previous 24-h avg NAAQS level of 140 ppb. Evidence was strongest for increased respiratory symptoms and respiratory-related hospital admissions and ED visits, especially in children. Due to inadequate examination, a key uncertainty was potential confounding by copollutants, particularly PM. However, controlled human exposure studies of individuals with asthma clearly show that respiratory effects are caused by 5−10 minute SO_2 exposures.

In contrast with asthma exacerbation, there was little information to assess whether short-term SO_2 exposure exacerbated allergy or chronic obstructive pulmonary disease (COPD) or increased risk of respiratory infection. However, there was some experimental evidence for respiratory effects in healthy humans (>1,000 ppb) and animal models (100 ppb) exposed to SO_2. Epidemiologic evidence in healthy populations was limited and inconsistent.

As described in the following sections, evidence from recent studies is generally consistent with that in the 2008 ISA and 1982 AQCD for Sulfur Oxides (U.S. EPA, 2008d, 1982a). To clearly characterize differences in the weight of evidence and the extent of coherence among disciplines and related outcomes, the sections are organized by respiratory outcome group [asthma exacerbation (Section 5.2.1.2), allergy exacerbation (Section 5.2.1.3), COPD exacerbation (Section 5.2.1.4), respiratory

infection (Section 5.2.1.5), aggregated respiratory conditions (Section 5.2.1.6), respiratory effects in the general population and healthy individuals (Section 5.2.1.7), and respiratory mortality (Section 5.2.1.8)]. Epidemiologic studies comprise most of the recent evidence base, and previous controlled human exposure and animal toxicological studies form the basis for characterizing and integrating evidence across disciplines. Recent epidemiologic evidence supports associations between ambient SO_2 concentrations and asthma-related symptoms, hospital admissions, and ED visits, but exposure measurement error and copollutant confounding remain uncertain. Recent epidemiologic studies add information on allergy and COPD exacerbation, respiratory infection, and respiratory effects in healthy populations, but relationships of these outcomes with short-term SO_2 exposure still are unclear because of inconsistent evidence or limited coherence among disciplines.

5.2.1.2 Asthma Exacerbation

Asthma is a chronic lung disease with a broad range of characteristics and disease severity. Its main features are airway obstruction that is generally reversible, airway inflammation, and increased airway responsiveness. SO_2 exposure has been demonstrated to induce clinical features of asthma exacerbation, including decreased lung function (e.g., decreased forced expiratory volume in 1 sec [FEV_1] or increased specific airway resistance [sRaw]), and increased symptoms (e.g., wheezing, cough, shortness of breath), as well as some subclinical effects such as inflammation. This section describes evidence for SO_2-associated lung function changes and respiratory symptoms in people with asthma, hospital admissions and emergency department visits for asthma and related respiratory conditions, and subclinical effects underlying asthma such as pulmonary inflammation and oxidative stress.

As detailed in the previous 2008 ISA for Sulfur Oxides (U.S. EPA, 2008d), controlled human exposure studies reported increased respiratory symptoms and decreased lung function after short-term exposures of 5−10 minutes to 0.2−0.6 ppm SO_2 during exercise or eucapnic hyperpnea (a rapid and deep breathing technique through a mouthpiece that prevents an imbalance of CO_2 due to hyperventilation) in adults and adolescents (12−18 years) with asthma. In contrast, the majority of the controlled human exposure studies evaluating the respiratory effects of SO_2 in healthy adults demonstrated increased airway resistance and decreased FEV_1 following exposures to concentrations >1.0−5.0 ppm (Section 5.2.1.7). While children may be especially susceptible to the respiratory effects of SO_2 for dosimetric reasons (Section 4.2.2), there are no available controlled human exposure studies in children under 12, partly due to ethical concerns.

Coherent with controlled human exposure findings, epidemiologic evidence indicated that short-term increases in ambient SO_2 concentration were associated with asthma-related hospital admissions, ED visits, and symptoms. The strongest evidence was for children, which is consistent with their greater oral breathing and higher ventilation rates relative to their size than adults and the consequent potential for them receiving a higher SO_2 dose to the tracheobronchial airways of the lower respiratory tract (Section 4.1.2, Section 4.2.2). Epidemiologic evidence for SO_2-related lung function decrements was inconsistent among both children and adults with asthma. A key uncertainty in the epidemiologic evidence was whether findings reflected an independent association for SO_2 because the studies assigned exposure from central site monitors (i.e., those used to determine attainment with the NAAQS, Section 3.3.1.1). Also, few of the studies examined potential confounding by $PM_{2.5}$ or other copollutants.

The 2008 SO_X ISA (U.S. EPA, 2008d) also provided limited evidence for a relationship between SO_2 concentrations and allergic responses and inflammation in individuals with asthma. Children and adults with atopy plus asthma were found to be at greater risk of SO_2-associated respiratory effects such as respiratory symptoms and lung function decrements. In addition, animal toxicological studies demonstrated that repeated exposure to SO_2 enhanced inflammation and allergic responses in animal models of allergic airway disease.

Together recent studies and the evidence presented in the 2008 ISA for Sulfur Oxides link short-term SO_2 exposure to asthma exacerbation. Most recent studies are epidemiologic, which continue to show ambient SO_2-associated increases in asthma symptoms, hospital admissions, and ED visits among children. However, exposure measurement error and copollutant confounding remain uncertainties in the epidemiologic evidence. A few recent animal toxicological studies add support for SO_2-induced allergic inflammation. While there are no recent controlled human exposure studies in individuals with asthma (see Section 5.2.1.7 for recent studies in healthy individuals), previous evidence from controlled human exposure studies provides support for an independent effect of SO_2 exposure on asthma exacerbation.

Lung Function Changes in Populations with Asthma

The 2008 SO_X ISA (U.S. EPA, 2008d) reported strong evidence for the effects of SO_2 exposure on decrements in lung function in controlled human exposure studies in adults with asthma under increased ventilation conditions. Controlled human exposure studies, none of which are new since the 2008 SO_X ISA (U.S. EPA, 2008d), also demonstrated a subset of individuals (i.e., responders) within this population who are particularly sensitive to the effects of SO_2 exposure. This finding is most evident in the recent

analysis of several published studies by Johns et al. (2010). Some additional data from the previous studies has also become available since the 2008 SO_X ISA and is summarized in Table 5-2, Table 5-3, and Table 5-4. Recent epidemiologic findings are inconsistent overall. A few recent epidemiologic studies add evidence for SO_2 measured at children's school or in copollutant models with PM, NO_2, or O_3, albeit with pollutants measured at central site monitors. There is a paucity of evidence from animal toxicological studies. While some animal toxicological studies of short-term exposure to SO_2 have examined changes in lung function, these experiments were conducted in naive animals rather than in models of allergic airway disease, which share many phenotypic features with asthma in humans.

Controlled Human Exposure Studies

Bronchoconstriction in individuals with asthma is the most sensitive indicator of SO_2-induced lung function effects. A characteristic feature of individuals with asthma is an increased propensity of their airways to narrow in response to bronchoconstrictive stimuli relative to nonatopic individuals without asthma. This characteristic is termed airway hyperresponsiveness (AHR). Different kinds of stimuli can elicit bronchoconstriction, but in general, they act on airway smooth muscle receptors (direct stimuli, e.g., methacholine) or act via the release of inflammatory mediators (indirect stimuli, e.g., allergens) (O'Byrne et al., 2009). SO_2 is a nonspecific bronchoconstrictive stimulus that is not easily classified as a direct or indirect, as discussed in Section 4.3.1.

Bronchoconstriction, evidenced by decrements in lung function, is observed in controlled human exposure studies after approximately 5−10-minute exposures and can occur at SO_2 concentrations as low as 0.2 ppm in exercising individuals with asthma; more consistent decrements are seen at concentrations of 0.4 ppm and greater (U.S. EPA, 2008d). In contrast, healthy adults are relatively insensitive to the respiratory effects of SO_2 below 1 ppm (Section 5.2.1.7). In all individuals, bronchoconstriction is mainly seen during conditions of increased ventilation rates, such as exercise or eucapnic hyperpnea. This effect is likely due to a shift from nasal breathing to oral/nasal breathing, which increases the concentration of SO_2 reaching the airways (Section 4.2.2). The majority of controlled human exposures to SO_2 were conducted with adult volunteers, although a limited number were also conducted with adolescents (12−18 years). Characteristics of controlled exposure studies in individuals with asthma are summarized in Table 5-1. 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.

Study	Disease Status; n; Sex; (Age[a])	Exposure Details (Concentration; Duration)	Outcomes Examined
Balmes et al. (1987)	Asthma; n = 8; 6 M, 2 F (23−39 yr)	0, 0.5, or 1 ppm SO_2 for 1, 3, and 5 min during eucapnic hyperpnea (60 L/min)	sRaw
Bethel et al. (1983)	Asthma; n = 10; 8 M, 2 F (22−36 yr)	0 or 0.5 ppm SO_2 for 5 min with exercise 750 kg m/min (125 watts)	sRaw
Bethel et al. (1984)	Asthma; n = 7; 5 M, 2 F (24−36 yr)	0.5 ppm SO_2 for 3 min with room temperature and cold air	sRaw
Bethel et al. (1985)	Asthma; n = 19; 16 M, 3 F (22−46 yr)	0 or 0.25 ppm SO_2 for 5 min during heavy exercise [bicycle, 750 (n = 19) or 1,000 (n = 9) kg m/min; 125 or 167 watts, respectively]	sRaw
Gong et al. (1995)	Asthma; n = 14; 12 M, 2 F (18−50 yr)	0 or 0.5, 1.0 ppm SO_2 with light, medium, and heavy exercise (average ventilation 30, 36, and 43 L/min) for 10 min	sRaw, FEV_1, symptoms, psychophysical (stamina) changes
Gong et al. (1996)	Asthma; n = 10; 2 M, 8 F (19−49 yr)	0 or 0.75 ppm SO_2 for 10 min with exercise (29 L/min) at 1, 12, 18, and 24 h after pretreatment with placebo or salmeterol (long-acting B_2-agonist)	FEV_1, symptoms
Gong et al. (2001)	Asthma; n = 12; 2 M, 10 F (20−48 yr)	0 or 0.75 ppm SO_2 for 10 min with exercise (35 L/min) with or w/o pretreatment to montelukast sodium (10 mg/d for 3 d)	sRaw, FEV_1, symptoms, eosinophil counts in induced sputum
Horstman et al. (1986)	(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_2 for 10 min with exercise (treadmill, 21 L/min per m^2 body surface area) (2) 2 ppm SO_2 for 10 min with exercise (treadmill, 21 L/min per m^2 body surface area)	sRaw
Horstman et al. (1988)	Asthma; n = 12; 12 M (22−37 yr)	0 or 1.0 ppm SO_2 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[a])	Exposure Details (Concentration; Duration)	Outcomes Examined
Jörres and Magnussen (1990)	Asthma; n = 14; 10 M, 4 F (21−55 yr, 34 ± 14 yr)	0 or 0.25 ppm NO_2, or 0.5 ppm SO_2 at rest followed by challenge with 0.75 ppm SO_2 during voluntary eucapnic hyperpnea. Ventilation increased in 15 L/min steps, each lasting 3 min	sRaw
Kehrl et al. (1987)	Asthma; n = 10; 10 M (20−30 yr)	0 or 1 ppm SO_2 for 1 h with exercise (3 × 10 min at 41 L/min on a treadmill)	sRaw
Koenig et al. (1980)	Asthma; n = 9; 7 M, 2 F (14−18 yr)	0 or 1 ppm SO_2 with 1 mg/m^3 of NaCl droplet aerosol, 1 mg/m^3 NaCl droplet aerosol for 60 min exposure with mouthpiece at rest	FEV_1, RT, FRC, V_{max50}, V_{max75}, symptoms
Koenig et al. (1981)	Asthma; n = 8; 6 M, 2 F (14−18 yr)	0 or 1 ppm SO_2 with 1 mg/m^3 of NaCl droplet aerosol, 1 mg/m^3 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_1, RT, FRC, V_{max50}, V_{max75}, symptoms
Koenig et al. (1983)	(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^3 of NaCl droplet aerosol, 1 ppm SO_2 + 1 mg/m^3 NaCl, 0.5 ppm SO_2 + 1 mg/m^3 NaCl for 30 min exposure via mouthpiece at rest followed by 10 min exercise on treadmill (five- to six-fold increase in V_E) (2) 0.5 ppm SO_2 + 1 mg/m^3 NaCl via a face mask with no nose clip with exercise conditions the same as above	FEV_1, RT, FRC, V_{max50}, V_{max75}, symptoms
Koenig et al. (1987)	Allergic w/EIB; n = 10; 3 M 7 F (13−17 yr)	0 or 0.75 ppm SO_2 (mouthpiece) with exercise (33.7 L/min) for 10 and 20 min prior pretreatment (placebo or 180 µg albuterol)	FEV_1, RT, FRC, symptoms
Koenig et al. (1988)	Asthma w/EIB; n = 8; 2 M, 6 F (13−17 yr)	1.0 ppm SO_2 10 min (mouthpiece, treadmill, 35 L/min) with pretreatment (placebo 20, 40, 60 mg cromolyn) 20 min prior, no control, air exposure	$FEV_{1,}$RT
Koenig et al. (1990)	Asthma w/EIB; n = 13; 8 M, 5 F (12−18 yr)	0.1 ppm SO_2 for 15 min preceded by air or 0.12 ppm O_3 for 45 min during intermittent exercise (2 × 15 min at 30 L/min on a treadmill), no control, air exposure	FEV_1, RT, FRC, V_{max50}, symptoms
Koenig et al. (1992)	Asthma; n = 8; 2 M, 6 F (18−46 yr; 27.5 ± 9.6 yr)	1 ppm SO_2 for 10 min with exercise ($\dot{V}_E$ = 13.4−31.3 L/min) with or w/o pretreatment to theophylline	FEV_1, RT

Table 5-1 (Continued): Study specific details from controlled human exposure studies of individuals with asthma.

Study	Disease Status; n; Sex; (Age[a])	Exposure Details (Concentration; Duration)	Outcomes Examined
Lazarus et al. (1997)	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_2 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
Linn et al. (1983b)	Asthma; n = 23; 13 M, 10 F (19−31 yr)	(1) 0, 0.2, 0.4, or 0.6 ppm SO_2 w/low humidity or high humidity for 10 min w/exercise (bicycle, 5 min 50 L/min) (2) 0 or 0.6 ppm SO_2 w/warm air or cold air w/exercise (bicycle, 50 L/min, ~5 min)	sRaw, sGaw, FVC, FEV_1, symptoms
Linn et al. (1983a)	Asthma; n = 23; 15 M, 8 F (18−30 yr, 23 ± 4 yr)	0 or 0.75 ppm SO_2 with unencumbered breathing and mouth only breathing (with exercise 40 L/m, 10 min bicycle)	sRaw, thoracic gas volume, symptoms, FVC, FEV_1, PEFR, V_{max50}, V_{max25}
Linn et al. (1984c)	Asthma; n = 24; 13 M, 11 F (19−31 yr)	0, 0.3, or 0.6 ppm SO_2 at 21°, 7°, and −6°C, rH 80% (bicycle 50 L/min, ~5 min)	sRaw, sGaw, symptoms
Linn et al. (1984a)	Asthma: n = 14; 12 M, 2 F (18−33 yr)	0 or 0.6 ppm SO_2 for 6 h with exercise on day 1 and 2 (2 × 5-min exercise, bicycle, 50 L/min per exposure)	sRaw, sGaw, symptoms
Linn et al. (1984b)	(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_2 at 5°C, 50 and 85% rH with exercise (5 min, 50 L/min) (2) 0 or 0.6 ppm SO_2 at 5 and 22°C, 85% rH with exercise (5 min, 50 L/min)	sRaw, sGaw, FEV_1, symptoms
Linn et al. (1985b)	Asthma; n = 22; 13 M, 9 F (18−33 yr)	0 or 0.6 ppm SO_2 at 21 and 38°C and 20 and 80% rH with exercise (~5 min, 50 L/min)	sRaw, sGaw, symptoms
Linn et al. (1985a)	COPD; n = 24; 15 M, 9 F (49−68 yr)	0, 0.4, or 0.8 ppm SO_2 for 1 h with exercise (2 × 15 min, bicycle, 18 L/min)	sRaw, FVC, FEV_1, MMFR, symptoms

Table 5-1 (Continued): Study specific details from controlled human exposure studies of individuals with asthma.

Study	Disease Status; n; Sex; (Age[a])	Exposure Details (Concentration; Duration)	Outcomes Examined
Linn et al. (1987)	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_2 1 h exposures 3 × 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_1, 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_1 induced by 3 min normocapnic hyperpnea with cold, dry air
Linn et al. (1988)	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_2 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
Linn et al. (1990)	Asthma; n = 21; 6 M, 15 F (19−48 yr)	0, 0.3, or 0.6 ppm SO_2 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
Magnussen et al. (1990)	Asthma; n = 46; 24 M, 22 F (28 ± 14 yr) Healthy; n = 12 (24 ± 5 yr)	0 or 0.5 ppm SO_2 10 min tidal breathing followed by 10 min of isocapnic hyperventilation (30 L/min) Histamine challenge—(8 mg/mL)	sRaw
Myers et al. (1986a)	Asthma; n = 10; 7 M, 3 F (19−40 yr)	0, 0.25, 0.5, 1, 2, 4, or 8 ppm SO_2 3 min sequential exposures (mouthpiece, 40 L/min) with pretreatment 30 min prior with cromolyn (placebo, 20, or 200 mg)	sRaw
Myers et al. (1986b)	(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_2 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[a])	Exposure Details (Concentration; Duration)	Outcomes Examined
Roger et al. (1985)	Asthma; n = 28; 28 M (19−33 yr)	75 min 0, 0.25, 0.5, or 1.0 ppm SO_2 Three 10 min periods of exercise 42.4 L/min	Raw; sRaw; FVC, FEV_1, FEF_{25-75}, FEF_{max}, FEF_{50}, FEF_{75},
Rubinstein et al. (1990)	Asthma; n = 9; 5 M, 4 F (23−34 yr)	0 or 0.3 ppm NO_2 during exercise followed by challenge with 0.25 to 4.0 ppm SO_2, in doubling dose increments, for 4 min each until sRaw increased by 8 SRaw units above baseline	sRaw, FVC, FEV_1, single-breath nitrogen test
Sheppard et al. (1983)	Asthma; n = 8; 4 M, 4 F (22−36 yr)	0.5 ppm SO_2 for 3 min eucapnic hyperpnea	sRaw, symptoms
Trenga et al. (1999)	Asthma; n = 47; 14 M, 33 F (18−39 yr)	0.5 ppm SO_2 for 10 min during moderate exercise	FEV_1, FVC, FEV_1/FVC, PEF, FEF_{25-75}, symptoms ratings
Trenga et al. (2001)	Asthma; n = 17; 5 M, 12 F (19−38 yr)	0.1 or 0.25 ppm SO_2 for 10 min w/moderate exercise (treadmill)	FVC, FEV_1, FEF_{25-75}, PEF, symptoms
Tunnicliffe et al. (2003)	Asthma; n = 12 (adults, 35.7 yr) Healthy; n = 12 (adults, 34.5 yr)	0 or 0.2 ppm SO_2 at rest	Symptoms, FEV_1, 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_1 = forced expiratory volume in 1 sec; FVC = forced vital capacity; $FEF_{25-75\%}$ = forced expiratory flow at 25−75% of forced vital capacity; $FEF_{50\%}$ = forced expiratory flow at 50% of forced vital capacity; $FEF_{75\%}$ = forced expiratory flow at 75% of forced vital capacity; FEF_{max} = 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_2 = nitrogen dioxide; O_3 = ozone; PEF = peak expiratory flow; PEFR = 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_2 = sulfur dioxide; V_E = minute volume; Vmax = maximal flow of expired vital capacity; V_{max75} = flow rate with 75% of FVC remaining to be expired; V_{max50} = flow rate with 50% of FVC remaining to be expired; V_{max25} = flow rate with 25% of FC remaining to be expired.

[a]Range or Mean ± SD.

Several investigators (Linn et al., 1990; Linn et al., 1988; Linn et al., 1987; Bethel et al., 1985; Linn et al., 1984a; Linn et al., 1983b) demonstrated ≥100% increase in sRaw or ≥15% decrease in FEV_1 after 5−10-minute exposures to low concentrations (0.2−0.3 ppm) of SO_2 in exercising adults with asthma, with effects being more pronounced following 5−10-minute exposures to 0.4−0.6 ppm SO_2 (Linn et al., 1990; Magnussen et al., 1990; Linn et al., 1988; Linn et al., 1987; Roger et al., 1985; Linn et al., 1983b).

SO_2-induced bronchoconstriction occurs rapidly and is transient with recovery following cessation of exposure. Bronchoconstriction occurs in as little as 2 minutes from the start of exposure in adults with asthma who have increased ventilation rates due to exercise or eucapnic hyperpnea (Horstman et al., 1988; Balmes et al., 1987; Sheppard et al., 1983). During exposure to SO_2 over a 30-minute period with continuous exercise, the response to SO_2 develops rapidly and is maintained throughout the 30-minute exposure (Kehrl et al., 1987; Linn et al., 1987; Linn et al., 1984c). Linn et al. (1984a) reported decrements in lung function in adults with asthma immediately after each exercise period (one early and one late into the exposure) in two 6-hour exposures to 0.6 ppm SO_2 on successive days. The decrements in lung function observed in the early and late exercise periods were not statistically significantly different from each other, and the response observed after the second day of SO_2 exposure was slightly less than the response observed after the first day of SO_2 exposure. These results demonstrate transient rather than cumulative bronchoconstriction effects. These effects are generally observed to diminish to baseline levels within 1 hour post exposure (Linn et al., 1987).

Other factors that affect responses to SO_2 include temperature and humidity. The majority of controlled human exposure studies were conducted at 20−25°C and at relative humidities ranging from ~25−90%. Some evidence indicates that the respiratory effects of SO_2 are exacerbated by colder and dryer conditions (Linn et al., 1985b; Bethel et al., 1984; Linn et al., 1984b).

Responders versus nonresponders to SO_2. At the time of the 2008 SO_X ISA (U.S. EPA, 2008d), it was well documented that some individuals have a greater response to SO_2 than others with similar disease status (Table 5-2) (Linn et al., 1990; Magnussen et al., 1990; Linn et al., 1988; Linn et al., 1987; Horstman et al., 1986; Bethel et al., 1985; 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_2 Conc (ppm)	Exposure Duration (min)	N	Ventil-ation (L/min)	Cumulative Percentage of Responders (Number of Subjects)[a]				Study	Respiratory Symptoms: Supporting Studies
				sRaw	≥100% ↑	≥200% ↑	≥300% ↑		
				FEV_1	≥15% ↓	≥20% ↓	≥30% ↓		
0.2	5	23	~48	sRaw	9% (2)[b]	0	0	Linn et al. (1983b)	Limited evidence of SO_2-induced increases in respiratory symptoms in some people with asthma: (Linn et al. (1990); Linn et al. (1988); Linn et al. (1987); Schachter et al. (1984); Linn et al. (1983b))
	10	40	~40	sRaw	7.5% (3)[c]	2.5% (1)[c]	0[c]	Linn et al. (1987)[c]	
	10	40	~40	FEV_1	9% (3.5)[c]	2.5% (1)[c]	1% (0.5)[c]	Linn et al. (1987)[c]	
0.25	5	19	~50−60	sRaw	32% (6)	16% (3)	0	Bethel et al. (1985)	
	5	9	~80−90	sRaw	22% (2)	0	0	Bethel et al. (1985)	
	10	28	~40	sRaw	4% (1)	0	0	Roger et al. (1985)	
0.3	10	20	~50	sRaw	10% (2)	5% (1)	5% (1)	Linn et al. (1988)[d]	
	10	21	~50	sRaw	33% (7)	10% (2)	0	Linn et al. (1990)[d]	
	10	20	~50	FEV_1	15% (3)	0	0	Linn et al. (1988)	
	10	21	~50	FEV_1	24% (5)	14% (3)	10% (2)	Linn et al. (1990)	
0.4	5	23	~48	sRaw	13% (3)	4% (1)	0	Linn et al. (1983b)	Stronger evidence with some statistically significant increases in respiratory symptoms: Balmes et al. (1987)[f], Gong et al. (1995) (Linn et al. (1987); Linn et al. (1983b)) Roger et al. (1985)
	10	40	~40	sRaw	24% (9.5)[c]	9% (3.5)[c]	4% (1.5)[c]	Linn et al. (1987)[c]	
	10	40	~40	FEV_1	27.5% (11)[c]	17.5% (7)[c]	10% (4)[c]	Linn et al. (1987)[c]	
0.5	5	10	~50−60	sRaw	60% (6)	40% (4)	20% (2)	Bethel et al. (1983)	
	10	28	~40	sRaw	18% (5)	4% (1)	4% (1)	Roger et al. (1985)	
	10	45	~30	sRaw	36% (16)	16% (7)	13% (6)	Magnussen et al. (1990)[f]	

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_2 Conc (ppm)	Exposure Duration (min)	N	Ventil-ation (L/min)	Cumulative Percentage of Responders (Number of Subjects)[a]				Study	Respiratory Symptoms: Supporting Studies
				sRaw	≥100% ↑	≥200% ↑	≥300% ↑		
				FEV_1	≥15% ↓	≥20% ↓	≥30% ↓		
0.6	5	23	~48	sRaw	39% (9)	26% (6)	17% (4)	Linn et al. (1983b)	Clear and consistent increases in SO_2-induced respiratory symptoms: (Linn et al. (1990); Linn et al. (1988); Linn et al. (1987); Linn et al. (1983b)), Gong et al. (1995), Horstman et al. (1988)
	10	40	~40	sRaw	34% (13.5)[c]	24% (9.5)[c]	19% (7.5)[c]	Linn et al. (1987)[c]	
	10	20	~50	sRaw	60% (12)	35% (7)	10% (2)	Linn et al. (1988)	
	10	21	~50	sRaw	62% (13)	29% (6)	14% (3)	Linn et al. (1990)	
	10	40	~40	FEV_1	47.5% (19)[c]	39% (15.5)[c]	17.5% (7)[c]	Linn et al. (1987)[c]	
	10	20	~50	FEV_1	55% (11)	55% (11)	5% (1)	Linn et al. (1988)	
	10	21	~50	FEV_1	43% (9)	38% (8)	14% (3)	Linn et al. (1990)	
1.0	10	28	~40	sRaw	50% (14)	25% (7)	14% (4)	Roger et al. (1985)[e]	
	10	10	~40	sRaw	60% (6)	20% (2)	0	Kehrl et al. (1987)	

Conc = concentration; FEV_1 = forced expiratory volume in 1 sec; sRaw = specific airway resistance; SO_2 = sulfur dioxide.

[a]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_1. 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_2 and the percent change relative to baseline with exercise/clean air).

[b]Numbers in parenthesis represent the number of subjects experiencing the indicated effect.

[c]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.

[d]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.

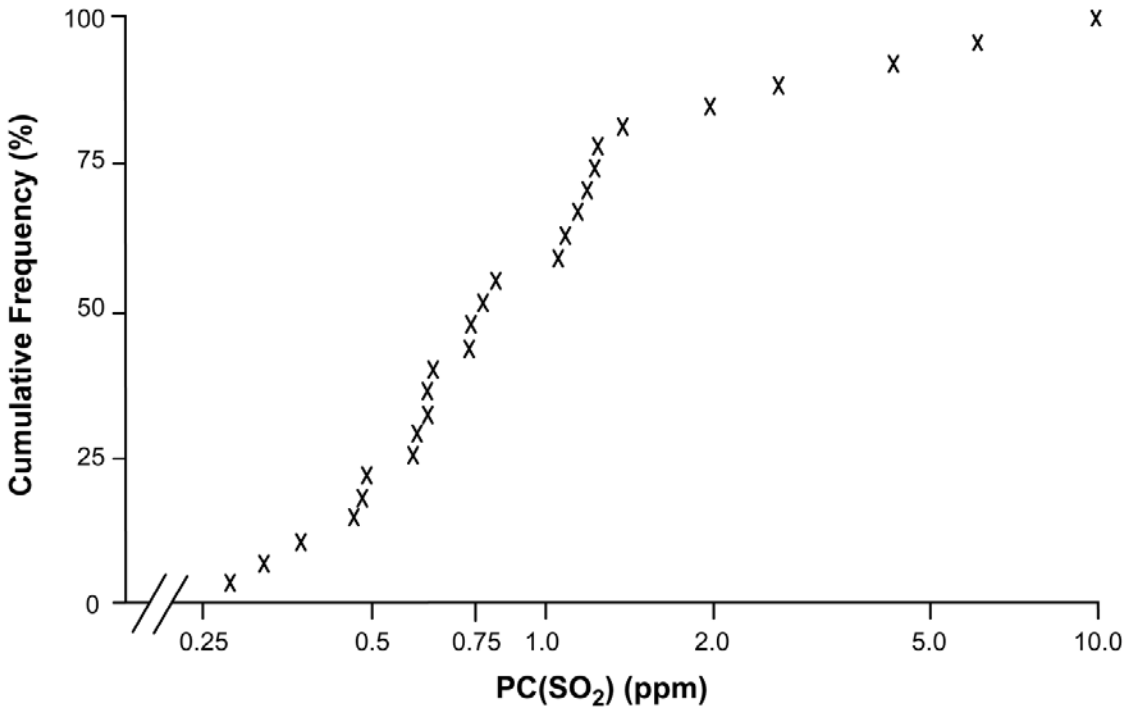
[e]One subject was not exposed to 1 ppm due to excessive wheezing and chest tightness experienced at 0.5 ppm. For this subject, the values used for 0.5 ppm were also used for 1.0 ppm under the assumption that the response at 1.0 ppm would be equal to or greater than the response at 0.5 ppm.

[f]Indicates studies in which exposures were conducted using a mouthpiece rather than a chamber.

Horstman et al. (1986) reported that individuals required different concentrations of SO_2 to produce a doubling of sRaw (≥100%) compared to clean air exposure [provocative concentration of SO_2, $PC(SO_2)$] (Figure 5-1). This study described the distribution of individual bronchial sensitivity to SO_2, measured by sRaw, in 27 subjects with asthma that were sensitive to methacholine; nonsensitive volunteers were excluded from further participation in the study. Individuals were exposed to concentrations of SO_2 between 0 and 2 ppm for 10 minutes under exercising conditions (V_E = 42 L/minute). While six of the subjects (22%) reached a $PC(SO_2)$ below 0.5 ppm SO_2, two subjects (7.4%) experienced a moderate decrease ≤0.3 ppm (Figure 5-1). On the other end of the spectrum, four subjects (14.8%) did not demonstrate ≥100% increase in sRaw even when exposed to 2.0 ppm SO_2 and eight (29.6%) subjects required an SO_2 concentration between 1.0 and 2.0 ppm to elicit a response. The authors noted that the effects of SO_2 on sRaw are similar to a variety of nonspecific bronchoconstrictive stimuli. However, they observed only a weak correlation between airway responsiveness to SO_2 and methacholine (r = 0.31, p = 0.12). This study demonstrates substantial interindividual variability in sensitivity to the bronchoconstrictive effects of SO_2 in exercising adults with asthma.

Completed after the 2008 SO_X ISA (U.S. EPA, 2008d), an analysis by Johns et al. (2010) of publicly available primary data from published studies clearly demonstrates disparate responses among 177 adults with asthma. Data from five studies of individuals with asthma exposed to multiple concentration of SO_2 for 5−10 minutes with elevated ventilation rates (Linn et al., 1990; Linn et al., 1988; Linn et al., 1987; Roger et al., 1985; Linn et al., 1983b) were analyzed after classifying individuals by responder status. Classification of responders versus nonresponders was based on the magnitude of sRaw and FEV_1 changes in response to the highest SO_2 concentration to which subjects were exposed (0.6 or 1.0 ppm). Responders were defined as subjects experiencing ≥100% increase in sRaw or ≥15% decrease in FEV_1 after exposure. Response status was assigned separately for sRaw and FEV_1. Among responders, significant decreases in FEV_1 were observed for concentrations as low as 0.3 ppm SO_2 (p = 0.005) (Table 5-3). In addition, marginally significant increases in sRaw were demonstrated at 0.3 ppm SO_2 (p = 0.009), with statistically significant increases observed at 0.4 and 0.5 ppm (p < 0.001) (Table 5-4). [Due to multiple comparisons, Johns et al. (2010) designated a critical p-value of 0.005 as significant, using the Bonferroni multiple comparison correction.] Overall, these data demonstrate a bimodal distribution of airway responsiveness to SO_2 in individuals with asthma, with one subpopulation that is insensitive to the bronchoconstrictive effects of SO_2 even at concentrations as high as 1.0 ppm, and another subpopulation that has an increased risk for bronchoconstriction at low concentrations of SO_2. The Winterton et al. (2001) study suggests that a TNF-α promoter polymorphism in

some individuals with asthma may be associated with increased airway responsiveness to SO_2.



PC = provocative concentration; SO_2 = sulfur dioxide.
Note: Each data point represents the PC(SO_2) 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.

A recent analysis of four previously published studies (Horstman et al., 1988; Horstman et al., 1986; Schachter et al., 1984; Sheppard et al., 1984) in which individuals with asthma were exposed to multiple SO_2 concentrations or had their response recorded over multiple durations of SO_2 exposure was provided by Goodman et al. (2015). However, the analysis conducted by Goodman et al. (2015) did not consider the log-normal distribution of airway responsiveness data and instead used an arithmetic mean and standard deviation in their analysis. Eight of 56 individuals were identified as sensitive to the effects of SO_2 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.

		FEV_1				
	SO_2 Concentration ppm	Number of Exposures	% Decrease	95% Confidence Limits		*p*-Value
				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[a,b]
	0.4	37	−17.4	−21.3	−13.6	<0.001[a,b]
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_1 = forced expiratory volume in 1 sec; ppm = parts per million; SO_2 = 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. (1987), Linn et al. (1988), and Linn et al. (1990).

[a]Indicates significance at 0.05 level using the Bonferroni multiple comparison correction.

[b]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.

		sRaw				
	SO_2 Concentration ppm	Number of Exposures	% Increase	95% Confidence Limits		*p*-Value
				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[a,b]
	0.5	14	68.0	33.2	102.8	<0.001[a,b]
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_2 = sulfur dioxide.

A 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).

[a]Indicates significance at 0.05 *p* level, using the Bonferroni multiple comparison correction.

[b]Indicates significance at 0.05 level using Dunnett's test.

Effects of asthma severity on SO_2-induced response. The influence of asthma severity on the degree of responsiveness to SO_2 exposure has been examined (Trenga et al., 1999; Linn et al., 1987). One study involved exposure to SO_2 under conditions of increased ventilation (i.e., exercise) (Linn et al., 1987). Adults with asthma were divided into two groups, minimal/mild and moderate/severe, mainly based on the individual's use of medication to control asthma. Individuals that did not regularly use asthma medication were classified as minimal/mild; however, even the moderate/severe group consisted of adults who had well-controlled asthma, were generally able to withhold medication, were not dependent on corticosteroids, and were able to engage in moderate to heavy levels of exercise. Thus, this moderate/severe group would likely be classified as moderate by

today's classification standards (Johns et al., 2010; Reddel, 2009). Linn et al. (1987) found similar relative decrements in lung function in response to SO_2 exposure between the groups. However, the moderate/severe group demonstrated larger absolute changes in lung function compared to the mild group (Linn et al., 1987). This greater decrement in lung function was attributable to a larger response to the exercise component of the exposure protocol in the moderate/severe group compared with the mild group. Trenga et al. (1999) found a correlation between asthma severity and response to SO_2. Adults with asthma were divided into four groups based on medication usage as an indicator of asthma severity. The role of exercise was not determined in this study, so it unclear whether individuals with more severe asthma had a greater response to exercise compared to individuals with less severe asthma. However, both studies suggest that adults with moderate/severe asthma may have more limited reserve to deal with an insult compared with individuals with mild asthma.

Asthma with medication. Asthma medications have been shown to mitigate SO_2-induced bronchoconstriction (U.S. EPA, 2008d). Medications evaluated include short-acting and long-acting beta-adrenergic bronchodilators (Gong et al., 1996; Linn et al., 1990; Linn et al., 1988; Koenig et al., 1987), cromolyn sodium (Koenig et al., 1988; Myers et al., 1986b), theophylline (Koenig et al., 1992), and leukotriene receptor antagonists (Gong et al., 2001; Lazarus et al., 1997). While these therapies have been shown to mitigate the respiratory effects of SO_2, they did not completely eliminate these effects in all studies.

Children and adolescents. Several studies have examined the responsiveness to SO_2 of adolescents (ages 12−18 years) with asthma or allergic with EIB (Koenig et al., 1990; Koenig et al., 1988; Koenig et al., 1987). Of these studies, only Koenig et al. (1987) included a control air exposure, so that the bronchoconstrictive effects of SO_2 itself (rather than, e.g., due to EIB), can be assessed. On average, based on the data provided in Table 1 of this paper, adolescents experienced a pre-to-post reduction in FEV_1 of 15.4% following exposure to 0.75 ppm SO_2 and a reduction in FEV_1 of 3.46% following air exposure. Although the adolescents in this study were allergic with EIB, they did not have extrinsic asthma. Nevertheless, they are discussed here because allergies affect airway responsiveness (Burrows et al., 1995) and because their response to SO_2 is similar to that observed in other studies of individuals with asthma. The pre-to-post reduction in FEV_1 of 15.4% following 0.75 ppm SO_2 observed by Koenig et al. (1987) is similar to the pre-to-post reduction in FEV_1 of 13.9% found in adolescents with asthma following exposure to 1.0 ppm SO_2 observed by Koenig et al. (1988). For potential comparison to the results of adolescents, three studies of adults with asthma were conducted at 0.75 ppm (Gong et al., 2001; Gong et al., 1996; Linn et al., 1983a). Of these, only Gong et al. (2001) provided pre-to-post data for both exposures to air and SO_2. Similar to the Koenig

et al. (1987) results, Gong et al. (2001) observed a pre-to-post reduction of 15.8% in FEV_1 following SO_2 exposure in adults based on Table 2 of their paper. Adjusted for the responses occurring with air exposure, Koenig et al. (1987) observed an 11.8% reduction in FEV_1 in adolescents, similar to the 12.7% reduction observed in adults by Gong et al. (2001). These two studies differ in that the adolescents were exposed via a mouthpiece, whereas the adults were exposed in a chamber without a mouthpiece. Breathing on a mouthpiece is expected to produce a somewhat larger FEV_1 decrement than unencumbered breathing (Linn et al., 1983a). Although generally similar effects of SO_2 on adolescents and adults have been observed, exact comparisons of SO_2 effects between adolescents and adults are not possible given the available data.

There is also evidence that adolescents (ages 12−18 years) with asthma or atopy are responsive to coexposures of SO_2 and sodium chloride (NaCl) droplet aerosol (Koenig et al., 1983, 1981; Koenig et al., 1980). Exposure concentrations in these studies ranged from 0.1 to 1.0 ppm SO_2. Koenig et al. (1983) observed average FEV_1 decrements of 15 and 23% in exercising adolescents (12 to 16 year old) with asthma after a 10-minute exposure to 0.5 ppm SO_2 or 1.0 ppm SO_2 plus 1 mg/m^3 NaCl droplet aerosols, respectively. No significant changes were observed following exposure to the NaCl droplet aerosol alone. However, the observed effect may be the result of the presence of hygroscopic particles that carry SO_2 deeper into the lung.

There are no controlled human exposure studies for children less than 12 years of age that were exposed to SO_2. However, the responsiveness of children to SO_2 relative to adolescents and adults may be inferred by the responses to other nonspecific bronchoconstrictive stimuli. Horstman et al. (1986) noted that the effects of SO_2 on sRaw are similar to that of a variety of nonspecific bronchoconstrictive stimuli. Indeed, SO_2 is a nonspecific bronchial challenge agent that has been used to assess changes in airway responsiveness of individuals with asthma following NO_2 and O_3 exposures (Trenga et al., 2001; Jörres and Magnussen, 1990; Rubinstein et al., 1990). Airway responsiveness to methacholine, a history of respiratory symptoms, and atopy were significant predictors of airway responsiveness to SO_2 in healthy adults Nowak et al. (1997). Thus, potential differences in airway responsiveness of children to SO_2 relative to adolescents and adults may be gleaned from the literature on airway responsiveness to other nonspecific stimuli such as methacholine.

A number of cross-sectional studies have assessed airway responsiveness of children with and without asthma to methacholine [e.g., (Mochizuki et al., 1995; Morikawa et al., 1994; Avital et al., 1991; Hopp et al., 1986; Hopp et al., 1985)]. Studies show a clear decrease in airway responsiveness of healthy children with increasing age beyond 5−7 years of age through adolescence (Mochizuki et al., 1995; Hopp et al., 1986; Hopp et al., 1985). In

studies of children with asthma, some have reported airway responsiveness increased with asthma severity but was not affected by age (Avital et al., 1991; Hopp et al., 1986), whereas others have found airway responsiveness to increase with asthma severity and decrease with age beyond 6−7 years of age (Mochizuki et al., 1995; Morikawa et al., 1994). The study by Mochizuki et al. (1995) suggested that airway responsiveness in both healthy children and those affected by asthma increases from ages 2−3 years up to 6−7 years, after which airway responsiveness begins decreasing.

More confidence in the effect of age on airway responsiveness may be placed on data from longitudinal studies than from the cross-sectional studies discussed above. In a longitudinal study of methacholine responsiveness conducted at 9, 11, 13, and 15 years of age, Le Souëf et al. (1995) found that responsiveness (1) decreases with age; (2) is greater in boys (n = 389) than girls (n = 429); and (3) is greater in those reporting wheeze, although responsiveness decreased with age in these individuals as well. Asthma prevalence and symptoms such as wheeze are greater in boys than girls during childhood and become similar or reversed around the time of puberty (Almqvist et al., 2008). In a subset of the cohort as used by Le Souëf et al. (1995), Burrows et al. (1995) investigated the effects of age (n = 573, 49% female), atopy (n = 558), and serum IgE (n = 473) on airway responsiveness. At 9 years of age, a larger fraction of boys experienced bronchial responsiveness than did girls. By the age of 15 years, there was little to no difference in responsiveness between the sexes. Relative to atopic children, those without atopy or with only minimal atopy had lower airway responsiveness and showed a more evident decrease in airway responsiveness with increasing age. In the most atopic children (41 of 558), about 40% experienced severe bronchial responsiveness, which did not decrease with age. Across all ranges of serum IgE, there was a decrease in responsiveness from age 9 to age 15 years. By 15 years of age, there was minimal bronchial reactivity in the children having the lowest IgE levels, and bronchial reactivity increased with increasing serum IgE levels ($p < 0.0001$). In biennial assessments of childhood responsiveness, Burrows et al. (1995) observed considerable intra-individual variability in bronchial reactivity, but they observed a statistically significant trend for the more allergic children to experience persistent bronchial hyperresponsiveness among their biennial assessments.

Under the assumption that bronchial responsiveness to methacholine is an appropriate surrogate for bronchial responsiveness to SO_2, these studies suggest that greater airway responsiveness to SO_2 occurs in school-aged children, particularly boys, than in adolescents. Additionally, the methacholine data also suggest that greater airway responsiveness to SO_2 in school-aged children and adolescents who are allergic or experience wheeze is expected to occur than in those without these conditions. Children, particularly boys, breathe more through the mouth than adults, and ventilation rates relative to body mass are greater in children than adults (see Section 4.1.2). Allergic

rhinitis can lead to increased nasal resistance, which also results in less nasal and more oral breathing. Obese children also tend to have increased nasal resistance, increased oral breathing, and increased ventilation rates relative to normal-weight children (see Section 4.1.2). Oral breathing allows greater SO_2 penetration into the lower airways, where it may cause bronchoconstriction, than does nasal breathing (see Section 4.2.2). Overall, school-aged children having asthma-like symptoms might be expected to experience greater responsiveness (i.e., larger decrements in pulmonary function) following exposure to SO_2 than normal-weight adolescents and adults.

Mixtures effects. The health effects of SO_2 can be potentially modified by the interaction with other pollutants during or prior to exposure. A few controlled human exposure studies have examined the interactive effects of O_3 and SO_2 both sequentially and in combination. Exercising adolescents with asthma exposed to 0.1 ppm SO_2 for 15 minutes after a 45-minute exposure to 0.12 ppm O_3 had a significant decrease (8%) in FEV_1 (8%) *($p < 0.05$)*, a significant increase in total respiratory resistance (R_T) (19%) *($p < 0.05$)*, and a significant decrease in maximal flow at 50% of expired vital capacity ($Vmax_{50}$) (15%) *($p < 0.05$)*, while air followed by SO_2, and O_3 followed by O_3 exposures did not cause significant changes in lung function (Koenig et al., 1990). In a more recent study in exercising adults with asthma, Trenga et al. (2001) observed greater decrements in lung function after 45 minutes of exposure to 0.12 ppm O_3 followed by 15 minutes of 0.25 ppm SO_2 compared to air followed by SO_2.

Jörres and Magnussen (1990) and Rubinstein et al. (1990) investigated the effects of prior NO_2 exposure on SO_2-induced bronchoconstriction in adults with asthma. While Jörres and Magnussen (1990) observed that tidal breathing of NO_2 increased airway responsiveness to subsequent hyperventilation of SO_2, Rubinstein et al. (1990) noted NO_2 induced greater airway responsiveness to inhaled SO_2 in only one subject.

While SO_2 acts as a nonspecific bronchial challenge agent that causes reductions in lung function in individuals with asthma after brief exposure, it can also increase airway responsiveness to subsequent exposures involving other stimuli such as allergens or methacholine. Two studies of adults with asthma provide evidence for AHR to allergens when exposure to SO_2 was in combination with NO_2 (Rusznak et al., 1996; Devalia et al., 1994). In the first of these studies, exposure to 0.2 ppm SO_2 or 0.4 ppm NO_2 did not affect airway responsiveness to house dust mite allergen immediately after a 6-hour exposure at rest. In considering the effect of SO_2 alone, because volunteers were exposed at rest, it is unlikely that enough SO_2 reached the bronchial airways to cause an effect. Following exposure to the two pollutants in combination, volunteers demonstrated an increased response to inhaled allergen (Devalia et al., 1994). Rusznak et al. (1996) confirmed these results in a similar study and found that AHR to dust mites persisted up

to 48-hours post-exposure. These results provide further evidence that SO_2 may elicit effects beyond the short time period typically associated with this pollutant.

Epidemiologic Studies

Unlike controlled human exposure studies, epidemiologic studies inconsistently indicate SO_2-related lung function decrements in populations with asthma. This applies to previous (U.S. EPA, 2008d) and recent (Table 5-5 and Table 5-6) studies as well as adults and children with asthma. Epidemiologic studies examined longer SO_2 averaging times and lags and had uncertainty in exposures estimated from central site monitors. For the few findings of SO_2-associated lung function decrements, confounding by moderately to highly correlated PM and NO_2 (r = 0.54−0.9) was not examined. A few recent studies address some of these uncertainties, but they persist in the evidence overall.

Adults. Previous studies were limited to Europe and Asia. A recent study shows an SO_2-associated decrease in lung function in adults with asthma in the U.S. (Qian et al., 2009b). Recent studies in Europe and Asia do not (Maestrelli et al., 2011; Wiwatanadate and Liwsrisakun, 2011; Canova et al., 2010) (Table 5-5). Mean and upper percentile SO_2 concentrations tended to be lower in recent studies than in previous studies (e.g., means for 24-h avg 0.87−4.8 ppb vs. 1.6−90 ppb). However, lower concentrations do not appear to account for the weak recent evidence in adults with asthma as previous studies with mean SO_2 concentrations of 5.2 to 90 ppb did not observe SO_2-associated lung function decrements (Park et al., 2005; Peters et al., 1996a). Recent studies did not differ in temporal variability (e.g., ratio of the mean concentration to standard deviation) in SO_2 concentrations, which is the basis of analysis in these repeated measure studies.

The U.S. multicity study provides supporting evidence but has the same uncertainty in the exposure estimate as do other studies in adults with asthma. All studies estimated SO_2 exposure from central site monitors, either a single monitor or average of many monitors. Ambient SO_2 concentrations tend to show high spatiotemporal variability within a city, and correlations with personal exposure are poorly characterized (Section 3.4.1.3). Studies did not discuss whether measurements at the monitors adequately represented the spatiotemporal variability in ambient SO_2 concentrations in the study area. Uncertainty is high in the U.S. study, which averaged SO_2 concentrations across monitors within 32 km of subjects' ZIP code centroid (Qian et al., 2009b). Ambient SO_2 concentrations show large, transient peaks (Section 2.5.3), which may be important based on results from controlled human exposure studies showing that 5- to 10-minute exposures to 200−600 ppb SO_2 induce rapid and short-lived lung function decrements. Epidemiologic studies examined same-day (lag 0) SO_2 concentrations, but the daily average. Daily average SO_2 concentrations may not represent peak exposures or capture the transient effects of peak exposures implicated in controlled human exposure studies.

Some recent studies that did not observe SO_2-related lung function decrements had small sample sizes (N = 19 or 32) (Maestrelli et al., 2011; Canova et al., 2010). However, it is unclear whether sample size explains the inconsistency among adults with asthma overall. Similarly sized studies (Boezen et al., 2005; Neukirch et al., 1998) observed associations, and larger studies do not show evidence for association (Wiwatanadate and Liwsrisakun, 2011; Park et al., 2005; Peters et al., 1996a). In panel studies, the number of repeated measurements is also important, and Canova et al. (2010) measured lung function for five 30-day periods. Many studies that had a large number of repeated measurements examined lung function measured by subjects at home not supervised by a trained technician. Results were inconsistent for both methodologies.

A few recent epidemiologic studies add information on response modification by asthma phenotype but produce no clear finding. Previous results support an SO_2 association with decreased lung function or increased airway responsiveness in adults with asthma plus atopy (Boezen et al., 2005; Taggart et al., 1996), but recent results do not (Maestrelli et al., 2011). A 10-ppb increase in 24-h avg SO_2 was associated with a −2.1 point change (95% CI: −6.6, 2.3) in percent predicted FEV_1. Of note, the previous studies specified examining adults with AHR. Similar to controlled human exposure studies, epidemiologic studies do not clearly show that SO_2-associated lung function decrements depend on asthma severity. An association was observed in adults with mild to moderate asthma (Neukirch et al., 1998), and the results varied among populations with more severe asthma (Maestrelli et al., 2011; Canova et al., 2010; Qian et al., 2009b). In contrast with the controlled human exposure studies, the U.S. asthma medication trial observed an SO_2-related decrease in lung function in adults randomized to daily inhaled corticosteroid use [−8.4 L/minute change in PEF (95% CI: −13, −3.4) per 10-ppb increase in 24-h avg SO_2] (Qian et al., 2009b). Decrements were not observed in the beta-agonist or placebo groups (Table 5-5). These two groups had more frequent asthma exacerbation during the study than the corticosteroid group but similar PEF and mean age (Lazarus et al., 2001). All three groups had persistent asthma. Thus, a clear explanation for the pattern of SO_2 associations is not apparent. There is no clear rationale for attributing null findings to the lack of analysis stratified by corticosteroid use, particularly for results that were adjusted for such use (Maestrelli et al., 2011; Canova et al., 2010).

Across studies, the potential influence of copollutants is largely unaddressed. No study in adults with asthma examined $PM_{2.5}$ total mass, and previous studies observed lung function decrements in association with larger sized PM metrics that were highly correlated with SO_2 concentrations (r = 0.8−0.9) and sulfate (Neukirch et al., 1998; Peters et al., 1996a). That some cities had a coal-fired power plant or used coal for heating may explain some of the high correlations with PM and moderate correlations with NO_2 (r = 0.54) (Neukirch et al., 1998; Taggart et al., 1996). Copollutant interactions were not

assessed. Only the recent U.S. study analyzed confounding, but the potential for confounding is unclear. SO_2 was moderately correlated with NO_2 (r = 0.58, no report on PM_{10}) but was associated with PEF in different medication use groups than NO_2 or PM_{10} (Qian et al., 2009b). SO_2 was associated with PEF in the corticosteroid group, and effect estimates decreased slightly with adjustment for PM_{10}, NO_2, or O_3 (Table 5-5). Associations for PM_{10} and NO_2 were observed in the beta-agonist and placebo groups, respectively, and were attenuated with SO_2 adjustment. However, inference from the results is weak due to numerous comparisons across pollutants, lags, and medication groups and questionable reliability in the exposures estimated from monitors up to 32 km away.

Children. As with adults, evidence from neither the 2008 ISA for Sulfur Oxides (U.S. EPA, 2008d) nor recent studies (Table 5-6) consistently links increases in ambient SO_2 concentration with lung function decrements in children with asthma, including recent U.S. multicity studies (Ierodiakonou et al., 2015; O'Connor et al., 2008). The inconsistency does not appear to be explained by lung function measured under supervised conditions or by subjects at home, asthma severity, or prevalence of asthma medication use. In contrast to adults with asthma, SO_2-associated lung function decrements were not observed in children with asthma who took inhaled corticosteroids (Ierodiakonou et al., 2015; Liu et al., 2009b). Among children with asthma in Windsor, ON, the association was limited to nonusers (Liu et al., 2009b). For some recent studies, including a U.S. multicity study, inference about an SO_2 effect is weak because the association was isolated to one lung function parameter or exposure lag among numerous lung function parameters, lags, pollutants, and/or asthma medication groups examined (Ierodiakonou et al., 2015; Wiwatanadate and Trakultivakorn, 2010). A few recent studies aimed to address uncertainty in the exposure estimates or copollutant confounding (Greenwald et al., 2013; Dales et al., 2009; Liu et al., 2009b) and provide limited indication of SO_2-associated lung function decrements.

Table 5-5 Recent epidemiologic studies of lung function in adults with asthma.

Study Population and Methodological Details	SO_2 Exposure Estimates (ppb)	SO_2 Averaging Time and Lag Day	Effect Estimate (95% CI) Single-Pollutant Model[a]	Copollutant Examination[a]
†Qian et al. (2009b) 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.	Monitors averaged within 32 km of subject ZIP code centroid. Mean (SD): 4.8 (3.9) 75th percentile: 6.2 Max: 32	24-h avg 0	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)	Copollutant model, ICS users, lag 0 with PM_{10}: −7.3 (−15, 0) with NO_2: −7.6 (−13, −1.8) with O_3: −6.5 (−12, −1.4) PM_{10} association in placebo group, NO_2 in beta-agonist group. No association with O_3. $PM_{2.5}$ not examined. NO_2 and PM_{10} associations attenuated with SO_2 adjustment. SO_2 moderately correlated with NO_2, r = 0.58. Correlation NR for PM_{10}.
		0−2 avg	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)	
†Maestrelli et al. (2011) 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 (>6 times per yr for 3 yr).	Two monitors in city Medians across seasons: 0.87−2.7 75th percentiles across seasons: 1.3−4.1	24-h avg 0	Change in % predicted FEV_1 All subjects: −2.1 (−6.6, 2.3) Nonsmokers: −11 (−40, 18)	No copollutant model CO associated with FEV_1. No association with personal or central site $PM_{2.5}$. No association for central site PM_{10}, NO_2, O_3. Copollutant correlations NR.
†Canova et al. (2010) 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_1. Part of same cohort as Maestrelli et al. (2011) above.	Two monitors in city Mean (SD): 1.4 (1.1) Max: 4.9	24-h avg 0, 1, 2, 3, 0−1 avg, 0−3 avg	Quantitative effect estimates NR. Figure shows negative but imprecise associations for PEF and FEV_1 with wide 95% CIs.	Copollutant model with CO CO association with PEF not FEV_1 robust to SO_2 adjustment. No association for PM_{10} or NO_2. $PM_{2.5}$ not examined. SO_2 moderately correlated with CO, PM_{10}, and NO_2. Spearman r = 0.50, 0.51, 0.54.

Table 5-5 (Continued): Recent epidemiologic studies of lung function in adults with asthma.

Study Population and Methodological Details	SO_2 Exposure Estimates (ppb)	SO_2 Averaging Time and Lag Day	Effect Estimate (95% CI) Single-Pollutant Model[a]	Copollutant Examination[a]
†Wiwatanadate and Liwsrisakun (2011) 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.	Monitor within 10 km of home Mean (SD): 1.7 (0.62) 90th percentile: 2.4 Max: 3.9	24-h avg 4	NR	Only multipollutant models analyzed SO_2 increment and units of PEF NR. with $PM_{2.5}$ and NO_2 Evening PEF: 0.90 (0.34, 1.5) Average PEF: 0.48 (0, 0.96) No associations with $PM_{2.5}$, PM_{10}, CO, O_3. SO_2 weakly correlated with NO_2, $PM_{2.5}$. r = 0.23, −0.07.

CI = confidence interval; CO = carbon monoxide; FEV_1 = forced expiratory volume in 1 sec; ICS = inhaled corticosteroid; N = sample size; NO_2 = nitrogen dioxide; NR = not reported; O_3 = ozone; PEF = peak expiratory flow; $PM_{2.5}$ = particulate matter with a nominal aerodynamic diameter less than or equal to 2.5 µm; PM_{10} = particulate matter with a nominal aerodynamic diameter less than or equal to 10 µm; r = correlation coefficient; SD = standard deviation; SO_2 = sulfur dioxide.

[a]Effect estimates are standardized to a 10-ppb increase in 24-h avg SO_2.

†Studies published since the 2008 Integrated Science Assessment for Sulfur Oxides.

For children in El Paso, TX, Greenwald et al. (2013) measured SO_2 at schools, which may better represent some component of exposure than a monitor not sited in a subject's microenvironment. For children attending the school near a major road, a 10-ppb increase in lag 0−3 avg SO_2 was associated with a −31% change (95% CI: −52, −2.0) in FEV_1. This is the largest effect estimate among children or adults with asthma, but a 10-ppb increase in 4-day avg SO_2 is unlikely in the area [school mean 0.84 (SD: 0.54) ppb]. Results are inconsistent for 24-h avg SO_2 assigned from monitors up to 2.3−50 km from children's homes or schools (Amadeo et al., 2015; Ierodiakonou et al., 2015; Dales et al., 2009; Liu et al., 2009b; O'Connor et al., 2008). Lung function decreased with increases in SO_2 concentrations at a monitor located a median distance of 2.3 km from children's homes (O'Connor et al., 2008) but not a monitor within 50 km of children's ZIP code centroid (Ierodiakonou et al., 2015) (Table 5-6). Studies did not describe the adequacy of monitors at these distances to represent temporal variation in SO_2 exposure. No association was observed with the change in PEF after a 6-minute exercise (Amadeo et al., 2015), but this protocol does not mimic controlled human exposure studies because PEF was examined in relation to 13-day avg SO_2.

In children with asthma, associations with lung function were mixed for temporally resolved SO_2 metrics. However, the extent to which concentrations at monitors up to 4.8−10 km from homes represent children's 1- to 12-hour exposures is not known. Previous studies observed an association with 1-h max SO_2 (Delfino et al., 2003b) but not 8-h max or 3-h avg (8−11 a.m.) SO_2 (Delfino et al., 2003a; Mortimer et al., 2002). Recent results also are mixed. Morning and bedtime FEV_1 were not associated with 8-hour or 12-hour overnight (12 a.m. or 8 p.m.−8 a.m.) or 12-hour daytime (8 a.m.−8 p.m.) avg SO_2 concentrations, but the diurnal change in FEV_1 decreased with an increase in 12-hour daytime avg SO_2 (Dales et al., 2009) (Table 5-6). Previous studies associated lung function decrements with lag 0 day SO_2 concentrations (Delfino et al., 2003b; Peters et al., 1996a). Recent studies point to associations with 3- to 5-day avg concentrations (Greenwald et al., 2013; Liu et al., 2009b; O'Connor et al., 2008), and effect estimates are larger than those for lag 0 or 1 (Table 5-6). There is limited support from a controlled human exposure study for lung function decreasing after exposure on 2 days. Repeated SO_2 exposures enhance allergic inflammation in rodents, and allergic inflammation-mediated lung function decrements could explain associations with multiday SO_2 concentrations. Most studies did not report the prevalence of atopy, but a U.S. multicity study observed an association in a population with 100% atopy and asthma (O'Connor et al., 2008). The results agree with previous findings in children with asthma 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_2 Exposure Estimates (ppb)	SO_2 Averaging Time and Lag Day	Effect Estimate (95% CI) Single-Pollutant Model[a]	Copollutant Examination[a]
†Greenwald et al. (2013) 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.	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 FEV_1 A: 15 (−60, 210) B: −31 (−52, −2.0)	No copollutant model Association with BC, NO_2, BTEX, cleaning product VOCs (a-pinene, dichlorobenzene, d-limonene) at school B. No association with $PM_{2.5}$. SO_2 weakly correlated with BC, NO_2, BTEX, cleaning product VOCs. Pearson r = −0.14, −0.22, −0.07, 0.14
†Dales et al. (2009) 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_1. 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	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	Percent change in FEV_1 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)	Copollutant model results in figure. SO_2 association with diurnal change in FEV_1 persists with adjustment for $PM_{2.5}$, NO_2, or O_3. NO_2 and $PM_{2.5}$ associations persist with adjustment for SO_2. No association with O_3. SO_2 moderately correlated with $PM_{2.5}$, weakly correlated with NO_2. Pearson r = 0.43, 0.31.
†Liu et al. (2009b), Liu (2013) 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 Dales et al. (2009) above.	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 FEV_1: −0.46 (−2.0, 1.1) $FEF_{25-75\%}$: −1.5 (−4.7, 2.0) Change in percent predicted FEV_1: −2.0 (−4.6, 0.74) $FEF_{25-75\%}$: −5.7 (−11, −2.2)	Copollutant model, lag 0−2 avg, $FEF_{25-75\%}$ with $PM_{2.5}$: 7.2 (−2.8, 18) with NO_2: −2.4 (−8.7, 4.3) with O_3: −5.4 (−11, −0.19) NO_2 and $PM_{2.5}$ associations persist with adjustment for SO_2. No association with O_3. SO_2 moderately correlated with $PM_{2.5}$, weakly correlated with NO_2 and O_3. Spearman r = 0.56, 0.18, −0.02.

Table 5-6 (Continued): Recent epidemiologic studies of lung function in children with asthma.

Study Population and Methodological Details	SO_2 Exposure Estimates (ppb)	SO_2 Averaging Time and Lag Day	Effect Estimate (95% CI) Single-Pollutant Model[a]	Copollutant Examination[a]
†O'Connor et al. (2008) 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_1/PEF. Recruited from intervention study.	Monitors averaged close to home and not near industry. Median 2.3 km to site. Quantitative SO_2 data NR.	24-h avg 1−5 avg	Change in percent predicted FEV_1: −1.29 (−2.04, −0.54) PEF: −1.73 (−2.49, −0.96) No association for lag 1.	No copollutant model Associations observed with $PM_{2.5}$, NO_2. Associations with CO and O_3 imprecise with wide 95% CIs. SO_2 weakly correlated with $PM_{2.5}$, moderately correlated with NO_2. r = 0.37, 0.59.
†Amadeo et al. (2015) Pointe-à-Pitre, Guadeloupe, 2008−2009 N = 71, ages 8−13 yr. Cross-sectional. Supervised spirometry. Recruited from schools.	Monitors in city Number and distance NR Mean (SD): 1.8 (1.4) Max: 4.9	24-h avg 0−13 avg	Change in prerun PEF (L/min) 93 (−28, 214) Percent change post 6-min run −1.6 (−36, 33)	No copollutant model No association observed with PM_{10}, NO_2, or O_3. $PM_{2.5}$ not examined. Copollutant correlations NR.
†Ierodiakonou et al. (2015) 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.	Nearest monitor within 50 km of ZIP code centroid. Medians across cities: 2−6 90th percentiles across cities: 5−24	24-h avg 0	Change in percent predicted Prebronchodilator FEV_1 All subjects 0.25 (−0.13, 0.63) ICS: 0.38 (−0.30, 1.1) Post-bronchodilator FEV_1 ICS: 0 (−0.73, 0.75) Change in methacholine that induces a 20% drop in FEV_1 Mast cell inhibitor: −13% (−25, 1.3)	No copollutant model Association with CO, not O_3 or NO_2. $PM_{2.5}$ not examined. SO_2 weakly to moderately correlated with CO, O_3, and NO_2 across cities. Spearman r = 0.19−0.34, −0.41 to −0.05, 0.15−0.54.

Table 5-6 (Continued): Recent epidemiologic studies of lung function in children with asthma.

Study Population and Methodological Details	SO_2 Exposure Estimates (ppb)	SO_2 Averaging Time and Lag Day	Effect Estimate (95% CI) Single-Pollutant Model[a]	Copollutant Examination[a]
†Wiwatanadate and Trakultivakorn (2010) 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 Mean (SD): 1.7 (0.62) 90th percentile: 2.4 Max: 3.9 ppb	24-h avg 0 4 0 4	Change in PEF (L/min) Evening PEF −8.1 (−25, 9.2) −21 (−38, −4.1) Daily average PEF −0.3 (−15, 15) −18 (−32, −2.8)	Copollutant model, lag 4, daily average PEF. with O_3, lag 5: −16 (−31, −1.1) O_3 association persists with adjustment for SO_2. No association with $PM_{2.5}$, CO, NO_2. SO_2 weakly correlated with O_3, $PM_{2.5}$, CO, NO_2. r = −0.04, −0.07, 0.38, 0.23

BC = black carbon; BTEX = benzene, toluene, ethylbenzene, xylene; CI = confidence interval; CO = carbon monoxide; $FEF_{25-75\%}$ = forced expiratory flow at 25−75% of forced vital capacity; FEV_1 = forced expiratory volume in 1 sec; ICS = inhaled corticosteroid; L/min = liters per min; N = sample size; NO_2 = nitrogen dioxide; NR = not reported; O_3 = ozone; PEF = peak expiratory flow; $PM_{2.5}$ = particulate matter with a nominal aerodynamic diameter less than or equal to 2.5 µm; PM_{10} = particulate matter with a nominal aerodynamic diameter less than or equal to 10 µm; r = correlation coefficient; SD = standard deviation; SO_2 = sulfur dioxide; VOC = volatile organic compound.

[a]Effect estimates are standardized to a 10-ppb increase in 8-h to 24-h avg SO_2.

†Studies published since the 2008 Integrated Science Assessment for Sulfur Oxides.

Where SO_2 was associated with lung function decrements in children with asthma, associations also were observed with $PM_{2.5}$, PM_{10}, sulfate, BC, OC, TSP, NO_2, or various VOCs (Greenwald et al., 2013; Dales et al., 2009; Liu et al., 2009b; O'Connor et al., 2008; Delfino et al., 2003b; Peters et al., 1996a). These copollutants were often moderately to highly correlated with SO_2 (r = 0.56−0.9), particularly in previous studies. SO_2 averaging times varied across studies, making it difficult to assess whether higher correlations are due to higher air pollution levels in the past. Copollutant confounding and interactions are poorly studied, and unstudied for children living near a coal-fired power plant (Peters et al., 1996a). O_3 may not influence the associations observed with SO_2. SO_2 and O_3 measurements at central site monitors were not correlated (r = −0.02), and SO_2 associations persisted with adjustment for O_3 (Dales et al., 2009; Liu et al., 2009b). A recent study adds information on SO_2 results adjusted for correlated copollutants. Among children with asthma in Windsor, ON, the SO_2 association persisted with adjustment for $PM_{2.5}$ or NO_2 for 12-h avg SO_2 (Dales et al., 2009) but not 24-h avg SO_2 (Liu, 2013; Liu et al., 2009b) (Table 5-6). Associations for $PM_{2.5}$ were robust to SO_2 adjustment, but inference about confounding is weak due to the moderate SO_2-$PM_{2.5}$ correlation (r = 0.56) and the potential differential exposure error for SO_2 and $PM_{2.5}$ measurements, which were made up to 10 km from subjects' homes. Weak inference also applies to results in a Los Angeles, CA cohort showing an imprecise association for SO_2 after adjustment for benzene [−34 L/minute change in PEF (95% CI: −120, 52) per 40-ppb increase in 1-h max SO_2] (Delfino et al., 2003b). SO_2 was highly correlated with 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

Controlled human exposure studies provide strong evidence for SO_2-induced lung function decrements in adults with asthma under increased ventilation conditions. Short-term exposures for 5−10 minutes to 0.2−0.3 ppm SO_2 resulted in 5−30% of exercising individuals with asthma experiencing moderate or greater decrements (defined in terms of a ≥15% decrease in FEV_1 or ≥100% increase in sRaw; Table 5-2). Exposures for 5−10-minutes to SO_2 at concentrations ≥0.4 ppm results in moderate or greater decrements in lung function in 20−60% of exercising individuals with asthma. A group of responders (defined as having ≥15% decrease in FEV_1 after exposure to 0.6 or 1.0 ppm SO_2) showed statistically significant decrements in FEV_1 following exposure for 5−10 minutes to 0.3 ppm SO_2 (Table 5-3). Less evidence is available from controlled human exposure studies to assess SO_2-induced lung function decrements in children with asthma. However, school-aged children, particularly boys and perhaps obese children, should be expected to experience greater responsiveness (i.e., larger decrements in lung function) following exposure to SO_2 than normal-weight adolescents and adults.

For both adults and children with asthma, epidemiologic evidence is inconsistent for lung function decrements associated with ambient SO_2 concentrations (Table 5-5 and Table 5-6), but most results indicate associations in populations with asthma plus atopy. In the few controlled human exposure and epidemiologic studies, findings of increased airway responsiveness could not be attributed to exposure to SO_2 alone versus a copollutant or mixture. A limitation across epidemiologic studies is the uncertainty in the SO_2 exposure estimates. A recent study observed an association with SO_2 measured at children's schools, but others used monitors located 2.3−50 km from subjects' homes or schools. It is unclear whether the SO_2 concentrations at central site monitors adequately represent the variation in personal exposure, especially if peak exposures are important as indicated by controlled human exposure studies. The influence of copollutants on epidemiologic results remains largely uncharacterized, including associations in populations with asthma plus atopy and populations living near SO_2 sources. SO_2-related lung function decrements in adults and children with asthma are inconsistently observed after adjustment for $PM_{2.5}$, PM_{10}, or NO_2, but the implications of these results are unclear because of uncertainty in the exposure estimates and potential differential exposure error.

Respiratory Symptoms in Populations with Asthma

The 2008 SO_X ISA (U.S. EPA, 2008d) reported strong evidence for the effects of SO_2 exposure on respiratory symptoms in controlled human exposure studies in individuals with asthma under increased ventilation conditions. No new controlled human exposure studies have been reported since the previous ISA. In contrast, previous and recent epidemiologic evidence for SO_2-associated increases in respiratory symptoms is weak in adults with asthma. However, epidemiologic evidence supports associations in children with asthma, and recent studies add evidence for estimates of SO_2 exposure at school and/or home. Overall, the influence of copollutants remains largely unexamined.

Controlled Human Exposure Studies

As reviewed in the 2008 ISA for Sulfur Oxides and the 1986 Supplement to the Second Addendum (U.S. EPA, 2008d, 1994), controlled human exposure studies demonstrate increases in incidence or severity of respiratory symptoms (i.e., cough, chest tightness, throat irritation) in individuals with asthma exposed to SO_2 concentrations between 0.2 and 0.6 ppm for 5−10 minutes during exercise (Table 5-2 and Table 5-7). Statistically significant increases are observed at SO_2 concentrations ≥0.4 ppm.

Table 5-7 Study-specific details from controlled human exposure studies of respiratory symptoms.

Study	Disease Status; n; Sex; (Age[a])	Exposure Details (Concentration; Duration)	Time of Symptom Assessment
Gong et al. (1995)	Asthma; n = 14; 12 M, 2 F; (27 ± 11 yr)	0, 0.5, or 1.0 ppm SO_2 with light, medium, and heavy exercise (average ventilation 30, 36, and 43 L/min) for 10 min	Before, during, and immediately after exposure
Gong et al. (1996)	Asthma; n = 10; 2 M, 8 F; (30.3 ± 9.2 yr)	0 or 0.75 ppm SO_2 with exercise (29 L/min) for up to 24 h with or w/o pretreatment with salmeterol (long-acting B_2-agonist)	Before and immediately after exposure
Gong et al. (2001)	Asthma; n = 11; 2 M, 9 F; (30.8 ± 11.3 yr)	0 or 0.75 ppm SO_2 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
Horstman et al. (1988)	Asthma; n = 12 M; (28.6 ± 5.5 yr)	0 or 1.0 ppm SO_2 for 0, 0.5, 1.0, 2.0, and 5.0 min with exercise (treadmill, 40 L/min)	Before and immediately after exposure
Magnussen et al. (1990)	Asthma; n = 46; 21 M, 25 F; (28 ± 14 yr)	0 or 0.5 ppm SO_2 for 20 min. 10 min rest followed by 10 min isocapnic hyperventilation (30 L/min)	Before exposure and immediately after hyperventilation
Kehrl et al. (1987)	Asthma; n = 10 M; (26.8 ± 4.4 yr)	0 or 1 ppm SO_2 for 1 h with exercise (3 × 10 min, 41 L/min, treadmill)	Before and during exposure/exercise
Koenig et al. (1980)	Asthma; n = 9; 7 M, 2 F; (15.7 ± 1.1 yr)	0 or 1 ppm SO_2 with 1 mg/m^3 of NaCl droplet aerosol, 1 mg/m^3 NaCl droplet aerosol for 60 min exposure with mouthpiece at rest	Before, during, and immediately after exposure
Koenig et al. (1981)	Asthma; n = 8; 6 M, 2 F; (14−18 yr)	0 or 1 ppm SO_2 with 1 mg/m^3 of NaCl droplet aerosol, 1 mg/m^3 NaCl droplet aerosol for 30 min exposure via mouthpiece at rest followed by 10 min exercise on a treadmill (sixfold increase in V_E)	Before, during, and immediately after exposure
Koenig et al. (1983)	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^3 of NaCl droplet aerosol, 1 ppm SO_2, 1 mg/m^3 NaCl, 0.5 ppm SO_2 + 1 mg/m^3 NaCl for 30 min exposure via mouthpiece at rest followed by 10 min exercise on treadmill (five- to sixfold increase in V_E) Phase 2: 0.5 ppm SO_2 + 1 mg/m^3 NaCl via a face mask with no nose clip with exercise conditions the same as Koenig et al. (1981)	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[a])	Exposure Details (Concentration; Duration)	Time of Symptom Assessment
Koenig et al. (1987)	Allergy with EIB; n = 10; 3 M, 7 F; (13−17 yr)	0 or 0.75 ppm SO_2 (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
Koenig et al. (1990)	Asthma with EIB; n = 13; 8 M, 5 F (14.3 ± 1.8 yr)	0.1 ppm SO_2 for 15 min preceded by air or 0.12 ppm O_3 for 45 min during intermittent exercise (2 × 15 min, 30 L/min, treadmill), no control, air exposure	Before and immediately after exposure
Koenig et al. (1992)	Asthma; n = 8; 2 M, 6 F; (27.5 ± 9.6 yr)	1 ppm SO_2 for 10 min with exercise ($\dot{V}_E$ = 13.4−31.3 L/min) with or w/o pretreatment to theophylline	Before and immediately after exposure
Linn et al. (1983b)	Asthma; n = 23; 13 M, 10 F; (23.3 ± 4.4 yr)	0, 0.2, 0.4, or 0.6 ppm SO_2 with low humidity or high humidity for 10 min with exercise (bicycle, 5 min 50 L/min) 0 or 0.6 ppm SO_2 with warm air or cold air with exercise (bicycle, 50 L/min, ~5 min)	Before and immediately after exposure
Linn et al. (1983a)	Asthma; n = 23; 15 M, 8 F (23 ± 4 yr)	0 or 0.75 ppm SO_2 with unencumbered breathing and mouth only breathing with exercise (40 L/m, 10 min, bicycle)	Before and immediately after exposure
Linn et al. (1984a)	Asthma; n = 14; 12 M, 2 F (24.1 ± 4.7 yr)	0, 0.3, or 0.6 ppm SO_2 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
Linn et al. (1984c)	Asthma; n = 24; 13 M, 11 F; (24.0 ± 4.3 yr)	0, 0.3, or 0.6 ppm SO_2 at 21°, 7 and −6°C and 80% rH with exercise (5 min, 50 L/min)	Before, immediately after, and 24 h after exposure

Linn et al. (1984b)	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_2 at 5°C, 50, and 85% rH with exercise (5 min, 50 L/min)
		Phase 2:
		0 and 0.6 ppm SO_2 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

Linn et al. (1985b)	Asthma; n = 22; 13 M, 9 F; (23.5 ± 4.0 yr)	0 or 0.6 ppm SO_2 at 21 and 38°C, 20 and 80% rH with exercise (~5 min, 50 L/min)	Before, immediately after, and 24 h after exposure
Linn et al. (1985a)	Asthma with COPD; n = 24; 15 M, 9 F; (60 yr; Range: 49−68 yr)	0, 0.4, or 0.8 ppm SO_2 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[a])	Exposure Details (Concentration; Duration)	Time of Symptom Assessment
Linn et al. (1987)	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_2 for 1 h with exercise (3 × 10-min, bicycle, ~40 L/min)	Before and during exposure (after first exercise and after last exercise)
Linn et al. (1988)	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_2 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
Linn et al. (1990)	Asthma; n = 21; 6 M, 15 F; (34.8 ± 8.9 yr)	0, 0.3, or 0.6 ppm SO_2 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
Myers et al. (1986a)	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_2 during sequential 3 min exposures, from 0.25 to 8 ppm	Before and after each 3-min exposure to an increasing SO_2 concentration
Sheppard et al. (1983)	Asthma; n = 8; 4 M, 4 F; (26.6 ± 4.3 yr)	0.5 ppm SO_2 for 3 min eucapnic hyperpnea	Before and immediately after exposure
Trenga et al. (1999)	Asthma; n = 47; 14 M, 33 F; (21.1 yr; Range: 18−39 yr)	0.5 ppm SO_2 for 10 min with moderate exercise	Before and immediately after exposure
Trenga et al. (2001)	Asthma; n = 17; 5 M, 12 F; (27.4 ± 6.3 yr)	0.5 ppm SO_2 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_3 = ozone; ppm = parts per million; rH = relative humidity; SD = standard deviation; SO_2 = sulfur dioxide; V_E = minute volume.

[a]Range or Mean ± SD.

Linn et al. (1983b) reported the severity of respiratory symptoms following 5-minute exposures to 0, 0.2, 0.4, and 0.6 ppm SO_2 in heavily exercising individuals with mild to moderate asthma. Total symptom score changes were significant ($0.01 < p < 0.05$) after 0.2 ppm SO_2 exposure, but when scores were separated by categories, significance was not reached until concentrations were ≥0.4 ppm SO_2. Subsequently, a similar study with a slightly lower level of exercise demonstrated that 43% of subjects with asthma experienced increases in respiratory symptoms after a 15-minute exposure to 0.6 ppm SO_2 (Linn et al., 1987). Smith (1993) provided additional support for increasing respiratory symptoms at concentrations as low as 0.4 ppm SO_2.

Additional studies examining concentrations of ≥0.5 ppm SO_2 demonstrated SO_2-induced increases in respiratory symptoms. Total and lower respiratory symptom scores were significantly increased with increasing SO_2 concentrations (0, 0.5, and 1.0 ppm SO_2) following 10-minute exposures with varying levels of exercise (Gong et al., 1995). Trenga et al. (1999) confirmed these results, observing a significant correlation between FEV_1 decrements and increases in respiratory symptoms following 10-minute exposures to 0.5 ppm SO_2 via mouthpiece. Respiratory symptoms have also been observed following exposure durations as low as 3 minutes to 0.5 ppm SO_2 via mouthpiece during eucapnic hyperpnea (V_E = 0 L/minute), in which seven out of eight individuals with asthma developed respiratory symptoms (Balmes et al., 1987).

As with lung function, increased respiratory symptoms in response to short-term exposure to SO_2 in individuals with asthma is dependent on exercise. Linn et al. (1983b) reported significant changes in total symptom scores after 0.2 ppm SO_2 exposure in heavily exercising individuals with asthma. In contrast, Tunnicliffe et al. (2003) found no association between respiratory symptoms (i.e., throat irritation, cough, wheeze) and 1-hour exposures to 0.2 ppm SO_2 in adults with asthma at rest.

Epidemiologic Studies

Compared with controlled human exposure studies, epidemiologic evidence for SO_2-associated increases in symptoms is variable, being supportive in children with asthma but weak in adults with asthma. A recent study not restricted to a certain lifestage does not support an association with asthma medication use but is limited by analysis of beta-agonist levels in wastewater rather than use ascertained for individual subjects and only reporting the lack of statistically significant associations (Fattore et al., 2016) (Table 5-8). The evidence base specifically in children with asthma is larger and more informative, providing results for home and/or school SO_2 exposure estimates and temporally resolved SO_2 metrics. Also, while they do not settle questions, studies in children with asthma aim to assess copollutant confounding and interactions. Although

the evidence overall is less consistent in recent than previous studies, the aforementioned strengths are features of many recent studies of children with asthma.

Adults. SO_2 concentrations were lower in recent than previous studies (0.87−2.7 ppb vs. 1.6−90 ppb for means), but this does not appear to explain the weak evidence because previous results also are inconsistent [Supplemental Figure 5S-1 (U.S. EPA, 2016g)]. All studies have uncertainty in the SO_2 exposure estimates assigned from a single central site monitor or averaged across multiple monitors. No study indicated whether measurements at the monitors adequately represented the spatiotemporal variability in ambient SO_2 concentrations in the study area or the temporal variation in people's exposures.

All epidemiologic studies of adults examined 24-h avg SO_2 concentrations, longer than the 5−10-minute exposures implicated in controlled human exposure studies (Table 5-2). Similar to previous studies, recent epidemiologic evidence does not indicate associations for respiratory symptoms with same-day (lag 0) SO_2 concentrations (Anyenda et al., 2016; Maestrelli et al., 2011). Atopy was prevalent in Maestrelli et al. (2011) (90%); previous findings supported an association in adults with atopy plus asthma (Boezen et al., 2005). A recent study linked an increase in SO_2 concentration to an increase in nighttime asthma symptoms with a 5-day lag (Wiwatanadate and Liwsrisakun, 2011), but inference is weak because results were inconsistent among the many lags, pollutants, and health effects examined. Also, SO_2 exposures were assessed from a monitor up to 10 km from subjects' homes. There is some consistency for SO_2 concentrations lagged 2 or 5 days or averaged over 3 or 5 days, including recent results (Anyenda et al., 2016) [Supplemental Figure 5S-1 (U.S. EPA, 2016g)]. In these studies, symptoms were also associated with moderately to highly correlated PM metrics (r = 0.60−0.9). Whether the magnitude of copollutant correlations influences the consistency of association for SO_2 with respiratory symptoms in adults with asthma cannot be determined in this small evidence base. As examined only in a recent study, SO_2 associations persisted with adjustment for PAH or NO_2 (Anyenda et al., 2016). However, uncertainty in the exposures estimated from a single central site monitor and a different site for PAH limits inferences that can be drawn about an independent association for SO_2. Controlled human exposure studies show symptoms to resolve once exposure ends, but SO_2-induced allergic inflammation could be a pathway by which SO_2 exposure induces symptoms after several days or over multiple days.

Table 5-8 Recent epidemiologic studies of respiratory symptoms in populations with asthma.

Study Population and Methodological Details	SO_2 Exposure Estimates (ppb)	SO_2 Averaging Time and Lag Day	Effect Estimate (95% CI) Single-Pollutant Model[a]	Copollutant Examination[a]
Adults With Asthma				
†Maestrelli et al. (2011) 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 (>6 times per yr for 3 yr).	Two monitors in city Medians across seasons: 0.87−2.7 75th percentiles across seasons: 1.3−4.1	24-h avg 0	Asthma control score Increase = better control All subjects: 0.77 (−1.1, 2.6) Nonsmokers: 0.10 (−2.2, 2.4) n = 22	No copollutant model Association observed with CO and personal PM_{10}. No association with personal or central site $PM_{2.5}$. No association with central site NO_2, O_3. Copollutant correlations NR.
†Wiwatanadate and Liwsrisakun (2011) 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.	Monitor within 10 km of home Mean (SD): 1.7 (0.62) 90th percentile: 2.4 Max: 3.9	24-h avg 2 5	SO_2 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)	Copollutant model with NO_2 SO_2 and NO_2 association reported not statistically significant. Quantitative results NR. Association observed with PM_{10} but no copollutant model. $PM_{2.5}$ not examined. SO_2 weakly correlated with NO_2, PM_{10}. r = 0.23 for both.
†Anyenda et al. (2016) Kanazawa, Japan, Jan−June 2011 N = 83, ages 23−84 yr. 54% atopy. Daily diary for mean 153 d. Recruited from hospital outpatients.	One monitor in city Mean (SD): 1.6 (1.3) Max: 7.3	24-h avg 0 2 0-2 avg	Cough 0.67 (0.34, 1.31) 2.19 (1.34, 3.54) 2.53 (1.05, 6.08)	Copollutant model, lag 2 with PAH: 1.98 (1.31, 3.05) with NO_2: 1.94 (1.16, 3.58) Adjustment for SO_2 does not alter PAH association but attenuates NO_2 association. SO_2 moderately correlated with PAH, NO_2. Spearman r = 0.60, 0.56.

Table 5-8 (Continued): Recent epidemiologic studies of respiratory symptoms in populations with asthma.

Study Population and Methodological Details	SO_2 Exposure Estimates (ppb)	SO_2 Averaging Time and Lag Day	Effect Estimate (95% CI) Single-Pollutant Model[a]	Copollutant Examination[a]
Children With Asthma				
†Spira-Cohen et al. (2011), Spira-Cohen (2013) 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.	Monitor at school Concentrations NR Most children walk to school	1-h max (a.m.) 0	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)	Copollutant model for cough with school EC: 1.32 (0.93, 1.87) No association with $PM_{2.5}$. EC association robust to SO_2 adjustment. School SO_2 moderately correlated with EC. r = 0.45.
†Velická et al. (2015) 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.	Five monitors and dispersion model 0.5 × 0.5 km resolution Weighted avg by time at home and school Median: 4.0 75th percentile: 12	24-h avg 0	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)	No copollutant model Associations observed with PM_{10} and NO_2. $PM_{2.5}$ not examined. Copollutant correlations NR.
†Dales et al. (2009) 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.	Two monitors averaged 99% homes within 10 km of sites Median: 4.5 95th percentile: 16	24-h avg	OR for SO_2 ≥8.8 vs. <2.3 ppb Chest tightness 1.30 (1.06, 1.58) ORs for difficulty breathing, cough, and wheeze reported not statistically significant.	No copollutant model Associations with $PM_{2.5}$, NO_2, O_3 reported not statistically significant. Quantitative results NR.
†O'Connor et al. (2008) 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.	Monitors averaged close to home and not near industry Median 2.3 km to site Quantitative SO_2 data NR.	24-h avg 1−19 avg	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)	No copollutant model Associations observed with NO_2 and CO. $PM_{2.5}$ associated with missed school. SO_2 moderately correlated with NO_2, weakly with CO and $PM_{2.5}$. r = 0.59, 0.32, 0.37.

Table 5-8 (Continued): Recent epidemiologic studies of respiratory symptoms in populations with asthma.

Study Population and Methodological Details	SO_2 Exposure Estimates (ppb)	SO_2 Averaging Time and Lag Day	Effect Estimate (95% CI) Single-Pollutant Model[a]	Copollutant Examination[a]
†Gent et al. (2009) 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.	Monitor 0.9−30 km of home Mean 10 km to site Concentrations NR	24-h avg 0	NR	Only multipollutant model analyzed with six $PM_{2.5}$ component factors Wheeze: 1.04 (0.92, 1.19) SO_2 moderately correlated with motor vehicle factor. r = 0.45.
Children and Adults with Asthma				
†Fattore et al. (2016) Milan, Italy, Sep−Dec 2013 N = 84 days Daily wastewater samples for 84 days analyzed for levels of the beta-agonist salbutamol.	3 monitors averaged Mean (SD): 2.2 (1.3) Max: 5.9	24-h avg 0 to 10 (single-day)	Beta-agonist levels in wastewater No quantitative results. RRs reported not statistically significant.	No copollutant model Associations observed with $PM_{2.5}$ and PM_{10}. SO_2 moderately correlated with $PM_{2.5}$ and PM_{10}. Pearson r = 0.66, 0.65.

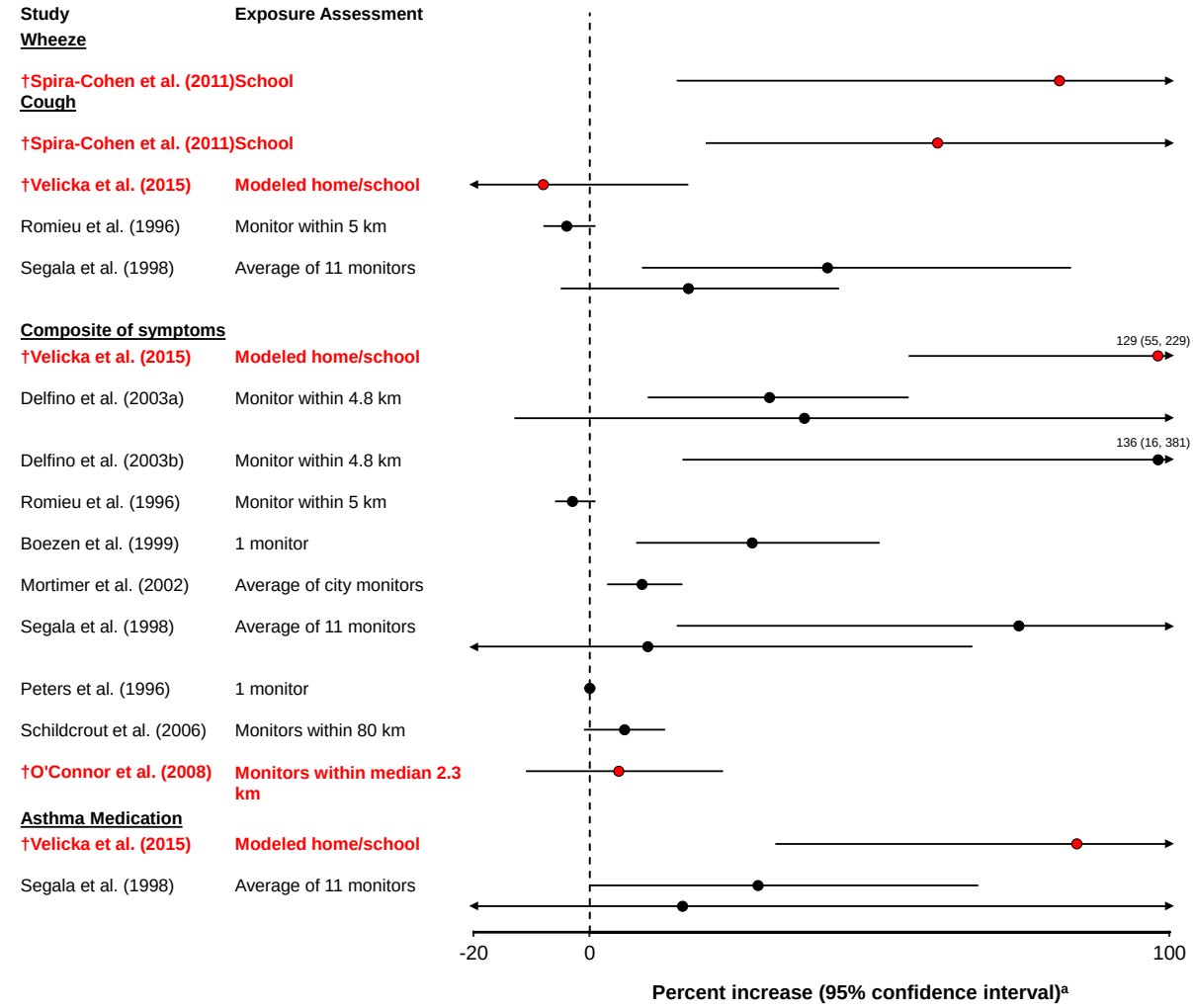
CI = confidence interval; CO = carbon monoxide; EC = elemental carbon; ED = emergency department; ICS = inhaled corticosteroids; N = sample size; NO_2 = nitrogen dioxide; NR = not reported; O_3 = ozone; OR = odds ratio; PAH = polycyclic aromatic hydrocarbon; $PM_{2.5}$ = particulate matter with a nominal aerodynamic diameter less than or equal to 2.5 µm; PM_{10} = particulate matter with a nominal aerodynamic diameter less than or equal to 10 µm; RR = relative risk; SD = standard deviation; SO_2 = sulfur dioxide.

[a]Effect estimates are standardized to a 10-ppb increase in 24-h avg SO_2 and 40-ppb increase in 1-h max SO_2.

†Studies published since the 2008 Integrated Science Assessment for Sulfur Oxides.

Children. As a whole, epidemiologic evidence indicates associations between higher SO_2 concentrations and increased respiratory symptoms in children with asthma, particularly when examined as a composite index of multiple symptoms (Figure 5-2). Associations also are observed for asthma medication use or activity restriction but not consistently for wheeze or cough. Results vary in magnitude and precision (Figure 5-2). In some study areas, the SO_2 concentrations were much lower (Spira-Cohen et al., 2011; Delfino et al., 2003a; Delfino et al., 2003b) or higher (Mortimer et al., 2002) than the 10-ppb increment used to standardize effect estimates. Although recent studies give inconsistent results (Table 5-8), associations are observed with SO_2 measured or modeled for school or home, which may represent exposure better than measurements at central site monitors. Recent studies reported lower SO_2 concentrations than many previous studies (for 24-h avg, median ~ 4 ppb vs. means 8.3 and 90 ppb). It is unclear whether the inconsistency is due to lower concentrations; previous studies observed associations in locations with similar SO_2 concentrations [median 24-h avg 2.2−7.4 ppb in Schildcrout et al. (2006), mean 8-h max 4.6 ppb in Delfino et al. (2003a), Delfino et al. (2003b)].

Spira-Cohen et al. (2011) is notable not only for monitoring SO_2 at schools but also for examining 1-h max concentrations. In the population of children in Bronx, NY, increases in SO_2 were linked to increased odds of cough and wheeze but not shortness of breath (Table 5-8). Previous U.S. studies also associated symptoms with temporally resolved SO_2 metrics [i.e., 1-h max, 8-h max, 3-h avg (8−11 a.m.)] but had more uncertainty in exposures estimated from monitors up to 4.8 km from children's homes/schools (Delfino et al., 2003a; Delfino et al., 2003b) or monitors averaged across the city (Mortimer et al., 2002). Spira-Cohen et al. (2011) did not report SO_2 concentrations to compare to previous studies but reported that most children walked to school, improving the relevance of 1-h max SO_2 concentrations at school to children's peak exposures. Velická et al. (2015) also aimed to improve exposure assessment for children in Ostrava, Czech Republic. A dispersion model and five monitors were used to estimate SO_2 concentrations at 0.5 km resolution and calculate a time-weighted 24-h avg for each child based on the school and home location. SO_2 was associated with breathing difficulty-wheeze, reliever inhaler use, and restricted activities, but not cough (Table 5-8). The study population had a high prevalence of atopy (79%); thus, results agree with Boezen et al. (1999) and Segala et al. (1998) but may have less uncertainty in exposure 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.
[a]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.

Other recent studies largely do not provide evidence for SO_2-associated increases in respiratory symptoms in children with asthma (Dales et al., 2009; Gent et al., 2009; O'Connor et al., 2008). But, they have more questionable implications due to (1) the large distance between the SO_2 monitor and children's homes (e.g., up to 10 km, median 2.3 km, mean 10 km); (2) a lack of quantitative results (Dales et al., 2009); (3) analysis of 19-day avg SO_2 concentrations, which are more subject to residual temporal confounding

(O'Connor et al., 2008); or (4) analysis of SO_2 only as part of a multipollutant model with six $PM_{2.5}$ component source factors (Gent et al., 2009).

For the associations observed between SO_2 and respiratory symptoms in children with asthma, including those with atopy, the influence of copollutants is poorly addressed. Symptoms were not associated with personal or school $PM_{2.5}$ but with other PM metrics: PM_{10}, EC, OC, BS, and TSP. Associations also were observed with NO_2, VOCs such as benzene and xylene, and O_3 (Table 5-8). Except for O_3, these copollutants were moderately to highly correlated with SO_2 (r = 0.45−0.9). Correlations were highest in previous studies, but recent studies did not report SO_2 concentrations (Spira-Cohen et al., 2011) or copollutant correlations (Velická et al., 2015) to assess whether the magnitude of correlation varied by SO_2 levels. Copollutant models were analyzed in few studies and for few copollutants. For a Los Angeles, CA cohort, no SO_2-VOC interaction was indicated, and SO_2 associations persisted with adjustment for benzene, xylene, or toluene for some but not all symptoms (Delfino et al., 2003a; Delfino et al., 2003b). Associations for VOCs were attenuated as well, and copollutant model results are uncertain because of the moderate to high correlations with SO_2 (r = 0.58−0.78) and because exposures were assessed from monitors 4.8 km from children's homes or schools. Potential exposure error also limits inference from results showing associations for joint increases in SO_2 with PM_{10}, NO_2, or CO that were similar to each single-pollutant association (Schildcrout et al., 2006). The recent Bronx, NY study analyzed copollutant models for school SO_2 and EC, which may have more comparable exposure error. SO_2 and EC were moderately correlated (r = 0.45), consistent with the location in a high diesel truck traffic area (Spira-Cohen et al., 2011). In the copollutant model, the odds ratio for cough was robust for EC but decreased in magnitude and precision for SO_2 from 1.60 (95% CI: 1.20, 2.12) to 1.32 (95% CI: 0.93, 1.87) per 40-ppb increase in 1-h max SO_2.

Summary of Respiratory Symptoms in Populations with Asthma

Controlled human exposure studies provide strong evidence for the effects of SO_2 exposure on respiratory symptoms in adults with asthma under increased ventilation conditions. Exposures for 5−10 minutes to 0.2−0.6 ppm SO_2 induced respiratory symptoms in exercising individuals with asthma, with the most consistent evidence from exposures to 0.4−0.6 ppm SO_2 (Table 5-2). Epidemiologic evidence in adults with asthma is weak, but increases in ambient SO_2 concentration are generally associated with increased risk of asthma symptoms in children (Figure 5-2; Table 5-8). Assessing coherence specifically with controlled human exposure studies of adolescents with asthma is difficult because those studies lacked an appropriate control exposure. Limited findings support associations in children and adults with asthma plus atopy.

Epidemiologic results in children are less consistent in recent than previous studies but support associations for 1-h max SO_2 measured at schools or 24-h avg SO_2 modeled for school and home. School or home SO_2 measures may better represent exposures than the concentrations at central site monitors examined in most studies, particularly for 1-h max. These SO_2 metrics are longer than the 5−10 minutes SO_2 exposures in controlled human exposure studies, which show transient responses. And, the role of confounding or an interaction with copollutants such as $PM_{2.5}$, EC, NO_2, and VOCs remains uncertain for epidemiologic associations, including those for populations with asthma plus atopy and for residents near a coal-fired power plant. However, evidence for allergic inflammation enhanced by repeated 1-hour exposures, albeit 2 ppm SO_2, to some extent supports the biological plausibility of SO_2-associated increases in respiratory symptoms, especially in populations with asthma plus atopy.

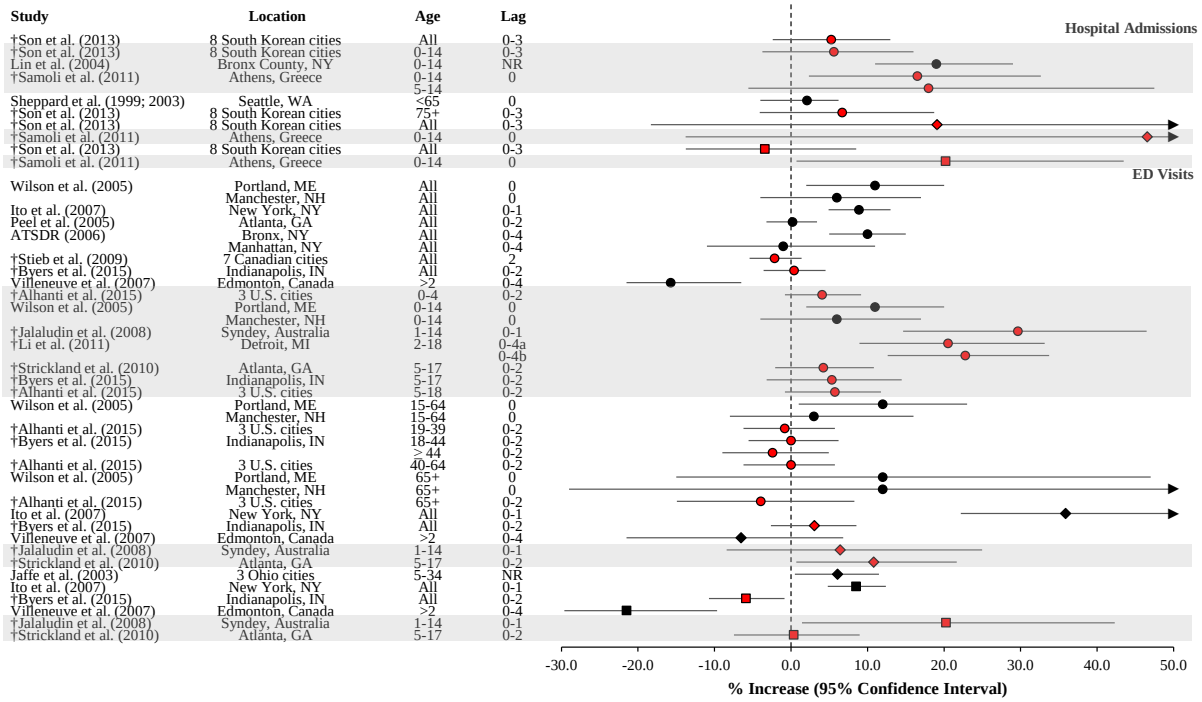
Hospital Admission and Emergency Department Visits for Asthma

Since the completion of the 2008 SO_X ISA, epidemiologic studies have continued to examine the association between short-term exposure to ambient SO_2 concentrations and respiratory-related hospital admissions and ED visits, but are primarily limited to single-city studies. The sections within this chapter detailing the respiratory-related hospital admissions and ED visits studies characterize recent studies in the context of the collective body of evidence evaluated in the 2008 SO_X ISA. The 2008 SO_X ISA (U.S. EPA, 2008d) included the first thorough evaluation of respiratory morbidity in the form of respiratory-related hospital admissions and ED visits, including asthma. These studies reported generally positive associations with short-term SO_2 exposures, with associations that are often larger in magnitude for children (Figure 5-3). Additionally, SO_2 associations with asthma hospital admissions and ED visits were often attenuated, but remained positive in copollutant models with PM, NO_2, or O_3.

Within this section focusing on asthma, as well as the rest of the chapter, respiratory-related hospital admissions and ED visit studies are evaluated separately because only a small percentage of respiratory-related ED visits result in hospital admission. Additionally, when evaluating asthma ED visit and hospital admission studies that focus on children (i.e., defined age ranges <18 years of age), it is important to note that it is often difficult to reliably diagnose asthma in children <5 years of age, which may add some uncertainty to the results including this age range (NAEPP, 2007).

For each of the studies evaluated in this section, Table 5-9 presents the air quality characteristics of each city, or across all cities, the exposure assignment approach used, and information on copollutants examined in each asthma hospital admission and ED visit study. Other recent studies of asthma hospital admissions and ED visits are not the

focus of this evaluation because they were conducted in small single-cities, encompassed a short study duration, had insufficient sample size, or did not examine potential copollutant confounding. The full list of these studies, as well as study specific details, 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_X 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_X ISA and studies published since the 2008 SO_X ISA.

Study	Location Years	Exposure Assignment	Metric	Mean Concentration ppb	Upper Percentile Concentrations ppb	Copollutants Examination
Hospital admissions						
Lin et al. (2004)	Bronx County, NY (1991−1993)	Avg of SO_2 concentrations from two monitoring sites	24-h avg	Cases: 16.8 Controls: 15.6	NR	NR
(Sheppard (2003); Sheppard et al. (1999))	Seattle, WA (1987−1994)	Avg of SO_2 concentrations from multiple monitors	24-h avg	8.0	75th: 10.0 90th: 13.0	Correlation (*r*): PM_{10}: 0.31 $PM_{2.5}$: 0.22 $PM_{10-2.5}$: 0.34 O_3: 0.07 CO: 0.24 Copollutant models: none
†Son et al. (2013)	Eight South Korean cities (2003−2008)	Avg of hourly ambient SO_2 concentrations from monitors in each city	24-h avg	3.2−7.3	NR	Correlation (*r*): PM_{10}: 0.5 O_3: −0.1 NO_2: 0.6 CO: 0.6 Copollutant models: none
†Zheng et al. (2015)	Meta-analysis (1988−2014)	NR	24-h avg	3.1−45.5[a]	NR	Correlations (*r*): NR Copollutant models: none
†Samoli et al. (2011)	Athens, Greece (2001−2004)	Avg of SO_2 concentrations across multiple monitors	24-h avg	6.4	75th: 8.4	Correlation (*r*): O_3: −0.19 NO_2: 0.55 Copollutant models: PM_{10}, SO_2, NO_2, O_3

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_X ISA and studies published since the 2008 SO_X ISA.

Study	Location Years	Exposure Assignment	Metric	Mean Concentration ppb	Upper Percentile Concentrations ppb	Copollutants Examination
ED visits						
Jaffe et al. (2003)	Cincinnati, Cleveland, and Columbus, OH (1991−1996)	When more than one monitoring station operating in a day, monitor reporting highest 24-h avg SO_2 concentration used	24-h avg	Cincinnati: 13.7 Cleveland: 15.0 Columbus: 4.2	Max: Cincinnati: 50 Cleveland: 64 Columbus: 22	Correlations (*r*) (range across cities) NO_2: 0.07−0.28 O_3: 0.14−0.26 PM_{10}: 0.29−0.42 Copollutant models: none
Ito et al. (2007)	New York, NY (1999−2002)	Average SO_2 concentrations across 19 monitors	24-h avg	7.8	75th: 10 95th: 17	Correlations (*r*): NR Copollutant models: $PM_{2.5}$, NO_2, O_3, CO
ATSDR (2006)	Bronx and Manhattan, NY (1999−2000)	SO_2 concentrations from one monitor in Bronx and one in Manhattan	24-h avg	Manhattan: 12 Bronx: 11	NR	Correlations (*r*): Bronx: O_3: −0.49 NO_2: 0.50 $PM_{2.5}$: 0.39 Max PM_{10}: 0.0.34 Manhattan: O_3: −0.40 NO_2: 0.47 $PM_{2.5}$: 0.26 PM_{10}: 0.24 Copollutant models: O_3, FRM and Max $PM_{2.5}$, NO_2

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_X ISA and studies published since the 2008 SO_X ISA.

Study	Location Years	Exposure Assignment	Metric	Mean Concentration ppb	Upper Percentile Concentrations ppb	Copollutants Examination
Peel et al. (2005)	Atlanta, GA (1993−2000)	Average of SO_2 concentrations from monitors for several monitoring networks	1-h max	16.5	90th: 39.0	Correlations (*r*): $PM_{2.5}$: 0.17 PM_{10}: 0.20 $PM_{10-2.5}$: 0.21 UFP: 0.24 $PM_{2.5}$ water soluble metals: 0.00 $PM_{2.5}$ sulfate: 0.08 $PM_{2.5}$ acidity: −0.03 $PM_{2.5}$ OC: 0.18 $PM_{2.5}$ EC: 0.20 Oxygenated HCs: 0.14 O_3: 0.19 CO: 0.26 NO_2: 0.34 Copollutant models: none
Wilson et al. (2005)	Portland, ME, and Manchester, NH (1996−2000)	SO_2 concentrations from one monitor in each city	24-h avg	Portland: 11.1 Manchester: 16.5	NR	Correlation (*r*) (Range across cities): O_3: 0.05−0.24 Copollutant models: none
†Stieb et al. (2009)	Seven Canadian cities (1992−2003)	Average SO_2 concentrations across all monitors in each city. Number of SO_2 monitors in each city ranged from 1−11.	24-h avg	2.6−10.0	75th: 3.3−13.4	Correlations (*r*) only reported by city and season Copollutant models: none
†Orazzo et al. (2009)	Six Italian cities (1996−2002)	Average of SO_2 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 (*r*): 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_X ISA and studies published since the 2008 SO_X ISA.

Study	Location Years	Exposure Assignment	Metric	Mean Concentration ppb	Upper Percentile Concentrations ppb	Copollutants Examination
†Alhanti et al. (2016)	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_2	1-h max	Atlanta: 10.7 Dallas: 2.7 St. Louis: 10.7	NR	Correlations (*r*): NR Copollutant models: none
†Zheng et al. (2015)	Meta-analysis (1988−2014)	NR	24-h avg	4.6−39.1[a]	NR	Correlations (*r*): NR Copollutant models: none
†Strickland et al. (2010)	Atlanta, GA (1993−2004)	Population-weighted average using data available from all monitors measuring SO_2	1-h max	All-year: 10.8 Warm (May−Oct): 9.6 Cold (Nov−Apr): 12.0	NR	Correlations (*r*): NR Copollutant models: none
†Li et al. (2011)	Detroit, MI (2004−2006)	Average of SO_2 concentrations across two monitors in Detroit metropolitan area that measure SO_2	24-h avg	3.8	75th: 5.1 Max: 27.3	Correlations (*r*), range across monitors: CO: 0.17−0.31 $PM_{2.5}$: 0.40−0.53 NO_2: 0.42−0.55 Copollutant models: none
†Byers et al. (2015)	Indianapolis, IN (2007−2011)	Double-weighted average (distance from monitor to ZIP code centroid and age-specific census population) of two SO_2 monitors	1-h max	All-year: 10.1 Warm: 10.5 Cold: 9.8	NR	Correlations (*r*): All-year: $PM_{2.5}$: 0.34 Warm: 1-h max O_3: 0.45 8-h max O_3: 0.42 $PM_{2.5}$: 0.38 Cold: $PM_{2.5}$: 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_X ISA and studies published since the 2008 SO_X ISA.

Study	Location Years	Exposure Assignment	Metric	Mean Concentration ppb	Upper Percentile Concentrations ppb	Copollutants Examination
†Villeneuve et al. (2007)	Edmonton, AB (1992−2002)	Average of SO_2 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 (*r*): NR Copollutant models: NR
†Jalaludin et al. (2008)	Sydney, Australia (1997−2001)	Average of SO_2 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 (*r*): (warm, cold) PM_{10}: 0.37, 0.46 $PM_{2.5}$: 0.27, 0.46 O_3: 0.45, −0.04 CO: 0.46, 0.51 NO_2: 0.52, 0.56 Copollutant models: PM_{10}, $PM_{2.5}$, O_3, CO, NO_2
†Smargiassi et al. (2009)	Montreal, QC (1996−2004)	SO_2 concentrations measured at two monitoring sites east and southwest of the refinery At-home estimates of daily exposure by estimating SO_2 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_X ISA and studies published since the 2008 SO_X ISA.

Study	Location Years	Exposure Assignment	Metric	Mean Concentration ppb	Upper Percentile Concentrations ppb	Copollutants Examination
†Winquist et al. (2014)	Atlanta, GA, U.S. (1998−2004)	Population-weighted average using data available from all monitors measuring SO_2	1-h max	Warm (May−Oct): 8.3 Cold (Nov−April): 10.8	75th: Warm: 11.4 Cold: 14.6	Correlations (*r*): Warm: O_3: 0.27 CO: 0.32 NO_2: 0.44 $PM_{2.5}$: 0.28 EC: 0.31 Sulfate: 0.24 Secondary $PM_{2.5}$: 0.24 Cold: O_3: 0.05 CO: 0.22 NO_2: 0.41 $PM_{2.5}$: 0.07 EC: 0.18 Sulfate: 0.02 Secondary $PM_{2.5}$: 0.08 Copollutant models: none
†Pearce et al. (2015)	Atlanta, GA	SO_2 concentrations from one monitor	1-h max	14.6	NR	Correlations (*r*): 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_X ISA and studies published since the 2008 SO_X ISA.

Study	Location Years	Exposure Assignment	Metric	Mean Concentration ppb	Upper Percentile Concentrations ppb	Copollutants Examination
Outpatient and physician visits						
†Burra et al. (2009)	Toronto, ON (1992−2001)	Average of SO_2 concentrations across six monitors	1-h max	9.7	75th: 12.0 95th: 35.0 Max: 62.0	Correlations (*r*): NR Copollutant models: none
†Sinclair et al. (2010)	Atlanta, GA, U.S. (1998−2002)	SO_2 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 (*r*): 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_2 = nitrogen dioxide; NR = not reported; O_3 = ozone; OC = organic carbon; PM_{10} = particulate matter with a nominal aerodynamic diameter less than or equal to 10 µm; $PM_{2.5}$ = particulate matter with a nominal aerodynamic diameter less than or equal to 2.5 µm; $PM_{10-2.5}$ = 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_2 = sulfur dioxide; UFP = ultrafine particle.

[a]Range of mean concentrations across all studies included in the meta-analysis.

† = studies published since the 2008 SO_X ISA.

Hospital Admissions

The 2008 SO_X ISA identified only two U.S.-based studies and no Canadian studies that examined the association between short-term SO_2 exposures and asthma hospital admissions. These studies reported positive associations; however, they were limited to studies of individual cities (Figure 5-3). The asthma hospital admission studies averaged SO_2 concentrations over multiple monitors and only examined 24-h avg exposure metrics, which may not adequately capture the spatial and temporal variability in SO_2 concentrations (Section 3.4.2.2 and Section 3.4.2.3). While correlations between 24-h avg and 1-h max SO_2 concentrations are high ($r > 0.75$) at most monitors, lower correlations may occur at some monitors and in individual studies, adding uncertainty to the ability of 24-h avg metrics to capture peak SO_2 concentrations. Additionally, relatively few studies have examined the potential confounding effects of other pollutants on the SO_2-asthma hospital admissions relationship.

To date a limited number of studies have been published since the 2008 SO_X ISA that focus on the relationship between short-term SO_2 exposures and asthma hospital

admissions. In a time-series study conducted in Athens, Greece, Samoli et al. (2011) evaluated the association between multiple ambient air pollutants and pediatric asthma hospital admissions for ages 0−14 years. In an all-year analysis, the authors reported a positive association with SO_2 [16.5 % (95% CI: 2.3, 32.6); lag 0 increase for a 10-ppb increase in 24-h avg SO_2 concentrations]. In copollutant analyses, the authors found SO_2 risk estimates to be robust in models with PM_{10} [13.0% (95% CI: −1.5, 29.7)] and O_3 [16.5% (95% CI: 2.3, 32.6)]. However, in models with NO_2 there was an increase in the SO_2 risk estimate [21.3% (95% CI: 1.1, 45.5)]. SO_2 was low ($r < 0.4$) to moderately (r ranging from 0.4−0.7) correlated with other pollutants examined in the study, with the highest correlation with NO_2 ($r = 0.55$).

The association between short-term SO_2 exposures and asthma hospital admissions was also examined by Son et al. (2013) in a study of eight South Korean cities. In addition to focusing on asthma, the authors examined allergic disease hospital admissions, which encompass asthma. For all ages, the authors reported a 5.3% increase (95% CI: −2.4, 13.0) in asthma hospital admissions for a 10-ppb increase in 24-h avg SO_2 concentrations and a 3.1% increase (95% CI: −3.7, 10.7) in allergic diseases hospital admissions. In analyses focusing on children (ages 0−14) and older adults (≥75 years of age), the authors reported associations that were larger in magnitude, compared to all ages for both asthma and allergic diseases hospital admissions (Figure 5-3).

The evidence from studies evaluated in the 2008 SO_X ISA, as well as recent studies indicating a positive association between short-term SO_2 exposure and asthma hospital admissions, is supported by a meta-analysis conducted by (Zheng et al., 2015) that focused on all studies examining air pollution and asthma hospital admissions and ED visits published between 1988 and 2014. For SO_2, the authors reported a 2.1% increase (95% CI: 0.5, 3.70) in asthma hospital admissions for a 10-ppb increase in 24-h avg SO_2 concentrations based on estimates from 31 studies. The results from Zheng et al. (2015) are smaller in magnitude compared to the other asthma hospital admission studies summarized in Figure 5-3, but this could be a reflection of the meta-analysis only including single-day lag estimates from each of the studies. The results of the meta-analysis were found to be robust in sensitivity analyses examining publication bias; however, the publication bias analysis was not conducted separately for asthma hospital admissions and ED visits results.

Emergency Department Visits

The majority of studies, examing respiratory-related hospital admissions and ED visits, have focused on asthma ED visits. Studies evaluated in the 2008 SO_X ISA were primarily limited to single-city studies that provided generally positive associations between SO_2 and asthma ED visits, with positive associations being reported in some study locations

and evidence of no association in other locations (Figure 5-3). Additionally, there was limited evidence for potential seasonal differences in SO_2 associations with asthma ED visits. As with the hospital admission studies, there has been limited analyses examining the potential confounding effects of copollutants on the SO_2-asthma ED visit relationship.

Recent studies that examined the association between short-term SO_2 exposures and asthma ED visits have primarily focused on either children or the entire population, with a few studies examining whether effects differ by lifestage. Additionally, unlike the hospital admission studies, the ED visit studies examined both 24-h avg and 1-h max exposure metrics, which can provide some additional insight, on a population level, into the short-term exposures that result in respiratory effects in controlled human exposure and animal toxicological studies (see previous subsections of Section 5.2.1.2).

Strickland et al. (2010) examined the association between SO_2 exposure and pediatric asthma ED visits (ages 5−17 years) in Atlanta, GA, using air quality data over the same years as Tolbert et al. (2007), who examined all respiratory ED visits. However, unlike Tolbert et al. (2007), who used a single-site monitor, Strickland et al. (2010) used population-weighting, a more refined exposure assignment approach, to combine daily pollutant concentrations across monitors. As discussed in Section 3.4.2, a study by Goldman et al. (2012) shows that the bias in health effect estimates decreases when using population-weighted averages for assigning exposure instead the values from a central site monitor. In Strickland et al. (2010), the authors developed a statistical model using hospital-specific, time-series data that is essentially equivalent to a time-stratified, case-crossover analysis (i.e., using interaction terms between year, month, and day-of-week to mimic the approach of selecting referent days within the same month and year as the case day). Strickland et al. (2010) observed a 4.2% (95% CI: −2.1, 10.8) increase in ED visits for a 40-ppb increase in 1-h max SO_2 concentrations at lag 0−2 days in an all-year analysis. The potential confounding effects of other pollutants on the SO_2-asthma ED visit relationship was not assessed in this study, and correlations between pollutants were not presented. However, when evaluating the correlation of pollutants examined over the same study years in Tolbert et al. (2007), SO_2 had a low correlation with all pollutants ($r \leq 0.36$).

Positive associations between short-term SO_2 exposures and pediatric asthma ED visits were also observed in a study conducted by Li et al. (2011) in Detroit, MI that focused on whether there was evidence of a threshold in the air pollution-asthma ED visit relationship. In the main nonthreshold analysis, the authors conducted both time-series and time-stratified case-crossover analyses. Li et al. (2011) observed similar results in both analyses, which indicated an association between SO_2 and asthma ED visits, [time series: 20.5% (95% CI: 8.9, 33.2); lag 0−4 for a 10-ppb increase in 24-h avg SO_2

concentrations; case-crossover: 22.8% (95% CI: 12.6, 33.7); lag 0−4]. The results of the U.S.-based studies focusing on children conducted by Strickland et al. (2010) and Li et al. (2011) are consistent with those of Jalaludin et al. (2008) in a study of children 1−14 years of age conducted in Sydney, Australia. In addition to conducting the analysis focusing on ages 1−14, the authors also examined whether risks varied among age ranges within this study population (Chapter 6). Jalaludin et al. (2008) examined single day lags ranging from 0 to 3 days as well as the average of 0−1 days. In the 1−14 years of age analysis, the authors observed slightly larger associations at lag 0−1 days [29.7% (95% CI: 14.7, 46.5)] compared to lag 0 [22.0% (95% CI: 9.1, 34.5)] for a 10-ppb increase in 24-h avg SO_2 concentrations. An examination of the potential confounding effects of other pollutants was assessed in copollutant models with PM_{10}, $PM_{2.5}$, O_3, CO, or NO_2 at lag 0. SO_2 was found to be weakly to moderately correlated with these pollutants, r = 0.27−0.52. Jalaludin et al. (2008) reported that the SO_2-asthma ED visit association was slightly attenuated, but remained positive in all copollutant models, with the magnitude of the association ranging from a 13.2−16.1% increase in asthma ED visits.

Byers et al. (2015) in a study conducted in Indianapolis, IN examined asthma ED visits across all ages as well as various lifestages (i.e., 5−17, 18−44, and ≥45 years of age). The authors used a double-weighted approach to assign exposure where they first weighted air pollution concentrations by distance from a monitor to the ZIP code centroid and then weighted concentrations by the age-specific census population. In an all-year analysis for all ages, the authors reported a 0.4% increase in asthma ED visits (95% CI: −3.6, 4.5) at lag 0−2 for a 40-ppb increase in 1-h max SO_2 concentrations, with evidence of a larger association when focusing on pediatric asthma ED visits [5.4% (95% CI: −3.2, 14.5); lag 0−2], which is consistent with Strickland et al. (2010), Li et al. (2011), and Jalaludin et al. (2008). Although copollutant analyses were not conducted, SO_2 was found to have a low correlation with $PM_{2.5}$ (r < 0.4) in all-year and seasonal analyses, and moderate correlation with 1-h max and 8-h max O_3 in warm season analyses (r = 0.42−0.45). Additionally, when examining SO_2 concentrations across the entire study period, the authors noted that only 36 days (i.e., 2.1% of days) had 1-h max SO_2 concentrations that exceeded the NAAQS.

Alhanti et al. (2016) also used the approach of assigning exposure using population-weighting similar to Strickland et al. (2010), but expanded the study area to include two additional cities, Dallas, TX and St. Louis, MO, as well as Atlanta, GA. The analysis focused on examining whether there was evidence of differential risk across lifestages (i.e., 0−4, 5−18, 19−39, 40−64, and 65+ years of age) for asthma ED visits across a number of air pollutants, including SO_2. Analyses were conducted for each individual city, and an overall estimate across all three cities was calculated by taking the inverse-variance weighted average of the city-specific risk estimate. Across the

individual cities, there was evidence of positive and negative associations for all age categories examined except ages 5−18 where positive associations were observed across all cities, which is consistent with the single-city studies detailed above. In the combined analysis across the three cities, Alhanti et al. (2016) reported positive associations for ages 0−4 [4.1% (95% CI: −0.8, 9.2); lag 0−2 for 40-ppb increase in 1-h max SO_2 concentrations] and 5−18 [5.7% (95% CI: −0.8, 11.8); lag 0−2] (Sarnat, 2016). In sensitivity analyses, the results were found to be robust to alternative model specifications for both control for temporal trends and weather covariates.

As detailed in the asthma hospital admissions section, Zheng et al. (2015) conducted a meta-analysis of asthma hospital admission and ED visit studies. In the analysis focusing on ED visit studies, the authors reported a 3.5% increase (95% CI: 1.9, 5.1) in asthma ED visits for a 10-ppb increase in 24-h avg SO_2 concentrations based on single-day lag estimates from 34 studies. This result is in the range of risk estimates reported in studies that observed positive associations between short-term SO_2 exposure and asthma ED visits (Figure 5-3).

Although a number of recent studies add to the evidence from the 2008 SO_X ISA indicating a positive association between asthma ED visits and short-term SO_2 exposures, not all studies have reported positive associations. Both Stieb et al. (2009) and Villeneuve et al. (2007), in studies conducted in seven Canadian cities and Edmonton, AB, respectively, did not observe evidence of a positive association between short-term SO_2 exposures and asthma ED visits (Figure 5-3). The evidence of no association was observed over multiple lag structures (i.e., both single and multiday lags) (Stieb et al., 2009; Villeneuve et al., 2007) as well as subdaily exposure metrics (i.e., 3-h avg pollutant concentrations) (Stieb et al., 2009).

Hospital Admissions and Emergency Department Visits for Respiratory Conditions Associated with Asthma

As stated previously, asthma is difficult to diagnose in children less than 5 years of age (NAEPP, 2007); however, asthma-like symptoms in children within this age range are often presented in the form of transient wheeze. Although studies that examine ED visits for wheeze do not directly inform upon the relationship between short-term SO_2 exposures and asthma, they can add supporting evidence. Orazzo et al. (2009) examined the association between short-term SO_2 exposures and wheeze ED visits, in children (ages 0−2 years) in six Italian cities. In a time-stratified case-crossover analysis, Orazzo et al. (2009) examined associations for multiday lags ranging from 0−1 to 0−6 days. The authors reported the strongest evidence for an association between short-term SO_2 exposures and wheeze ED visits at lags of 0−3 to 0−6 days with estimates ranging from

2.1 to 4.3%, respectively, for a 10-ppb increase in 24-h avg SO_2 concentrations. Within this study, copollutant analyses or correlations with other pollutants were not presented.

Smargiassi et al. (2009) also provided additional information on whether there is an association between short-term SO_2 exposures and health effects that may be closely related to asthma. The distinction between asthma and asthma-related outcomes is made in this case because the study focused on asthma hospital admissions and ED visits in children 2−4 years of age. This age range may not necessarily represent an asthma exacerbation in the same context as those studies discussed earlier in this section that include older individuals in whom asthma is more easily diagnosed. Within this study, the authors examined the influence of a point source of SO_2 (i.e., stack emissions from a refinery) in Montreal on asthma hospital admissions and ED visits using data from two fixed-site monitors as well as estimates of SO_2 concentrations from a dispersion model, AERMOD. The authors examined both daily mean and daily peak SO_2 concentrations. When comparing SO_2 concentrations at one monitoring site east of the refinery with those obtained via AERMOD the authors observed a modest correlation (daily mean SO_2, $r = 0.43$; daily peak SO_2, $r = 0.36$). An examination of hospital admissions and ED visits for both monitor locations, east and southwest of the refinery, found that associations were slightly larger in magnitude for the same-day daily peak [hospital admissions: 1.46 (95% CI: 1.10, 1.93); ED visits: 1.18 (95% CI: 1.05, 1.33) for a 40-ppb increase in 1-h max SO_2 concentrations] compared to daily mean concentrations [hospital admissions: 1.36 (95% CI: 1.05, 1.81); ED visits: 1.15 (95% CI: 1.02, 1.27) for a 10-ppb increase in 24-h avg SO_2 concentrations] in an unadjusted model at lag 0. When examining associations using SO_2 concentrations from the fixed monitoring sites, Smargiassi et al. (2009) did not find consistent evidence of an increase in asthma hospital admissions or ED visits, which is indicative of the fact that a monitor located far from a point source may not adequately capture population exposures for residences of interest located closer to that source (see Section 3.4.2). The authors also examined an adjusted model to control for daily weather variables and all other regional pollutants (i.e., $PM_{2.5}$, SO_2, NO_2, and O_3), but these results are not presented because, as discussed within this ISA, the evaluation of potential copollutant confounding is limited to two-pollutant models because the results from multipollutant models are difficult to interpret due to multicollinearity between pollutants. However, the results from the unadjusted (i.e., single-pollutant model) and adjusted models were generally similar.

Outpatient and Physician Visits Studies of Asthma

Several recent studies examined the association between ambient SO_2 concentrations and physician or outpatient (nonhospital, non-ED) visits for asthma. In Toronto, Burra et al. (2009) examined asthma physician visits among patients aged 1−17 and 18−64 years in a

study focusing on differences by sex and income within each age category. For children, the authors reported evidence of consistent positive associations between short-term increases in SO_2 concentrations and asthma physician visits for most of the single and multiday lags examined (i.e., 0, 0−1, 0−2, 0−3), with no evidence of an association for a 0−4 day lag. In the analysis of adults, a similar pattern of associations was observed; however, there was no evidence of an association at the two longest lags examined, 0−3 and 0−4 days.

In a study conducted in Atlanta, GA, Sinclair et al. (2010) examined the association between multiple respiratory outcomes, including asthma and outpatient visits from a managed care organization. The authors separated the analysis into two time periods (the first 25 months of the study period and the second 28 months of the study period) in order to compare the air pollutant concentrations and relationships between air pollutants and acute respiratory visits for the 25-month time period examined in Sinclair and Tolsma (2004) (i.e., August 1998−August 2000), and an additional 28-month time period of available data from the Atlanta Aerosol Research and Inhalation Epidemiology Study (ARIES) (i.e., September 2000−December 2002). As detailed in Table 5-9, SO_2 concentrations were relatively similar between periods, differing by less than 2 ppb. A comparison of the two time periods indicated that risk estimates across outcomes tended to be larger in the earlier 25-month period compared to the later 28-month period, with evidence of consistent positive associations across the lags examined for asthma (both child and adult), but confidence intervals were relatively large.

Examination of Seasonal Differences

In addition to examining the association between short-term SO_2 exposures and asthma hospital admissions and ED visits in all-year analyses, some studies also conducted seasonal analyses. When evaluating these studies, it is important to note that the difference in the geographic locations examined across studies complicates the ability to draw overall conclusions regarding the seasonal patterns of associations.

In the study of eight South Korean cities, Son et al. (2013) examined potential seasonal differences across respiratory hospital admission outcomes. For asthma and allergic disease hospital admissions, the association with SO_2 was largest in magnitude during the summer, although confidence intervals were quite large [asthma: 19.1% (95% CI: −18.3, 73.9), lag 0−3; allergic disease: 21.9% (95% CI: −6.7, 58.6), lag 0−3 for a 10-ppb increase in 24-h avg SO_2 concentrations]. Across the eight cities, mean 24-h avg SO_2 concentrations were lowest during the summer season (4.4 ppb compared to a range of 4.8 to 7.0 in the other seasons), which was also observed for NO_2, PM_{10}, and CO. The seasonal asthma hospital admission results of Son et al. (2013) are similar to those reported in Samoli et al. (2011) in a study conducted in Athens, Greece. Samoli et al.

(2011) observed the largest magnitude of an association during the summer months [46.6% (95% CI: −13.8, 149.3); lag 0 for a 10-ppb increase in 24-h avg SO_2 concentrations], but also reported a similar association in the autumn months [42.6 % (95% CI: −0.5, 104.4); lag 0]. Although positive, associations for the winter and spring months were smaller in magnitude, 20.2 and 31.8%, respectively.

The initial indication of larger associations during the summer for asthma hospital admissions is further supported by the analysis of Strickland et al. (2010) examining short-term SO_2 exposures and pediatric asthma ED visits in Atlanta. The authors reported evidence of asthma ED visit associations larger in magnitude during the summer [10.8% (95% CI: 0.7, 21.7); lag 0−2 for a 40-ppb increase in 1-h max SO_2 concentrations], with no evidence of an association during the winter [0.4% (95% CI: −7.5, 9.0)]. These results are consistent with (Byers et al., 2015), who reported associations larger in magnitude in the summer for all ages [3.1% (95% CI: −2.6, 8.6); lag 0−2 for a 40-ppb increase in 1-h max SO_2 concentrations], and particularly children 5−17 years of age [13.0% (95% CI: 0.8, 26.8); lag 0−2], and no evidence of an association in the cold season across all ages examined. However, in another study focusing on asthma physician visits in Atlanta, Sinclair et al. (2010) reported inconsistent evidence of seasonal differences in risk estimates, with the pattern of associations being different in each of the time periods examined in the study. It is important to note that the results of Sinclair et al. (2010) may be a reflection of the severity of asthma exacerbations requiring medical attention and people proceeding directly to a hospital for treatment instead of first visiting a physician. Therefore, the study may not be able to adequately capture associations, and specifically, any potential seasonal differences.

The meta-analysis conducted by (Zheng et al., 2015) provides some additional supporting evidence for potential seasonal differences in SO_2-asthma hospital admission and ED visit associations. In a combined analysis including both asthma hospital admission and ED visit studies that reported seasonal results, Zheng et al. (2015) reported slightly larger associations in the warm [4.8% (95% CI: 2.7, 7.0) for a 10-ppb increase in 24-h avg SO_2 concentrations] compared to the cold season [3.2% (95% CI: 0.5, 5.9)], but confidence intervals did overlap.

Although there is some evidence for larger associations during the summer, studies conducted by Villeneuve et al. (2007) in Edmonton, AB and Jalaludin et al. (2008) in Sydney, Australia present conflicting results. As stated above, Villeneuve et al. (2007) did not find evidence of an association between short-term SO_2 exposures and asthma ED visits, including in seasonal analysis, while Jalaludin et al. (2008) reported evidence of larger associations during the cold months (May−October) compared to the warm months (November−April) (Figure 5-3).

Overall, the results of Samoli et al. (2011), Son et al. (2013), Strickland et al. (2010), and Byers et al. (2015) suggest that associations are larger in magnitude during the summer season, but this conclusion should be viewed with caution because the results of each study are highly imprecise, as reflected by the wide confidence intervals for each seasonal result. Additionally, the interpretation of results from these studies is complicated by the lack of copollutant analyses, and the results from Villeneuve et al. (2007) and Jalaludin et al. (2008) that do not find evidence of larger associations during the summer or warm season.

Lag Structure of Associations

When examining associations between air pollution and a specific health outcome, such as respiratory-related hospital admissions, it is informative to assess whether exposure to an air pollutant results in an immediate, delayed, or prolonged effect on health. Recent studies that examine both multiple single- and multiday lags can help provide information on whether there is a specific exposure window(s) that contribute to SO_2-related asthma hospital admissions and ED visits.

Son et al. (2013) examined the lag structure of associations for multiple respiratory-related hospital admissions, including asthma and allergic disease, by analyzing both single- and multiday lags. Across single-day lags of 0 to 3 days, positive associations were observed across each lag, but the magnitude of the association varied across single-day lags for each outcome. For both asthma and allergic disease hospital admissions, the largest association, in terms of magnitude, for SO_2 was observed for each of the multiday lags examined, with the largest occurring at lag 0−3 days [asthma: 5.3% (95% CI: −2.4, 13.0); allergic disease: 3.1% (95% CI: −3.7, 10.7) for a 10-ppb increase in 24-h avg SO_2 concentrations].

Studies conducted by Samoli et al. (2011) and Jalaludin et al. (2008) report evidence for the strongest SO_2-asthma hospital admission and ED visit associations occurring rather immediately (lag 0) as well as over the first few days after exposure, average of lags from 0 up to 2 days. Samoli et al. (2011) in the examination of single- and multiday lags for associations between SO_2 and asthma hospital admissions in Athens, Greece found associations of similar magnitude at lag 0 and a 0−2 day distributed lag, but the distributed lag association was imprecise (i.e., larger confidence intervals) (quantitative results not presented). The associations reported for single-day lags of 1 and 2 days were small and close to null. Jalaludin et al. (2008) in a study in Sydney, Australia found when examining single-day lags of 0 to 3 days that asthma ED visit associations were largest for lag 0 [22.0% (95% CI: 9.1, 34.5) for a 10-ppb increase in 24-h avg SO_2 concentrations] and 1 day [16.1% (95% CI: 5.1, 26.5)]. This is further reflected in the

largest SO_2 association being observed for the multiday lag of 0−1 days [29.7% (95% CI: 14.7, 46.5)].

Only a limited number of studies have examined the lag structure of associations and the results across studies are not fully supported by the rest of the literature base. Villeneuve et al. (2007), when studying asthma ED visits in seven Canadian cities, examined single-day lags of 0 and 1 day, along with multiday lags of 0−2 and 0−4 days. The authors reported no evidence of an association between short-term SO_2 exposures and asthma ED visits at any lag. Additionally, Orazzo et al. (2009) in the study of wheeze ED visits in six Italian cities, examined multiday lags ranging from 0−1 to 0−6 days. Across the lags examined, the authors reported evidence of increasing magnitude of the association as the length of the multiday lag increased, with lag 0−6 days showing the largest association.

Exposure Assignment

Questions often arise in air pollution epidemiologic studies about the method used to assign exposure (see Section 3.3.3). Strickland et al. (2011), using ED visit data from Atlanta, GA, assessed the effect of various exposure assignment approaches on the relationship between short-term air pollution exposures and asthma ED visits. The authors used warm season data from Strickland et al. (2010) to examine the relative influence of different exposure assignment approaches (i.e., central monitor, unweighted average across available monitors, and population-weighted average) on the magnitude and direction of associations between SO_2 and pediatric asthma ED visits. SO_2 exhibited a relatively low chi-square goodness-of-fit statistic compared with other pollutants, which the authors attributed to spatial heterogeneity in SO_2 concentrations (Section 3.4.2.2). Strickland et al. (2011) reported that effect estimates per IQR increase in SO_2 were similar across the metrics; however, based on a standardized increment (i.e., 20 ppb in the study), the magnitude of the association between SO_2 and pediatric asthma ED visits varied [central monitor 3.0% (95% CI: −0.4, 8.4); unweighted average 12.8% (95% CI: 2.8, 23.4); population-weighted average 10.9% (95% CI: 0.8, 21.9) for a 40-ppb increase in 1-h max SO_2 concentrations at lag 0−2 days]. The difference in associations observed across the various exposure assignment approaches when using the standardized increment can be attributed to the value (i.e., a 1-h max SO_2 concentration of 20 ppb) not reflecting an increase in SO_2 concentrations that is reflective of the SO_2 distribution in Atlanta (e.g., in the study the standardized increment for 1-h max SO_2 is 20 ppb, but the IQR, which is often used to calculate the relative risk, differs across the exposure assignment approaches, varying from 9.6 to 13.9 ppb). Although the Strickland et al. (2011) study was only conducted in one city, the study suggests that it is appropriate to consider the distribution of air pollutant concentrations when calculating a relative risk

(i.e., IQR), but also that the different approaches used to assign exposure across the studies evaluated may alter the magnitude, not direction, of the associations observed.

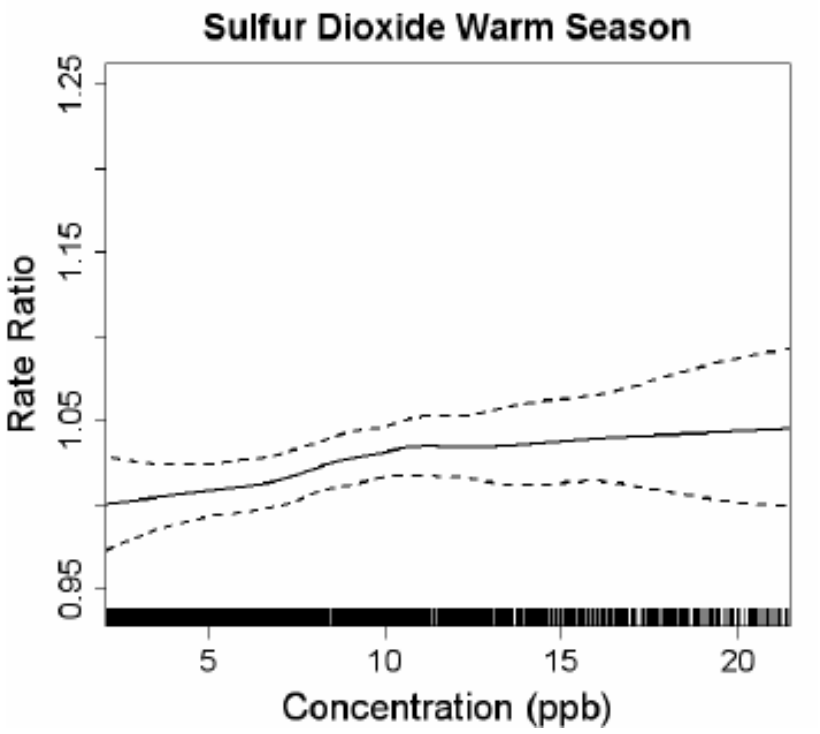
Concentration-Response Relationship

To date, few studies have examined the C-R relationship between SO_2 exposures and respiratory morbidity. In recent studies, Strickland et al. (2010) and Li et al. (2011) examined the shape of the SO_2-pediatric asthma ED visit relationship using different analytical approaches.

Strickland et al. (2010) examined the C-R relationship by conducting quintile and locally weighted scatterplot smoothing (LOESS) C-R analyses. In the quintile analysis, SO_2 associations were examined in both the warm and cold seasons; however, no associations were observed for the cold season for any quintile. Focusing on the warm season, the authors found evidence of an increase in the magnitude of the association for concentrations within the range of 7 to <24.2 ppb, relative to the first quintile (i.e., SO_2 concentrations <3.1 ppb). The smallest associations were observed for the 5th quintile, which represented concentrations ranging from 24.2 to ≤149 ppb; however, this quintile represented the extreme end of the distribution of SO_2 concentrations where data density was low. Additionally, the LOESS C-R relationship analysis provides evidence of a linear relationship between short-term SO_2 exposures and asthma ED visits along the distribution of concentrations from the 5th (2.1 ppb) to 95th (21.5 ppb) percentile (Sacks, 2015) (Figure 5-4). Collectively, these analyses do not provide evidence of a threshold.

In a study conducted in Detroit, MI, Li et al. (2011) examined whether there is evidence of a nonlinear C-R relationship for air pollutants and pediatric asthma ED visits. Associations with SO_2 were examined in both a time-series and time-stratified, case-crossover study design assuming (1) a linear relationship and (2) a nonlinear relationship starting at 8 ppb [i.e., the maximum likelihood estimate within the 10th to 95th percentile concentration where a change in linearity may occur (~91st percentile)]. It is important to note the analysis that assumed a nonlinear relationship did not assume zero risk below the inflection point. The focus of the analysis was on identifying whether risk increased above that observed in the linear models at SO_2 concentrations above 8 ppb. In the analyses assuming linearity, the authors examined single-day lags of 3 and 5 days and multiday lags of 0−2 and 0−4 days. Positive associations were observed for all lags examined and were relatively consistent across models, with the strongest association for a 0−4 day lag [time series: 20.5% (95% CI: 8.9, 33.2); case-crossover: 22.8% (95% CI: 12.6, 33.7) for a 10-ppb increase in 24-h avg SO_2 concentrations]. In the models that assumed a nonlinear relationship, the authors did not observe evidence of increased risk above ~8 ppb. However, it is important to note that the data density is low

at concentrations greater than 8 ppb, as reflected by this value representing the ~91st percentile of SO_2 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.

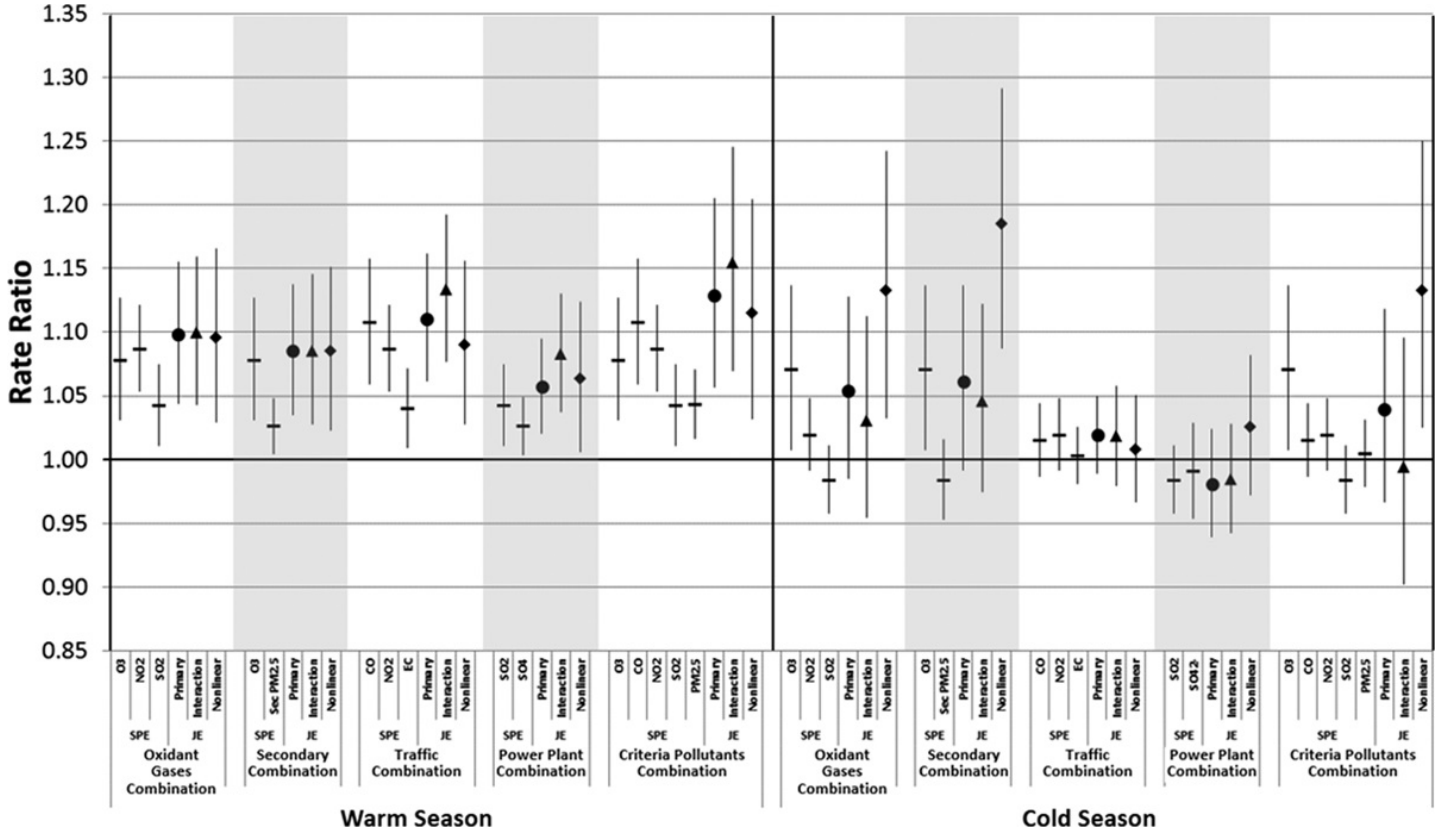
Sulfur Dioxide within the Multipollutant Mixture

An important question often encountered during the review of any criteria air pollutant, is whether the pollutant has an independent effect on human health. However, ambient exposures to criteria air pollutants are in the form of mixtures, which make answering this question difficult. Epidemiologic studies traditionally attempt to identify the independent effect of a criteria air pollutant through the use of copollutant models, but these methods do not consider the broader air pollution mixture. Recent studies conducted by Winquist et al. (2014) and Pearce et al. (2015) using pediatric asthma ED visits data from Atlanta assessed whether specific mixtures are more strongly associated

with health effects compared to others. Although the primary objective of these types of studies is not to directly assess the independent effects of a pollutant, they can inform the understanding of the role of SO_2 in the air pollution mixture (e.g., contributing to an additive or synergistic effect).

Winquist et al. (2014) examined multipollutant mixtures by focusing on the joint effect (i.e., the combined effect of multiple pollutants) of pollutants often associated with specific air pollution sources. Associations between short-term SO_2 exposures and pediatric asthma ED visits (i.e., ages 5−17) were examined in single-pollutant models and also in a multipollutant context in joint models for pollutant combinations representative of irritant gases (i.e., O_3, NO_2, and SO_2), power plants (i.e., SO_2 and SO_4^{2-}), and NAAQS pollutants (i.e., O_3, CO, NO_2, SO_2, and $PM_{2.5}$). It is important to note that the pollutant combination analyses attempt to address a different question (i.e., what is the risk associated with exposure to a combination of pollutants?) than a traditional copollutant analysis, which focuses on identifying the independent effect of a pollutant. Using the model detailed in Strickland et al. (2010), the authors examined the relationship between each combination and pediatric asthma ED visits using a Poisson model in the context of a time-referent case-crossover analysis. The authors reported results for an IQR increase for lag 0−2 days in single-pollutant analyses as well as three types of joint effect models [i.e., no interaction terms (primary), first-order multiplicative interactions between pollutants (interactions), and nonlinear pollutant terms (nonlinear)] (Figure 5-5).

In single-pollutant analyses, SO_2 associations were smaller in magnitude compared to the other pollutants that comprised each pollutant combination, but the uncertainty surrounding each SO_2 estimate was relatively small. Across pollutant combinations that contained SO_2, joint effect models reported consistent positive associations with pediatric asthma ED visits in the warm season. Additionally, for each pollutant combination the association observed was larger in magnitude than any single-pollutant association, including SO_2, but not equivalent to the sum of each individual pollutant association for a specific combination. In the warm season analyses, associations across the different joint effect models were relatively similar. Overall, the results during the cold season were more variable.



JE = joint model estimate; NO_2 = nitrogen dioxide; O_3 = ozone; PM_{25} = particulate matter with a nominal aerodynamic diameter less than or equal to 2.5 μm; SO_2 = sulfur dioxide; SPE = single-pollutant model estimate.

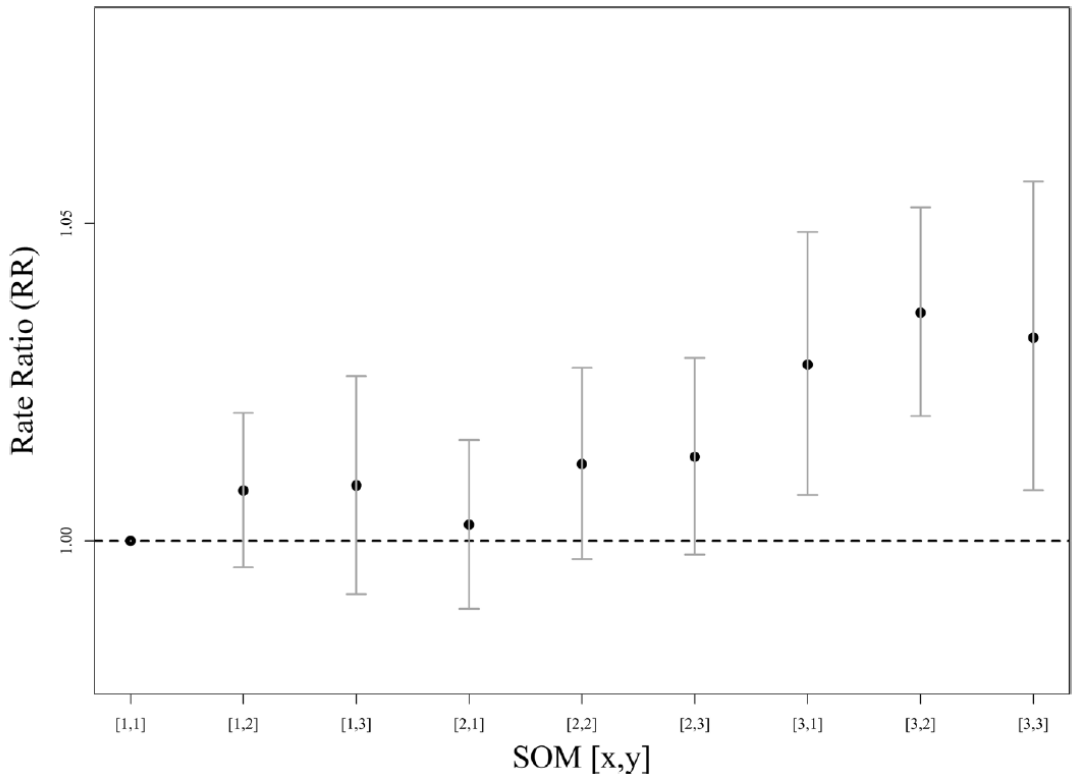
Note: Interquartile range for 1-h max SO_2 concentrations = 10.51 ppb.

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.

Pearce et al. (2015) took a different approach to examining multipollutant mixtures by using an unsupervised learning tool, the self-organizing map (SOM), which is similar to cluster analysis. Using air pollution concentrations for 10 pollutants from a single monitor, the authors identified nine distinct day types representative of air quality in Atlanta during the study period. These unique days were then used as indicator variables to examine associations with pediatric asthma ED visits using the same statistical approach as Strickland et al. (2010) and Winquist et al. (2014). Across the nine SOMs, some pollutant combinations represented days consisting of high single pollutant extremes, which included a day with high 1-h max SO_2 concentrations (i.e., mean concentration of 48.8 ppb and concentrations ranging from 8.5−23.7 ppb for all other SOMs). In analyses of all SOMs focusing on lag 1, the strongest associations were observed for days representing above average concentrations for all pollutants, and for days representing a collection of primary (i.e., CO, NO_2, NO_X, EC, and OC) or secondary pollutants (i.e., O_3, NH_4^+, and SO_4^{2+}) (Figure 5-6). Additional evidence of associations with pediatric asthma ED visits was observed for days with single pollutant extremes, including days with high SO_2 concentrations and generally lower concentrations for all other pollutants Figure 5-6). Interestingly, when comparing SOMs results with single-pollutant results in sensitivity analyses, the authors reported a null association with SO_2 at lag 1. This result differs from that observed in Strickland et al. (2010) and Winquist et al. (2014), but the difference could be due to the fact that Pearce et al. (2015) focused only on lag 1 because they were examining distinct pollution profiles that often do not occur on multiple days in a row. In contrast, Strickland et al. (2010) and Winquist et al. (2014) examined associations over a multiday average of 0−2 days. Additionally, the difference between the SOM and single-pollutant SO_2 result could be because the SOM with high SO_2 concentrations was better able to capture the immediate respiratory response due to higher peak concentrations, which would be consistent with the effects observed in controlled human exposure and animal toxicological studies.

Although the single-pollutant results of Winquist et al. (2014) and Pearce et al. (2015) differ due to the lags examined, the studies contribute to evidence that SO_2 alone and in combination with other pollutants is associated with asthma ED visits. The studies also highlight the difficulty in separating out the independent effect of a pollutant that is part 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

Recent studies that examined the association between short-term SO_2 exposure and asthma hospital admissions and ED visits generally report positive associations in studies examining all ages, children (i.e., <18 years of age), and older adults (i.e., 65 years of age and older) (Figure 5-3). The pattern of associations observed across studies focusing on all ages as well as age-stratified analyses is consistent with those studies evaluated in the 2008 SO_X ISA. Across asthma hospital admission and ED visit studies that evaluated the lag structure of associations, the most consistent evidence indicated that associations were largest in magnitude for multiday lags that encompassed the first few days after exposure (i.e., average of 0−2 and 0−3 day lags). This evidence generally supports the

timing of SO_2 effects observed in the controlled human exposure and animal toxicological studies (Section 5.2.1.2). The examination of potential copollutant confounding was rather limited in the body of studies that focused on asthma hospital admissions and ED visits. Across studies, SO_2 was found to be low ($r < 0.4$) to moderately ($r = 0.4–0.7$) correlated with other pollutants examined. Evidence from these studies is consistent with those studies evaluated in the 2008 SO_X ISA and adds to the body of evidence indicating that SO_2-asthma hospital admission and ED visit associations remain relatively unchanged in magnitude in copollutant models.

A number of recent studies also examined whether there was evidence that the association between short-term SO_2 exposures and asthma hospital admissions and ED visits was modified by season or some other individual- or population-level factor (Chapter 6). An examination of seasonal differences in SO_2-asthma hospital admission and ED visit associations provide some evidence of SO_2 effects being larger in magnitude in the summer or warm season, but the lack of this pattern across all studies that conducted seasonal analyses suggests that seasonal associations may vary by geographic location. Studies of individual- and population-level factors provide evidence of differences in associations by lifestage, with larger SO_2 effects for children and older adults, and more limited evidence for differences by sex (Chapter 6).

Additionally, some recent studies examined various study design issues, including model specification and exposure assignment. An examination of model specification, as detailed in Section 5.2.1.6, indicates that the relationship between short-term SO_2 exposures and respiratory-related hospital admissions, including those for asthma and allergic disease, are sensitive to using less than 7 degrees of freedom (df) per year to account for temporal trends, but robust to alternative lags and df ranging from 3 to 6 for weather covariates (Son et al., 2013). The results of Son et al. (2013) are supported by the sensitivity analyses examining model specification conducted by Alhanti et al. (2016) for asthma ED visits where the results were relatively consistent when the number of df for temporal trends was increased and alternative covariates for weather used. An examination of various exposure assignment approaches, including single central site, average of multiple monitors, and population-weighted average, suggests that each approach may influence the magnitude, but not direction, of the SO_2-asthma ED visit risk estimate (Strickland et al., 2011).

Finally, a few recent studies examined whether the shape of the SO_2-asthma ED visits relationship is linear or provides evidence of a threshold. These studies provide initial evidence of a linear, no-threshold relationship between short-term SO_2 exposures and asthma ED visits (Li et al., 2011; Strickland et al., 2010).

Subclinical Effects Underlying Asthma Exacerbation: Pulmonary Inflammation and Oxidative Stress

Pulmonary inflammation is a key subclinical effect in the pathogenesis of asthma. It consists of both acute and chronic responses and involves the orchestrated interplay of the respiratory epithelium and both the innate and adaptive immune system. The immunohistopathologic features of chronic inflammation involve infiltration of inflammatory cells such as eosinophils, lymphocytes, mast cells, and macrophages and the release of inflammatory mediators such as cytokines and leukotrienes. Oxidative stress is also relevant to asthma exacerbation. For example, many transcription factors regulating the expression of pro-inflammatory cytokines are redox sensitive.

This section characterizes the evidence on SO_2 exposure effects on pulmonary inflammation and oxidative stress in humans with asthma and in animal models of allergic airway disease (see Section 5.2.1.7 for healthy humans and animal models). The 2008 SO_X ISA (U.S. EPA, 2008d) concluded that evidence from the limited number of controlled human exposure, epidemiologic, and animal toxicological studies was insufficient to determine that exposure to SO_2 at current ambient concentrations was associated with inflammation in the airway. However, several studies provided evidence for subclinical effects related to allergic inflammation. There are no recent controlled human exposure studies, but there is additional investigation in epidemiologic and animal toxicological studies. Epidemiologic results are inconsistent for pulmonary inflammation and oxidative stress, including those for SO_2 measured at or near children's schools. However, recent findings in rats link short-term SO_2 exposure to allergic inflammation.

Controlled Human Exposure Studies

Pulmonary inflammation following 5−10 minute exposure to SO_2 was discussed in the previous ISA; no new studies were available for review. Briefly, Tunnicliffe et al. (2003) measured levels of exhaled NO (eNO), an indirect marker for pulmonary inflammation, in individuals with asthma before and after a 1 hour exposure to 0.2 ppm SO_2 under resting conditions. NALF levels of the antioxidants, ascorbic and uric acid, were also measured pre- and post-exposure. No statistically significant differences were observed between pre- and post-exposure for any of these indicators. Because subjects were exposed at rest and exposed to low concentrations, it is unlikely that enough SO_2 reached the airways to cause an effect. Gong et al. (2001) evaluated the response of individuals with asthma to 0.75 ppm SO_2 during exercise. In addition to changes in lung function and symptoms, there was a statistically significant increase in eosinophil count in induced sputum 2 hours after a 10-minute exposure. This response was significantly dampened by pretreatment with a leukotriene receptor antagonist. These results provided some evidence that SO_2 elicits an inflammatory response in the airways of individuals with

asthma that extends beyond the immediate bronchoconstriction response typically associated with SO_2 exposure. Additionally, this study provides further evidence that the bronchoconstriction response is only partially due to neural reflexes and that inflammatory mediators play an important role (Section 4.3.1).

Epidemiologic Studies

Recent epidemiologic evidence is inconsistent for associations of short-term increases in ambient SO_2 concentration with pulmonary inflammation and oxidative stress in adults and children with asthma (Table 5-10). Outcomes were assessed at varying frequency: daily, weekly, or seasonally. All studies examined eNO. Higher eNO has been linked to higher eosinophil counts (Brody et al., 2013) as well as prevalence and exacerbation of asthma (Soto-Ramos et al., 2013; Carraro et al., 2007; Jones et al., 2001; Kharitonov and Barnes, 2000). An SO_2-associated increase in eNO was observed in a population of adults with asthma with high prevalence of atopy (90%) (Maestrelli et al., 2011) (Table 5-10). Maestrelli et al. (2011) did not observe associations with lung function or asthma control score, but their results for pulmonary inflammation agree with results for lung function and symptoms in other populations with asthma plus atopy. Their results are also supported by findings that allergic inflammation in rats persists 24 hours after SO_2 exposures repeated over many days. The multicity U.S. asthma medication trial observed imprecise associations for eNO with wide 95% CIs in the ICS, beta-agonist, and placebo groups (Qian et al., 2009a). Both studies of adults with asthma estimated SO_2 exposure from central site monitors. Neither indicated whether the measurements adequately represented the spatiotemporal variability in SO_2 concentrations in the study area, and the U.S. study averaged concentrations from monitors within 32 km of each subject's ZIP code centroid.

Two recent studies measured SO_2 at or 0.65 km from children's schools (Greenwald et al., 2013; Lin et al., 2011b), which may better represent some component of subjects' exposure. Results are inconsistent. Percent changes in eNO were 31 (95% CI: −24, 119) per 10-ppb increase in SO_2 measured at a school in El Paso, TX (Greenwald et al., 2013) and 5.5 (95% CI: 2.7, 8.3) per 10-ppb increase in SO_2 measured near a school in Beijing, China before and after the 2008 Olympics (Lin et al., 2011b). Among children with asthma not using ICS in Windsor, ON, SO_2 concentrations at a monitor within 10 km of homes were not associated with eNO but were associated with markers of oxidative stress in exhaled breath condensate (EBC) (Liu et al., 2009b). The school-based studies differed in lags examined, and an association was observed with lag 0 SO_2 (Lin et al., 2011b) but not lag 0−3 avg SO_2 (Greenwald et al., 2013). For SO_2 measured at central site monitors, associations were observed with both lag 0 and lag 0−2 avg concentrations (Liu et al., 2009b). Prevalence of atopy was not reported for the study populations of children.

Copollutant confounding is an uncertainty in addition to inconsistent findings for SO_2 associations with pulmonary inflammation and oxidative stress in children and adults with asthma. Associations were observed with $PM_{2.5}$, BC, CO, O_3, and NO_2 (Lin et al., 2011b; Maestrelli et al., 2011; Liu et al., 2009b). Only Liu et al. (2009b) reported SO_2-copollutant correlations, indicating the potential for confounding with $PM_{2.5}$ (r = 0.56), less so with NO_2 (r = 0.18), and likely not with O_3 (r = −0.02). Maestrelli et al. (2011) did not examine copollutant models, and results in children with asthma are conflicting. For pollutants measured 0.65 km from school, SO_2 associations with eNO persisted with adjustment for $PM_{2.5}$ or BC but nevertheless decreased (Lin et al., 2011b). The effect estimate decreased for $PM_{2.5}$ but was robust for BC. Based on pollutants measured up to 10 km from home, the SO_2 association with oxidative stress decreased with adjustment for NO_2 and became imprecise with adjustment for $PM_{2.5}$ (Liu et al., 2009b) (Table 5-10). However, inference about SO_2 associations is weak because of uncertainty in the SO_2 exposure estimates and because $PM_{2.5}$ and NO_2 associations decreased with SO_2 adjustment.

Animal Toxicological Studies

The 2008 SO_X ISA (U.S. EPA, 2008d) discussed several studies that investigated the effects of exposure to SO_2 on inflammatory responses. While one study failed to demonstrate inflammation following a single subacute exposure to 1 ppm SO_2 (U.S. EPA, 2008d), other studies found that repeated SO_2 exposure enhanced the development of an allergic phenotype and altered physiologic responses in animal models of allergic airway disease. These studies demonstrating effects of repeated SO_2 exposures in models of allergic airway disease are listed in Table 5-11 and described here. In addition, other studies involving repeated SO_2 exposures in naive rats, including studies that demonstrate increased sensitivity to allergens, have been conducted and are described below in 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_2 Exposure Estimates (ppb)	SO_2 Averaging Time and Lag Day	Effect Estimate (95% CI) Single-Pollutant Model[a]	Copollutant Examination[a]
Adults with Asthma				
†Qian et al. (2009b) 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.	Monitors averaged within 32 km of subject ZIP code centroid. Mean (SD): 5.3 (4.4) 75th percentile: 7.6 Max: 27	24-h avg 0 0−3 avg	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)	Copollutant model, all subjects, lag 0 with PM_{10}: 0.16 (−0.08, 0.40) with NO_2: 0 (−0.18, 0.18) with O_3: 0.05 (−0.12, 0.22) NO_2 and PM_{10} associations persist with SO_2 adjustment. No association with O_3. SO_2 moderately correlated with NO_2, r = 0.58. Correlation NR for PM_{10}.
†Maestrelli et al. (2011) 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 (>6 times per yr for 3 yr).	Two monitors in city Medians across seasons: 0.87−2.7 75th percentiles across seasons: 1.3−4.1	24-h avg 0	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	No copollutant model Association observed with CO and O_3. No association with personal or central site $PM_{2.5}$ or PM_{10}. No association for central site NO_2. Copollutant correlations NR.

Table 5-10 (Continued): Recent epidemiologic studies of pulmonary inflammation and oxidative stress in populations with asthma.

Study Population and Methodological Details	SO_2 Exposure Estimates (ppb)	SO_2 Averaging Time and Lag Day	Effect Estimate (95% CI) Single-Pollutant Model[a]	Copollutant Examination[a]
Children with Asthma				
†Greenwald et al. (2013) 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_2, BTEX, cleaning product VOCs (a-pinene, dichlorobenzene, d-limonene) at school B. No association with $PM_{2.5}$. SO_2 weakly correlated with BC, NO_2, BTEX, cleaning product VOCs. Pearson r = −0.14, −0.22, −0.07, 0.14.
†Lin et al. (2011b) 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 $PM_{2.5}$ Results presented only in a figure. SO_2 associations persist but decrease in magnitude with adjustment for BC or $PM_{2.5}$. BC association not altered by SO_2 adjustment; $PM_{2.5}$ association slightly attenuated. Associations observed for CO and NO_2. Copollutant correlations NR.
†Liu et al. (2009b), Liu (2013) 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 $PM_{2.5}$: 53 (−21, 158) with NO_2: 51 (0.93, 112) with O_3: 74 (26, 128) $PM_{2.5}$ and NO_2 association attenuated with SO_2 adjustment. SO_2 moderately correlated with $PM_{2.5}$, weakly correlated with NO_2 and O_3. 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_2 = nitrogen dioxide; O_3 = ozone; $PM_{2.5}$ = particulate matter with nominal aerodynamic diameter less than or equal to 2.5 µm; PM_{10} = particulate matter with nominal aerodynamic diameter less than or equal to 10 µm; SO_2 = sulfur dioxide; TBARS = thiobarbituric acid reactive substances.

[a]Effect estimates are standardized to a 10-ppb increase in 24-h avg SO_2.

†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
Li et al. (2007)	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_2 for 1 h/d for 7 d, or (3) SO_2 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
Li et al. (2008)	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_2 for 1 h/d for 7 d, or (3) SO_2 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
Xie et al. (2009)	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_2 for 1 h/d for 7 d, or (3) SO_2 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
Li et al. (2014)	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_2 for 1 h/d for 7 d, or (3) SO_2 exposure followed by ovalbumin aerosol challenge 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 of NFκB, IκBα, IKKβ, IL-6, IL-4, TNFα, FOXp3 EMSA NFκB 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-γ = interferon gamma; IgE = immunoglobulin E; 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; p53 = tumor protein p53; SD = standard deviation; SO_2 = sulfur dioxide; TNF-α = tumor necrosis factor alpha.

Repeated exposure to SO_2 promoted an allergic phenotype when ovalbumin sensitization and challenge preceded SO_2 exposure. As described in the 2008 SO_X ISA (U.S. EPA, 2008d), Li et al. (2007) demonstrated that rats, which were first sensitized and challenged with ovalbumin and subsequently exposed to 2 ppm SO_2 for 1 hour/day for 7 days, had an increased number of inflammatory cells in BALF and an enhanced histopathological response compared with those treated with ovalbumin or SO_2 alone. Similarly, ICAM-1, a protein involved in regulating inflammation, and MUC5AC, a mucin protein, were upregulated in lungs and trachea to a greater extent in rats treated with ovalbumin and SO_2 than in those treated with ovalbumin or SO_2 alone. A follow-up study involving the same exposure regimen (2 ppm SO_2 for 1 hour) in the same allergic animal model (rats sensitized and challenge with ovalbumin) also found that repeated SO_2 exposure enhanced inflammatory and allergic responses to ovalbumin (Li et al., 2014). Numbers of eosinophils, lymphocytes and macrophages were greater in BALF of SO_2-exposed and ovalbumin-treated animals than in animals treated only with ovalbumin. In addition, SO_2 exposure enhanced upregulation and activation of NFκB, a transcription factor involved in inflammation and upregulation of the cytokines IL-6 and IL-4 in lung tissue in this model of allergic airway disease. Furthermore, BALF levels of IL-6 and IL-4 were increased to a greater extent in SO_2-exposed and ovalbumin-treated animals compared with ovalbumin treatment alone. These results indicate that repeated SO_2 exposure enhanced activation of the NFκB inflammatory pathway and upregulation of inflammatory cytokines in ovalbumin-treated animals. Furthermore, SO_2 exposure

enhanced the effects of ovalbumin on levels of IFN-γ (decreased) and IL-4 (increased) in BALF and on IgE levels in serum (increased). Because levels of IL-4 are indicative of Th2 status and levels of IFN-γ are indicative of Th1 status, these results suggest a shift in Th1/Th2 balance away from Th2 in rats made allergic to ovalbumin, an effect exacerbated by SO_2 exposure. These Th2-related changes are consistent with the observed increases in serum IgE and BALF eosinophils in ovalbumin-treated animals, effects which were also enhanced by SO_2 exposure. Alternatively, Th2-related changes may reflect a Type 2 immune response mediated by group 2 innate lymphoid cells. Taken together, these results indicate that repeated exposure to SO_2 exacerbated inflammatory and allergic responses in this animal model.

Two other follow-up studies by the same laboratory examined the effects of inhaled SO_2 on the asthma-related genes encoding epidermal growth factor (EGF), epidermal growth factor receptor (EGFR), and cyclooxygenase-2 (COX-2) and on apoptosis-related genes and proteins in this same model based on sensitization with ovalbumin (Xie et al., 2009; Li et al., 2008). While EGF and EGFR are related to mucus production and airway remodeling, COX-2 is related to inflammation and apoptosis and may play a role in regulating airway inflammation. SO_2 exposure enhanced the effects of ovalbumin challenge in this model, resulting in greater increases in mRNA and protein levels of EGF, EGFR, and COX-2 in the trachea compared with ovalbumin challenge alone. SO_2 exposure enhanced other effects of ovalbumin in this model, resulting in a greater decline in mRNA and protein levels of p53 and bax and a greater increase in mRNA and protein levels of bcl-2 in the lungs compared with ovalbumin challenge alone. The increased ratio of bcl-2:bax, an indicator of susceptibility to apoptosis, observed following ovalbumin challenge, was similarly enhanced by SO_2. Thus, repeated exposure to SO_2 may impact numerous processes that may be involved in inflammation and/or airway remodeling in allergic airway disease.

Summary of Subclinical Effects Underlying Asthma Exacerbation

Whereas previous evidence was limited and inconsistent, recent evidence from experimental studies supports a relationship between short-term exposure to SO_2 and allergic responses related to asthma. This includes findings of eosinophilic inflammation in individuals with asthma exposed acutely to SO_2. In addition, enhanced inflammation and allergic responses were demonstrated in animals made allergic to ovalbumin and exposed repeatedly to SO_2. Epidemiologic findings are inconsistent overall, including recent results based on SO_2 measured at or near children's schools. However, coherent with experimental studies, an SO_2-associated increase in pulmonary inflammation was observed in adults with asthma plus atopy. Copollutant confounding is not addressed in these results, but the evidence from animal toxicological studies provides some biological

plausibility for an effect of SO_2 exposure, particularly because effects in rats were shown to occur with repeated exposures and 24 hours after exposure ended. The evidence for SO_2-related allergic inflammation also supports evidence across disciplines for SO_2 effects on asthma symptoms, hospital admissions, and ED visits, as well as lung function decrements in people with asthma.

Summary of Asthma Exacerbation

The 2008 ISA for Sulfur Oxides did not explicitly draw a conclusion about a relationship between short-term SO_2 exposure and asthma exacerbation but described strong support from controlled human exposure studies for SO_2-induced lung function decrements and increases in respiratory symptoms in adults with asthma when ventilation rates were increased. Such effects in adolescents with asthma are less clear due to a paucity of data, but effects appear similar to adults. There are no laboratory studies of children exposed to SO_2; however, a number of studies have assessed airway responsiveness of children and adults exposed to the bronchoconstrictive stimuli methacholine. Based largely on those studies, school-aged children, particularly boys and perhaps obese children, might be expected to have greater responses (i.e., larger decrements in lung function) following exposure to SO_2 than adolescents and adults.

In adults with asthma, short-term exposures for 5−10 minutes to 0.2−0.3 ppm SO_2 resulted in 5−30% of exercising individuals experiencing moderate or greater decrements (i.e., ≥15% decrease in FEV_1 or ≥100% increase in sRaw; Table 5-2). Decrements in FEV_1 at 0.3 ppm SO_2 were statistically significant in responsive individuals (defined as those having an FEV_1 decrease of ≥15% after exposure to 0.6 or 1.0 ppm SO_2; Table 5-3). At concentrations greater than or equal to 0.4 ppm, 20−60% of asthmatics experienced SO_2-induced decrements in lung function, which were frequently accompanied by respiratory symptoms. There is a clear concentration-response relationship for exposures to SO_2 between 0.2 and 1.0 ppm, both in terms of increasing severity of effect and percentage of asthmatics affected. These concentrations are in the range of the highest 5-minute ambient SO_2 concentrations in some U.S. cities during 2010−2012 (Table 2-9).

Epidemiologic evidence generally supports SO_2-associated increases in asthma hospital admissions and ED visits, particularly in children (Figure 5-3), and respiratory symptoms in children with asthma (Figure 5-2; Table 5-8). Epidemiologic evidence is inconsistent for SO_2 associations with lung function decrements in adults and children with asthma (Table 5-6 and Table 5-7). For the limited results from previous epidemiologic and controlled human exposure studies on airway responsiveness (i.e., response to methacholine), an independent effect of SO_2 is unclear. Two controlled human exposure

studies demonstrated increased airway responsiveness to subsequent allergen challenge for at least 48 hours following SO_2 exposure in combination with a copollutant (i.e., NO_2). Most epidemiologic studies estimated SO_2 exposure from central site monitors. A few recent studies aimed to address the uncertainty in exposure estimates and observed asthma-related effects in association with SO_2 measured or modeled at or near school or homes. Studies did not statistically correct for measurement error, but in this new research area, a method has not been reported for short-term SO_2 exposure (Section 3.4.4). As in the 2008 ISA for Sulfur Oxides, copollutant confounding is unresolved in the epidemiologic evidence. Many recent studies continue to indicate that SO_2 associations with asthma hospital admissions and ED visits remain relatively unchanged in magnitude in copollutant models, but SO_2 associations with asthma symptoms and pulmonary inflammation often did not persist after adjustment for $PM_{2.5}$, EC/BC, or NO_2. The role of SO_2 in ambient multipollutant mixtures is not clearly elucidated. Controlled human exposure studies show asthma-related effects when SO_2 exposure occurs with O_3 or NO_2, and limited epidemiologic examination shows associations for multipollutant mixtures that contain SO_2. However, associations for mixtures containing SO_2 are similar to those for SO_2, CO, NO_2, PM_{10}, or $PM_{2.5}$ or less than the sum of single-pollutant effect estimates, indicating an overlap in associations for copollutants.

Expanded evidence for SO_2-induced allergic inflammation supports an effect of SO_2 exposure on asthma exacerbation. Epidemiologic findings of SO_2-associated increases in pulmonary inflammation are inconsistent, but enhanced allergic inflammation and allergic responses are demonstrated in a previous controlled human exposure study of adults with asthma plus atopy and multiple recent studies from a single laboratory in rats made allergic to ovalbumin and exposed repeatedly to 2 ppm SO_2. These findings provide some support for the epidemiologic associations for SO_2 with decreased lung function as well as increased airway responsiveness, respiratory symptoms, and pulmonary inflammation observed in most studies of children and adults with asthma plus atopy.

Much of the epidemiologic evidence for SO_2-associated asthma exacerbation is for 24-h avg SO_2 concentrations. Although 24-h avg and 1-h max SO_2 concentrations are correlated at the same monitor, it is not clear whether this correlation applies across a community. Some recent studies add evidence for association for asthma symptoms and ED visits with increases in 1-h max SO_2 concentrations, including SO_2 measured at schools. For lung function decrements, pulmonary inflammation, and asthma hospital admission and ED visit studies, several results indicate associations for 3- or 4-day avg SO_2 concentrations. The evidence for enhanced allergic inflammation, which is seen after repeated 2 ppm SO_2 exposures and 24 hours after exposure ended, somewhat supports the biological plausibility of epidemiologic associations with asthma-related outcomes.

Moreover, controlled human exposure studies clearly demonstrate that SO_2 exposures of 0.2−0.6 ppm can induce effects related to asthma exacerbation.

5.2.1.3 Allergy Exacerbation

The evidence described in the preceding section for SO_2 and allergen coexposure enhancing inflammation in rodent models of allergic airway disease indicates that SO_2 exposure may increase the sensitivity of people with allergic asthma to an allergen. This evidence also suggests the potential for SO_2 exposure to affect respiratory responses in people with allergy but not asthma. The 2008 ISA for Sulfur Oxides did not make distinct statements about a relationship with SO_2 exposure, but relevant epidemiologic studies had inconsistent findings. Recent epidemiologic evidence is also uncertain, including that for school SO_2 measurements.

Lung Function in Populations with Allergy

Previous epidemiologic studies examined children or adults with allergy but no asthma, defined by high serum IgE levels but no bronchial hyperresponsiveness, and did not indicate associations between short-term increases in ambient SO_2 concentration and decreases in lung function (Boezen et al., 2005; Boezen et al., 1999). The same studies observed associations for groups with asthma plus allergy. Previous findings were based on 24-h avg SO_2 measured at a single site in each city. The only available recent study measured SO_2 at children's schools (Correia-Deur et al., 2012), which may better represent some component of subjects' exposures. Also, the temporally resolved 2-h avg metric is more comparable to the exposure durations examined in experimental studies. In this group of children with allergy in São Paolo, Brazil, SO_2 had an imprecise association with PEF with a wide 95% CI [−0.82% (95% CI: −1.9, 0.31) per 10-ppb increase in 2-h avg SO_2]. Results were similar for allergy defined by high serum IgE levels alone like previous studies and by multiple criteria (i.e., high IgE levels, positive skin prick test, and high blood eosinophil levels). There was evidence for an association among all children (with and without allergy), but that was attenuated in copollutant models with PM_{10}, NO_2, or CO. Correlations with SO_2 were not reported.

Respiratory Symptoms and Physician Visits in Populations with Allergy

Limited to epidemiologic studies, evidence for an association between short-term SO_2 exposure and allergy symptoms is inconsistent. Nonspecific upper and lower respiratory symptoms were examined in children and adults with high IgE levels but no bronchial

hyperresponsiveness, and associations with SO_2 were inconsistent (Boezen et al., 2005; Boezen et al., 1999). For symptoms specific to allergy, Villeneuve et al. (2006b) observed an SO_2-associated increase in physician visits for allergic rhinitis in older adults. Recent findings for allergic rhinitis or eczema in children are mixed. However, inference about an SO_2 effect is weak both for results indicating an association (Kim et al., 2016a) and results not indicating an association (Annesi-Maesano et al., 2012; Linares et al., 2010). Limitations include cross-sectional design (Annesi-Maesano et al., 2012; Linares et al., 2010), analysis of a multipollutant model with NO_2, O_3, PM_{10}, and pollen (Kim et al., 2016a; Annesi-Maesano et al., 2012), lack of consideration of confounding by meteorological factors (Kim et al., 2016a), or inclusion of children with and without allergy in analysis of eczema (Linares et al., 2010). For results supporting a relationship with allergy symptoms, associations were observed with same-day (lag 0) 24-h avg SO_2 concentrations. These concentrations were from a single monitor in the city, and information was not reported on the extent to which the measurements represented the spatiotemporal variability in SO_2 concentrations in the study area. Associations were observed with copollutants such as NO_2, PM_{10}, and BS, although these results were inconsistent as well (Villeneuve et al., 2006b; Boezen et al., 2005; Boezen et al., 1999). Correlations with SO_2 concentrations were not reported, and copollutant models were not analyzed. Thus, the extent to which the supporting findings may indicate an independent association for SO_2 is unclear.

Subclinical Effects Underlying Allergy Exacerbation

In addition to the animal toxicological evidence for SO_2-enhanced allergic inflammation, a previous epidemiologic study of children with atopy found an SO_2-associated decrease in blood eosinophil number, which was presumed to reflect increased recruitment to the airways (Soyseth et al., 1995). Exposure assessment from a monitor 2 km from most subjects' homes is an uncertainty, as is confounding by PM. The study was conducted in a European city with an aluminum smelter that emitted SO_2 and PM, and PM was not examined for association with eosinophils.

5.2.1.4 Chronic Obstructive Pulmonary Disease Exacerbation

COPD is a lung disease characterized by deterioration of lung tissue and airflow limitation. Reduced airflow can decrease lung function, and clinical symptoms demonstrating exacerbation of COPD include cough, dyspnea, sputum production, and shortness of breath. Severe exacerbation can lead to hospital admissions or ED visits. This spectrum of outcomes has been evaluated in relation to short-term SO_2 exposure,

and evidence across outcomes and disciplines is inconsistent. This applies to the small body of studies available for the 2008 ISA for Sulfur Oxides (U.S. EPA, 2008d) as well as the few available recent studies. Recent findings come from epidemiologic studies, and most are for hospital admissions and ED visits.

Lung Function and Respiratory Symptoms

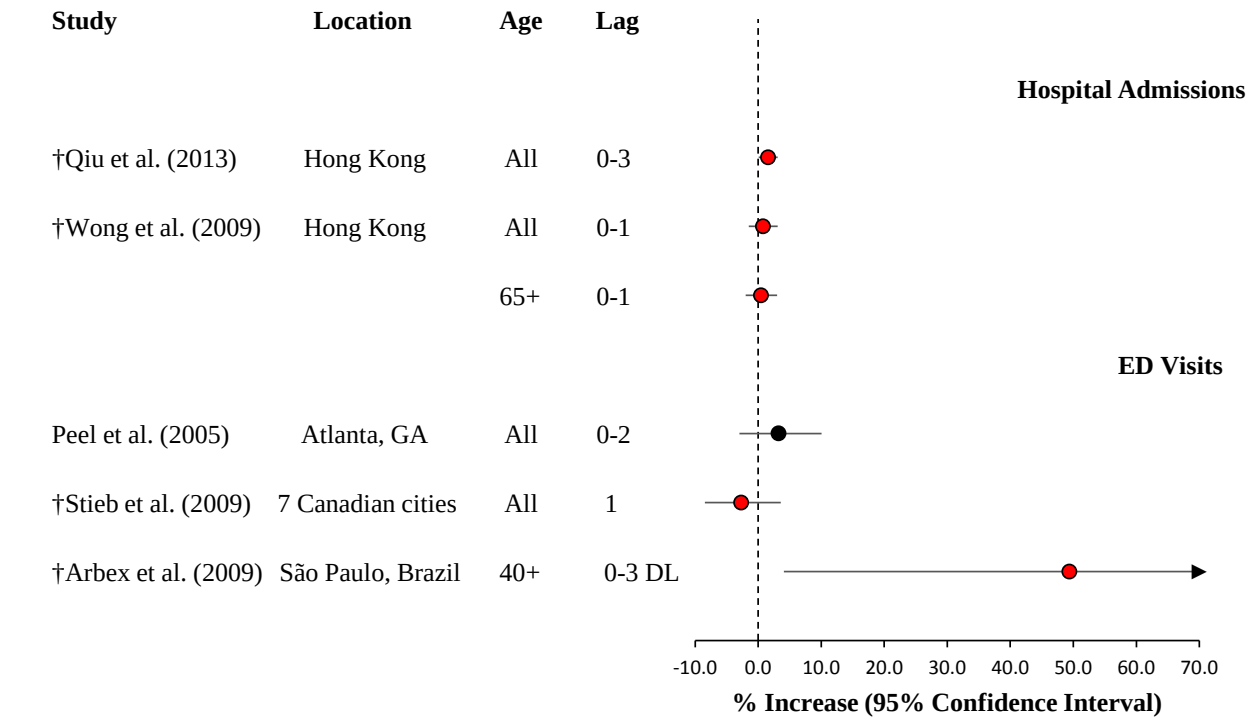
Evidence from a controlled human exposure study and epidemiologic studies does not support an effect of SO_2 exposure on lung function in adults with COPD. Recent epidemiologic studies add information on respiratory symptoms and mostly do not indicate an association with ambient SO_2 concentrations.

Linn et al. (1985a) reported that a 15-minute exposure to 0.4 and 0.8 ppm SO_2 had no effect on lung function in older adults with physician-diagnosed COPD. These adults were much older than the adults with asthma (Table 5-2) or healthy adults (Table 5-15) examined in controlled human exposure studies. Also, the level of exercise in adults with COPD ($\dot{V}_E$ = 18 L/minute) was lower than that of individuals with asthma, which effectively lowers the SO_2 dose delivered to the lungs (Section 4.2.2). Neither the previous nor recent epidemiologic study observed SO_2-associated decrements in lung function in adults with COPD (Peacock et al., 2011; Harre et al., 1997). Both studies estimated SO_2 exposure from a central site monitor(s), and examined 24-h avg concentrations lagged 1 day. Whereas previous results were based on a multipollutant model (with PM_{10}, NO_2, O_3), which often is unreliable, recent results were based on a single-pollutant model. Associations were imprecise with wide 95% CIs [e.g., 0.31 L/minute (95% CI: −0.10, 0.72) change in PEF per 10-ppb increase in SO_2 and OR 1.01 (95% CI: 0.89, 1.15) for PEF decrement greater than 20%] (Peacock et al., 2011). Mean and 75th percentile SO_2 concentrations were 7.5 and 9.3 ppb, respectively. SO_2 mostly was not associated with dyspnea, sputum changes, wheeze/tight chest, or other respiratory symptoms (Wu et al., 2016; Peacock et al., 2011). Wu et al. (2016) examined a period of higher SO_2 concentration (median 17 ppb and 75th percentile 27 ppb) and observed dyspnea to increase with an increase in 3- to 6-day avg SO_2 (OR: 1.88 [95% CI: 1.06, 3.34] per 10-ppb increase in 3-day avg SO_2). However, there was a wide range of distance from subjects to the monitor (1.6−8.8 km), and associations also were observed with moderately correlated (r = 0.51−0.68) $PM_{2.5}$, PM_{10}, and NO_2.

Hospital Admissions and Emergency Department Visits

Of the studies evaluated in the 2008 SO_X ISA, only one U.S. or Canadian-based study examined the association between short-term SO_2 exposure and COPD hospital

admissions or ED visits (Figure 5-7). Recent studies add to the initial evidence, which generally indicates no association between short-term SO_2 exposures and COPD hospital admissions and ED visits. Additionally, most studies averaged SO_2 concentrations over multiple monitors and examined 24-h avg exposure metrics, which, may not adequately capture the spatial and temporal variability in SO_2 concentrations (Section 3.4.2.). For each of the studies evaluated in this section, Table 5-12 presents the air quality characteristics of each city or across all cities, the exposure assignment approach used, and information on copollutants examined in each COPD hospital admission and ED visit study. Other recent studies of COPD hospital admissions and ED visits are not the focus of this evaluation because of various study design issues, as initially detailed in Section 5.2.1.2, but the full list of these studies, as well as study-specific details, 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. 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 SOx 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_X ISA and studies published since the 2008 SO_X ISA.

Study	Location Years	Exposure Assignment	Metric	Mean Concentration ppb	Upper Percentile Concentrations ppb	Copollutants Examined
Hospital admissions						
†(Qiu et al. (2013b); Ko et al. (2007a))	Hong Kong, China (1998−2007)	Average of SO_2 concentrations from 10 monitoring stations	24-h avg	7.4	NR	Correlations (*r*): O_3: 0.173 Copollutant models: PM_{10}
†Wong et al. (2009)	Hong Kong, China (1996−2002)	Average of SO_2 concentrations from eight monitoring stations	24-h avg	6.8	75th: 8.4 Max: 41.8	Correlations (*r*): NR Copollutant models: none
ED visits						
Peel et al. (2005)	Atlanta, GA (1993−2000)	Average of SO_2 concentrations across monitors for several monitoring networks	1-h max	16.5	90th: 39.0	Correlations (*r*): $PM_{2.5}$: 0.17 PM_{10}: 0.20 $PM_{10-2.5}$: 0.21 UFP: 0.24 $PM_{2.5}$ water soluble metals: 0.00 $PM_{2.5}$ sulfate: 0.08 $PM_{2.5}$ acidity: −0.03 $PM_{2.5}$ OC: 0.18 $PM_{2.5}$ EC: 0.20 Oxygenated HCs: 0.14 O_3: 0.19 CO: 0.26 NO_2: 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_X ISA and studies published since the 2008 SO_X ISA.

Study	Location Years	Exposure Assignment	Metric	Mean Concentration ppb	Upper Percentile Concentrations ppb	Copollutants Examined
†(Stieb et al. (2009))	Seven Canadian cities (1992−2003)	Average SO_2 concentrations across all monitors in each city. Number of SO_2 monitors in each city ranged from 1−11.	24-h avg	2.6−10.0	75th: 3.3−13.4	Correlations (*r*) only reported by city and season. Copollutant models: none
†(Arbex et al. (2009))	São Paulo, Brazil (2001−2003)	Average of SO_2 concentrations across 13 monitoring stations	24-h avg	5.3	75th: 6.6 Max: 16.4	Correlations (*r*): PM_{10}: 0.77 NO_2: 0.63 CO: 0.52 Copollutant models: none

CO = carbon monoxide; EC = elemental carbon; HC = hydrocarbon; NR = not reported; O_3 = ozone; OC =organic carbon; NO_2 = nitrogen dioxide; PM_{10} = particulate matter with nominal aerodynamic diameter less than or equal to 10 µm; $PM_{2.5}$ = particulate matter with nominal aerodynamic diameter less than or equal to 2.5 µm; $PM_{10-2.5}$ = 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_2 = sulfur dioxide; UFP = ultrafine particle.

† = Studies published since the 2008 ISA for Sulfur Oxides.

Hospital Admissions

Of the studies evaluated in the 2008 SO_X ISA, relatively few examined the association between short-term SO_2 exposure and COPD hospital admissions, and evidence of an association was inconsistent across studies. Although several recent studies assessed the relationship between short-term SO_2 exposures and COPD hospital admissions, the overall body of evidence remains limited.

Wong et al. (2009) in a study that examined the potential modification of the relationship between air pollution and respiratory-related hospital admissions by influenza, also focused on cause-specific respiratory hospital admissions, including COPD. When focusing on the baseline effect of short-term SO_2 exposures on COPD hospital admissions, the authors found limited evidence of an association at lag 0−1 days for a 10-ppb increase in 24-h avg SO_2 concentrations in analyses of both all ages [0.8% (95% CI: −1.5, 3.1)] and individuals over the age of 65 [0.5% (95% CI: −2.0, 3.0)].

In an additional study conducted in Hong Kong, Qiu et al. (2013b) focused on whether there is evidence of modification of the air pollution-COPD hospital admissions relationship by season and humidity. Compared to Wong et al. (2009), Qiu et al. (2013b) included 5 additional years of recent data through the year 2007. In single-pollutant models focusing on the association between short-term SO_2 exposures and COPD hospital admissions, for a multiday lag of 0−3 days, the authors reported a 1.6% increase (95% CI: 0.1, 3.1) for a 10-ppb increase in 24-h avg SO_2 concentrations. The magnitude of the SO_2 association was found to differ between Qiu et al. (2013b) and Wong et al. (2009), but the reason for the difference remains unclear, considering that similar data sources were used in each study. It is important to note that neither study conducted copollutant analyses for the entire study duration nor provided detailed information on the correlation between the air pollutants examined to help in the assessment of whether SO_2 has an independent effect on COPD hospital admissions.

Emergency Department Visits

The 2008 SO_X ISA identified relatively few studies that examined the association between short-term SO_2 exposure and COPD ED visits, and across studies there was inconsistent evidence of an association. Although recent studies continued to assess the relationship between short-term SO_2 exposures and COPD ED visits, the overall body of evidence remains limited.

In the seven Canadian cities study discussed previously, and consistent with the asthma ED visits results, Stieb et al. (2009) did not find any evidence of associations between 24-h avg SO_2 and COPD ED visits at single-day lags of 0 to 2 days. Additionally, there was no evidence of consistent associations between any pollutant and COPD ED visits at subdaily time scales (i.e., 3-h avg of ED visits vs. 3-h avg pollutant concentrations).

Arbex et al. (2009) also examined the association between COPD and several ambient air pollutants, including SO_2, in a single-city study conducted in São Paulo, Brazil for individuals over the age of 40 years. The authors examined associations between short-term SO_2 exposures and COPD ED visits in both at single-day lags (0 to 6 days) and in a polynomial distributed lag model (0−6 days). The authors found evidence that the magnitude of the association was larger at multiday lags compared to single-day lags, with the lag of 0−3 days from the distributed lag model [49.4% (95% CI: 4.1, 113.7) for a 10-ppb increase in 24-h avg SO_2 concentrations] most representative of the pattern of associations across single-day lags. Although the 0−6-day distributed lag model had the largest risk estimate, it was not supported by the single-day lag results that showed the strongest associations at lags of 0 and 1 day. It is important to note that Arbex et al. (2009) did not conduct copollutant analyses, but unlike correlations with SO_2 observed in other locations, SO_2 was highly correlated with PM_{10} (r = 0.77) and moderately

correlated with NO_2 (r = 0.63) and CO (r = 0.52) in this study. The results of Arbex et al. (2009) provide evidence of a potentially prolonged SO_2 effect on COPD ED visits; however, the results should be viewed with caution because effect estimates are not precise, time series is short, and there is potential for copollutants confounding.

Seasonal Analyses

Traditionally, epidemiologic studies have examined potential seasonal differences in associations by stratifying by season. In the study of air pollution and COPD hospital admissions in Hong Kong, Qiu et al. (2013b) examined potential seasonal differences in associations by this traditional approach but also examined whether the combination of season and humidity modify the air pollution-health effect association. In seasonal analyses, the authors found a stronger association at lag 0−3 for a 10-ppb increase in 24-h avg SO_2 concentrations during the cool season (November−April) [2.7% (95% CI: 0.5, 4.9)] compared to the warm season (May−October) [0.6% (95% CI: −1.1, 2.3)]. Qiu et al. (2013b) then examined whether the seasonal differences in associations observed were due to low humidity days (i.e., relative humidity <80%) or high humidity days (i.e., relative humidity ≥80%) by examining the interaction between the various combinations of season and humidity. When focusing on the combined effect of season and humidity, SO_2 concentrations were found to be highest on days with low humidity in both seasons. In the warm season, there was no evidence of an association regardless of whether the interaction between season and low or high humidity days were examined. In the cold season, at lag 0−3 for a 10-ppb increase in 24-h avg SO_2 concentrations, Qiu et al. (2013b) reported the strongest association during days with low humidity [5.3% (95% CI: 2.4, 8.3)] compared to high humidity [0.5% (95% CI: −2.6, 3.7)], suggesting that the combination of season and humidity plays a role in the relationship between air pollution and health effects. However, when examining copollutant models with PM_{10}, associations in all season and humidity combinations were attenuated, with only the association in the cool season and low humidity combination remaining positive, albeit with large uncertainty estimates [0.8% (95% CI: −2.1, 3.9); lag 0−3 for a 10-ppb increase in 24-h avg SO_2 concentrations]. The results from Qiu et al. (2013b) are consistent with evidence from controlled human exposure studies demonstrating that SO_2 responses are exacerbated in colder and dryer conditions (Section 5.2.1.2). However, these studies focused on lung function changes in people with asthma and it is unclear how these results correspond to results from an epidemiologic study of COPD hospital admissions. Additionally, it is important to note the potential influence of geographic location on the results from studies that examine the seasonal patterns of associations.

Lag Structure of Associations

Only a limited number of studies examined the lag structure of associations for SO_2-related COPD hospital admissions and ED visits. Qiu et al. (2013b) in the examination of air pollution and COPD hospital admissions in Hong Kong conducted analyses to evaluate associations with SO_2 at both single-day and multiday lags of 0−3 days. The authors found the strongest evidence for an SO_2-COPD hospital admission association at a multiday lag of 0−3 days, with additional evidence of positive associations at single-day lags of 1 day and 3 days.

Arbex et al. (2009), when examining associations between SO_2 exposure and COPD ED visits in São Paulo, Brazil, focused on both single-day lags (0 to 6 days) and a polynomial distributed lag (0−6 day) model. The authors found evidence that the magnitude of the association was larger at multiday lags compared to single-day lags, and the magnitude of the association increased as the number of lag days examined increased, specifically across lags of 0−1, 0−2, and 0−5 days. However, the 0−5-day distributed lag model results were not supported by the single-day lag results, which indicated that the effect of SO_2 on COPD ED visits was rather immediate, occurring in the range of lag 0 and 1 days. Collectively, the results of Qiu et al. (2013b) and Arbex et al. (2009) provide initial evidence suggesting a potential prolonged effect of SO_2 on COPD hospital admissions and ED visits. However, the collective evidence indicating a potential association between short-term SO_2 exposures and COPD hospital admissions and ED visits remains relatively small.

Summary of Chronic Obstructive Pulmonary Disease Exacerbation

Across disciplines and outcomes, evidence from previous and recent studies does not clearly support a relationship between short-term SO_2 exposure and COPD exacerbation. The evidence base is relatively small and mostly comprises epidemiologic studies. Neither the single controlled human exposure study nor the few epidemiologic studies indicate SO_2-related lung function changes in adults with COPD, and recent epidemiologic studies mostly reported no association with an array of respiratory symptoms, including sputum changes and dyspnea, which are characteristic of COPD exacerbation. There is similarly inconsistent evidence for association between short-term increases in ambient SO_2 concentration and hospital admissions and ED visits for COPD (Figure 5-7). Hospital admissions, ED visits, lung function, and symptoms were examined in relation to 24-h avg SO_2 concentrations, but an association was not observed with 1-h max SO_2 either. The supporting evidence is limited largely to an association of COPD hospital admissions and ED visits with same-day and 4-day avg SO_2 concentrations. All epidemiologic studies estimated SO_2 exposure from central site

monitors. SO_2 generally has low to moderate spatial correlations across urban geographical scales, and the potential error in the exposure estimates in adequately representing the spatiotemporal variability is uncharacterized in the evidence (Section 3.4.2.2). The uncertainty in exposure estimates especially applies to 1-h max SO_2. COPD hospital admissions were associated with PM_{10}, NO_2, and O_3. PM_{10} was highly correlated with SO_2 (r = 0.77) or when analyzed in a copollutant model, attenuated the SO_2 association and produced wide 95% CIs. The copollutant model results have unclear implication due to uncertainty in the exposure estimates and unreported SO_2-PM_{10} correlation. Overall, there is inconsistent evidence for an effect of SO_2 exposure on COPD exacerbation, and for the limited supporting evidence, an effect of SO_2 exposure that is independent of copollutants is unclear.

5.2.1.5 Respiratory Infection

The respiratory tract is protected from exogenous pathogens and particles through various lung host defense mechanisms that include mucociliary clearance, phagocytosis by alveolar macrophages, and innate and adaptive immunity. There is a paucity of evidence related to host defense from animal toxicological experiments using ambient-relevant concentrations of SO_2. Several studies of short-term exposure to SO_2 were reported in the 1982 AQCD (U.S. EPA, 1982a) and discussed in the 2008 SO_X ISA (U.S. EPA, 2008d). Findings of short-term studies included some effects of 0.1−1 ppm SO_2 on the clearance of labeled particles. No new animal studies of the effects of SO_2 exposure on lung host defense have been conducted since the previous review. A small number of previous epidemiologic studies reported SO_2-associated increases in respiratory infections as self-reported or indicated by hospital admissions and ED visits. However, many results were noted as being unreliable because they were based on statistical methods prone to bias.

Recent contributions to the evidence are limited to epidemiologic studies, and the evaluation of this evidence focuses on hospital admissions and ED visits. There are recent studies of self-reported infections, and they inconsistently show associations with ambient SO_2 concentrations, [Supplemental Figure 5S-2 (U.S. EPA, 2016h)]. Results based on school or home SO_2 exposure estimates are limited by their cross-sectional design or examination of nonspecific symptoms such as fever. Other studies do not provide insight over studies of hospital admissions and ED visits on issues such as exposure measurement error, copollutant confounding, or potentially relevant exposure durations and concentrations. Recent studies of respiratory infection hospital admissions and ED visits provide some evidence for association with ambient SO_2 concentrations. However, copollutant confounding remains an uncertainty.

Hospital Admissions and Emergency Department Visits

The 2008 SO_X ISA contained limited evidence of an association between short-term SO_2 concentrations and respiratory conditions other than asthma or COPD. Although some studies evaluated respiratory infections, including respiratory tract infections and pneumonia, the majority of studies used generalized additive models with default convergence criteria in the analysis, and this statistical approach was shown to inaccurately calculate effect estimates and to underestimate standard errors. Additionally, of the studies evaluated in the 2008 SO_X ISA, only one study was conducted in the U.S. or Canada [i.e., (Peel et al., 2005)]. Recent studies have examined a variety of outcomes indicative of respiratory infection; however, none have examined the same respiratory infection outcome. Additionally, most studies averaged SO_2 concentrations over multiple monitors and examined 24-h avg exposure metrics, which may not adequately capture the spatial and temporal variability in SO_2 concentrations (Section 3.4.2). For each of the studies evaluated in this section, Table 5-13 presents the air quality characteristics of each city, or across all cities, the exposure assignment approach used, and information on copollutants examined in each respiratory infection hospital admission and ED visit study. Other recent studies of respiratory infection hospital admissions and ED visits are not the focus of this evaluation because of various study design issues, as initially detailed in Section 5.2.1.2, but the full list of these studies, as well as study specific details, can be found in Supplemental Table 5S-5 (U.S. EPA, 2016m).

Hospital Admissions

Although recent studies have continued to examine the association between short-term SO_2 exposures and respiratory infection hospital admissions, the overall evidence remains limited, primarily due to the variety of respiratory infection outcomes examined. In a study conducted in Ho Chi Minh City, Vietnam Mehta et al. (2013) and HEI (2012) examined the association between short-term air pollution exposures and pediatric (ages 28 days−5 years) hospital admissions for acute lower respiratory infections (ALRI, including bronchiolitis and pneumonia). In a time-stratified, case-crossover analysis focusing only on the average of a 1−6 day lag, the study authors reported a positive association, with large uncertainty estimates, between SO_2 and ALRI hospital admissions in the all-year analysis [7.0% (95% CI: −3.0, 19.1) for a 10-ppb increase in 24-h avg SO_2 concentrations]. A larger association was observed in the time-series analysis (HEI, 2012) (Figure 5-8). When examining copollutant models with PM_{10} and O_3, SO_2 associations increased slightly, with the percent increase ranging from 7.5−8.0%, respectively. However, in models with NO_2, the SO_2 association was attenuated, but remained positive [4.9% (95% CI: −6.0, 17.0) for a 10-ppb increase in 24-h avg SO_2 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_X ISA and studies published since the 2008 SO_X ISA.

Study	Location (Years)	Type of Visit (ICD 9/10)	Exposure Assignment	Metric	Mean Concentration ppb	Upper Percentile of Concentrations ppb	Copollutants Examined
Hospital admissions							
†HEI (2012) Mehta et al. (2013)	Ho Chi Minh City, Vietnam (2003−2005)	Acute lower respiratory infection (J13−16, 18, 21)	Average of SO_2 concentrations across nine monitors	24-h avg	8.2	Max: 30.5	Correlations (*r*): Dry season: PM_{10}: 0.32 O_3: 0.19 NO_2: 0.29 Rainy season: PM_{10}: 0.36 O_3: 0.65 NO_2: 0.01 Copollutant models: NO_2, PM_{10}, O_3
†Ségala et al. (2008)	Paris, France (1997−2001)	Bronchiolitis	Average SO_2 concentrations across 30 monitors	24-h avg	4.0	Max: 27.4	Correlations (*r*): BS: 0.76 PM_{10}: 0.73 NO_2: 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_X ISA and studies published since the 2008 SO_X ISA.

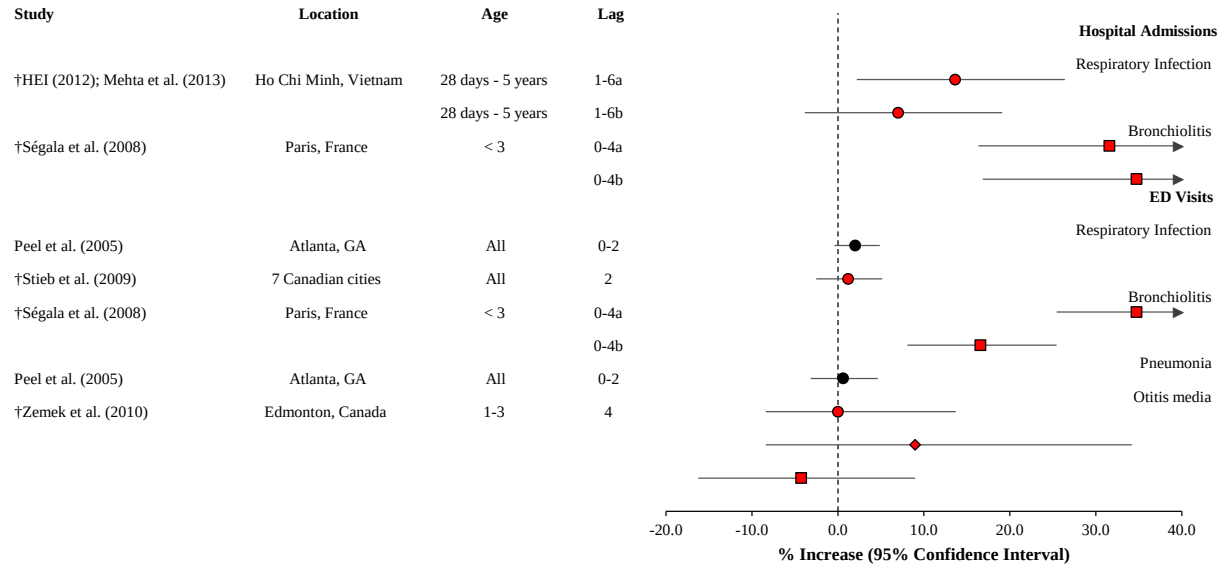
Study	Location (Years)	Type of Visit (ICD 9/10)	Exposure Assignment	Metric	Mean Concentration ppb	Upper Percentile of Concentrations ppb	Copollutants Examined
ED visits							
Peel et al. (2005)	Atlanta, GA (1993−2000)	Pneumonia (480−486)	Average of SO_2 concentrations from monitors for several monitoring networks	1-h max	16.5	90th: 39.0	Correlations (*r*): $PM_{2.5}$: 0.17 PM_{10}: 0.20 $PM_{10-2.5}$: 0.21 UFP: 0.24 $PM_{2.5}$ water soluble metals: 0.00 $PM_{2.5}$ sulfate: 0.08 $PM_{2.5}$ acidity: −0.03 $PM_{2.5}$ OC: 0.18 $PM_{2.5}$ EC: 0.20 Oxygenated HCs: 0.14 O_3: 0.19 CO: 0.26 NO_2: 0.34 Copollutant models: none
†Stieb et al. (2009)	Seven Canadian cities (1992−2003)	Respiratory infection (464, 466, 480−487)	Average SO_2 concentrations across all monitors in each city. Number of SO_2 monitors in each city ranged from 1−11.	24-h avg	2.6−10.0	75th: 3.3−13.4	Correlations (*r*) 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_X ISA and studies published since the 2008 SO_X ISA.

Study	Location (Years)	Type of Visit (ICD 9/10)	Exposure Assignment	Metric	Mean Concentration ppb	Upper Percentile of Concentrations ppb	Copollutants Examined
†Ségala et al. (2008)	Paris, France (1997−2001)	Bronchiolitis	Average SO_2 concentrations across 30 monitors	24-h avg	4.0	Max: 27.4	Correlations (*r*): BS: 0.76 PM_{10}: 0.73 NO_2: 0.78 Copollutant models: none
†Zemek et al. (2010)	Edmonton, AB (1992−2002)	Otitis media (382.9)	Average of SO_2 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 (*r*): NR Copollutant models: none
Outpatient and physician visits							
†Sinclair et al. (2010)	Atlanta, GA (1998−2002)	Upper respiratory infection Lower respiratory infection	SO_2 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 (*r*): 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_2 = nitrogen dioxide; O_3 = ozone; OC = organic carbon; PM = particulate matter; NR = not reported; *r* = correlation coefficient; SEARCH = Southeast Aerosol Research Characterization; SO_2 = 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_X 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.

In another study that also examined respiratory infections (i.e., bronchiolitis) in children, Ségala et al. (2008) focused on associations with winter (October−January) air pollution because that is when respiratory syncytial virus (RSV) activity peaks. It has been hypothesized that air pollution exposures may increase the risk of respiratory infections, including bronchiolitis due to RSV (Ségala et al., 2008). Focusing on children <3 years of age in Paris, France, the study authors conducted a bidirectional case-crossover analysis along with a time-series analysis to examine air pollution associations with bronchiolitis hospital admissions and ED visits (see ED visits section below). Although the authors specified that the bidirectional case-crossover approach was used to "avoid time-trend bias," it must be noted that the bidirectional approach has been shown to bias results (Ségala et al., 2008; Levy et al., 2001). In the case-crossover analysis, SO_2 was associated with bronchiolitis hospital admissions at lag 0−4 days for a 10-ppb increase in 24-h avg SO_2 concentrations [34.8% (95% CI: 19.5, 47.8)] with a similar risk estimate observed

for the time-series analysis [31.6% (95% CI: 13.7, 51.2)]. Although a positive association was observed, the authors did not conduct copollutant analyses. This omission complicates the interpretation of the results because SO_2 was highly correlated with the other pollutants examined, with correlations ranging from r = 0.73−0.87.

Emergency Department Visits

Similar to respiratory infection hospital admissions, recent studies have examined respiratory infection ED visits; however, these studies overall have not consistently examined the same respiratory infection outcomes (Figure 5-8). In their study of seven Canadian cities, Stieb et al. (2009) also examined the association between short-term SO_2 exposure and respiratory infection ED visits. The authors reported a positive association at a 2-day lag [1.2% (95% CI: −2.5, 5.2) for a 10-ppb increase in 24-h avg SO_2 concentrations], but there was uncertainty surrounding this result and there was no evidence of an association at single-day lags of 0 and 1 days. However, Ségala et al. (2008), in addition to examining bronchiolitis hospital admissions, also examined bronchiolitis ED visits. The authors reported evidence of an association between short-term SO_2 exposures and bronchiolitis ED visits [34.7% (95% CI: 25.5, 44.5); lag 0−4 for a 10-ppb increase in 24-h avg SO_2 concentrations]. However, as mentioned previously, the interpretation of these results is complicated by the lack of copollutant analyses and the high correlation between the pollutants examined (r = 0.73 to 0.87), along with the use of a bidirectional case-crossover approach.

In an additional study conducted in Edmonton, AB, Zemek et al. (2010) examined a new outcome for SO_2, otitis media (i.e., ear infections) ED visits, for ages 1−3 years. Associations were examined for single-day lags of 0 to 4 days in all-year as well as seasonal analyses. The authors found no evidence of an association between short-term SO_2 exposures and increases in ED visits for otitis media at any single-day lag in the all-year analysis.

Physician/Outpatient Visits

In a study conducted in Atlanta, GA as discussed in Section 5.2.1.2, Sinclair et al. (2010) examined the association between air pollution and respiratory infection (e.g., upper respiratory infections, lower respiratory infections) outpatient visits from a managed care organization. As detailed previously, the authors separated the analysis into two time periods - the first 25 months of the study period (i.e., August 1998−August 2000) and the second 28 months of the study period (i.e., September 2000−December 2002). A comparison of the two time periods indicated that risk estimates across outcomes tended to be larger in the earlier 25-month period compared to the later 28-month period. An examination of the respiratory infection outcomes found no evidence of an

association for upper respiratory infections at any lag and a positive association for lower respiratory infections for only lag 0−2.

Multiday Lags

In the case of respiratory infection hospital admission and ED visit studies, none of the studies evaluated conducted an extensive analysis of the lag structure of associations. However, Ségala et al. (2008) in a study of acute bronchiolitis examined multiday lags of 0−1 and 0−4 days, which does provide some indication of the lag structure of associations. The authors found relatively similar associations for both multiday lags, but the association was slightly larger for lag 0−4 days (i.e., 31.6 vs. 34.8%). These initial results indicate a potential prolonged effect of SO_2 that could lead to a respiratory infection hospital admission or ED visit.

Seasonal Analyses

A few of the recent studies that examined respiratory infection-related hospital admissions and ED visits also examined whether there was evidence of seasonal differences in associations. It should be noted that interpreting the results from these studies is complicated by the different geographic locations as well as the respiratory infection outcome examined in each study. Mehta et al. (2013) in the study of ALRI hospital admissions in Vietnam examined potential seasonal differences in associations by dividing the year into the dry (November−April) and rainy seasons (May−October). Within these seasons, SO_2 concentrations differed drastically, with mean 24-h avg SO_2 concentrations being 10.1 ppb in the dry season and 5.7 ppb in the rainy season. In seasonal analyses, Mehta et al. (2013) reported that SO_2 was consistently associated with ALRI hospital admissions in the dry season [16.1% (95% CI: 1.2, 33.3) for a 10-ppb increase in 24-h avg SO_2 concentrations, lag 1−6 day avg], with no evidence of an association in the rainy season. Of the other pollutants that were found to be positively associated with ALRI hospital admissions during the dry season (i.e., PM_{10} and NO_2), none were associated during the rainy season. In copollutant analyses for the dry season, SO_2 was robust to the inclusion of PM_{10} and O_3 in the model, with the magnitude of the effect remaining similar, 15.0 and 15.8%, respectively. However, in models with NO_2, the SO_2-ALRI hospital admission association was attenuated, but remained positive with large uncertainty estimates [10.0% (95% CI: −4.6, 26.9) for a 10-ppb increase in 24-h avg SO_2 concentrations, lag 1−6 day avg].

Additionally, Zemek et al. (2010) in the study of otitis media ED visits in Alberta, reported that the magnitude of the association was larger, albeit with wide confidence intervals, in the warm months (April−September), 9.0% (95% CI: −8.4, 34.2), compared

to the cold months, (October−March), −4.3% (95% CI: −16.30, 9.0) at lag 4 for a 10-ppb increase in 24-h avg SO_2 concentrations.

Summary of Respiratory Infection

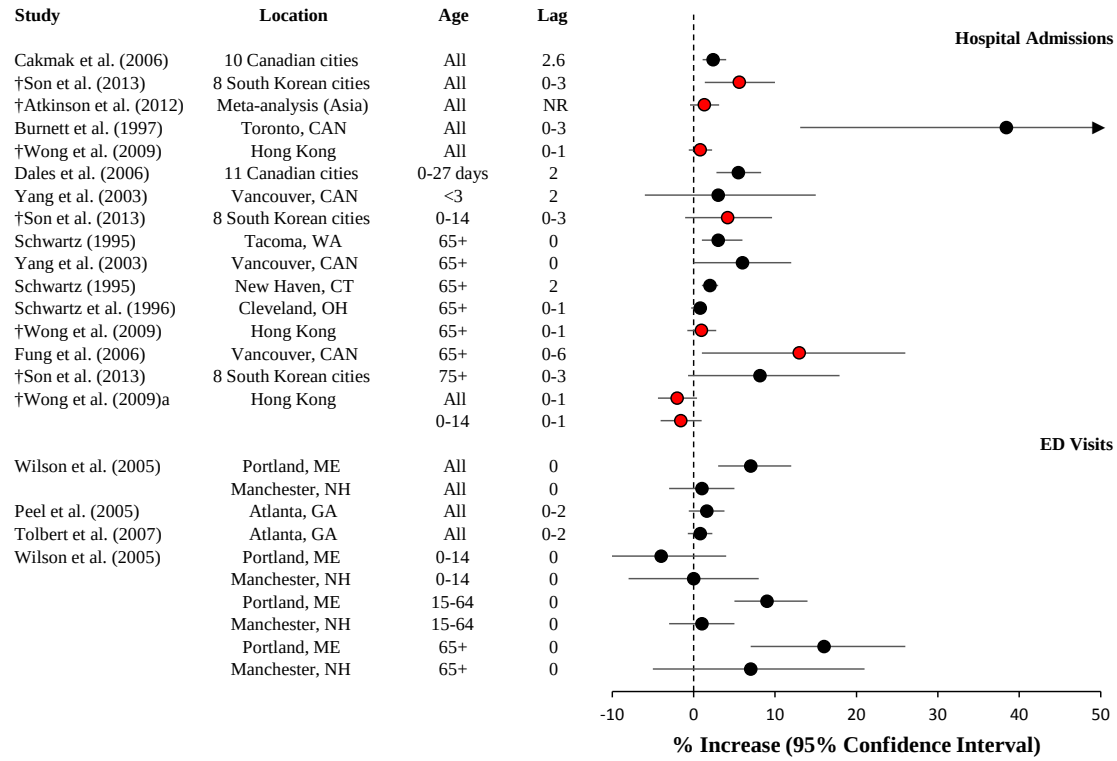
Recent evidence, which comes from epidemiologic studies, expands on that presented in the 2008 ISA for Sulfur Oxides and provides some, but not entirely consistent, support for an association between ambient SO_2 concentrations and respiratory infection. Whereas cross-sectional studies do not consistently link SO_2 exposures estimated for school or home to respiratory infections self-reported by children [Supplemental Figure 5S-2 (U.S. EPA, 2016h)], some evidence points to an association with hospital admission and ED visits (Figure 5-8). Associations are observed for all respiratory infections combined and bronchiolitis but not pneumonia or otitis media. The lack of multiple studies examining the same respiratory infection outcome complicates the interpretation of the collective body of evidence, specifically because the etiologies of upper and lower respiratory infections are vastly different.

Most supporting evidence points to associations with 24-h avg SO_2 concentrations averaged over 3 to 7 days, but an association was observed with temporally resolved 1-h max as well. The relatively small number of studies does not provide a strong basis for drawing inferences about the lag structure of associations with respiratory infection or potential seasonal differences in associations. An examination of potential factors that could modify the SO_2-respiratory infection hospital admission or ED visit association finds differences by SES but inconsistent differences by sex (Chapter 6). Recent studies continued to rely on central site monitors. SO_2 generally has low to moderate spatial correlations across urban geographical scales, which could contribute to some degree of exposure error (Section 3.4.2.2). Another uncertainty that persists in the recent evidence is copollutant confounding. Respiratory infection hospital admissions and ED visits were associated with $PM_{2.5}$, PM_{10}, BS, and NO_2. High SO_2-copollutant correlations were observed (r = 0.73−0.78). Correlations were low in some locations (r = 0.17−0.34) (Table 5-13), but these may not adequately reflect correlation in exposure due to differential measurement error, particularly for copollutants with different averaging times. New information from copollutant models shows an SO_2 association that is attenuated and made imprecise with adjustment for NO_2, but uncertainty in the exposure estimates weakens inference about independent associations. Information to assess the biological plausibility of epidemiologic findings is limited. There is some evidence in rodents that SO_2 exposures of 0.1−1 ppm diminish clearance of particles, but responses to infectious agents have not been examined in relation to ambient-relevant exposures.

5.2.1.6 Aggregated Respiratory Conditions

In addition to individual respiratory conditions, epidemiologic studies examined respiratory effects as an aggregate of multiple respiratory conditions (e.g., asthma, COPD, respiratory infections). Epidemiologic studies examining the association between short-term SO_2 exposures and respiratory-related hospital admissions or ED visits, including those discussed earlier in this chapter, were not available until after the completion of the 1986 Supplement to the Second Addendum of the 1982 SO_X AQCD (U.S. EPA, 1994). Therefore, the 2008 SO_X ISA (U.S. EPA, 2008d) included the first thorough evaluation of respiratory morbidity in the form of respiratory-related hospital admissions and ED visits. Of the studies evaluated, the majority consisted of single-city, time-series studies that primarily examined all respiratory disease or asthma hospital admissions or ED visits, with a more limited number of studies examining other respiratory outcomes, as discussed in previous sections. Additionally, most studies averaged SO_2 concentrations over multiple monitors and examined 24-h avg exposure metrics, which may not adequately capture the spatial and temporal variability in SO_2 concentrations (Section 3.4.2). The studies that examined all respiratory disease hospital admissions and ED visits generally reported positive associations (Figure 5-9). These associations were found to remain generally positive with some evidence of an attenuation of the association in models with gaseous pollutants (i.e., NO_2 and O_3) and particulate matter (U.S. EPA, 2008d).

Since the completion of the 2008 SO_X ISA, recent studies have examined the association between short-term exposure to ambient SO_2 and all respiratory disease hospital admissions and ED visits. For each of the studies evaluated in this section, Table 5-14 presents the air quality characteristics of each city or across all cities, the exposure assignment approach used, and information on copollutants examined in each hospital admission and ED visit study that examined all respiratory diseases. Other recent studies that have examined all respiratory disease hospital admissions and ED visits are not the focus of this evaluation because of various study design issues, as initially detailed in Section 5.2.1.2, but the full list of these studies, as well as study specific details, 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. 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_X 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_X ISA and studies published since the 2008 SO_X ISA.

Study	Location Years	Exposure Assignment	Metric	Mean Concentration ppb)	Upper Percentile of Concentrations ppb)	Copollutants Examined
Hospital admissions						
Cakmak et al. (2006)	10 Canadian cities (1993−2000)	Average of SO_2 concentrations across all monitors in each city	24-h avg	4.6	Max: 14−75	Correlations (r): NR Copollutant models: none
Dales et al. (2006)	11 Canadian cities (1986−2000)	Average of SO_2 concentrations across all monitors in each city	24-h avg	4.3[a]	95th: 3.5−23.5	Correlations (*r*): PM_{10}: −0.09 to 0.61 O_3: −0.41 to 0.13 NO_2: 0.20 to 0.67 CO: 0.19 to 0.66 Copollutant models: none
Burnett et al. (1997)	Toronto, ON (1992−1994)	Average of SO_2 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^+: 0.45 SO_4: 0.42 PM_{10}: 0.55 $PM_{2.5}$: 0.49 $PM_{10-2.5}$: 0.44 COH: 0.50 O_3: 0.18 NO_2: 0.46 CO: 0.37 Copollutant models: COH, PM_{10}, $PM_{10-2.5}$, $PM_{2.5}$

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_X ISA and studies published since the 2008 SO_X ISA.

Study	Location Years	Exposure Assignment	Metric	Mean Concentration ppb)	Upper Percentile of Concentrations ppb)	Copollutants Examined
Fung et al. (2006)	Vancouver, BC (1995−1999)	Average of SO_2 concentrations across all monitors within Vancouver	24-h avg	3.46	Max: 12.5	Correlations (*r*): CO: 0.61 COH: 0.65 O_3: −0.35 NO_2: 0.57 PM_{10}: 0.61 $PM_{2.5}$: 0.42 $PM_{10-2.5}$: 0.57 Copollutant models: none
Schwartz (1995)	New Haven, CT Tacoma, WA (1988−1990)	Average of SO_2 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 (*r*): NR Copollutant models: PM_{10}, O_3
Schwartz et al. (1996)	Cleveland, OH (1988−1990)	Average of SO_2 concentrations across all monitors	24-h avg	35.0	75th: 45.0 90th: 61.0	Correlations (*r*): NR Copollutant models: none
Yang et al. (2003b)	Vancouver, BC (1986−1998)	Average of SO_2 concentrations across four monitors	24-h avg	4.8	75th: 6.3 Max: 24.0	Correlation (*r*): O_3: −0.37 Copollutant models: O_3
†Son et al. (2013)	Eight South Korean cities (2003−2008)	Average of hourly ambient SO_2 concentrations from monitors in each city	24-h avg	3.2−7.3	NR	Correlation (*r*): PM_{10}: 0.5 O_3: −0.1 NO_2: 0.6 Copollutant models: none
†Atkinson et al. (2012)	Meta-analysis (Asia) (1980−2007)	NR	24-h avg	NR	NR	Correlation (*r*): 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_X ISA and studies published since the 2008 SO_X ISA.

Study	Location Years	Exposure Assignment	Metric	Mean Concentration ppb)	Upper Percentile of Concentrations ppb)	Copollutants Examined
†Wong et al. (2009)	Hong Kong, China (1996−2002)	Average of SO_2 concentrations from eight monitoring stations	24-h avg	6.8	75th: 8.4 Max: 41.8	Correlation (*r*): NR Copollutant models: none
ED visits						
Peel et al. (2005)	Atlanta, GA (1993−2000)	Average of SO_2 concentrations from monitors for several monitoring networks	1-h max	16.5	90th: 39.0	Correlations (*r*): $PM_{2.5}$: 0.17 PM_{10}: 0.20 $PM_{10-2.5}$: 0.21 UFP: 0.24 $PM_{2.5}$ water soluble metals: 0.00 $PM_{2.5}$ sulfate: 0.08 $PM_{2.5}$ acidity: −0.03 $PM_{2.5}$ OC: 0.18 $PM_{2.5}$ EC: 0.20 Oxygenated HCs: 0.14 O_3: 0.19 CO: 0.26 NO_2: 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_X ISA and studies published since the 2008 SO_X ISA.

Study	Location Years	Exposure Assignment	Metric	Mean Concentration ppb)	Upper Percentile of Concentrations ppb)	Copollutants Examined
Tolbert et al. (2007)	Atlanta, GA (1993−2004)	Average of SO_2 concentrations from monitors for several monitoring networks	1-h max	14.9	75th: 20.0 90th: 35.0	Correlations (*r*): PM_{10}: 0.21 O_3: 0.21 NO_2: 0.36 CO: 0.28 $PM_{10-2.5}$: 0.16 $PM_{2.5}$: 0.17 $PM_{2.5}$ SO4: 0.09 $PM_{2.5}$ EC: 0.22 $PM_{2.5}$ OC: 0.17 $PM_{2.5}$ TC: 0.19 $PM_{2.5}$ water soluble metals: 0.06 Organic hydrocarbon: 0.05 Copollutant models: none
Wilson et al. (2005)	Portland, ME Manchester, NH (1996−2000)	SO_2 concentrations from one monitor in each city	24-h avg	Portland: 11.1 Manchester: 16.5	NR	Correlation (*r*): Portland O_3: 0.05 Manchester O_3: 0.01 Copollutant models: none

CO = carbon monoxide; COH = coefficient of haze; EC = elemental carbon; H^+ = hydrogen ion; HC = hydrocarbon; OC = organic carbon; NO_2 = nitrogen dioxide; NR = not reported; O_3 = ozone; PM_{10} = particulate matter with a nominal aerodynamic diameter less than or equal to 10 µm; $PM_{2.5}$ = particulate matter with a nominal aerodynamic diameter less than or equal to 2.5 µm; $PM_{10-2.5}$ = 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_2 = sulfur dioxide; SO_4 = sulfate; TC = total hydrocarbon; UFP = ultrafine particle.

† studies published since the 2008 SO_X ISA.

Hospital Admissions

A recent multicity study conducted in Korea (Son et al., 2013) and a single-city study conducted in Hong Kong (Wong et al., 2009) provide additional insight into the relationship between short-term SO_2 exposures and hospital admissions for all respiratory diseases.

Son et al. (2013) examined the association between short-term exposures to air pollution and respiratory-related hospital admissions in eight South Korean cities. It is important to note that South Korea has unique demographic characteristics with some indicators more in line with other developed countries (e.g., life expectancy, percent of population living in urban areas), but because it represents a rapidly developing Asian country, it is likely to have different air pollution, social, and health patterns than less industrialized Asian nations or Western nations that developed earlier (Son et al., 2013). In a time-series analysis using a two-stage Bayesian hierarchical model, Son et al. (2013) examined both single-day lags and multiday lags up to 3 days (i.e., lag 0−3). For a lag of 0−3 days the authors reported a 5.6% increase (95% CI: 1.4, 10.0) in respiratory disease hospital admissions for a 10-ppb increase in 24-h avg SO_2 concentrations. The authors did not conduct copollutant analyses; however, SO_2 was found to be moderately correlated with PM_{10} (r = 0.5), NO_2 (r = 0.6), and CO (r = 0.6). The results of Son et al. (2013) add additional support to the results from the multicity studies evaluated in the 2008 SO_X ISA [i.e., (Cakmak et al. (2006); Dales et al. (2006))] in terms of the lag in which the strongest associations were observed and the magnitude of the association (Figure 5-9).

A greater degree of variability in the magnitude of the association between short-term SO_2 exposures and all respiratory hospital admissions was observed when evaluating single-city studies in the 2008 SO_X ISA (Figure 5-9). Wong et al. (2009) in a study conducted in Hong Kong reported results consistent with these earlier single-city studies for individuals over the age of 65 [1.0% (95% CI: −0.8, 2.8) for a 10-ppb increase in 24-h avg SO_2 concentrations at lag 0−1]. However, compared to studies that examined all ages, the magnitude of the association was much smaller [0.8% (95% CI: −0.6, 2.3) for a 10-ppb increase in 24-h avg SO_2 concentrations at lag 0−1]. Wong et al. (2009) also examined acute respiratory disease, which represents a smaller subset of outcomes within all respiratory diseases. When focusing on only acute respiratory disease, Wong et al. (2009) reported no evidence of an association at a 0−1 day lag for all ages [−2.0% (95% CI: −4.4, 0.4) for a 10-ppb increase in 24-h avg SO_2 concentrations].

The all-respiratory-disease hospital admissions results of Son et al. (2013) and Wong et al. (2009) are supported by the results of a meta-analysis conducted by Atkinson et al. (2012) that focused on studies conducted in Asian cities since 1980. The six estimates

from studies that examined the association between SO_2 and all respiratory hospital admissions were included in a random effects model, which yielded a 1.3% increase in respiratory hospital admissions (95% CI: −0.4, 3.2) for a 10-ppb increase in 24-h avg SO_2 concentrations. However, Atkinson et al. (2012) found some evidence of publication bias for associations between SO_2 and respiratory hospital admissions.

Emergency Department Visits

The 2008 SO_X ISA evaluated a few studies that examined the association between short-term SO_2 exposures and all respiratory ED visits [Figure 5-9, Supplemental Table 5S-8 (U.S. EPA, 2016o)]. These studies reported evidence of a positive association, but the magnitude of the association varied across study locations. However, these studies were limited in that they did not examine copollutant confounding. Recent studies that examined the association between air pollution and all respiratory ED visits have not examined associations with SO_2.

Model Specification—Sensitivity Analyses

A question that often arises when evaluating studies that examine the association between air pollution and a health effect is whether the statistical model employed adequately controls for the potential confounding effects of temporal trends and meteorological conditions. Son et al. (2013), in the study of eight South Korean cities, conducted sensitivity analyses to identify whether risk estimates changed depending on the df used to control for temporal trends and meteorological covariates (i.e., temperature, humidity, and barometric pressure). The authors reported that the association between short-term SO_2 exposures and all of the respiratory hospital admission outcomes examined (i.e., all respiratory diseases, allergic disease, and asthma) was sensitive to using less than 7 df per year, indicating inadequate control for temporal trends, but was stable when using 7−10 df per year. These results suggest that at least 7 df per year are needed to adequately account for temporal trends when examining the relationship between short-term SO_2 exposures and respiratory disease hospital admissions. However, additional studies have not systematically examined this issue for SO_2.

In an additional sensitivity analysis focusing on meteorological covariates (i.e., temperature, relative humidity, and barometric pressure), Son et al. (2013) examined whether risk estimates were sensitive to the degree of smoothing used and to the lag structure. The authors found that when varying the number of df for each covariate from 3 to 6 df and varying the lag structure (i.e., lag 0 and lag 0−3 days), the SO_2 association remained robust for all respiratory hospital admission outcomes.

Lag Structure of Associations

As stated previously, when examining associations between air pollution and a specific health outcome, it is informative to assess whether there is a specific exposure window for SO_2 that results in the strongest association with the health outcome of interest. In the examination of all respiratory disease hospital admissions, Son et al. (2013) focused on both single-day and multiday lags to address whether there is evidence of an immediate or persistent effect of SO_2. Across single-day lags of 0 to 3 days, positive associations were observed across each lag with the magnitude of the association being relatively similar across each lag (i.e., 2.4% for lag 0 and 2.1% for lags 1 to 3 days for a 10-ppb increase in 24-h avg SO_2 concentrations). When examining multiday lags of 0−1, 0−2, and 0−3 days, the authors reported an increase in the magnitude of the association as the length of the multiday lag increased with a 3.5% increase reported at lag 0−1 and a 5.6% increase reported for lag 0−3 days. Therefore, the limited evidence suggests that SO_2 effects occur within the first few days after exposure, but also that SO_2 effects on respiratory disease hospital admissions may persist over several days.

Examination of Seasonal Differences

Of the studies that examined all respiratory disease hospital admissions or ED visits, only Son et al. (2013) in the analysis of eight South Korean cities examined potential seasonal differences in SO_2 associations. However, it is important to note the potential influence of geographic location on the results from studies that examine potential seasonal differences in associations. For all outcomes examined, including respiratory diseases, the association with SO_2 was largest in magnitude during the summer, although confidence intervals were quite large [respiratory diseases: 21.5% (95% CI: −0.7, 48.3), lag 0−3, for a 10-ppb increase in 24-h avg SO_2 concentrations] with additional evidence of a positive association in the fall [8.9% (95% CI: −1.4, 20.7), lag 0−3, for a 10-ppb increase in 24-h avg SO_2 concentrations]. There was no evidence of an association between short-term SO_2 exposures and respiratory disease hospital admissions in either the spring or winter seasons. Across the eight cities, mean 24-h avg SO_2 concentrations were lowest during the summer season (4.4 ppb compared to a range of 4.8 to 7.0 in the other seasons) as was also the case for NO_2 and CO.

Summary of Aggregate Respiratory Conditions

Recent studies add to the evidence detailed in the 2008 SO_X ISA that indicated a generally positive association between short-term SO_2 exposures and respiratory disease hospital admissions and ED visits (Figure 5-9). These recent studies provide some insight

into previously identified limitations (i.e., model specification, lag structure of associations, and potential seasonal differences) in the SO_2-respiratory disease hospital admission and ED visits relationship. Initial evidence from a limited number of studies suggests that SO_2 associations are robust to alternative model specifications for weather covariates and that SO_2 associations are relatively stable in the range of df per year indicative of reasonable control for temporal trends (i.e., 7−10 df per year); however, more studies are needed to confirm these findings. Additionally, an examination of the lag structure of associations is in line with the results reported in studies that focused on a priori lags [i.e., associations tend to be strongest within the first few days after exposure, primarily within the range of 0 to 3 days (Figure 5-9)]. The potential seasonal patterns in SO_2 associations remain unclear due to the variability in SO_2 associations observed across different geographic locations, as reflected in studies of other respiratory hospital admission and ED visit outcomes. Some studies have also examined whether there is evidence that specific factors modify the SO_2-respiratory disease hospital admission or ED visit relationship and have found some evidence for potential differences by lifestage and influenza intensity (see Chapter 6). Studies of all respiratory hospital admissions and ED visits have not conducted extensive analyses to examine potential copollutant confounding. However, studies that reported SO_2 correlations with other pollutants found low ($r < 0.4$) to moderate ($r = 0.4−0.7$) correlations. Overall, the results of recent studies are limited in that they do not further inform the understanding of potential confounding by copollutants on the relationship between short-term SO_2 concentrations and respiratory disease hospital admissions and ED visits.

5.2.1.7 Respiratory Effects in General Populations and Healthy Individuals

The 2008 SO_X ISA (U.S. EPA, 2008d) reported respiratory effects of SO_2 in general populations and healthy individuals but did not make specific conclusions about the relationship. Respiratory effects were demonstrated in healthy individuals following SO_2 exposures ≥1.0 ppm in controlled human exposure studies. Animal toxicological studies demonstrated bronchoconstriction after a single SO_2 exposure and increased airway responsiveness and inflammation after repeated SO_2 exposures. Epidemiologic evidence was weak. The few recent toxicological studies corroborate previous results, but recent epidemiologic and controlled human exposure studies provide inconsistent results, including new results for pulmonary inflammation.

Lung Function Changes in General Populations and Healthy Individuals

Compared with evidence for lung function changes in individuals with asthma, evidence for SO_2-induced lung function effects in healthy individuals is weak. Most of the controlled human exposure studies evaluating these effects in healthy individuals were discussed in the 1982 SO_X AQCD (U.S. EPA, 1982a). While some studies showed that transient decreases in lung function can occur at concentrations of 1.0 ppm SO_2 under exercising or forced oral breathing conditions, the evidence was more consistent for exposures >1.0 ppm (U.S. EPA, 2008d). Epidemiologic associations between ambient SO_2 concentrations and lung function continue to be inconsistent in children. While recent results indicate associations in adults, inferences about SO_2 exposure still are weak because of uncertainty in the exposure estimates and copollutant confounding.

Controlled Human Exposure Studies

Evidence from controlled human exposure studies evaluating SO_2-induced lung function changes in healthy adults was extensively discussed in the 1982 AQCD (U.S. EPA, 1982a). In general, these studies demonstrated respiratory effects such as increased airway resistance and decreased FEV_1 following exposures to concentrations >1.0−5.0 ppm, while some studies demonstrated respiratory effects at 1.0 ppm.

Lung function changes in response to SO_2 exposure in controlled human exposure studies have been investigated since the early 1950s. Respiratory effects including increased respiration rates, decrements in peak flow, bronchoconstriction, and increased airway resistance have been observed in healthy human volunteers at concentrations ≥1.0 ppm (Lawther et al., 1975; Andersen et al., 1974; Snell and Luchsinger, 1969; Abe, 1967; Frank et al., 1962; Sim and Pattle, 1957; Lawther, 1955; Amdur et al., 1953). Although bronchoconstriction was observed in healthy subjects exposed to concentrations ≥5.0 ppm, shallow rapid respiration and increased pulse rate, decreased maximum expiratory flow from one-half vital capacity, and increased sRaw were observed following exposures as low as 1.0 ppm (Lawther et al., 1975; Snell and Luchsinger, 1969; Amdur et al., 1953). Overall, only these few studies have reported SO_2-induced respiratory effects in healthy individuals for 5−10-minute exposures at concentrations ≥1.0 ppm SO_2.

A limited number of studies examined lung function changes in healthy populations in response to ≥1 hour exposures to SO_2. Controlled human exposure studies examining lung function changes in healthy individuals exposed to SO_2 are summarized in Table 5-15. Andersen et al. (1974) reported that exposures of up to 6 hours to 1.0 ppm SO_2 in resting healthy adults induced decreases in $FEF_{25–75}$ and to a lesser extent FEV_1. Another human exposure study (van Thriel et al., 2010) reported that healthy subjects

exposed to SO_2 concentrations of 0.5, 1.0, or 2.0 ppm for 4 hours while exercising did not show changes in FEV_1. However, lung function measurements in this study were not performed between 40−100 minutes after exercise and more sensitive measures such as shallow rapid respiration or FEF_{25-75} were not reported. Healthy individuals at rest or exercising exhibited no changes in several measures of lung function following a 1 hour exposure to 0.2−0.6 ppm SO_2 (Tunnicliffe et al., 2003; Linn et al., 1987).

The interaction of SO_2 exposure with O_3 was reported in two studies. Hazucha and Bates (1975) demonstrated that a combined 2 hours exposure to low concentrations of O_3 (0.37 ppm) and SO_2 (0.37 ppm) has a greater effect on lung function than exposure to either agent alone in exercising adults. However using a similar study design, Bedi et al. (1979) did not observe a greater effect of the combined exposures compared with exposure to only O_3; exposure to SO_2 alone had no effect.

Epidemiologic Studies

Previous epidemiologic evidence was inconsistent for an association between ambient SO_2 concentrations and lung function in healthy adults or children and people recruited from the general population (U.S. EPA, 2008d). Studies mostly estimated SO_2 exposure from central site monitors and did not report whether the measurements well captured the spatiotemporal variability in the study areas. Some recent studies measured SO_2 at subjects' locations and observed associations with lung function decrements in adults but not consistently in children. Most studies examined 24-h avg SO_2 concentrations, which are much longer than the 5−10 minute exposures inducing lung function decrements in experimental studies. Inconsistency also is observed among recent results for temporally resolved metrics such as 1-h max and 1- to 10-h avg SO_2 concentrations, which is similar to controlled human exposure findings for 1- to 6-hour exposures to SO_2.

Adults. Among previous studies, an SO_2-associated decrease in lung function was observed in adults in Beijing, China where coal was used for domestic heating (Xu et al., 1991). Recent results are based on much lower SO_2 concentrations [means 7.3−8.6 ppb vs. 6.8−49 ppb in Xu et al. (1991)]. Associations are observed with lung function decrements in adults without respiratory disease (Table 5-16), with some based on 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
Andersen et al. (1974)	Healthy; n = 15; 15 M; 20−28 yr	0, 1, 5, or 25 ppm SO_2 for 6 h at rest	Nasal mucociliary flow Area of the nasal airway Airway resistance (FEV_1, $FEF_{25-75\%}$) Nasal removal of SO_2 Discomfort level symptoms
Linn et al. (1987)	Healthy; n = 24; 15 M, 9 F; 18−37 yr	0, 0.2, 0.4, or 0.6 ppm SO_2 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_1, 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
Raulf-Heimsoth et al. (2010)	Healthy; n = 16; 8 M, 8 F; 19−36 yr	0, 0.5, 1.0, or 2.0 SO_2 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
Tunnicliffe et al. (2003)	Asthma; n = 12 adults, 35.7 yr Healthy; n = 12 adults, 34.5 yr	0 or 0.2 ppm SO_2 for 1 h at rest	Symptoms, FEV_1, FVC, MMEF, exhaled NO, ascorbic and uric acid in nasal lavage fluid
van Thriel et al. (2010)	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_2 for 4 h with exercise for 15 min (bicycle, 75 Watts) two times during each session	Symptoms, FEV_1

EBC = exhaled breath condensate; EKG = electrocardiogram; F = female; $FEF_{25-75\%}$ = forced expiratory flow at 25−75% of exhaled volume; FEV = forced expiratory volume; FEV_1 = 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_2 = sulfur dioxide; sRaw = specific airway resistance.

The exposure characterization of Dales et al. (2013) is judged to be good because SO_2 was measured on site of adults' scripted exposures near (0.87 km) and away from (4.5 km at a college campus) a steel plant in Ontario. Another strength was the well-defined 8-hour exposure duration and lag between exposure and lung function testing. Higher SO_2 concentrations averaged over 10 hours (8 a.m.−6 p.m.) were

associated with decreases in several lung function parameters measured just after exposure (Table 5-16). For example, a 10-ppb increase in SO_2 was linked to a −0.50% FEV_1 change (95% CI: −1.0, 0.05). Son et al. (2010) also examined air pollution from industry, in this case a petrochemical complex in Ulsan, South Korea. Ambient SO_2 concentrations across the study area were highly variable. Between-monitor correlation varied widely (0−0.8), even for those 5 km apart, and the mean decreased from about 0.4 to 0.2 with increasing distance up to 20 km. Investigators aimed to capture this spatiotemporal variability by combining SO_2 measurements across monitors with inverse distance weighting or kriging. These metrics and that for the nearest monitor to the subjects' home, all 24-h avg SO_2, were associated with FVC but not FEV_1 (Table 5-16). The implications overall are unclear because many subjects lived far from a monitor, and potential confounding by meteorological factors and season were not considered. Both studies observed associations with copollutants among $PM_{2.5}$, PM_{10}, UFP, CO, NO_2, and O_3. Correlations among copollutants and analyses of confounding or interactions were not reported for personal exposures near the steel plant (Dales et al., 2013). For the study near the petrochemical complex, the decrease in FEV_1 for kriged SO_2 was larger after CO adjustment (Son et al., 2010) (Table 5-16). The effect estimate for CO became null, but the range of between-monitor correlations was 0−0.8. The effect estimate for SO_2 was attenuated with adjustment for O_3, which could be influenced by differential exposure measurement error. Between-monitor correlations were 0.4 to 0.8 for O_3.

Other studies reported SO_2-associated lung function decrements, but inference about SO_2 is weaker (Steinvil et al., 2009; Min et al., 2008a). Associations were observed for SO_2 after adjustment for NO_2 or CO, but correlations with SO_2 were 0.62−0.70, and single-pollutant associations for SO_2 were in opposing directions across lags and limited to lags of 3 or more days (Steinvil et al., 2009). Associations were observed with 1-h avg SO_2 concentrations lagged 5−30 hours, but confounding by meteorological factors was not considered (Min et al., 2008a). Also, both studies had cross-sectional design and estimated SO_2 exposure from monitors up to 11 km or unspecified distance from homes.

Children. Similar to previous studies, many recent studies of children examined populations with high prevalence (8−35%) of respiratory disease, such as asthma, and populations outside the U.S. and Canada. As examined in several recent studies, SO_2 at schools was inconsistently associated with lung function (Table 5-17). Previously, 1-h max SO_2 concentrations at school were not associated with lung function. Additional results for temporally resolved SO_2 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_2 Exposure Estimates (ppb)	SO_2 Averaging Time and Lag Day	Effect Estimate (95% CI) Single-Pollutant Model[a]	Copollutant Examination[a]
†Dales et al. (2013) 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.	Monitor on site of outdoor exposures Mean (SD) Near steel plant 7.8 (13) College campus 1.6 (4.2)	10-h avg (8 a.m.−6 p.m.) Lag 0 h	Percent change FEV_1: −0.50 (−1.0, 0.05) FVC: −0.45 (−1.1, 0.19) FEV_1/FVC: −0.15 (−0.31, 0.01) $FEF_{25-75\%}$: −0.44 (−0.74, −0.14) Total lung capacity −0.42 (−0.70, −0.13) Residual volume −2.1 (−4.1, −0.18)	No copollutant model Associations observed with $PM_{2.5}$, UFP, NO_2, and O_3. All pollutants higher at steel plant than at college campus. Copollutant correlations NR.
†Son et al. (2010) Ulsan, South Korea, 2003−2007 N = 2,102, ages 7−97 yr. Mean age 45 yr. Mean percent predicted FEV_1 83%. Cross-sectional. Supervised spirometry. Recruited from a meeting of residents near a petrochemical complex. Did not examine confounding by meteorological factors or season.	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	24-h avg 0−2 avg	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_1 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)	Copollutant model, lag 0−2 avg FVC Kriging with O_3: −1.8 (−4.0, 0.46) with CO: −8.8 (−11, −6.3) O_3 association persists with SO_2 adjustment. CO association attenuated. Association also observed with PM_{10} and NO_2 but no copollutant model. $PM_{2.5}$ not examined. Copollutant correlations NR.

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_2 Exposure Estimates (ppb)	SO_2 Averaging Time and Lag Day	Effect Estimate (95% CI) Single-Pollutant Model[a]	Copollutant Examination[a]
†Steinvil et al. (2009) 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 0 5 0−6 avg 0 5 0−6 avg 0 5 0−6 avg	Change in FEV_1 (mL) 93 (−90, 277) −300 (−487, −113) −447 (−750, −143) Change in FVC (mL) 53 (−167, 273) −373 (−600, −147) −560 (−927, −193) Percent change in FEV_1/FVC 716 (−6.5, 4,233) 237 (−79, 2,195) 220 (−217, 657)	Copollutant model, lag 5, FEV_1 (mL) with O_3: −220 (−413, −33) with NO_2: −280 (−527, −33) with CO: −247 (−473, −20) NO_2 and CO association attenuated with SO_2 adjustment. No association with O_3. SO_2 highly correlated with NO_2, moderately correlated with CO, weakly correlated with O_3. r = 0.70, 0.62, −0.24.
†Min et al. (2008a) 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 Lag 1 h	Results presented only in figure. Associations observed only in smokers. FEV_1 and FVC decrease after lag of 5−6 h. No association after 30 h.	No copollutants examined.

CI = confidence interval; CO = carbon monoxide; $FEF_{25-75\%}$ = forced expiratory flow at 25−75% of forced vital capacity; FEV_1 = forced expiratory volume in 1 sec; FVC = forced vital capacity; IDW = inverse distance weighting; max = maximum; mL = millilitres; N = sample size; NO_2 = nitrogen dioxide; NR = not reported; r = correlation coefficient; O_3 = ozone; $PM_{2.5}$ = particulate matter with nominal aerodynamic diameter less than or equal to 2.5 µm; PM_{10} = particulate matter with nominal aerodynamic diameter less than or equal to 10 µm; SD = standard deviation; SO_2 = sulfur dioxide, UFP = ultrafine particles.

[a]Effect estimates are standardized to a 10-ppb increase in 1-h to 24-h avg SO_2.

†Studies published since the 2008 Integrated Science Assessment for Sulfur Oxides.

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Table 5-17 Recent epidemiologic studies of lung function in healthy children and children in the general population.

Study Population and Methodological Details	SO_2 Exposure Estimates (ppb)	SO_2 Averaging Time and Lag Day	Effect Estimate (95% CI) Single-Pollutant Model[a]	Copollutant Examination[a]
†Correia-Deur et al. (2012) 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.	Monitor at school Mean (SD): 8.8 (3.3) 75th percentile: 11 90th percentile: 13	2-h avg 0 24-h avg 0	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	Copollutant model for group that included 65 children with atopy. SO_2 association near null with adjustment for PM_{10}, NO_2, or CO. SO_2 highly correlated with PM_{10}, moderately correlated with NO_2 & CO. Pearson r = 0.75, 0.60, 0.60
†Altuğ et al. (2014) Eskisehir, Turkey, Feb−Mar 2007 N = 535, ages 9−13 yr Cross-sectional. Supervised spirometry. Recruited from schools from participants of a larger study.	Monitor at school Mean and max Suburban: 21, 29 Urban: 29, 44 Urban-traffic: 22, 27	24-h avg 0−6 avg	Relative ratio for change Subjects without URS FVC: 1.00 (0.97, 1.03) FEV_1: 1.00 (0.97, 1.03) PEF: 1.00 (0.97, 1.03) MMEF: 1.00 (0.92, 1.08) Subjects with URS FVC: 1.00 (0.97, 1.03) FEV_1: 1.00 (0.97, 1.03) PEF: 1.00 (0.97, 1.03) MMEF: 1.03 (0.95, 1.11)	No copollutant model No association with O_3 or NO_2. $PM_{2.5}$ and PM_{10} not examined. SO_2 moderately correlated with NO_2, negatively correlated with O_3 in winter. r = 0.49, −0.40.

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_2 Exposure Estimates (ppb)	SO_2 Averaging Time and Lag Day	Effect Estimate (95% CI) Single-Pollutant Model[a]	Copollutant Examination[a]
†Altuğ et al. (2013) 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.	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	24-h avg 0−6 avg	OR for impaired lung function (predicted values <85% for FEV_1 or FVC or <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)	Copollutant model, girls, summer with O_3: 1.08 (0.63, 1.91) with NO_2: 1.14 (0.65, 1.99) O_3 association persists with SO_2 adjustment. No association for NO_2 overall. $PM_{2.5}$ and PM_{10} not examined. SO_2 moderately correlated with NO_2 and negatively correlated with O_3 in winter. r = 0.49, −0.40. Summer correlations NR.
†Castro et al. (2009) Rio de Janeiro, Brazil, 2004 N = 118, ages 6−15 yr. 18% asthma. Daily measures for 6 wk. Supervised PEF. Recruited from schools.	Monitor at school Mean (SD): 7.1 (6.8) 90th percentile: 16 Max: 37	24-h avg 1 2 3 0−1 avg 0−2 avg	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)	No copollutant model Associations observed with PM_{10} and CO but not NO_2. $PM_{2.5}$ not examined. Copollutant correlations NR.
†Chang et al. (2012b) Taipei, Taiwan, 1996−1997 N = 2,919, ages 12−16 yr. Cross-sectional. Supervised spirometry. Recruited from schools.	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	4-h avg 0 10-h avg 1 1-h max 0 1	Change in FEV_1 (mL) 0.4 (−32, 33) −117 (−193, −42) 3.6 (−21, 28) −85 (−129, −41)	No copollutant model Associations observed with PM_{10}, NO_2, CO, O_3. $PM_{2.5}$ not examined. Copollutant correlations NR.

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_2 Exposure Estimates (ppb)	SO_2 Averaging Time and Lag Day	Effect Estimate (95% CI) Single-Pollutant Model[a]	Copollutant Examination[a]
†Linares et al. (2010) 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	Monitors within 2 km of school Means spring−winter School 1: 12, 12, 10, 9.8 School 2: 9.1, 8.7, 10, 13	24-h avg 0	Units not reported FVC: −0.06 (−0.13, 0) FEV_1: −0.01 (−0.01, −0.00) PEF: −0.03 (−0.05, 0) FEV_1/FVC: −0.07 (−0.18, 0.03)	No copollutant model Associations observed with PM_{10} and O_3 but not NO_2. $PM_{2.5}$ not examined. Copollutant correlations NR.
†Reddy et al. (2012) 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.	Monitor at school Mean (SD): 5.8 (0.2) Max: 41	24-h avg 0−4 avg 3	Percent change FEV_1 diurnal variability (increase = poorer function) By *GSTM1* gene variant Null: −1.2 (−3.0, 0.54) Positive: 1.1 (0.45, 2.7) By *GSTP1* gene variant AG/GG: 3.1 (1.6, 4.7) AA: −0.73 (−2.2, 0.70)	No copollutant model Association observed with PM_{10} in *GSTP1* AG/GG group. NO_2 association in AA group. $PM_{2.5}$ not examined. Copollutant correlations NR.
†Makamure et al. (2016a) Durban, South Africa, 2004−2005 N = 71, ages 9−11 yr. 35% asthma. Part of the same cohort as Reddy et al. (2012) 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 1	Percent change FEV_1 diurnal variability (increase = poorer function) All subjects: 1.6 (−0.03, 3.3) By *CD14* gene variant CC: −1.5 (−3.4, −0.37) CT/TT: −3.6 (−7.1, −0.17)	No copollutant model Association observed with PM_{10} in CD14 CC group. No association with NO_2. $PM_{2.5}$ not examined. Copollutant correlations NR.

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_2 Exposure Estimates (ppb)	SO_2 Averaging Time and Lag Day	Effect Estimate (95% CI) Single-Pollutant Model[a]	Copollutant Examination[a]
†Makamure et al. (2016b) Durban, South Africa, 2004−2005 N = 104, ages 9−11 yr. 39% asthma. Part of the same cohort as Reddy et al. (2012) 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 1 2	Percent change FEV_1 diurnal variability (increase = poorer function) By *TNF-α* gene variant AA/GA: 2.3 (−0.29, 5.0) GG: 0.83 (−1.32, 3.0) AA/GA: 2.7 (0.52, 4.8) GG: 0.24 (−1.19, 1.68)	No copollutant model Association observed with NO_2 at lag 1 and NO at lag 2. No association with PM_{10} in AA/GA group. $PM_{2.5}$ not examined. Copollutant correlations NR.
†Amadeo et al. (2015) 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	1-h max 0 24-h avg 0−13 avg	All subjects Percent change post 6-min run 43 (−3,787, 3,873) Children without asthma Change in prerun PEF (L/min) 18 (−84, 119) Percent change post 6-min run 4.5 (−24, 33)	No copollutant model Association observed with 24-h avg O_3 measured at central site not PM_{10} or NO_2. $PM_{2.5}$ not examined. Copollutant correlations NR.

CI = confidence interval; CO = carbon monoxide; FEV_1 = forced expiratory volume in 1 sec; FVC = forced vital capacity; MMEF = maximum midexpiratory flow; N = sample size; NO_2 = nitrogen dioxide; NR = not reported; O_3 = ozone; OR = odds ratio; PEF = peak expiratory flow; $PM_{2.5}$ = particulate matter with nominal aerodynamic diameter less than or equal to 2.5 µm; PM_{10} = particulate matter with nominal aerodynamic diameter less than or equal to 10 µm; *r* = correlation coefficient; SD = standard deviation; SO_2 = sulfur dioxide; TNF-α = tumor necrosis factor-alpha; URS = upper respiratory symptoms.

[a]Effect estimates are standardized to a 10-ppb increase in 1-h to 24-h avg SO_2 or a 40-ppb increase in 1-h max SO_2.

†Studies published since the 2008 Integrated Science Assessment for Sulfur Oxides.

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For SO_2 measured at schools, there is no evidence for association with lung function in groups of children without respiratory disease or symptoms in Turkey or Brazil (Altuğ et al., 2014; Correia-Deur et al., 2012). Altuğ et al. (2014) examined only 1-wk avg SO_2, but Correia-Deur et al. (2012) was noteworthy for examining multiple averaging times and lags (i.e., 3- to 10-day avg). PEF also was measured at school and analyzed with the preceding 2-h avg SO_2 concentrations. The association was imprecise [−0.24% change (95% CI: −1.4, 0.96) in PEF per 10-ppb increase in SO_2]. Another strength of this study over similar ones is its repeated-measures design and clinical assessment of children's respiratory health status. Among the studies of school SO_2, an association with lung function was observed in another cohort of children from Brazil (Castro et al., 2009). The impact of the 18% of children with asthma on these results is unknown. The effect estimate was largest for 2-day avg SO_2 concentrations and imprecise for lag 1 and 2 (Table 5-17). Missing SO_2 concentration data for 52% of days could be one reason for the imprecision.

Some results for SO_2 measured at children's schools have more ambiguous implication (Makamure et al., 2016a, b; Altuğ et al., 2013; Reddy et al., 2012) (Table 5-17). For children in Turkey, lung function was analyzed dichotomously based on a cutpoint of 85 or 75% of the predicted value (Altuğ et al., 2013). Healthy children may not experience such decrements, and the 7% of the cohort with asthma may influence results. In a South African cohort, results were in opposing directions across the many comparisons made among lung function parameters, pollutants, exposure lags, and gene variants (Makamure et al., 2016a, b; Reddy et al., 2012). For example, an association for SO_2 was found in children with the GSTP1 variant with reduced oxidative metabolism activity but children with the GSTM1 variant with normal activity (Table 5-17 and Section 6.4). Confounding by meteorology was not considered in either cohort.

For exposures estimated from central site monitors, lung function associations were inconsistent for 1-h max SO_2 (Amadeo et al., 2015; Chang et al., 2012b), which may be more variable within a community and subject to greater exposure error. For children in Taiwan, a 40-ppb increase in 1-h max SO_2 lagged 1 day was associated with a −85 mL (95% CI: −129, −41) change in FEV_1 (Chang et al., 2012b). SO_2 concentrations were averaged from five monitors within 2 km of children's schools. For children in Guadeloupe, West Indies, the distance to monitors was not reported. Daily 1-h max SO_2 concentrations were not associated with PEF (Amadeo et al., 2015). Although PEF was measured before and after a 6-minute exercise period, which is akin to procedures in controlled human exposure studies, the SO_2 metric was not likely matched temporally with PEF measurements. Lung function in populations of children with low or no prevalence of asthma was inconsistently associated with 24-h avg SO_2 measured at central site monitors (Amadeo et al., 2015; Linares et al., 2010), although the null

findings are for 13-day avg SO_2 (Amadeo et al., 2015). Airway responsiveness increased with increases in 24-h avg SO_2 in a population of children with 8% asthma and 18% atopy (Soyseth et al., 1995). SO_2 exposures were estimated from monitors within 2 km of homes, which is similar to studies observing associations with 24-h avg and 1-h max SO_2 (Chang et al., 2012b; Linares et al., 2010).

For the few associations observed for SO_2 with lung function or airway responsiveness, the potential for copollutant confounding or interactions is not addressed, including the study conducted near an aluminum smelter that also emitted PM (Soyseth et al., 1995). Associations were observed for PM_{10}, CO, NO_2, and O_3 measured at schools and central site monitors, but neither correlations with SO_2 nor copollutant model results were reported (Chang et al., 2012b; Linares et al., 2010; Castro et al., 2009). Altuğ et al. (2014) reported a moderate correlation with NO_2 of 0.49 and observed no association for either NO_2 or SO_2. Copollutant models were analyzed for long-term SO_2, which was not associated with lung function decrements in single-pollutant models (Linares et al., 2010). Importantly, none of the studies examined $PM_{2.5}$

Animal Toxicological Studies

Lung function was examined in numerous studies reported in the 1982 SO_X AQCD (U.S. EPA, 1982a) and the 2008 SO_X ISA (U.S. EPA, 2008d). The majority of these were conducted in naive animals rather than in animal models of allergic airway disease. Bronchoconstriction, indicated by increased pulmonary resistance, was identified as the most sensitive indicator of lung function effects of acute SO_2 exposure, based on the observation of increased pulmonary resistance in guinea pigs that were acutely exposed to 0.16 ppm SO_2 (U.S. EPA, 2008d, 1982a). The 2008 SO_X ISA (U.S. EPA, 2008d) reported a few additional studies conducted at concentrations below 2 ppm. Animal toxicological studies examining lung function changes in naive animals exposed to SO_2 are summarized in Table 5-18. Increased pulmonary resistance and decreased dynamic compliance were observed in conscious guinea pigs exposed to 1 ppm SO_2 for 1 hour (Amdur et al., 1983). Effects were seen immediately after exposure and were not present 1 hour post-exposure. No changes in tidal volume, minute volume, or breathing frequency were found. These same investigators also exposed guinea pigs to 1 ppm SO_2 for 3 hours/day for 6 days (Conner et al., 1985). No changes were observed in lung function or respiratory parameters (i.e., diffusing capacity for CO, functional reserve capacity, vital capacity, total lung capacity, respiratory frequency, tidal volume, pulmonary resistance, or pulmonary compliance). In another study, Barthelemy et al. (1988) demonstrated a 16% increase in airway resistance following a 45-minute exposure of anesthetized rabbits to 0.5 ppm SO_2 via an endotracheal tube. This latter exposure is 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
Amdur et al. (1983)	Hartley guinea pig; n = 8−23/group; M; age NR; 200−300 g;	≈1 ppm (2.62 mg/m^3); 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
Conner et al. (1985)	Hartley guinea pig; n ≤ 18/group/time point; M; age NR; 250−320 g;	1 ppm (2.62 mg/m^3); 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
Barthelemy et al. (1988)	Rabbit; n = 5−9/group; sex NR; adult; mean 2.0 kg; rabbits were mechanically ventilated	0.5 ppm (1.3 mg/m^3) for 45 min; intratracheal	Endpoints examined 5 min before and up to 1 h post-exposure. Lung function—pulmonary resistance
Amdur et al. (1988)	Guinea pig; n = 8	1 ppm for 1 h	Endpoints examined 2 h following exposure Airway responsiveness to acetylcholine
Riedel et al. (1988)	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_2 and continued for 14 d 4 groups: Control 0.1 ppm SO_2 4.3 ppm SO_2 16.6 ppm SO_2	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
Park et al. (2001)	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_2 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_2 = sulfur dioxide.

The 2008 SO_X ISA (U.S. EPA, 2008d) also described studies that examined airway responsiveness following SO_2 exposure. In several different animal species, a single exposure to SO_2 at a concentration up to 10 ppm failed to increase airway responsiveness to a challenge agent. These studies were mainly conducted in naive animals rather than in models of allergic airways disease. Only one was conducted at a SO_2 concentration of less than 2 ppm. This study found no change in airway responsiveness to acetylcholine measured 2 hours following a 1-hour exposure in guinea pigs to 1 ppm SO_2 (Amdur et al., 1988). However, two toxicological studies (Park et al., 2001) (Riedel et al., 1988) described in the 2008 SO_X ISA (U.S. EPA, 2008d), provide evidence that repeated SO_2 exposure of guinea pigs to concentrations as low as 0.1 ppm enhanced AHR following subsequent sensitization and challenge with ovalbumin.

Summary of Lung Function Changes in General Populations and Healthy Individuals

Across disciplines, there is limited evidence that short-term SO_2 exposure induces lung function changes in healthy people. Evidence from controlled human exposure studies of healthy individuals shows that transient decreases in lung function can occur at concentrations of 1.0 ppm SO_2 under exercising or forced oral breathing conditions, but the evidence is more consistent for exposures >1.0 ppm. Animal toxicological studies demonstrated that acute exposure of guinea pigs to 0.16−1.0 ppm SO_2 results in increased airway resistance and repeated exposure of guinea pigs to concentrations of SO_2 as low as 0.1 ppm led to an enhancement of AHR following sensitization and challenge with an allergen. Epidemiologic studies do not clearly indicate SO_2-associated decreases in lung function in healthy adults or children or groups from the general population with varying

prevalence of respiratory disease. Results are mixed for SO_2 measured at subjects' locations and at central site monitors. Similar to experimental studies in healthy humans and animals without allergen challenge plus 1- to 6-hour SO_2 exposures, epidemiologic findings are mixed for temporally resolved metrics such as 1-h max or 1- to 4-h avg SO_2. Associations were observed for populations living in locations with steel, aluminum, or petrochemical industry or coal heating, but SO_2 was one of many pollutants implicated.

Respiratory Symptoms in General Populations and Healthy Individuals

Respiratory symptoms in relation to short-term SO_2 exposure have been investigated in a limited number of studies of general populations or healthy individuals. The 2008 SO_X ISA (U.S. EPA, 2008d) described some controlled human exposure and epidemiologic studies of respiratory symptoms among children or adults without asthma. Most controlled human exposure studies reported no respiratory symptoms at concentrations up to 2.0 ppm. Evidence from both previous and recent epidemiologic studies is inconsistent.

Controlled Human Exposure Studies

Controlled human exposure studies examining respiratory symptoms in healthy individuals exposed to SO_2 are summarized in Table 5-15. Briefly, Tunnicliffe et al. (2003) found no association between respiratory symptoms (i.e., throat irritation, cough, and wheeze) and 1-hour exposures at rest to 0.2 ppm SO_2 in either healthy adults or those with asthma. Similarly, Andersen et al. (1974) reported no change in respiratory symptoms in resting adults exposed to 1.0 ppm SO_2 for 6 hours. A more recent study in which exercising healthy adults were exposed to SO_2 concentrations as high as 2.0 ppm for 4 hours confirms these null findings (van Thriel et al., 2010).

Epidemiologic Studies

Associations for ambient SO_2 with respiratory symptoms in populations of healthy adults and children are inconsistent. Most results are from Europe and Asia. There are more studies of children than adults, but studies of adults focus on healthy individuals. Many previous studies of children examined populations with 5−81% chronic wheeze, asthma, or atopy, although results were inconsistent for healthy children as well (Boezen et al., 1999; Neas et al., 1995). Some recent studies examine populations of children with low (0.6−4%) prevalence of respiratory disease, but like previous studies do not consistently associate increases in SO_2 concentrations with respiratory symptoms (Table 5-19). Previous results were largely based on 24-h avg SO_2 concentrations measured at central site monitors. Many recent studies have improved exposure assessment, examining temporally resolved 1-hour SO_2 concentrations for adults or SO_2 concentrations at

children's schools. These associations with respiratory symptoms also are inconsistent. Other uncertainties include confounding by meteorological factors and copollutants.

For adults, a study on Miyakejima Island, Japan 5 years after a volcano eruption provided information on effects related to SO_2 concentrations and durations comparable to those examined in experimental studies (Ishigami et al., 2008). Incidence of many symptoms increased at 1-h avg SO_2 concentrations above 100 ppb and 1-h max concentrations above 600 ppb than concentrations less than 10 ppb (reference category) (Table 5-19). Although temporally resolved metrics were analyzed, inference about an SO_2 effect is weak. SO_2 concentrations were measured within 2 km of volunteer workers' home and work site, no other air pollutants or other potential confounders were examined, and 80% of concentrations were in the reference category. Results linking long-term air pollution from volcanoes to respiratory symptoms also are uncertain because they are based on ecological comparisons of areas with low and high air pollution mixtures in which SO_2 is one constituent (Section 5.2.2.1).

For children, associations with SO_2 concentrations were inconsistent within studies among the array of symptoms examined (Table 5-19). Results across studies were consistent for wheeze, an asthma symptom that is less likely to be experienced by healthy children. A study in South Korea has many limitations including estimating SO_2 exposure from central site monitors at an unspecified distance from children and observing only a few isolated associations among the numerous pollutants, symptoms, exposure lags, and cities examined (Moon et al., 2009). Other studies had cross-sectional design and measured SO_2 at school or within 2 km from school (Altuğ et al., 2014; Linares et al., 2010; Zhao et al., 2008). A study in China examined high SO_2 concentrations similar to those in the Japanese volcano study. Mean school SO_2 concentrations were 101 ppb indoors and 271 ppb outdoors. Indoor, but not outdoor, 1-wk avg SO_2 concentrations were associated with symptoms (Zhao et al., 2008) (Table 5-19). Temporal mismatch is likely between current SO_2 measurements and symptoms at any time in the preceding 12 months. The other study with 1-wk avg school SO_2 measures, conducted in Turkey, observed an association with any shortness of breath or wheeze in the previous 7 days but not throat symptoms, runny nose, or medication use concurrently or in the previous 7 days (Altuğ et al., 2014). It is not clear whether the single positive association applied to the entire population, the 7% with asthma, or 27% with hay fever. Among mostly healthy children (0.6% asthma) in Mexico, lag 0 SO_2 concentration was associated with wheeze, but SO_2 was measured up to 2 km from children's schools (Linares et al., 2010). SO_2 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_2 Exposure Estimates (ppb)	SO_2 Averaging Time and Lag Day	Effect Estimate (95% CI) Single-Pollutant Model[a]	Copollutant Examination
Adults				
†Ishigami et al. (2008) 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	
Children				
†Zhao et al. (2008) 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_2 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 0−6 avg	Outdoor SO_2 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) Indoor SO_2 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)	No copollutant model Indoor NO_2 and formaldehyde associated with symptoms. $PM_{2.5}$ not examined. SO_2 highly correlated with NO_2. r = 0.74.

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_2 Exposure Estimates (ppb)	SO_2 Averaging Time and Lag Day	Effect Estimate (95% CI) Single-Pollutant Model[a]	Copollutant Examination
†Altuğ et al. (2014) 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.	Monitor at school Mean and max Suburban: 21, 29 Urban: 29, 44 Urban-traffic: 22, 27	24-h avg 0−6 avg	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)	No copollutant model O_3 and NO_2 not associated with symptoms. $PM_{2.5}$ not examined. SO_2 weakly correlated with O_3, moderately correlated with NO_2. r = 0.40, 0.49.
†Linares et al. (2010) Salamanca, Mexico, Mar 2004−Feb 2005 N = 464, ages 6−14 yr. 0.6% asthma. Cross-sectional. Recruited from schools.	Monitors within 2 km of school Means spring−winter School 1: 12, 12, 10, 9.8 School 2: 9.1, 8.7, 10, 13	24-h avg 0	Wheezing OR: 1.06 (1.00, 1.11) Rhinorrhea OR: 0.98 (0.92, 1.05) Dyspnea OR: 1.02 (0.97, 1.07)	No copollutant model PM_{10} and O_3 but not NO_2 associated with symptoms. $PM_{2.5}$ not examined. Copollutant correlations NR.
†Moon et al. (2009) Seoul, Incheon, Busan, Jeju, South Korea, 2003 N = 696, ages < 13 yr Daily diaries for 2 mo. Recruited from schools.	Monitors in city Number and distance NR Means NR Max: 38	24-h avg 0	LRS OR: 1.00 (0.93, 1.08) URS OR: 1.11 (1.03, 1.20)	No copollutant model PM_{10} and CO associated with symptoms. $PM_{2.5}$ not examined. Copollutant correlations NR.

CI = confidence interval; CO = carbon monoxide; LRS = lower respiratory symptoms; N = sample size; NO_2 = nitrogen dioxide; NR = not reported; O_3 = ozone; OR = odds ratio; $PM_{2.5}$ = particulate matter with a nominal aerodynamic diameter less than or equal to 2.5 µm; PM_{10} = 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_2 = sulfur dioxide; URS = upper respiratory symptoms.

[a]Effect estimates are standardized to a 10-ppb increase in 1-h avg and 24-h avg SO_2 and a 40-ppb increase in 1-h max SO_2.

†Studies published since the 2008 Integrated Science Assessment for Sulfur Oxides.

For the few observations of SO_2-associated increases in respiratory symptoms in healthy adults and children, the potential for copollutant confounding was not examined. PM_{10}, CO, and formaldehyde were also associated with symptoms; $PM_{2.5}$ was not examined (Table 5-19). Most studies did not report copollutant correlations, and none examined copollutant models. Symptoms were not associated with outdoor NO_2 (Altuğ et al., 2014; Linares et al., 2010; Zhao et al., 2008), but an association was observed with indoor NO_2 (Zhao et al., 2008). Indoor school SO_2 and NO_2 were highly correlated (r = 0.74), and it is not clear the extent to which the association with breathlessness can be attributed independently to SO_2 or NO_2 or to a combined effect of those and other copollutants.

Summary of Respiratory Symptoms in General Populations and Healthy Individuals

There is little evidence for an effect of short-term SO_2 exposure on respiratory symptoms in healthy individuals. Controlled human exposure studies of healthy adults did not demonstrate effects for 1- to 6-hour SO_2 exposures up to 2 ppm, and epidemiologic findings are inconsistent for healthy adults and children. For epidemiologic studies, there is uncertain representativeness of SO_2 exposures estimated from central site monitors. However, as shown in recent studies, respiratory symptoms are also inconsistently associated with SO_2 measured at children's schools. A biological explanation for associations observed with 1-wk avg SO_2 concentrations is unclear. For associations observed with 1-h avg or max concentrations and the evidence overall, potential for confounding by $PM_{2.5}$, PM_{10}, NO_2, CO, and formaldehyde is not addressed.

Subclinical Respiratory Effects in Healthy Individuals

Pulmonary inflammation is a key subclinical effect in the pathogenesis of asthma and other respiratory diseases. It consists of both acute and chronic responses and involves the orchestrated interplay of the respiratory epithelium and both the innate and adaptive immune system. The immunohistopathologic features of chronic inflammation involve the infiltration of inflammatory cells such as eosinophils, lymphocytes, mast cells, and macrophages and the release of inflammatory mediators such as cytokines and leukotrienes. The 2008 ISA for Sulfur Oxides described limited evidence from animal toxicological studies for SO_2-induced pulmonary inflammation and allergic sensitization in rodents exposed to allergen. Recent controlled human exposure and epidemiologic studies add to the evidence base and do not clearly support SO_2-related pulmonary inflammation in healthy populations.

Controlled Human Exposure Studies

A recent controlled human exposure study examined eNO and other biomarkers of pulmonary inflammation in the NALF and EBC after exposures to 0, 0.5, 1, and 2 ppm SO_2 for 4 hours in exercising healthy adults (Raulf-Heimsoth et al., 2010). Data demonstrated no statistically significant changes in eNO; leukotriene B4, prostaglandin E2, and 8-iso-prostaglandin F2 alpha in EBC; or substance P, interleukin-8 (IL-8), and brain derived neurotrophic factor in NALF after SO_2 exposures, compared to air.

Epidemiologic Studies

Unlike the study reviewed in the 2008 ISA for Sulfur Oxides (Adamkiewicz et al., 2004), recent studies measured SO_2 near subjects' homes, schools, or work. SO_2 concentrations at a site within 1 km of most homes were not associated with pulmonary inflammation in a population of children with high prevalence (33%) of asthma or atopy (Chen et al., 2012a). Previous results were similar for a population of older adults that included people with respiratory disease. Recent examination of healthy adults and children in Beijing, China indicates SO_2-associated increases in pulmonary inflammation or oxidative stress. These recent studies were conducted before, during, and after the 2008 Olympics (Roy et al., 2014; Lin et al., 2011b). Concentrations of SO_2 and other pollutants were lower during the Olympics than before or after (e.g., mean 24-h avg 3.0 vs. 7.5 and 6.8 ppb). During a winter 2007 period, mean 24-h avg SO_2 concentrations were 45 ppb (Lin et al., 2011b). Pollutants were measured 0.65 km from the school that study children attended and the hospital where most of the study adults worked. A 10-ppb increase in lag 0 24-h avg SO_2 was associated with a 7.6% (95% CI: 5.9, 9.3) increase in eNO of children (Lin et al., 2011b) and, in adults, a 0.67 standard deviation (95% CI: 0.48, 0.86) increase in an index of pulmonary inflammation and oxidative stress combining eNO and EBC markers (Roy et al., 2014). Associations were also observed with $PM_{2.5}$, sulfate, EC/BC, CO, NO_2, and OC. Copollutant models were analyzed for children, in which SO_2 effect estimates remained positive but decreased substantially with adjustment for $PM_{2.5}$ or BC (Lin et al., 2011b). Conversely, the effect estimate for BC was robust to adjustment for SO_2. Correlations with SO_2 concentrations were not reported, but inference from copollutant models is likely better for pollutants measured close to school than at central site monitors due to more comparable exposure measurement error. Confounding by other copollutants was not examined.

Animal Toxicological Studies

The 2008 SO_X ISA (U.S. EPA, 2008d) described several animal toxicological studies that examined the effects of repeated exposure to SO_2 on inflammation. These and other animal toxicological studies examining inflammation in naive animals exposed to SO_2

are summarized in Table 5-20. Repeated exposure to SO_2 was found to promote allergic sensitization and enhanced allergen-induced bronchial obstruction in guinea pigs. In the first of these studies, Riedel et al. (1988) examined the effect of SO_2 exposure on local bronchial sensitization to inhaled antigen. Guinea pigs were exposed by inhalation to 0.1, 4.3, and 16.6 ppm SO_2 for 8 hours/day for 5 days. During the last 3 days, SO_2 exposure was followed by exposure to nebulized ovalbumin for 45 minutes. Following bronchial provocation with inhaled ovalbumin (0.1%) 1 week later, bronchial obstruction was measured by examining the respiratory loop obtained by whole-body plethysmography. In addition, specific antibodies against ovalbumin were measured in serum and BALF. Results showed significantly higher bronchial obstruction in animals exposed to both SO_2, at all concentration levels, and ovalbumin compared with animals exposed only to ovalbumin. In addition, significant increases in anti-ovalbumin IgG antibodies were detected in BALF of animals exposed to 0.1, 4.3, and 16.6 ppm SO_2 and in serum from animals exposed to 4.3 and 16.6 ppm SO_2 and ovalbumin compared with controls exposed only to ovalbumin. These results demonstrated that repeated exposure to SO_2 enhanced allergic sensitization and bronchial obstruction in the guinea pig at a concentration as low as 0.1 ppm.

In the second study, guinea pigs were exposed to 0.1 ppm SO_2 for 5 hours/day for 5 days and sensitized with 0.1% ovalbumin aerosols for 45 minutes on days 4 and 5 (Park et al., 2001). One week later, animals were subjected to bronchial challenge with 0.1% ovalbumin and lung function was evaluated 24 hours later by whole-body plethysmography. The results demonstrated a significant increase in enhanced pause (Penh), a measure of airway obstruction, in animals exposed to both SO_2 and ovalbumin but not in animals treated with ovalbumin or SO_2 alone. In animals treated with both SO_2 and albumin, increased numbers of eosinophils were found in lavage fluid. In addition, infiltration of inflammatory cells, bronchiolar epithelial cell damage, and plugging of the airway lumen with mucus and cells were observed in bronchial tissues. These cellular changes were not observed in animals treated with ovalbumin or SO_2 alone. Results indicate that repeated exposure to near-ambient levels of SO_2 may play a role in allergic sensitization and in exacerbating allergic inflammatory responses in the guinea pig. Furthermore, increases in bronchial obstruction suggest that SO_2 exposure induced an increase in airway responsiveness in the animals subsequently made allergic to 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
Conner et al. (1989)	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
Riedel et al. (1988)	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_2 and continued for 14 d Four groups: Control 0.1 ppm SO_2 4.3 ppm SO_2 16.6 ppm SO_2	Endpoints examined 48 h after the last provocation. Serum—anti IgG levels BALF—anti IgG levels
Park et al. (2001)	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_2 Four groups: Control Ovalbumin SO_2 Ovalbumin/SO_2	Endpoints examined 24 h after the bronchial challenge. BALF—differential cell counts cells Lung and bronchial tissue—histopathology
Li et al. (2007)	Rats (Wistar); n = 6/group; M; age NR	2 ppm SO_2 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
Li et al. (2014)	Rats (Wistar); n = 6/group; M; age NR; 180−200 g	2 ppm SO_2 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_2 = sulfur dioxide; TNFα = tumor necrosis factor alpha.

Park et al. (2001) demonstrated that repeated exposure of guinea pigs to 0.1 ppm SO_2 alone did not lead to allergic inflammation or morphologic changes in the lung although it enhanced the allergic inflammation due to subsequent sensitization and challenge with ovalbumin. Conner et al. (1989) found no changes in total cells and neutrophils in BALF from guinea pigs exposed repeatedly to 1 ppm SO_2. In contrast, found that repeated exposure of rats to 2 ppm SO_2 resulted in mild pathologic changes in the lung, including inflammatory cell influx and smooth muscle hyperplasia (Li et al., 2014; Li et al., 2007). Several other indicators of inflammation and immune response were not changed by exposure to SO_2 alone.

Summary of Subclinical Respiratory Effects in Healthy Individuals

There is limited evidence for inflammatory and other subclinical respiratory effects in healthy populations following short-term exposure to SO_2, primarily from animal toxicological studies involving allergen sensitization. As newly informed by recent studies, SO_2 is not clearly related to pulmonary inflammation in healthy populations in controlled human exposure or epidemiologic studies. Associations were observed in some epidemiologic studies, but confounding by $PM_{2.5}$, sulfate, BC, or NO_2 is not well addressed. Studies in animals demonstrated that repeated exposure of guinea pigs to 0.1 or 1 ppm SO_2 had no effect on inflammation. However, when followed by sensitization with an allergen, exposure of guinea pigs to 0.1 ppm SO_2 enhanced allergic sensitization, allergic inflammatory responses, and airway responsiveness to that allergen. These results

point to the potential for SO_2 exposure to increase sensitivity to an allergen, which differ from the inflammatory responses examined in healthy humans. In addition, repeated exposure of rats to 2 ppm SO_2 resulted in inflammation and smooth muscle hyperplasia, early indicators of airway remodeling.

5.2.1.8 Respiratory Mortality

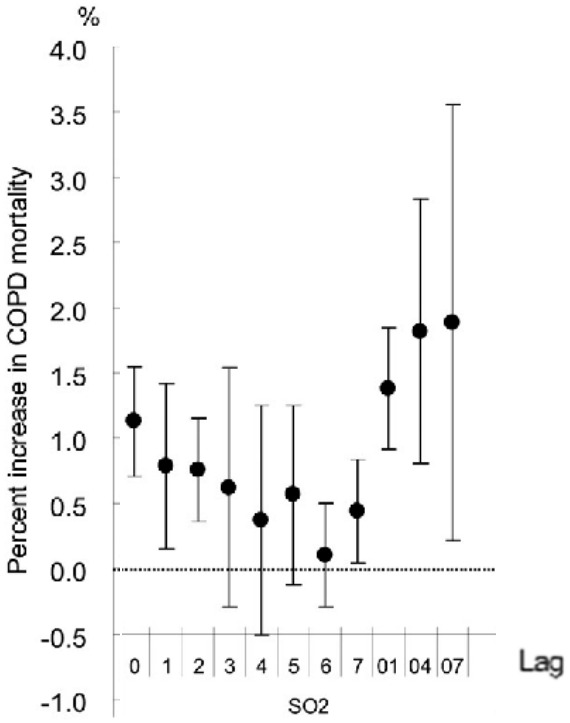
Studies evaluated in the 2008 SO_X ISA that examined the association between short-term SO_2 exposure and cause-specific mortality found consistent positive associations with respiratory mortality using a 24-h avg exposure metric with some evidence indicating that the magnitude of the association was larger compared to all-cause and cardiovascular mortality. Recent multicity studies conducted in Asia (Chen et al., 2012b; Kan et al., 2010b) and Italy (Bellini et al., 2007), a meta-analysis of studies conducted in Asia (Atkinson et al., 2012), and a four-city study conducted in China that focused specifically on COPD mortality (Meng et al., 2013) add to the initial body of evidence indicating larger respiratory mortality effects (Section 5.5.1.3, Figure 5-18).

Studies evaluated in and prior to the 2008 SO_X ISA that examined the association between short-term SO_2 exposures and respiratory mortality focused exclusively on single-pollutant analyses. Therefore, questions arose regarding the independent effect of SO_2 on respiratory mortality, and whether associations remained robust in copollutant models. A few recent multicity studies conducted in China (Meng et al., 2013; Chen et al., 2012b) and multiple Asian cities (Kan et al., 2010b) examined both of these questions. Chen et al. (2012b) found that the SO_2-respiratory mortality association was attenuated, but remained positive in copollutant models with PM_{10} [2.03% (95% CI: 0.89, 3.17) for a 10-ppb increase in 24-h avg SO_2 concentrations at lag 0−1 days] and NO_2 [1.16% (95% CI: −0.03, 2.37) for a 10-ppb increase in 24-h avg SO_2 concentrations at lag 0−1 days]. These results are similar to what the authors reported when examining the SO_2-total mortality association in models with PM_{10} (i.e., ~40% reduction), but more attenuation was observed in models with NO_2 (i.e., ~80% reduction for total mortality and 65% reduction for respiratory mortality) (Section 5.5.1.4). Kan et al. (2010b), as part of the Public Health and Air Pollution in Asia (PAPA) study, also examined the effect of copollutants (i.e., NO_2, PM_{10}, and O_3), but only in each city individually. The study authors found that although the SO_2-respiratory mortality association remained positive in copollutant models, there was evidence of an attenuation of the association in models with PM_{10} and more so in models with NO_2 (Figure 5-10). Meng et al. (2013) in a four-city analysis of COPD mortality in China reported evidence consistent with Chen et al. (2012b) and Kan et al. (2010b). The authors observed a 3.7% (95% CI: 2.4, 4.9) increase in COPD mortality for a 10-ppb increase in 24-h avg SO_2 concentrations at lag

0−1 days. However, compared to the results for respiratory mortality from copollutant models reported in Chen et al. (2012b), Meng et al. (2013) found a larger degree of attenuation in models with PM_{10}, ~50% reduction [1.9% (95% CI: 0.3, 3.5)] and NO_2, ~99% reduction [0.0% (95% CI: −1.8, 1.9)] compared to the SO_2 results from the single pollutant model. The larger degree of attenuation of the SO_2-COPD mortality association in Meng et al. (2013), compared to respiratory mortality in Chen et al. (2012b) could be a reflection of the smaller sample size and smaller number of cities included in the analysis. Overall, the studies that examined the potential confounding effects of copollutants on the SO_2-respiratory mortality relationship show results consistent with what has been observed for total mortality. However, the overall assessment of potential copollutant confounding remains limited, and it is unclear how the results observed in Asia translate to other locations, specifically due to the unique air pollution mixture and higher concentrations observed in Asian cities.

Of the studies evaluated, only Bellini et al. (2007) (in a multicity study conducted in Italy) examined potential seasonal differences in the SO_2-cause-specific mortality relationship. Bellini et al. (2007) reported that risk estimates for respiratory mortality were dramatically increased in the summer from 4.1 to 12.0% for a 10-ppb increase in 24-h avg SO_2 concentrations at lag 0−1, respectively, with the all-year and winter results being similar. These results are consistent with the seasonal pattern of SO_2 associations observed in Bellini et al. (2007) for total and cardiovascular mortality. However, it remains unclear whether this seasonal pattern of SO_2-respiratory mortality associations is observed in other locations.

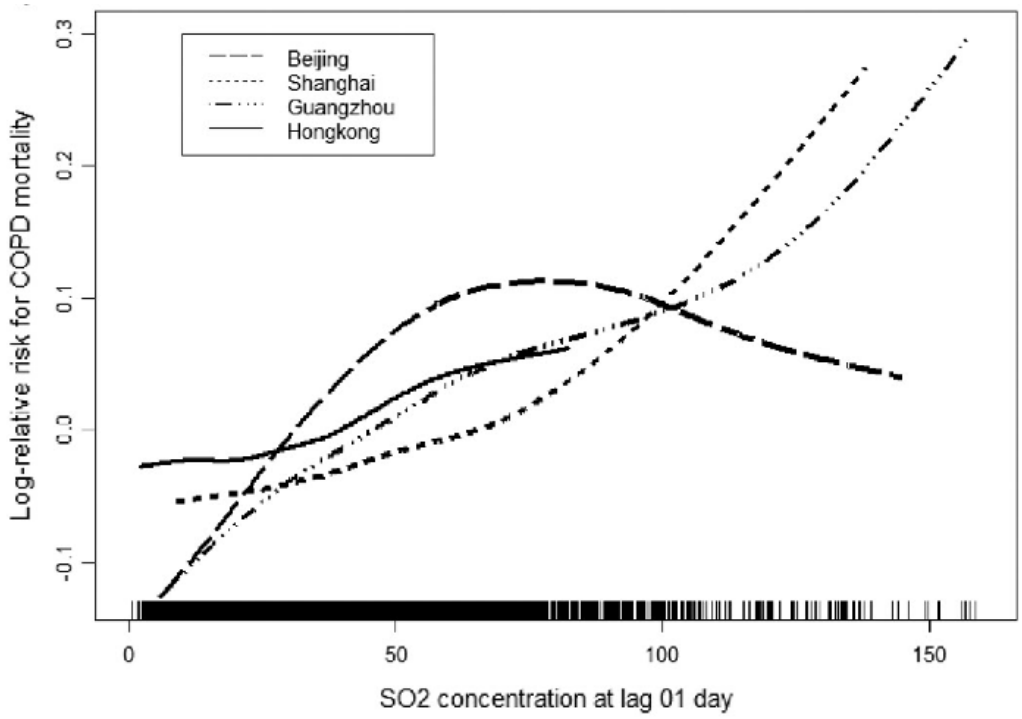
An uncertainty that often arises when examining the relationship between short-term air pollution exposures and cause-specific mortality is whether the lag structure of associations and the C-R relationship is consistent with what is observed for total mortality. Meng et al. (2013) addressed both the lag structure of associations and the C-R relationship in a study of short-term air pollution exposures and COPD mortality in four Chinese cities. Although not explicitly part of the China Air Pollution and Health Effects Study (CAPES) study, Meng et al. (2013) focused on four CAPES cities over the same time period as Chen et al. (2012b). In comparison to Chen et al. (2012b), who found a steady decline in risk estimates at single-day lags of 0 to 7 days with the largest effect at lag 0−1, Meng et al. (2013) observed a steady decline over single lag days, but some indication of larger associations, although highly uncertain, at longer multiday lags (i.e., 0−4 and 0−7 days) (Figure 5-10). Note that Chen et al. (2012b) did not examine multiday lags longer than 0−1 days, but the magnitude of the association for all respiratory mortality [3.3% (95% CI: 2.1, 4.6) for a 10-ppb increase in 24-h avg SO_2 concentrations] is similar to that reported in Meng et al. (2013) for COPD [3.7% (95% CI: 2.4, 4.9)].



COPD = chronic obstructive pulmonary disease; SO_2 = 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/m³ (3.62 ppb) increase in 24-h avg sulfur dioxide concentrations at various single and multiday lags.

Meng et al. (2013) also examined the shape of the SO_2-COPD mortality C-R relationship. To examine the assumption of linearity, the authors modeled the relationship between air pollution exposures and COPD mortality using a natural spline with 3 df. Meng et al. (2013) then computed the difference between the deviance of the linear and spline models to assess whether there was evidence of nonlinearity in the SO_2-COPD relationship. As depicted in Figure 5-11, the authors found no evidence that the spline model resulted in a better fit of the SO_2-mortality relationship compared to the linear model. However, the authors did not present confidence intervals for each of the C-R curves, which complicates the interpretation of the results.



COPD = chronic obstructive pulmonary disease; SO_2 = 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.

Overall, recent multicity studies report evidence of consistent positive associations between short-term SO_2 concentrations and respiratory mortality, which is consistent with those studies evaluated in the 2008 SO_X ISA. Unlike studies evaluated in the 2008 SO_X ISA, recent studies examined whether copollutants confound the relationship between short-term SO_2 concentrations and respiratory mortality. Overall, these studies reported evidence that the SO_2-respiratory mortality association was attenuated in models with NO_2 and PM_{10}, but the analyses are limited to Asian cities where the air pollution mixture and concentrations are different than those reported in other areas of the world. Additional analyses focusing on seasonal patterns of associations, lag structure of associations, and the C-R relationship are limited in number, but suggest evidence of: larger associations in the summer/warm season, larger and more precise associations at shorter lag periods (in the range of 0 and 1 days), and a linear, no threshold C-R relationship, respectively. However, for both total and cause-specific mortality, the overall assessment of linearity in the C-R relationship is based on a very limited exploration of alternatives.

5.2.1.9 Summary and Causal Determination

Strong evidence indicates that there is a causal relationship between short-term SO_2 exposure and respiratory effects, particularly for respiratory effects in the at-risk population of individuals with asthma. This determination is based on the consistency of SO_2-induced bronchoconstriction in exercising individuals with asthma in controlled human studies, coherence of asthma-related effects among multiple lines of evidence, and biological plausibility for effects specifically related to asthma exacerbation. There is limited support for a relationship between short-term SO_2 exposure and other respiratory effects, including exacerbation of COPD, allergy exacerbation, respiratory infection, respiratory effects in healthy populations, and respiratory mortality. The limited and inconsistent evidence for these nonasthma-related respiratory effects does not contribute heavily to the causal determination.

The determination of a causal relationship is the same as the conclusion of the 2008 SO_X ISA (U.S. EPA, 2008d). The evidence for this conclusion was heavily based on controlled human exposure studies that showed lung function decrements and respiratory symptoms in adult individuals with asthma exposed to SO_2 for 5−10 minutes under increased ventilation conditions. These findings are consistent with the current understanding of biological plausibility described in the mode of action section (Section 4.3.6). Previous epidemiologic studies provided supporting evidence indicating associations between short-term increases in ambient SO_2 concentration and respiratory-related ED visits and hospital admissions as well as respiratory symptoms. The evidence for a causal relationship is detailed below using the framework described in the Preamble to the ISAs (U.S. EPA, 2015b). While new evidence adds to the existing body of evidence, the determination remains largely based on previous controlled human exposure studies. The key evidence as it relates to the causal framework is presented in Table 5-21.

Evidence for Asthma Exacerbation

A causal relationship between short-term SO_2 exposure and respiratory effects is primarily supported by evidence from controlled human exposure studies of respiratory effects in adults with asthma. These studies consistently demonstrated that the majority of individuals with asthma experience a moderate or greater decrement in lung function, as defined by a ≥100% increase in sRaw or ≥15% decrease in FEV_1. This decrement is frequently accompanied by respiratory symptoms following exposures of 5−10 minutes, with elevated ventilation rates at concentrations of 0.4−0.6 ppm (Johns et al., 2010; Linn et al., 1990; Linn et al., 1988; Balmes et al., 1987; Linn et al., 1987; Horstman et al., 1986; Linn et al., 1983b). A fraction of the population with asthma (~5−30%) has also

been observed to have decrements in lung function at lower SO_2 concentrations (0.2−0.3 ppm) (Linn et al., 1990; Linn et al., 1988; Linn et al., 1987; Bethel et al., 1985). Although the degree of lung function decrements are considered moderate, they are less likely to be accompanied by respiratory symptoms at these lower concentrations (Linn et al., 1990; Linn et al., 1988; Linn et al., 1987; Roger et al., 1985; Linn et al., 1983b). A group of responders (defined as having ≥15% decrease in FEV_1 after exposure to 0.6 or 1.0 ppm SO_2) showed statistically significant decrements in FEV_1 following 5−10 minute exposure to 0.3 ppm SO_2 (Johns et al., 2010) (Table 5-3). While SO_2-induced respiratory effects have been examined in individuals classified as having mild and moderate asthma, these individuals are relatively healthy. Thus, extrapolating to individuals with severe asthma is difficult because such individuals cannot be tested in an exposure chamber due to the severity of their disease. Therefore, it is unknown whether people with severe asthma are at increased risk to respiratory effects due to short-term SO_2 exposure. The same may be said about children with asthma. There are no laboratory studies of children exposed to SO_2, but a number of studies have assessed airway responsiveness of children and adults exposed to the bronchoconstrictive stimuli methacholine. Based largely on those studies, school-aged children, particularly boys and perhaps obese children, would be expected to have greater responses (i.e., larger decrements in lung function) following exposure to SO_2 than adolescents and adults.

The coherence of epidemiologic findings (Section 5.2.1.2) is supporting evidence for a causal relationship. Epidemiologic evidence for lung function changes in adults and children with asthma is inconsistent. However, short-term increases in ambient SO_2 concentration are associated with increases in asthma hospital admissions and ED visits among all ages, children (i.e., <18 years of age) and older adults (i.e., 65 years of age and older) (Figure 5-3), as well as asthma symptoms in children (Velická et al., 2015; Spira-Cohen et al., 2011). Epidemiologic associations between short-term increases in ambient SO_2 concentration and respiratory mortality provide support for a potential continuum of effects between respiratory morbidity and respiratory mortality.

Most epidemiologic studies indicating associations between short-term SO_2 exposures and asthma exacerbation assigned exposure using SO_2 concentrations measured at central site monitors. The use of central site monitors to assign exposure, particularly to 1-h max SO_2, may introduce exposure measurement error if the spatiotemporal variability in SO_2 concentrations is not captured. Studies did not statistically correct for measurement error, but in this new research area, a method has not been reported for short-term SO_2 exposure (Section 3.4.4). A few recent results reduce the uncertainty with SO_2 measured or modeled at or near children's school or home (Velická et al., 2015; Spira-Cohen et al., 2011). Additional uncertainty exists regarding potential copollutant confounding. In many studies, SO_2 was moderately to highly correlated with $PM_{2.5}$, larger sized PM,

EC/BC, NO_2, and VOCs (r = 0.4−0.9). The few available results show association with sulfate. A small number of studies examined copollutant models. Some associations were relatively unchanged in magnitude after adjustment for a copollutant; others did not persist. However, inference from copollutant models is limited given potential differences in exposure measurement error for SO_2 compared to NO_2, CO, PM, and O_3 and in many cases, high copollutant correlations. Copollutant interactions are not well studied. Some controlled human exposure studies demonstrate increased asthma-related effects with coexposure to SO_2 and NO_2 or O_3. Limited epidemiologic evidence shows increased asthma-related effects with joint increases in SO_2 and copollutants but does not clearly show a joint association that is greater than a single-pollutant association.

There is supportive evidence for a relationship between short-term SO_2 exposure and airway responsiveness and pulmonary inflammation. Limited epidemiologic evidence points to associations with increased airway responsiveness in adults with asthma plus atopy (Taggart et al., 1996). Gong et al. (2001) demonstrated an increase in airway eosinophils in adults with asthma 2 hours after a 10-minute exposure to 0.75 ppm SO_2. This effect, along with bronchoconstriction, was attenuated by pretreatment with a leukotriene receptor antagonist. Other pharmacologic studies have demonstrated the importance of inflammatory mediators in mediating SO_2 exposure-induced bronchoconstriction in people with asthma (Section 4.3.1). Further support for an important role of airway inflammation, including allergic inflammation, is provided by animal toxicological studies of repeated SO_2 exposure in allergic animals that are used to model the asthmatic phenotype (Li et al., 2014; Li et al., 2007). In addition, repeated exposure of naive animals promoted allergic sensitization and enhanced allergic inflammation and airway responsiveness to an allergen (Park et al., 2001; Riedel et al., 1988). These latter studies point to a possible increased sensitivity to allergens following SO_2 exposure.

Evidence for Other Respiratory Effects

Epidemiologic studies demonstrate some associations of ambient SO_2 concentrations with hospital admissions and ED visits for all respiratory causes combined (Figure 5-9). While these results suggest that the respiratory effects of short-term SO_2 exposure could extend beyond exacerbation of asthma, evidence across disciplines is inconsistent and/or lacks biological plausibility for conditions such as allergy exacerbation (Section 5.2.1.3), COPD exacerbation (Section 5.2.1.4), and respiratory infection (Section 5.2.1.5). Where epidemiologic associations were found, potential copollutant confounding is uncertain. For COPD exacerbation, a controlled human exposure study demonstrated no effect of SO_2 exposure, and epidemiologic associations are inconsistent for lung function, respiratory symptoms, hospital admissions, and ED visits. Some evidence supports

SO_2-associated increases in hospital admissions and ED visits due to respiratory infections. However, the lack of multiple studies examining the same respiratory infection outcome, inconsistent findings for self-reported infections in children, and the lack of evidence from controlled human exposure and animal toxicological studies produces uncertainty as to whether a relationship exists. Controlled human exposure studies in healthy individuals provide evidence for transient decreases in lung function with ≥1 ppm SO_2 exposures for 5−10 minutes under exercising or a forced oral breathing condition with no evidence for increased respiratory symptoms. Epidemiologic evidence is inconsistent for SO_2 associations with lung function, respiratory symptoms, and pulmonary inflammation in healthy children and adults.

Conclusion

The evidence integrated across disciplines supports a causal relationship between short-term SO_2 exposure and respiratory effects, particularly asthma exacerbation. This determination is primarily based on decreased lung function and increased respiratory symptoms observed in controlled human exposure studies in adults with asthma. Epidemiologic studies of asthma hospital admissions and ED visits and asthma symptoms in children provide supporting evidence. Supportive evidence for a relationship between short-term SO_2 exposure and pulmonary inflammation and AHR, is provided by controlled human exposure, epidemiologic, and toxicological studies. Evidence for an effect of SO_2 exposure on allergy exacerbation, COPD exacerbation, respiratory infection, respiratory effects in healthy populations, and respiratory mortality is inconsistent within and across disciplines and outcomes, and there is uncertainty related to potential confounding by copollutants. The limited and inconsistent evidence for these nonasthma-related respiratory effects does not contribute heavily to the causal determination.

Table 5-21 Summary of evidence for a causal relationship between short-term sulfur dioxide exposure and respiratory effects.

Rationale for Causal Determination[a]	Key Evidence[b]	Key References[b]	SO_2 Concentrations Associated with Effects[c]
Asthma exacerbation			
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	Section 5.2.1.2 Table 5-2	400−600 ppb
	A group of responders (defined as having ≥15% decrease in FEV_1 after exposure to 0.6 or 1.0 ppm SO_2) showed statistically significant decrements in FEV_1 following 5-10 min of exposure to 0.3 ppm SO_2	Section 5.2.1.2 Table 5-3	300 ppb
	Decreased lung function following exposures of 5-10 min in 5-30% of exercising individuals with asthma	Section 5.2.1.2 Table 5-2	200−300 ppb
	Increased respiratory symptoms following exposure of 5−10 min in exercising individuals with asthma	Section 5.2.1.2 Table 5-2	400−1,000 ppb
Generally supporting evidence from multiple epidemiologic studies at relevant SO_2 concentrations	Increase in asthma hospital admissions and ED visits in single- and multi-city studies, among all ages, children and older adults	Section 5.2.1.2	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_2 exposure estimates	†Spira-Cohen et al. (2011), †Velická et al. (2015) Section 5.2.1.2	24-h avg: median 4.0 ppb
Uncertainty regarding exposure measurement error	SO_2 exposures estimated from central site monitors may not capture spatiotemporal variability of SO_2 across a community	Section 3.4.2	
Uncertainty regarding potential copollutant confounding	Some SO_2 associations were relatively unchanged in magnitude in copollutant models with NO_2, $PM_{2.5}$, or PM_{10}. Others were attenuated. Differential exposure measurement error limits inference. SO_2 showed a wide correlation with copollutants across studies (r = 0.4−0.9).	Attenuated: †Spira-Cohen et al. (2011) Section 5.2.1.2, Section 3.4.3	
	Neural reflexes and/or inflammation lead to bronchoconstriction.	Section 4.3.6	

Table 5-21 (Continued): Summary of evidence for a causal relationship between short-term sulfur dioxide exposure and respiratory effects.

Rationale for Causal Determination[a]	Key Evidence[b]	Key References[b]	SO_2 Concentrations Associated with Effects[c]
Evidence for key events in proposed mode of action	Increased airway eosinophils in adults with asthma exposed to SO_2 Enhanced allergic inflammation in rats previously sensitized with an allergen and then repeatedly exposed to SO_2.	Gong et al. (2001), Li et al. (2007), †Li et al. (2014)	750−2,000 ppb
	Enhancement of allergic sensitization, allergic inflammation and airway responsiveness in guinea pigs exposed to SO_2 repeatedly over several days and subsequently sensitized and challenged with an allergen	Park et al. (2001), Riedel et al. (1988)	100 ppb
	Allergic inflammation leads to increased airway responsiveness. Association with airway responsiveness among adults with asthma plus atopy	Taggart et al. (1996)	24-h avg: max 39 ppb
Other respiratory effects			
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	Section 5.2.1.3, Section 5.2.1.4, Section 5.2.1.5, Section 5.2.1.6, and Section 5.2.1.7	
Respiratory mortality			
Consistent epidemiologic evidence from multiple studies at relevant SO_2 concentrations	Increases in respiratory mortality in multicity studies conducted in the U.S., Canada, Europe, and Asia	Section 5.2.1.8 and Section 5.5.1.3 Figure 5-8 and Figure 5-16	Mean 24-h avg: U.S., Canada, Europe: 0.4−28.2[d] ppb Asia: 0.7−>200 ppb Table 5-39
Uncertainty regarding potential confounding by copollutants	No copollutant models with $PM_{2.5}$. SO_2 associations remained positive but decreased in magnitude with adjustment for PM_{10} or NO_2, suggesting confounding. Studies limited to areas with high SO_2 concentrations, which complicates the interpretation of independent association for SO_2.	Section 5.2.1.8, Section 3.4.3	

Table 5-21 (Continued): Summary of evidence for a causal relationship between short-term sulfur dioxide exposure and respiratory effects.

Rationale for Causal Determination[a]	Key Evidence[b]	Key References[b]	SO_2 Concentrations Associated with Effects[c]
Uncertainty regarding exposure measurement error	SO_2 exposures estimated from central site monitors may not capture spatiotemporal variability of SO_2 across a community.	Section 3.4.2	

COPD = chronic obstructive pulmonary disease; ED = emergency department; NO_2 = nitrogen dioxide; PM_{10} = particulate matter with a nominal aerodynamic diameter less than or equal to 10 µm; $PM_{2.5}$ = particulate matter with a nominal aerodynamic diameter less than or equal to 2.5 µm; *r* = correlation coefficient; SO_2 = sulfur dioxide.

[a]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).

[b]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.

[c]Describes the SO_2 concentrations with which the evidence is substantiated (for experimental studies, below 2,000 ppb).

[d]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

The 2008 SO_X ISA (U.S. EPA, 2008d) reviewed the epidemiologic and toxicological evidence for long-term exposure to SO_2 and respiratory effects and concluded that the evidence was inadequate to infer a causal relationship. Although some positive associations with asthma prevalence, bronchitis, symptoms, and lung function were observed among children, uncertainties made it difficult at that time to assess the evidence as a whole. Uncertainties related to assessing the consistency of findings across a diverse set of respiratory outcomes, the potential for exposure measurement error to influence results, and the lack of information available to assess the impact of copollutant confounding were cited in the document. The studies of long-term exposure to SO_2 and respiratory morbidity that were considered in the last review are found in Supplemental Table 5S-9 (U.S. EPA, 2015f). Animal toxicological studies of the effects of long-term exposure to SO_2, which were reviewed in the 2008 SO_X ISA (U.S. EPA, 2008d), examined lung function, morphology, and host defense. Most of these studies involved SO_2 concentrations well above 2 ppm. Recent toxicological studies add to this database.

Both older and more recent epidemiologic and toxicological studies that evaluate the relationship between long-term SO_2 exposure and asthma (Section 5.2.2.1), allergy (Section 5.2.2.2), lung function (Section 5.2.2.3), respiratory infection (Section 5.2.2.4), other respiratory diseases (Section 5.2.2.5), and respiratory mortality (Section 5.2.2.6) are discussed below. Recent cohort studies of asthma incidence (Nishimura et al., 2013; Clark et al., 2010) use a longitudinal design, a methodological enhancement over the

cross-sectional studies of asthma prevalence available in the 2008 SO_X ISA (U.S. EPA, 2008d). A recent study (Ierodiakonou et al., 2015) using a longitudinal design provides the first epidemiological report relating SO_2 exposure to AHR in human subjects with asthma. Uncertainties related to exposure estimates based on IDW concentrations or other estimates based on monitors (see Section 3.3.1) may limit the inferences that can be made for these recent studies. The majority of other recent and earlier epidemiologic studies used cross-sectional designs evaluating prevalence. Results were generally positive, although the strength of the associations varied across studies. The designs used (i.e., ecological, cross-sectional) limit the contribution of these studies to possible inferences about causality of relationships between long-term SO_2 exposure and respiratory effects. The caution expressed in the 2008 SO_X ISA (U.S. EPA, 2008d) related to the limitation of attributing an independent effect to SO_2 (due to the relationship of SO_2 levels to PM levels) is still a concern. The evidence base does not include studies evaluating concentration-responses, and few studies provide copollutant model analyses. The 2008 SO_X ISA (U.S. EPA, 2008d) found that animal toxicological studies did not provide sufficient evidence to assess the effects of long-term SO_2 exposure on lung function, morphology, or host defense. The one new subchronic animal toxicological study that is discussed in this review found effects of SO_2 exposure on airway responsiveness, airway remodeling, and allergic inflammation. Short-term toxicological studies also provide some evidence for these responses to SO_2 exposure.

5.2.2.1 Development and Severity of Asthma

Development of Asthma

Asthma is described by the National Heart, Lung, and Blood Institute (NHLBI NAEPP, 2007) as a chronic inflammatory disease of the airways that develops over time. Pulmonary inflammation can induce AHR, resulting in bronchoconstriction (bronchial smooth muscle contraction), and in turn, episodes of shortness of breath, coughing, wheezing, and chest tightness. When asthma advances in its development to the stage when the symptoms lead people to seek medical treatment, a diagnosis of asthma can result. Epidemiologic studies of SO_2 used self- or parental report of a diagnosis to define asthma. Epidemiologic studies reviewed in the 2008 SO_X ISA (U.S. EPA, 2008d) were limited to those with cross-sectional designs [Supplemental Table 5S-9 (U.S. EPA, 2015f)]. The majority of these studies reported positive associations of long-term SO_2 exposure with asthma prevalence. A few recent longitudinal epidemiologic studies support associations with asthma incidence and provide coherent evidence for associations with respiratory symptoms in healthy populations. Uncertainty remains in

the adequacy of SO_2 exposure estimates and copollutant confounding. However, some support for an effect of SO_2 exposure comes from a recent toxicological study showing SO_2-induced AHR.

Epidemiologic Studies

A strength of recent epidemiologic studies of asthma development is their longitudinal design (see Table 5-22). The follow-up of children over time to mark the first record of a physician diagnosis with no prior record of diagnosis can better characterize the temporal sequence between SO_2 exposure and the incidence of asthma. In this regard, longitudinal studies can better distinguish between onset of asthma and the exacerbation of asthma. In a large multicity study (N = 4,320 from Chicago, IL, Bronx, NY, Houston, TX, San Francisco Bay Area, CA, and the territory of Puerto Rico), Nishimura et al. (2013) observed that for SO_2 exposures during the first year of life the OR and 95% CI for asthma incidence was 0.95 (0.59−1.47) per 5 ppb change. SO_2 exposure during the first 3 years of life produced an OR and 95% CI for asthma incidence of 1.16 (0.73−1.84) per 5 ppb SO_2. SO_2 exposures were estimated using the IDW average of the four monitors within 50 km of the subject's residence. Selection bias due to differential loss to follow-up is not an issue given the retrospective design.

In a study of the British Columbia Birth Cohort (n =3,394 asthma cases), Clark et al. (2010) used IDW estimate-based concentrations from the three closest monitors within 50 km of the participants postal code to estimate SO_2 exposure. These authors observed an adjusted OR (95% CI) per 5 ppb of 1.48 (1.3−1.9) due to average exposures both during pregnancy and the first year of life. Conducted in Southwest British Columbia, the study had 14 SO_2 monitors available to provide data. Clark et al. (2010) conducted a quartile analysis to explore the exposure-response relationship and observed that the trend across quartiles was not linear (i.e., for the first-year exposure model the second quartile was smaller, negative with confidence intervals less than 1.0, than the positive first and last quartiles), lessening the strength of the association. In this nested case-control study (n = 37,401), medical records of children ages 3−4 years (born 1999−2000) were reviewed for asthma diagnosis (Clark et al., 2010). Selection bias due to differential loss to follow-up is not an issue, because of the records-based analysis used.

Table 5-22 Selected epidemiologic studies of long-term exposure to SO_2 and the development of asthma and intervention studies/natural experiments.

Study/Population	Location (Years)	Mean SO_2 ppb	Exposure Assessment	Selected Effect Estimates (95% CI)[a]
Longitudinal studies of the development of asthma				
†Nishimura et al. (2013) 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. Copollutant 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.
†Clark et al. (2010) 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. Copollutant 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_2 and the development of asthma and intervention studies/natural experiments.

Study/Population	Location (Years)	Mean SO_2 ppb	Exposure Assessment	Selected Effect Estimates (95% CI)[a]
†(Chiang et al. (2016a), 2016b)) Recruited 587 children aged between 11 and 14 yr from junior high schools in each of 9 townships. N = 587 Incidence rates for asthma (ICD-9; 493) were obtained from the Taiwan Health Insurance Database.	Taiwan, near a petrochemical complex which yields a diverse pollution mix. 1999 to 2010	The three-year average of the 99th percentage of SO_2 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_2 concentrations above 75 ppb each year in the HE areas and 2 hours in LE areas.	Two air quality monitoring stations, part of the Taiwan Environmental Protection Administration (TEPA), provided the SO_2 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. Copollutant correlations NR.	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.
Intervention studies and natural experiments				
Peters et al. (1996b) Children N = 3,521	Hong Kong, China (Kwai Tsing and Southern districts) Period of study: 1989−1991	Annual avg (µg/m^3): Southern 1989: 11 1990: 8 1991: 7 Kwai Tsing 1989: 111 1990: 67 1991: 23	Pre- and post-regulation concentrations compared in natural experiment; SO_2 emissions were reduced by 80% post-regulation.	Associations between respiratory symptoms and living in polluted areas observed and greater decline in symptoms post-regulation. Covariate adjustment: age, gender, environmental tobacco smoking in the family home, housing and father's education.
†Wong et al. (1998) Children (9—12 yr) N = 423	Hong Kong, China (Kwai Tsing and Southern districts) Period of study: 1989−1991	Annual avg (µg/m^3): Southern 1989: 11 1990: 8 1991: 7 Kwai Tsing 1989: 111 1990: 67 1991: 23	Pre- and post-regulation concentrations compared in natural experiment; SO_2 emissions were reduced by 80% post-regulation.	Decreased bronchial responsiveness observed post-intervention.

Table 5-22 (Continued): Selected epidemiologic studies of long term exposure to SO_2 and the development of asthma and intervention studies/natural experiments.

Study/Population	Location (Years)	Mean SO_2 ppb	Exposure Assessment	Selected Effect Estimates (95% CI)[a]
†Iwasawa et al. (2009) Miyake adults (N= 823)	Miyakejima Island, Japan, near Mt. Oyama volcano 2004−2006	31, post volcano (range: 19−45) Inhabited areas were classified into one lower SO_2 and three higher SO_2 areas to gauge exposure.	Seven monitors in residential areas used to estimate 2 yr avg; Natural experiment comparing symptom prevalence pre- and post-volcano eruption. Copollutant correlations: NR	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.
†Iwasawa et al. (2015) 120 Miyake school children	Feb. 2005 to Nov. 2011	Average concentrations (ppb) of SO_2 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.	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.	Prevalence of respiratory symptoms (cough, phlegm, wheeze, shortness of breath) was increased in areas with higher post-volcano SO_2 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.
†Longo et al. (2008) †Longo (2009) Adults (≥20 yr) N = 115 exposed N = 110 unexposed	Kilauea volcano, Hawaii Apr. to Jun. 2004	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.	Ambient and indoor SO_2 concentrations measured using a network of 70 passive samplers over a 3 wk sample period. Copollutant correlations: NR	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.

Table 5-22 (Continued): Selected epidemiologic studies of long term exposure to SO_2 and the development of asthma and intervention studies/natural experiments.

Study/Population	Location (Years)	Mean SO_2 ppb	Exposure Assessment	Selected Effect Estimates (95% CI)[a]
†Tam et al. (2016) 1,836 4th/5th graders mean age 10,1 yr	Kilauea volcano, Hawaii 2002 to 2005	SO_2, $PM_{2.5}$, and particulate acid in four exposure zones. Mean (SD) SO_2 across zones ranged from 0.3 to 10.1 ppb.	SO_2 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_2 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_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; IDW = inverse distance weighting; N = population number; NR = not reported; $PM_{2.5}$ = particulate matter with a nominal aerodynamic diameter less than or equal to 2.5 μm; SD = standard deviation; SES = socioeconomic status; SO_2 = sulfur dioxide.

[a]Effect estimates are standardized per 5-ppb increase in SO_2 concentrations unless otherwise noted.

†Studies published since the 2008 ISA for Sulfur Oxides.

Asthma incidence for school children from the Taiwan Health Insurance Database was evaluated contrasting high and low air pollution areas near a petrochemical complex for three time periods after the opening of the complex. The areas were indexed by 3-year annual average levels of the 99th % of SO_2 levels and periods above 75 ppb (Chiang et al., 2016a, b). The HRs were positive with wide confidence intervals for the three periods. Caution is required in inferences about an SO_2 effect because the areas examined represent complicated mixes from petrochemical complexes, the uncertainty for exposure error is high to include area comparisons rather than individual level comparisons, and the absence of evaluation for potential asthma risk factors.

The use of questionnaires in these studies to ascertain parents' report of physician-diagnosed asthma, a strength of the study design (Burr, 1992; Ferris, 1978), adds to the strength of inference about associations with SO_2. A limitation of these longitudinal studies include the potential for measurement error related to the use of IDW for SO_2 exposure estimates and comparison of high and low concentration areas (see Section 3.3.2). Validation of SO_2 exposures was not discussed for these studies. The standard increment used in the current ISA, 5 ppb for an annual average, is larger than the mean exposures in these studies, especially so for Clark et al. (2010) where the mean exposure and SD are 1.98 (0.97) ppb. Additionally, the strongest associations observed in both studies were with NO_2 concentration. Correlations between pollutant

concentrations were not reported by (Chiang et al. (2016a); Nishimura et al. (2013)), while Clark et al. (2010) noted that correlations between pollutant concentrations were generally high, but did not provide quantitative data. These studies suggest the potential for a relationship between long-term SO_2 exposure and the development of asthma. However, these results do little to reduce uncertainty related to potential copollutant confounding.

These studies considered confounding by asthma risk factors, which may be related to $PM_{2.5}$ exposure. All used information on maternal smoking. Clark et al. (2010) and Nishimura et al. (2013) examined parental education level. Nishimura et al. (2013) considered family history of allergy. These are key risk factors for asthma (Paaso et al., 2014). Other potentially important risk factors that do not appear to have been considered in these studies include respiratory infections, dampness, gas stove, pets, and daycare attendance (Gehring et al., 2010). Obesity identified as a potential risk factor for asthma in children (Gilliland et al., 2003; Gold et al., 2003) was not evaluated in these studies. However Borrell et al. (2013) examined obesity in the cohorts studied by Nishimura et al. (2013) in a nonpollution study.

Several recent studies presented in Supplemental Table 5S-10 (U.S. EPA, 2016p) also examine the association of long-term exposure to SO_2 with the prevalence of asthma in cross-sectional designs with various SO_2 exposure estimates as discussed in the table. While these studies involve uncertainties, most (Liu et al., 2016; Deng et al., 2015a; Liu et al., 2014a; Dong et al., 2013c; Dong et al., 2013b; Kara et al., 2013; Deger et al., 2012; Portnov et al., 2012; Akinbami et al., 2010; Sahsuvaroglu et al., 2009), but not all (Portnov et al., 2012), reported positive associations. These studies are consistent with similar studies in the 2008 SO_X ISA (U.S. EPA, 2008d). Deng et al. (2015a) used multipollutant models and reported that adjusting SO_2 for PM_{10} only slightly changes asthma risk. However, adjusting SO_2 for NO_2 substantially changed the SO_2 result. In addition, Liu et al. (2016) found that adjusting the effect in the single adjusted model for SO_2 was attenuated when further adjusted for NO_2 and PM_{10}. No longitudinal study of asthma incidence evaluates copollutant models. Thus, within the recent epidemiologic evidence base, studies provide limited new data to reduce the uncertainty related to whether the effect was from SO_2 or another pollutant. Studies of asthma incidence strengthen the inference by addressing the temporality of exposure and response.

Supportive evidence for a relationship between long-term SO_2 exposure and the development of asthma is provided by cross-sectional studies of respiratory symptoms related to asthma. In the 2008 SO_X ISA (U.S. EPA, 2008d), studies examining an array of respiratory symptoms related to SO_2 exposure are presented in Supplemental Table 5S-11 (U.S. EPA, 2016q) and others are noted in the text of the 2008 SO_X ISA (U.S. EPA,

2008d; Ware et al., 1986; Chapman et al., 1985; Dodge et al., 1985). These cross-sectional studies used fixed site monitors for the SO_2 exposure estimate. While associations were generally positive, some inverse or null associations were also observed. Recent studies evaluating the relationship between long-term SO_2 exposure and the prevalence of asthma symptoms [Supplemental Table 5S-10 (U.S. EPA, 2016p)] also found positive associations (Altuğ et al., 2013; Pan et al., 2010; Arnedo-Pena et al., 2009).

Additional epidemiologic evidence for a link between long-term exposure to SO_2 and the development of asthma may come from intervention or natural experiment studies (see Table 5-22). Physicians diagnose asthma, in part, based on the occurrence or exacerbation of asthma symptoms, such as cough and wheeze, and the level of bronchial hyperreactivity (BHR) in the subjects. Decline in such symptoms and BHR in relation to a decline of a pollutant level may support a relationship between asthma development and exposure to pollutants such as SO_2. Decreases in respiratory symptoms, including any wheeze or asthmatic symptoms, wheezing, and cough and sore throat, in 3,521 healthy children (mean age of 9.51 years) were associated with decreases in SO_2 concentrations in Hong Kong due to a government restriction of sulfur content of fuels as discussed in the 2008 SO_X ISA [see Peters et al. (1996b), within U.S. EPA (2008d)] . During the same period, Wong et al. (1998) examined the effect of the same decrease in SO_2 concentrations on BHR in children aged 9−12 who were non-wheezing and did not have asthma at study entry. In the cohort analysis, which compared measurements made before the intervention and 1 year afterwards, BHR declined. The subjective health measures seen in Peters et al. (1996b) were corroborated by the objective data of the histamine challenge test in Wong et al. (1998). These results should be interpreted with caution given the uncertainty of whether changes in BHR and respiratory symptoms were independently related to SO_2 in light of the concomitant decline in sulfate respirable suspended particles (RSP) (<10 µm). Over the study period, SO_2 declined about 80% (from about 111 to 23 µg/m^3 while annual mean sulfate concentrations in RSP fell from 12.5 to 7.7 µg/m^3. It is difficult to determine whether one was more important than the other. However, these studies add to the information base relating long-term SO_2 exposure and asthma-related outcomes.

Recent cross-sectional studies that estimated long-term SO_2 exposure from volcano emissions in Japan and Hawaii were conducted (Table 5-22). Iwasawa et al. (2009) observed increased frequencies of phlegm and minor effects on the respiratory system among both adults and children residing near the Mt. Ōyama volcano in Japan across four inhabitant areas with varying SO_2 levels. Iwasawa et al. (2015) further followed the children yearly from 2006 to 2011, finding the prevalence of respiratory symptoms (cough, phlegm, wheeze, shortness of breath) to be related to the higher SO_2 exposure.

Studies conducted near the Kīlauea volcano in Hawaii observed an adjusted increase in cough on most days for 3 consecutive months or more per year in children and adults (Longo, 2009; Longo and Yang, 2008; Longo et al., 2008). Tam et al. (2016) related cough to a mixture containing acidic respirable particulates, but not to SO_2 exposure directly, in children near the Kilauea volcano. As a whole, these studies are supportive of a link between SO_2 exposure and respiratory symptoms. However, such studies compare areas of high volcano emissions to areas of lower emissions (indexed by SO_2 concentration) and thus, results may be confounded by copollutant exposures.

Severity of Asthma

NHLBI NAEPP (2007) identifies stages of asthma such as mild, moderate, moderate-persistent, and severe. When going from mild to severe, the likelihood of acute exacerbations increases. Stages of worsening of asthma are usually based on severity scores as used in the following studies [Supplemental Table 5S-10, (U.S. EPA, 2016p)]. Rage et al. (2009) examined severity of asthma in adults. Long-term SO_2 exposure was correlated with a higher asthma severity score. Ozone showed the strongest relationship while NO_2 was unrelated. In 17--year-old male military recruits, Greenberg et al. (2016) related asthma severity to SO_2 measured as low, intermediate, and high. The observed associations between asthma severity and air pollution support the notion that air pollutants may increase asthma severity. However, the uncertainty related to these effects potentially being influenced by short-term exposure needs to be examined. Deger et al. (2012) examined the prevalence of active and poor asthma control in children and observed an association with long-term SO_2 exposure among children with active asthma and a more marked association among children with poor asthma control. No other pollutants were examined. Adjusting for child's age and sex, parental atopy and environmental tobacco smoke exposure slightly decreased the association, and stratification according to age (<6 years and ≥6 years) showed that associations with SO_2 were mainly observed in the older age group. Adjusting for socioeconomic status (i.e., household income and maternal educational level) had limited influence on the results of the analyses (<5%).

AHR is a key component of asthma. In a recent study, long-term exposures to SO_2 were associated with increased methacholine responsiveness determined by FEV_1 decreasing by 20% or more [provocative concentration 20 (PC_{20})] (Ierodiakonou et al., 2015), but results have uncertain inference because exposures were estimated from monitors up to 50 km from subjects' ZIP code centroid. Further, a very large number of comparisons were made among pollutants, exposure lags, lung function parameters, cities, and asthma medication groups, and there is higher probability that the few associations observed are due to chance. The PC_{20} percent change per interquartile range (2 ppb 4-month moving

average) was −6% (95% CI, −11% to −1.5%) in 2,661 observations in the Childhood Asthma Management Program (CAMP), a randomized clinical trial involving eight cities in North America. The PC_{20} standardized to per 5 ppb is −15% (−27.5 to −3.75%). Four-month average SO_2 was not associated with changes in lung function measured before or after bronchodilator treatment. Health outcome results for 1-day and 1-week exposure periods are discussed earlier in Section 5.2.1.2; only the 4-month moving average results are discussed here. The original health study, a longitudinal prospective cohort study with repeated measures but without a pollution component, was designed to examine the long-term safety and effectiveness of daily inhaled anti-inflammatory medication in children with mild to moderate asthma diagnosed and was sponsored by the NHLB. The children were 5 to 12 years of age and hyperresponsive to methacholine at study entry. Recruitment occurred from late December 1993 to early September 1995 (CAMP Research Group, 1999; Cherniack et al., 1999) at two HMO's and six academic institutions.

Monitoring data on 24-h avg concentrations of pollutants ozone, CO, NO_2, and SO_2 were obtained for each metropolitan area from the Aerometric Information Retrieval System for the U.S. cities and from the Air Quality and Reporting Unit for Toronto were linked to the ZIP code of the subject's address at study entry. There is uncertainty in the measurement estimate and a potential for measurement error. Distance or proximity of sites to subjects is not known. For long-term studies bias can go in either direction. Thus, the evidence base for a relationship between long-term SO_2 exposure and AHR is limited.

Animal Toxicological Studies

A single animal study of chronic SO_2 exposure-related effects on lung morphology was discussed in the 2008 SO_X ISA (U.S. EPA, 2008d). Study characteristics are summarized in Table 5-23. Smith et al. (1989) found that rats exposed to 1 ppm of SO_2 had an increased incidence of bronchiolar epithelial hyperplasia and increased numbers of nonciliated epithelial cells after 4 months of exposure. However, these effects were not present at 8 months of exposure, suggesting that repair and/or adaptation may have taken place.

Table 5-23 Study-specific details from animal toxicological studies.

Study	Species (strain); n; Sex; Lifestage/Age	Exposure Details (Concentration; Duration)	Endpoints Examined
Smith et al. (1989)	Rats (Sprague-Dawley); n = 12−15 per data point; M; young adult; normal or elastase-impaired	1 ppm (2.62 mg/m^3) SO_2 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_2 washout Morphological effects Lung function—residual volume, functional residual capacity, quasi-static compliance, residual volume/total lung capacity, N_2 washout Endpoints examined after sacrifice Morphology
Song et al. (2012)	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_2 for 4 h/d for 4 wk beginning at 15 d Exposure groups: (1) Control (2) SO_2 alone (3) Ovalbumin alone (4) Ovalbumin + SO_2	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_2 = nitrogen; SD = standard deviation; SO_2 = sulfur dioxide.

No studies on airway responsiveness or pulmonary inflammatory responses to long-term exposure to SO_2 concentrations of 2 ppm and lower were discussed in the 2008 SO_X ISA (U.S. EPA, 2008d). One new animal toxicological study of subchronic SO_2 exposure has become available since the last review. Key findings are discussed here, and study characteristics are summarized in Table 5-23. Song et al. (2012) found that airway responsiveness was enhanced in a model of allergic airways disease using rats that were first sensitized and challenged with ovalbumin and then exposed to 2 ppm SO_2 for 4 hours/day for 28 days. Airway responsiveness was not changed with exposure to SO_2 alone in naive rats. However, Song et al. (2012) observed hyperemia in the lung

parenchyma and inflammation in the airways of naive rats exposed only to SO_2. SO_2 exposure also increased the inflammatory responses in rats made allergic to ovalbumin. Airway remodeling was found in ovalbumin-treated rats with and without exposure to SO_2. A more pronounced increase in the airway smooth muscle layer was found in the ovalbumin/SO_2 group compared to the ovalbumin group. The authors concluded that the effects of SO_2 on airway responsiveness and airway remodeling were dependent on ovalbumin sensitization and challenge. Song et al. (2012) also measured concentrations of IL-4 and IFN-γ in the BALF and serum of rats exposed to SO_2, with and without prior sensitization and challenge with ovalbumin. Concentrations of IL-4 in the BALF were increased in the ovalbumin and the SO_2 groups, with the greatest increase occurring in the combined ovalbumin/SO_2 group. An increase in IL-4 in serum occurred only in the ovalbumin/SO_2 group. Concentrations of IFN-γ in the BALF were decreased in the ovalbumin, SO_2, and ovalbumin/SO_2 groups. A decrease in serum IFN-γ was observed in the ovalbumin and ovalbumin/SO_2 groups. IL-4 is a Th2 cytokine associated with allergic responses, while IFN-γ is a Th1 cytokine. An increase in the ratio of Th2 to Th1 cytokines indicates Th2 polarization (or possibly a Type 2 immune response mediated by group 2 innate lymphoid cells), a key step in allergic sensitization. As discussed in prior sections, these findings provide evidence that repeated SO_2 exposure enhances allergic responses, airway remodeling, and airway responsiveness in this model of allergic airway disease. Furthermore, repeated SO_2 exposure in naive rats increased levels of the Th2 cytokine IL-4, decreased levels of the Th1 cytokine IFN-γ in the BALF, and increased airway inflammation suggesting that SO_2 exposure may on its own induce allergic sensitization. Because allergic sensitization, airway remodeling, and AHR are key events (or endpoints) in the proposed mode of action for the development of asthma (Section 4.3.6), these results suggest that long-term exposure to SO_2 may lead to the development of an asthma-like phenotype in this animal model involving newborn rats.

Summary of Asthma Development and Severity

Recent epidemiologic evidence from a limited number of longitudinal studies report associations between asthma incidence among children and long-term SO_2 exposures. Additional supportive evidence for a link between long-term SO_2 exposure and the development of asthma is provided by cross-sectional studies of asthma prevalence. The longitudinal studies help reduce the uncertainty associated with the temporality of exposure and response that is inherent in cross-sectional study designs. This evidence is coherent with animal toxicological evidence of inflammation, allergic sensitization and other allergic responses, airway remodeling, and AHR, which are key events (or endpoints) in the proposed mode of action for the development of asthma (Section 4.3.6). The animal toxicological evidence provides support for an independent effect of SO_2 and

strengthens the link between long-term exposure to SO_2 and the development of asthma in children. Additional evidence supportive of this link comes from cross-sectional studies of respiratory symptoms and respiratory allergies among children and from natural experiments. Thus, multiple lines of evidence suggest that long-term SO_2 exposure results in a coherent and biologically plausible sequence of events that culminates in the development of asthma, especially allergic asthma, in children.

The potential for a relationship between long-term SO_2 exposure and severity of asthma has been examined in a few studies. One study in adults correlated exposure with higher asthma severity scores. A study in children found a more marked association in those with poor asthma control. AHR, measured as PC_{20}, worsened with long-term SO_2 exposure in a multicity cohort of children. Thus, evidence of asthma control and increased AHR provides suggestive but limited support for this relationship.

5.2.2.2 Development of Allergy

There is some evidence for a potential relationship between long-term SO_2 exposure and indicators or respiratory allergies and inflammation among children. Several recent cross-sectional studies examined the prevalence of respiratory allergies using different markers for respiratory allergies including IgE antibodies, rhinitis, eczema, sensitization to pollen, and hay fever related to long-term SO_2 exposure (Liu et al., 2016; Chan et al., 2013; Bhattacharyya and Shapiro, 2010; Penard-Morand et al., 2010; Parker et al., 2009; Nordling et al., 2008) **[**see Supplemental Table 5S-11 (U.S. EPA, 2016q)]. Positive results were observed for children using these various indicators of allergy. Further, a very weak relationship was found Dales et al. (2008) between long-term SO_2 exposure and eNO, an indicator of inflammation [see Supplemental Table 5S-11 (U.S. EPA, 2016q)].

Recent studies examine two-pollutant models for allergic rhinitis prevalence. Results for allergic rhinitis prevalence based on responses from ISAAC questionnaire data in Changsha China (Chan et al., 2013) did not find an association for SO_2 for site-specific background SO_2 and allergic rhinitis in children 3−6 year old, but did find an association for age-related accumulative exposure in a single pollutant model using the closest monitor to kindergartens. The two-pollutant model with PM_{10} was attenuated. For SO_2 exposures during the first year of life in Shanghai, China, Liu et al. (2016) found an association with allergic rhinitis in children at age 6 which was attenuated when adjusted for other pollutants using district monitors. These findings suggest the possibility that chronic exposure to SO_2 may play a role in the development of allergic conditions based on results for various allergic markers. The cross-sectional design of these studies makes

these relationships uncertain and the exposure estimates from monitors is subject to the possibility of measurement error and uncertainties informing the representativeness of the exposure estimates in the studies as discussed in Section 3.4.2. Thus, the evidence base for a relationship between long-term SO_2 exposure and allergic rhinitis response is limited and two-pollutant model begin to characterize the role of SO_2 exposure.

5.2.2.3 Lung Function

Epidemiologic Studies

Longitudinal epidemiologic studies examine associations between long-term SO_2 exposure and decrements in lung function. Lung function grows through early adulthood with growth and development, then declines with aging (Stanojevic et al., 2008; Zeman and Bennett, 2006; Thurlbeck, 1982). Thus, a relationship between long-term SO_2 exposure and decreased lung function over time in school-age children into early adulthood would be an indicator of decreased lung development.

As discussed in the 2008 SO_X ISA (U.S. EPA, 2008d), earlier cross-sectional studies (Dockery et al., 1989; Schwartz, 1989) found no association between long-term SO_2 exposure and lung function in U.S. children. A longitudinal cohort study (Frischer et al., 1999) reported that long-term SO_2 exposure was associated with decrements in lung function in the summer but not in the winter. In Poland, a prospective cohort study of children (Jedrychowski et al., 1999) found decrements in lung function growth related to a polluted area where concentrations of both TSP and SO_2 were high compared to a cleaner area where concentrations of both TSP and SO_2 were low, thus not providing results specifically for SO_2. In a cross-sectional study in adults in Switzerland, Ackermann-Liebrich et al. (1997) observed an association between SO_2 concentration and lung function, but after controlling for PM_{10}, this association was no longer evident. In the former East Germany from 1992 to 1999, Frye et al. (2003) reported improvements in lung function associated with declines in SO_2 concentrations in 2,493 children over three cross-sectional surveys. These studies are presented in Supplemental Table 5S-9 (U.S. EPA, 2015f).

Recent studies in children and adults add to this evidence base [see Supplemental Table 5S-12 (U.S. EPA, 2016r)**]**. In a repeated measure prospective study of the TCHS cohort, Hwang et al. (2015a) examined lung function growth for a 2 year period from age 12 to 14 years. No association was found for SO_2 exposure and FEV_1 or FVC for boys and girls, but a deficit was observed for boys for $FEF_{25–75}$. A single measure longitudinal study in several U.S. cites observed for first year of life exposures a suggestive

association for SO_2 and FEV_1. Neophytou et al. (2016) examined the same cohort that Nishimura et al. (2013) did as discussed earlier in this section for asthma incidence in the same cities with the same SO_2 exposure method evaluating the same confounding factors plus obesity. For each 1 ppb increase of SO_2 percent change in FEV_1 and the 95% CI were −1.01 (−3.25, 1.27).

In a cross-sectional, longitudinal repeated-measures study of children, Linares et al. (2010) reported a decline in FEV_1 related to long-term SO_2 exposure in the entire study group. This study included children from two schools in different locations relative to a petrochemical zone. In an analysis of the children by sex, in one- and two-pollutant analysis of PM_{10} and O_3, the outcome was attenuated. In a cross-sectional study of children in 14 communities in Taiwan, Lee et al. (2011c) found a reduction in FEV_1 related to long-term SO_2 exposure with larger reductions related to NO_2 and CO exposure. Yogev-Baggio et al. (2010) related the effect of the interaction, $NO_X \times SO_2$ "event," to reduction in FEV_1 in children in Israel near a coal-fired power plant. In a cross-sectional study of 32,712 adults in England, Forbes et al. (2009c) related FEV_1 effects to exposure to SO_2, PM_{10}, and NO_2, but not O_3. A U.K. study of alpha-1-antitrypsin deficiency and COPD (Wood et al., 2010) found reduced FEV_1 in relation to SO_2 concentration but a more rapid decline in relation to PM_{10} concentration. Dales et al. (2008) found a weak decline in FEV_1 and FVC related to long-term SO_2 exposure in school children in Windsor, ON using a cross-sectional prevalence design.

The majority of the recent studies and earlier studies used cross-sectional designs. Some studies took into account potentially confounding covariates detailed in the Supplemental Table 5S-12 (U.S. EPA, 2016r). Neophytou et al. (2016) controlled for age, height, and calendar time, allowing for nonlinear effects, indicator variables for sex, race/ethnicity, and continuous variables for SES (composite score variable), and numbers of smokers in the household and also assessed effect modification by sex, obesity, SES, atopy, and parental asthma. The designs used in most of the recent studies (i.e., ecological, cross-sectional, single measure) limit the possible inferences about the relationship between long-term SO_2 exposure and lung function. The evidence does not include studies evaluating concentration-responses. The one study conducting a copollutant analysis found attenuation of the effect with adjustment for PM_{10}. Thus, recent studies do not add information that changes conclusions made in the 2008 SO_X ISA (U.S. EPA, 2008d) that there is not clear evidence that long-term SO_2 exposure is related to lung function changes.

Animal Toxicological Studies

A single long-term study with SO_2 exposure concentrations at or below 2 ppm was discussed in the 2008 SO_X ISA (U.S. EPA, 2008d). Study characteristics are summarized in Table 5-23. Smith et al. (1989) found that rats exposed to 1 ppm SO_2 for 4 months had decreased residual volume and quasi-static compliance when treated with saline (control). Rats treated with elastase (a model of emphysema) and exposed to 1 ppm SO_2 for 4 months had a decreased ratio of residual volume to total lung capacity and decreased alveolar plateau of the single-breath nitrogen (N_2) washout (N_2-slope), indicating a worsening of the emphysema. However, Smith et al. (1989) concluded that the effects of SO_2 on lung function measurements were very minor in the saline (control) group and likely due to chance alone (residual volume) or to unusually high control values (quasi-static compliance).

Summary of Lung Function

Several studies evaluated the relationship between long-term SO_2 exposure and decrements in lung function. Evidence supporting this relationship is limited because associations were inconsistent and because both PM and SO_2 were at high concentrations in the same areas, which does not allow determination of individual SO_2 effects. Potential confounding of long-term SO_2 exposure-related decrements in lung function and lung development by other pollutants, especially PM, was evaluated in only one study. This study found an attenuation of the effect in copollutant analyses. No changes in lung function were found in long-term animal toxicological studies at relevant SO_2 concentrations. The recent studies support conclusions of no association between long-term SO_2 exposure and lung function in children made in the 2008 SO_X ISA (U.S. EPA, 2008d).

5.2.2.4 Respiratory Infection

Epidemiologic Studies

Studies have also examined the association of long-term exposure to SO_2 with infant bronchiolitis, otitis media, and pneumonia in children, hospital admission for community-acquired pneumonia in adults aged 65 years or more, and tuberculosis in adults. Infant bronchiolitis was examined in British Columbia by Karr et al. (2009). These authors observed an association with lifetime exposure to SO_2 after adjustment for an array of confounders [Supplemental Table 5S-11 (U.S. EPA, 2016q)]. The largest associations were observed with NO_2 and CO concentrations. MacIntyre et al. (2011)

found no increased risk for otitis media in relation to long-term SO_2 exposure in a study of children up to the age of 2 in British Columbia, while Bhattacharyya and Shapiro (2010) found a strong relationship with long-term SO_2 exposure in the U.S. National Health Interview Survey of 126,060 children ages 3−6 years. Lu et al. (2014) observed that the prevalence of pneumonia in children 3 to 6 year old was related to long-term SO_2 exposure. Liu et al. (2016) reported that doctor-diagnosed pneumonia in children 4−6 years old was related to SO_2 exposure during the first year of life. Neupane et al. (2010) estimated long-term SO_2 exposure at the residence for both the case and control subjects with bicubic splined (SPL) and IDW methods for the 2-yr avg for 2001 and 2002, obtaining means of 4.65 ppb and 5.80 ppb, respectively, but with a twofold greater range for SPL. Adjusted estimates of associations for SO_2 with hospitalization from community-acquired pneumonia were positive for SPL but not for IDW. The incidence of tuberculosis was associated with an increase of SO_2 in adult males (Hwang et al., 2014) but not in a study in California (Smith et al., 2016). Although limited in number, by inconsistency, and by their cross-sectional design, these studies suggest a potential relationship between long-term exposure to SO_2 and respiratory infections due to various infectious agents.

Animal Toxicological Studies

No new animal studies of the effects of long-term SO_2 exposure on lung host defense have been conducted since the previous review. Several studies of short- and long-term exposure to SO_2 were reported in the 1982 AQCD (U.S. EPA, 1982a) and discussed in the 2008 SO_X ISA (U.S. EPA, 2008d). Short-term exposure studies found some effects of 0.1−1 ppm SO_2 on the clearance of labeled particles. Long-term exposure studies found decreased tracheal mucus flow at a concentration of 1 ppm SO_2, but no effects on susceptibility to bacterial infection or alterations in the pulmonary immune system at concentrations of 2 ppm or less.

Summary of Respiratory Infection

Evidence for prevalence of infant bronchiolitis and/or respiratory infections consists of generally positive associations found in cross-sectional studies. Thus, they provide a limited evidence base in number and design. While some animal toxicological studies reported alterations in specific host defense mechanisms, there is no evidence to support increases in bacterial or viral infections in animals exposed to SO_2 at relevant concentrations.

5.2.2.5 Development of Other Respiratory Diseases: Chronic Bronchitis, Chronic Obstructive Pulmonary Disease, and Acute Respiratory Distress Syndrome

Chronic bronchitis consists of symptoms, including daily cough and/or congestion or phlegm for 3 months in a row. While these symptoms may have started with acute exacerbation, they are likely to represent chronic indolent symptoms. As discussed in the 2008 SO_X ISA (U.S. EPA, 2008d), earlier cross-sectional studies observed positive relationships between long-term SO_2 exposure estimates derived from fixed site monitors and chronic bronchitis as presented in Supplemental Table 5S-11 (U.S. EPA, 2016q). Recent cross-sectional studies of the association of long-term exposure to SO_2 with the prevalence of bronchitis also observed positive relationships after adjustment for potential confounders. In addition, a recent COPD incidence study in a national English cohort (Atkinson et al., 2015), discussed in Supplemental Table 5S-11 (U.S. EPA, 2016q), reported a positive association in an adjusted HR model with SO_2 exposure averaged over 3 years determined by dispersion models. Assessment of model validity using national network sites and separate verification sites yielded poor R^2 values for SO_2 of 0 and 0.39, respectively. Other limitations of this study include a short follow-up time and the failure to confirm the 36% of incident hospital admissions for COPD by a general practitioner diagnosis.

A relationship between Acute Respiratory Distress Syndrome (ARDS) and long-term SO_2 exposure has recently been studied (Ware et al., 1986) as discussed in Supplementary Table 5S-11 (U.S. EPA, 2016q). SO_2 and $PM_{2.5}$ were not associated with ARDS.

5.2.2.6 Respiratory Mortality

Recent studies provide some evidence that respiratory mortality may be more consistently associated with long-term exposure to SO_2 than other causes of death (Section 5.5.2 and Figure 5-27). There is uncertainty in the small, positive associations between long-term exposure to SO_2 and respiratory mortality observed in these studies, because the exposure assessment and statistical methods are not adequate for studying a highly spatially and temporally heterogeneous pollutant like SO_2. Additionally, there is little evidence of respiratory health effects in adults in relation to long-term SO_2 exposure that could provide coherence with the observed associations with respiratory mortalities.

5.2.2.7 Summary and Causal Determination

Overall, the evidence is suggestive of, but not sufficient to infer, a causal relationship between long-term SO_2 exposure and respiratory effects, mainly the development of

asthma in children. This conclusion represents a change from "inadequate to infer a causal association" for respiratory effects as stated in the 2008 SO_X ISA (U.S. EPA, 2008d).

Recent epidemiologic evidence from a limited number of longitudinal studies report associations between asthma incidence among children and long-term SO_2 exposures. The longitudinal studies address the temporality of exposure and response and help to reduce the uncertainty associated with temporality that is inherent in cross-sectional study designs. The evidence from longitudinal studies is coherent with animal toxicological evidence of allergic sensitization, airway remodeling, and enhanced airway responsiveness, which are key events (or endpoints) in the proposed mode of action for the development of asthma. The animal toxicological evidence provides support for an independent effect of SO_2 and a possible relationship between long-term exposure to SO_2 and the development of asthma in children. Some evidence of a link between long-term exposure to SO_2 and respiratory symptoms and/or respiratory allergies among children further supports this relationship. The potential for SO_2 to serve as an indicator for other pollutants or mixture related to PM is an uncertainty that applies to the new body of epidemiologic evidence across the respiratory effects examined.

The key evidence supporting the causal determination is detailed below using the framework described in Table I of the Preamble to the ISAs (U.S. EPA, 2015b) and is presented in Table 5-24.

Evidence for the Development of Asthma

A limited number of longitudinal studies demonstrate associations between ambient SO_2 concentrations measured in the first year of life and/or over the first 3 years of life in children and asthma incidence such as (Clark et al., 2010) and (Nishimura et al., 2013) (Section 5.5.2.1). Results are fairly consistent between studies with one based on several different locations across the U.S., another over a large area in Canada, and one in Taiwan, involving a large number of participants. Uncertainties and the potential for measurement error related to the use of IDW and area comparisons in these studies may limit inferences that can be made (Section 3.4.2). Additional supportive evidence for a link between long-term SO_2 exposure and the development of asthma is provided by cross-sectional studies of asthma prevalence, respiratory symptoms, and markers of respiratory allergies among children (Section 5.2.2.2). Findings of studies evaluating respiratory symptoms are supportive of the development of asthma; however, they may also reflect other respiratory conditions. Intervention and natural experiment studies also indicate a possible relationship between long-term exposure to SO_2 and the development 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[a]	Key Evidence[b]	Key References[b]	SO_2 Concentrations Associated with Effects[c]
Development and severity of asthma			
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	Nishimura et al. (2013) Clark et al. (2010)	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	Section 5.2.2.1	
	Supporting evidence for respiratory symptoms and markers of respiratory allergies among children in cross-sectional studies	Section 5.2.2.1 and Section 5.2.2.2	
	Supporting evidence from intervention studies and natural experiments	Section 5.2.2.1	
	Evidence for increases in asthma severity as indicated by asthma severity score, degree of asthma control, and AHR	Section 5.2.2.1	
Uncertainty regarding potential for measurement error in exposure estimates	Use of IDW in asthma incidence studies and fixed monitoring sites in cross-sectional studies	Section 3.4.2	
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	Section 3.4.3 (Liu et al. (2016); Deng et al. (2015a))	

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[a]	Key Evidence[b]	Key References[b]	SO_2 Concentrations Associated with Effects[c]
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	Song et al. (2012)	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	Li et al. (2007) Li et al. (2014)	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	Riedel et al. (1988) Park et al. (2001)	100 ppb 100 ppb
	Enhanced inflammation and allergic responses in rats previously sensitized with an allergen and then repeatedly exposed	Li et al. (2007) Li et al. (2014)	2,000 ppb
Some evidence for key events in proposed mode of action	Inflammation, allergic sensitization, AHR, airway remodeling	Section 4.3.6	
Development of allergy			
Limited epidemiologic evidence but uncertainty regarding SO_2 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	Section 5.2.2.2	
Lung function			
Inconsistent epidemiologic evidence among children from quality studies and uncertainty regarding SO_2 independent effects	In cohort studies, associations inconsistent with adjustment for PM and by season	Neophytou et al. (2016) Jedrychowski et al. (1999) Frischer et al. (1999)	
	Inconsistent results from cross-sectional studies	Dockery et al. (1989) Schwartz (1989) Ackermann-Liebrich et al. (1997) Frye et al. (2003)	

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[a]	Key Evidence[b]	Key References[b]	SO_2 Concentrations Associated with Effects[c]
Respiratory infection			
Limited epidemiologic evidence; uncertainty regarding SO_2 independent effects	Generally positive associations in cross-sectional studies. Uncertainty in temporality, exposures estimated from monitors in the community, and copollutant confounding	Section 5.2.2.4	
Limited animal toxicological evidence	Altered clearance of particles and decreased tracheal mucus flow	U.S. EPA (1982a)	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		
Development of other respiratory diseases			
Limited epidemiologic evidence but uncertainty regarding SO_2 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	Section 5.2.2.5	
Respiratory mortality			
Generally consistent epidemiologic evidence	Small, positive associations between long-term exposure to SO_2 and respiratory mortality in several cohorts, even after adjustment for common potential confounders	Hart et al. (2011), Nafstad et al. (2004), Elliott et al. (2007), Cao et al. (2011), Carey et al. (2013), Dong et al. (2012), Katanoda et al. (2011)	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	Section 5.2.2.6	

AHR = airway hyper-responsiveness; IDW = inverse distance weighting; PM = particulate matter; SD = standard deviation; SO_2 = sulfur dioxide.

[a]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).

[b]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.

[c]Describes the SO_2 concentrations with which the evidence is substantiated (for experimental studies, ≤2,000 ppb).

Epidemiologic studies of asthma development in children have not clearly characterized potential confounding by other pollutants or mixtures of pollutants. This uncertainty was present in the previous review, and there is no new information from incidence studies to help reduce this uncertainty. No studies of asthma incidence have evaluated copollutant models to address copollutant confounding, making it difficult to evaluate the independent effect of SO_2 within the epidemiologic evidence base for incidence. A limited number of recent cross-sectional studies of asthma prevalence involving two-pollutant models provide preliminary information to characterize the role of long-term SO_2 exposure. In studies that examined both SO_2 and $PM_{2.5}$, positive associations were observed between $PM_{2.5}$ concentrations and asthma development; the effects were similar in magnitude to those for SO_2 (Nishimura et al., 2013; Clark et al., 2010). Correlations between SO_2 and $PM_{2.5}$ were not reported in these studies. Thus, results from these two studies do not reduce the uncertainty related to potential copollutant confounding.

The uncertainties in the epidemiologic evidence base is reduced, in part, by the biological plausibility provided by findings from experimental studies that demonstrate SO_2-induced effects on key events or endpoints that are part of the proposed mode of action for development of asthma [i.e., allergic sensitization, airway remodeling and AHR (Section 4.3.6)]. An experimental study in newborn rats, which were not previously sensitized and challenged with an allergen (i.e. naive animals), found that repeated acute SO_2 exposures over several weeks led to airway inflammation and Th2 polarization (or other Type 2 immune responses), important steps in allergic sensitization [(Song et al., 2012); (see Section 5.2.2.1)]. Repeated SO_2 exposure in the newborn rats, which were previously sensitized and challenged with an allergen (i.e., allergic animals), resulted in enhanced allergic airway inflammation and some evidence of airway remodeling and AHR. Additional evidence comes from experimental studies in adult animals involving short-term exposure to SO_2 over several days. In naive rats, airway inflammation and morphologic responses indicative of airway remodeling were seen (Section 5.2.1.7). Furthermore, enhancement of allergic sensitization and other inflammatory responses were observed along with AHR in guinea pigs exposed repeatedly to SO_2 for several days and subsequently sensitized and challenged with an allergen (Section 5.2.1.7). Similarly, SO_2 exposure enhanced airway inflammation in rats previously sensitized with an allergen (Section 5.2.1.2).

Evidence for the Severity of Asthma

A few studies provide evidence for a potential relationship between long-term SO_2 exposure and the severity of asthma, as indicated by asthma severity scores, asthma control, and AHR (Section 5.2.2.1).

Evidence for the Development of Allergies

Epidemiologic evidence from a few long-term studies provides a link between long-term SO_2 exposure and respiratory allergies and allergic rhinitis among children (Section 5.2.2.2). However, uncertainties remain given the cross-sectional design of these studies. Two pollutant models have begun to address the role of SO_2 exposure in the development of allergic rhinitis.

Evidence for Lung Function

Several studies evaluated the relationship between long-term SO_2 exposure and decrements in lung function (Section 5.2.2.3). Evidence supporting this relationship is limited because associations were inconsistent and because both PM and SO_2 were at high concentrations in the same areas, precluding determination of individual SO_2 effects. Potential confounding of long-term SO_2 exposure-related decrements in lung function and lung development by other pollutants, especially PM, was evaluated in only one study. This study found an attenuation of the effect in two-pollutant analyses. No changes in lung function were found in long-term animal toxicological studies at relevant SO_2 concentrations. The recent studies support conclusions made in the 2008 SO_X ISA (U.S. EPA, 2008d) that the available evidence was inadequate to infer a causal relationship between long-term exposure to SO_2 at ambient concentrations and changes in lung function.

Evidence for Respiratory Infection

Respiratory infection related to long-term SO_2 exposure is discussed in Section 5.2.2.4. A limited number of the cross-sectional studies examined indicate associations between long-term SO_2 exposure and bronchitis or respiratory infection due to various infectious agents; findings were generally positive. While some animal toxicological studies reported alterations in specific host defense mechanisms, there is no evidence to support increases in bacterial or viral infections in animals exposed to SO_2 at relevant concentrations.

Evidence for the Development of Other Respiratory Diseases

Evidence for prevalence of bronchitis and/or COPD consists of generally positive associations found in cross-sectional studies (Section 5.2.2.5).

Evidence for Respiratory Mortality

Small positive associations between long-term exposure to SO_2 and respiratory mortality among adults were found in several cohort studies after adjustment for common potential confounders (Section 5.2.2.6). There is little evidence of respiratory health effects in adults in relation to long-term SO_2 exposure that could provide coherence with the observed associations with respiratory mortality among adults.

Conclusion

Taken together, epidemiologic and animal toxicological studies provide evidence that is suggestive of, but not sufficient to infer, a causal relationship between long-term SO_2 exposure and respiratory effects (see Table 5-24). The strongest evidence is provided by coherence of findings of epidemiologic studies showing associations between long-term SO_2 exposure and increases in asthma incidence among children and findings of animal toxicological studies that provide a pathophysiologic basis for the development of asthma. These latter studies demonstrated that repeated SO_2 exposure over several weeks resulted in Th2 polarization (or other Type 2 immune responses) and airway inflammation, key steps in allergic sensitization, in naive newborn animals. In addition, repeated SO_2 exposure over several weeks resulted in enhanced airway inflammation and some evidence of airway remodeling and AHR in allergic newborn animals. Toxicological studies involving repeated exposure to SO_2 over several days provide additional evidence of these effects. However, because the animal toxicological evidence is limited, particularly for long-term exposure, some uncertainty remains regarding an independent effect of long-term SO_2 exposure on the development of asthma. In addition, potential confounding by other pollutants is unexamined, and largely unavailable, for epidemiologic studies of asthma among children. However, multiple lines of evidence suggest that long-term SO_2 exposure results in a coherent and biologically plausible sequence of events that culminates in the development of asthma, especially allergic asthma, in children.

5.3 Cardiovascular Effects

5.3.1 Short-Term Exposure

5.3.1.1 Introduction

The 2008 ISA for Sulfur Oxides (U.S. EPA, 2008d) reviewed studies published through 2006 and concluded that "the evidence as a whole is inadequate to infer a causal relationship" between short-term exposure to SO_2 and cardiovascular health effects. Specifically, the 2008 ISA for Sulfur Oxides found a lack of consistency with regard to short-term exposure to SO_2 and markers of HRV, cardiac repolarization, discharges of implantable cardioverter defibrillators (ICDs), blood pressure, blood markers of cardiovascular disease risk, the triggering of a myocardial infarction, or ED visits or hospital admission for cardiovascular diseases. This section reviews the published studies pertaining to the cardiovascular effects of short-term exposure (i.e., up to 1 month) to SO_2 in humans and animals. There are no toxicological studies evaluating cardiovascular effects following 5−10 minute exposures to SO_2. With few exceptions, most epidemiologic studies model the association of 24-h avg SO_2 concentration with cardiovascular outcomes. With the existing body of evidence serving as the foundation, emphasis has been placed on studies published since the 2008 ISA for Sulfur Oxides (U.S. EPA, 2008d).

To clearly characterize the evidence underlying causality, the discussion of the evidence is organized into groups of related outcomes [myocardial infarction and ischemic heart disease (Section 5.3.1.2), arrhythmia and cardiac arrest (Section 5.3.1.3), cerebrovascular disease (Section 5.3.1.4), hypertension (Section 5.3.1.5), venous thromboembolism (Section 5.3.1.6), heart failure (Section 5.3.1.7), aggregated cardiovascular disease (Section 5.3.1.8), and cardiovascular mortality (Section 5.3.1.9)]. Evidence for subclinical effects (e.g., heart rate variability, blood biomarkers of cardiovascular effects) of short-term exposure to SO_2 that potentially underlie the triggering or indication of various clinical events are discussed in Section 5.3.1.10, and may provide biological plausibility for multiple outcomes. When considered with the evidence reviewed in the 2008 ISA for Sulfur Oxides, recent epidemiologic studies add to the evidence for effects of SO_2 exposure on a broader array of cardiovascular effects and mortality. Still, substantial uncertainties remain concerning exposure measurement error, the lack of mechanistic evidence to describe a role for SO_2 in the initiation of key events in a proposed mode of action, and potential confounding by copollutants. The majority of the

recent evidence is from epidemiologic studies, which examined the association of SO_2 exposure with MI, cerebrovascular disease and other cardiovascular effects.

The previous ISA included a small number of animal toxicological studies of blood pressure (Section 5.3.1.5), HR and HRV (Section 5.3.1.10), and arrhythmia frequency (Section 5.3.1.3) and controlled human exposure studies that examined effects on the autonomic nervous system (Section 5.3.1.10) from short-term exposure to SO_2. Since the 2008 ISA for Sulfur Oxides (U.S. EPA, 2008d), no controlled human exposure studies and few animal toxicological studies have investigated the effects of short-term SO_2 exposure on the cardiovascular system. Results from the experimental studies included in the past and current reviews that evaluated cardiovascular effects of short-term SO_2 exposures of less than 2,000 ppb are summarized in the relevant outcome section and additional study details are summarized in Supplemental Table 5S-13 (U.S. EPA, 2016s).

Studies examining cardiovascular effects of sulfite exposure (via i.p., i.v., etc.) are not included in this section because these studies generally involve exposures to sulfite that are higher than what is expected to occur following inhalation of SO_2 at ambient relevant concentrations. Some studies using prolonged exposures to 300 ppb and higher concentrations of SO_2 reported measurable changes in the concentrations of sulfite/S-sulfonate in plasma and tissues. A positive correlation was found between the concentration of inhaled SO_2 and plasma sulfite/S-sulfonate levels in humans exposed continuously to SO_2 (300−6,000 ppb) (Gunnison and Palmes, 1974). Similarly, a recent report in mice exposed to 5,000−20,000 ppb SO_2 for 7 days found a concentration-dependent increase in sulfite/S-sulfonate levels in lung, heart, and brain compared to controls (Meng et al., 2005b). These studies suggest that prolonged exposure to SO_2 at concentrations higher than typically found in ambient air may increase circulating sulfite, but these changes would be expected to be far less following ambient exposures of shorter duration. The literature on the distribution and metabolism of sulfite is discussed in Section 4.2.3 and Section 4.2.4. The potential role of sulfite in the induction of systemic effects, such as effects of the cardiovascular system, is discussed in Section 4.3.4.

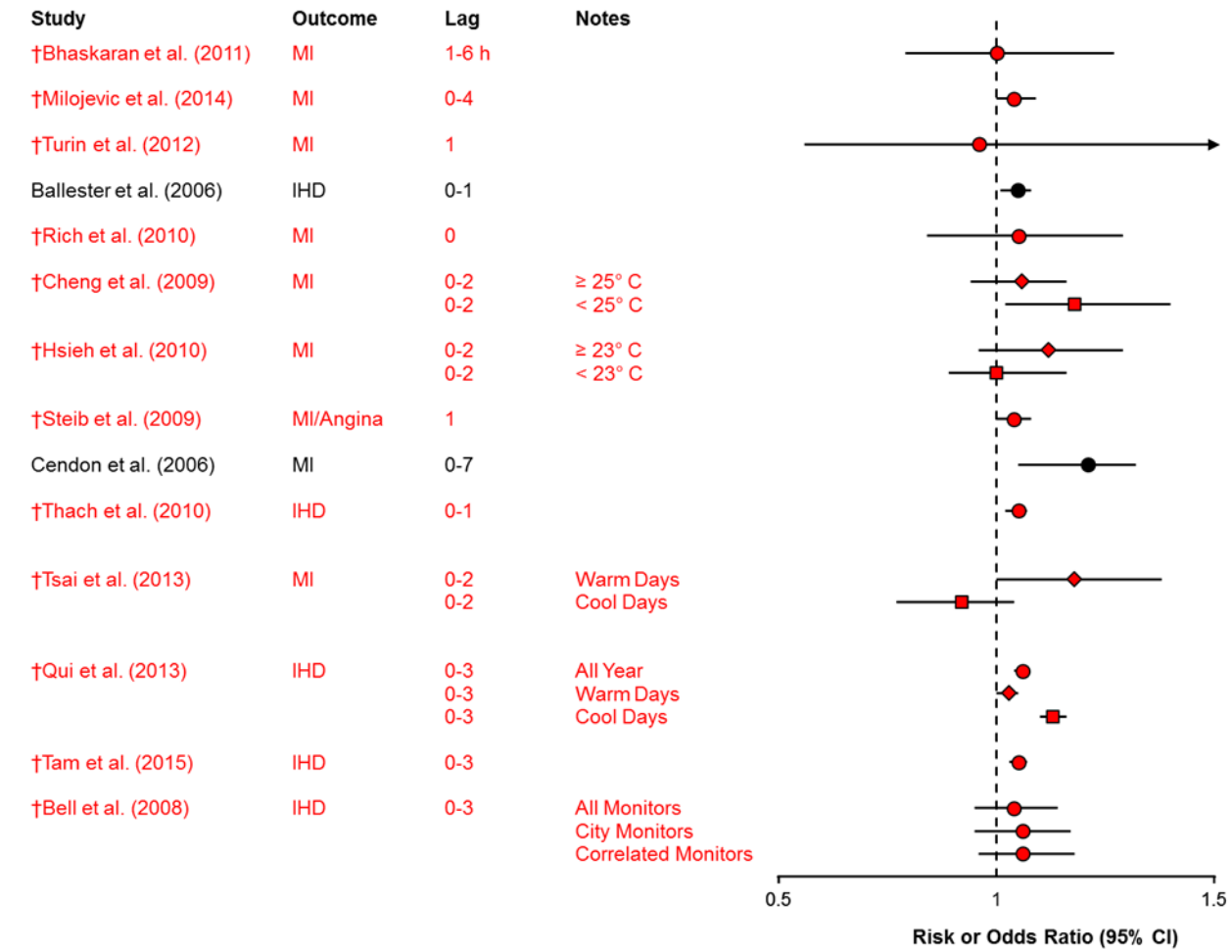
5.3.1.2 Myocardial Infarction and Ischemic Heart Disease

Several lines of evidence are discussed in evaluating the relationship between short-term SO_2 exposure and MI. An MI, or heart attack, occurs as a consequence of IHD, resulting in insufficient blood flow to the heart that overwhelms myocardial repair mechanisms and leads to muscle tissue death. ICD codes for MI are classified within the group of IHDs, thus studies in which IHD is evaluated will include any patients diagnosed with an

MI. Finally, acute MI may be characterized by ST-segment depression, a nonspecific marker of myocardial ischemia. The evaluation of evidence supporting a relationship between short-term SO_2 exposure and the triggering of an MI includes hospitalization and ED visits for MI or IHD and ST-segment amplitude changes.

The epidemiologic data available for review by the 2008 ISA for Sulfur Oxides (U.S. EPA, 2008d) did not indicate an association between SO_2 and risk of MI. A number of additional studies based on administrative data of hospital admissions or ED visits or on clinical data are now available in Figure 5-12. The air quality characteristics of the city, or across all cities, and the exposure assignment approach used in each MI-related hospital admission and ED visit study evaluated in this section are presented in Table 5-25. The recent clinical registry studies provide inconsistent evidence for an association between MI and ambient SO_2, while multicity and single-city hospital admission and ED visit studies provide generally consistent evidence of an association. However, potential copollutant confounding and limited mechanistic evidence are still key uncertainties that make it difficult to interpret the results of these studies. Additionally, most studies examined 24-h avg exposure metrics for SO_2, which may not adequately capture the spatial and temporal variability in SO_2 concentrations (Section 3.4.2).

Some studies rely on clinical registries, which are generally less susceptible to misclassification of the outcome. Using data from the Myocardial Ischaemia National Audit Project (MINAP) clinical registry, Bhaskaran et al. (2011) reported that hourly ambient SO_2 concentrations were not associated with risk of MI in a case-crossover study of 15 conurbations in England and Wales between 2003 and 2006. While no associations were reported in the population overall, there was some evidence of an association in subgroup analyses within older age groups (60−69, 70−79, and 80+) at inconsistent lag times. This study is unique because it included detailed data on the timing of MI onset in more than 79,000 patients, which allowed examination of the association with ambient SO_2 in the hours preceding MI. Milojevic et al. (2014) also used data from MINAP, from 2003 to 2009, and observed stronger evidence of an association between SO_2 concentrations and MI [4.3% (95% CI: −0.25, 8.8%) increase in risk of MI per 10-ppb increase in 24-h avg SO_2 at lag 0−4]. Turin et al. (2012) did not observe any association using data from the Takashima County Stroke and Acute Myocardial Infarction Registry in central Japan, although this study was likely underpowered to detect an association of the expected magnitude. None of the clinical registry studies examined copollutant models.



CI = confidence interval.

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-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
†Bhaskaran et al. (2011)	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
†Milojevic et al. (2014)	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
†Turin et al. (2012)	Takashima County, Japan (1988−2004)	Nearest monitor to Takashima County (20 km)	24-h avg	Mean: 3.9	75th: 4.8
Ballester et al. (2006)	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
†Rich et al. (2010)	New Jersey (2004−2006)	Closest of 14 monitor (those >10 km from monitor excluded)	24-h avg	NR	NR
†Cheng et al. (2009)	Kaohsiung, Taiwan (1996−2006)	Average across six monitoring stations	24-h avg	Mean: 9.33	75th: 11.69 Max: 31.26
†Hsieh et al. (2010)	Taipei, Taiwan (1996−2006)	Average across six monitoring stations	24-h avg	Mean: 4.36	75th: 5.48 Max: 17.82
†Stieb et al. (2009)	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
Cendon et al. (2006)	São Paulo, Brazil (1998−1999)	Average across 13 monitoring stations	24-h avg	Mean: 5.6	95th: 12.1
†Thach et al. (2010)	Hong Kong, China (1996−2002)	Average across eight monitoring stations	24-h avg	Mean: 6.8	NR
†Tsai et al. (2012)	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
†Qiu et al. (2013a)	Hong Kong, China (1998, 2007)	Average across 14 monitoring stations	24-h avg	Mean: 7.4	NR
†San Tam et al. (2015)	Hong Kong, China (2001−2010)	Average across 13 monitoring stations	24-h avg	Mean: 7.6	75th: 9.3 Max: 51.9
†Bell et al. (2008)	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.

One prominent study from the previous 2008 ISA for Sulfur Oxides (U.S. EPA, 2008d) was conducted in 14 cities across Spain and found a 4.5% (95% CI: 1.3, 8.1%) increase in hospital admissions per 10-ppb shift in SO_2 for the composite endpoint of IHD, arrhythmias, and heart failure (Ballester et al., 2006). This association was still positive, but attenuated and no longer statistically significant after adjustment for CO or NO_2. It was lessened in magnitude, but more precise, with adjustment for TSP or O_3 in copollutant models (no quantitative results; results presented graphically). Several additional ED visit and hospital admission studies are now available. In a study of hospitalization in New Jersey, Rich et al. (2010) did not report strong evidence for an association between SO_2 and risk of hospital admissions for MI [OR: 1.05 (95% CI: 0.84, 1.29) per 10-ppb increase in 24-h avg SO_2 on the same day]. The inclusion of $PM_{2.5}$ in a copollutant model did not reveal a positive association for SO_2 [OR: 0.91 (95% CI: 0.69, 1.21)]. In Kaohsiung, Taiwan, Cheng et al. (2009) reported an association between SO_2 concentrations and hospital admissions for MI, but only on days when the mean ambient temperature was <25°C. However, in copollutant models adjusting for PM_{10}, NO_2, or CO, SO_2 was no longer associated with increased admissions. Conversely, in Taipei, Taiwan, Hsieh et al. (2010) only observed an association between SO_2 and MI on warm days (≥23°C). Similar to the findings of Cheng et al. (2009), this association was no longer positive after adjustment for PM_{10}, NO_2, O_3, or CO in copollutants models. Most other studies have not considered copollutant models.

A study using data from 14 hospitals in seven Canadian cities found a 4.2% (95% CI: 0.4, 8.0%) increase in risk of ED visits for the composite endpoint of acute MI or angina per

10-ppb increase in SO_2 on the previous day (Stieb et al., 2009). Most (San Tam et al., 2015; Qiu et al., 2013a; Tsai et al., 2012; Thach et al., 2010; Cendon et al., 2006; Martins et al., 2006) but not all (Bell et al., 2008) studies using data from individual cities have found associations between SO_2 concentrations and risk of hospital admissions or ED visits for ischemic heart disease or MI. None of the single-city studies evaluated potential copollutant confounding, and all of the studies in this section used fixed site monitors to measure ambient SO_2. The limitations of these monitors in capturing spatial variation in SO_2 has been noted previously (Section 3.4.2).

ST-Segment Changes

ST-segment changes (either ST-segment elevation or depression) on the electrocardiogram are considered a nonspecific marker of myocardial ischemia. While the 2008 ISA for Sulfur Oxides did not review any epidemiologic studies of ambient SO_2 concentrations and markers of myocardial ischemia, one subsequent study reported an association. Chuang et al. (2008) conducted a repeated-measures study in adults with a history of coronary heart disease (CHD) and examined the association between ambient pollutants and ST-segment level changes. This study found an odds ratio of 3.0 (95% CI: 1.8, 5.5) for ST-segment depression of $\geq$0.1 mm per 10-ppb increase in SO_2 over the previous 24 hours. This finding was generally unchanged after additional control for $PM_{2.5}$ and BC in copollutant models.

Summary of Ischemic Heart Disease and Myocardial Infarction

In summary, while evidence from epidemiologic studies suggests a potential association between ambient SO_2 concentrations and rates of hospital admissions or ED visits for MI or ischemic heart diseases in single-pollutant models, these associations may be the result of confounding by other pollutants. While three studies based on clinical data report inconsistent evidence regarding associations between ambient SO_2 concentrations and risk of MI, the majority of studies relying on MI hospital admission and ED visit data observed either seasonal or year-round associations with SO_2. However, some of these associations were either attenuated or no longer present after controlling for potential copollutant confounding (Hsieh et al., 2010; Cheng et al., 2009; Ballester et al., 2006), leaving uncertainties regarding the independent effect of short-term SO_2 exposure. In congruence with the evidence from hospital admission and ED visit studies, there was limited evidence from a single study indicating that SO_2 may be associated with ST-segment changes on the electrocardiogram in patients with a history of coronary heart disease. Most studies examined 24-h avg exposure metrics for SO_2, which may not adequately capture the spatial and temporal variability in SO_2 concentrations

(Section 5.2.1.2). No experimental studies have been conducted to evaluate measures of ischemic heart disease or MI following short-term SO_2 exposure. Overall, despite some epidemiologic evidence of an association between short-term exposure to SO_2 and hospital admissions and ED visits for ischemic heart disease and MI, uncertainties regarding copollutant confounding continue to impede the determination of an independent SO_2 effect.

5.3.1.3 Arrhythmias and Cardiac Arrest

The 2008 ISA for Sulfur Oxides (U.S. EPA, 2008d) concluded that the evidence available at the time did not suggest that SO_2 has an effect on cardiac arrhythmias. There continues to be essentially no epidemiologic or toxicological evidence suggestive of such a relationship.

Metzger et al. (2007) examined 518 patients with ICDs with 6,287 tachyarrhythmic event-days over a 10-year period in Atlanta, Georgia and found no association between SO_2 concentrations and the risk of tachyarrhythmias, either overall or in analyses limited to more severe tachyarrhythmic events, or stratified by season or the presence of a recent past arrhythmic event (results for this study and other studies in this section can be found in Table 5-26). A similar study in London, England also found limited evidence of an association between SO_2 concentrations and arrhythmic risk (Anderson et al., 2010). Anderson et al. (2010) reported an increase in risk of ICD activations corresponding to an increase in ambient SO_2, but the association was imprecise [OR: 1.35 (95% CI: 0.75, 2.41) per 10-ppb increase in SO_2 at lag days 0−1]. Similarly, a study in Boston, Massachusetts observed an association between ambient SO_2 and ICD activations that was even more imprecise [32.0% (95% CI: −48.5, 336.2%) increase in ICD activations per 10-ppb increase in SO_2 concentrations at lag 1] (Link et al., 2013). Additionally, a multicity study in Canada (Stieb et al., 2009) and a large single-city study in Taipei, Taiwan (Tsai et al., 2009) have reported finding no association between SO_2 and ED visits for arrhythmias, while a large single-city study in Shanghai, China reported a positive association that was attenuated and no longer positive in a copollutant model adjusted for NO_2 (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_2 (ppb)	Exposure Assessment	Selected Effect Estimates[a] (95% CI)
†Metzger et al. (2007)	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)
†Anderson et al. (2010)	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_{10}: 0.48, $PM_{2.5}$: 0.42, BS: 0.35, SO_4^{2-}: 0.19, PNC: 0.29, NO_2: 0.60, NO: 0.44, NO_X: 0.49, O_3: −0.36
†Link et al. (2013)	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_2: 0.05 to 0.69, O_3: −0.52 to −0.18, PM_{10}: 0.27 to 0.55, $PM_{2.5}$: 0.01 to 0.67
†Stieb et al. (2009)	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_{10}: 0.52, NO_2: 0.43, CO: 0.24, O_3: 0.09
†Tsai et al. (2009)	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_{10}: 0.52, NO_2: 0.43, CO: 0.24, O_3: 0.09
†Zhao et al. (2014)	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_2 (ppb)	Exposure Assessment	Selected Effect Estimates[a] (95% CI)
†Dennekamp et al. (2010)	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)
†Silverman et al. (2010)	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_2 concentrations. OHCA positively but imprecisely (i.e., wide 95% CI) associated with ambient SO_2 during the warm season
†Straney et al. (2014)	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)
†Rosenthal et al. (2013)	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)
†Kang et al. (2016)	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_2 = nitrogen dioxide; NO_X = the sum of NO and NO_2; O_3 = ozone; OHCA = out-of-hospital cardiac arrhythmias; OR = odds ratio; PM_{10} = particulate matter with a nominal aerodynamic diameter less than or equal to 10 µm; $PM_{2.5}$ = particulate matter with a nominal aerodynamic diameter less than or equal to 2.5 µm; PNC = particle number concentration; SO_2 = sulfur dioxide; SO_4^{2-} = sulfate.

All Lag times are in days, unless otherwise noted.

†Studies published since the 2008 ISA for Sulfur Oxides.

[a]Effect estimates are standardized to a 10-ppb or 40-ppb increase in SO_2 concentration for 24-h avg and 1-h max metrics, respectively.

The majority of out-of-hospital cardiac arrests (OHCA) are due to cardiac arrhythmias. Dennekamp et al. (2010) considered the association between ambient pollutants and OHCA among 8,434 cases identified through the Victorian Cardiac Arrest Registry in Melbourne, Australia and found null and/or imprecise associations (e.g., wide 95% CIs) between SO_2 concentrations and risk of OHCA. A similar approach was used by Silverman et al. (2010) with data from 8,216 OHCAs in New York City. Quantitative

results for SO_2 were not provided, but graphs showed a null association between OHCA and year-round SO_2 concentrations. Silverman et al. (2010) also presented season-specific analyses graphically, demonstrating that out-of-hospital cardiac arrests were positively but imprecisely (i.e., wide 95% CI) associated with SO_2 concentrations during the warm season. Two additional case-crossover studies of OHCA in Perth, Australia (Straney et al., 2014) and Helsinki, Finland (Rosenthal et al., 2013) observed null associations with ambient SO_2. In contrast, Kang et al. (2016) observed an association between 24-h avg SO_2 and OHCA in Seoul, South Korea at individual lag days 0 through 3 (no quantitative results; results presented graphically).

One animal toxicological study (Nadziejko et al., 2004) evaluated arrhythmia frequency in rats following short-term SO_2 exposure and reported no significant changes in spontaneous arrhythmias (irregular, delayed, or premature beats).

In summary, studies of patients with implantable cardioverter defibrillators, hospital admissions for arrhythmias, and out of hospital cardiac arrest do not provide evidence to support the presence of an association between ambient SO_2 concentrations and arrhythmias. Most of these studies have been focused on other pollutants and therefore have not explored whether such an association might exist in certain subgroups. Additionally, the majority of studies used central site monitors to estimate ambient SO_2 exposure, which have noted limitations in capturing spatial variation in SO_2 that generally lead to attenuation and loss of precision in the effect estimates (Section 3.4.4). One toxicological study also found no evidence for arrhythmias following short-term SO_2 exposure.

5.3.1.4 Cerebrovascular Diseases and Stroke

Results among the studies reviewed in the 2008 ISA for Sulfur Oxides were inconsistent with regard to the association between ambient SO_2 concentrations and hospital admissions or ED visits for cerebrovascular diseases or stroke (a specific form of cerebrovascular disease). Many additional studies are now available for consideration (study details and results presented in Table 5-27 and Figure 5-13). In Edmonton, AB, Szyszkowicz (2008) reported that risk of ED visits for ischemic stroke was linked to SO_2 concentrations, but this association was observed only in subgroup analyses stratified by sex, season, and age. A subsequent study in Vancouver, BC, found that SO_2 was associated with risk of ED visits for ischemic stroke in the population overall [OR: 2.09 (95% CI: 1.23, 3.52) per 10-ppb increase in SO_2 at lag 3] (Szyszkowicz et al., 2012a). The association was generally unchanged after adjustment for O_3 in a copollutant model, and attenuated, although still positive, after adjustment for CO [OR: 1.73 (95% CI: 1.00,

3.10)]. Chen et al. (2014b) also observed an association between SO_2 and ischemic stroke at longer lags in Edmonton, AB. In Brazil, Costa Nascimento et al. (2012) observed a 7.8% (95% CI: 0.0, 16.5%) increase in risk of hospital admissions of stroke per 10-ppb increase in 24-h avg SO_2 at lag 0. Zheng et al. (2013) reported a small but precise association between SO_2 concentrations and risk of hospital admission for cerebrovascular disease [1.7% increase (95% CI: 0.5, 2.8%) per 10-ppb increase in 24-h avg SO_2 at lag 2] in Lanzhou, a heavily polluted city in China with a high observed mean daily concentration of SO_2 (30.19 ppb) over the 5-year study period. The association was as strong, or stronger, after adjustment for PM_{10} [1.8% increase (95% CI: 0.4, 3.2%)] or NO_2 [2.6% increase (95% CI: 1.4, 3.7%)] in copollutant models. In central Japan, Turin et al. (2012) found that the risk of hemorrhagic stroke was associated with SO_2 concentrations, but found no association with other types of stroke. However, the 95% CI for the hemorrhagic stroke association was wide, indicating an imprecise association, and copollutant confounding was not considered.

In contrast to the studies that reported some evidence of an association between SO_2 concentrations and cerebrovascular disease, a number of studies observed null or imprecise associations. In an effort to reduce uncertainty related to the use of central site monitors, Bell et al. (2008) estimated SO_2 exposure over the entire Taipei, Taiwan area (average of 13 monitors), within Taipei City only (average of 5 monitors), and using a subset of monitors where all pairs of monitors had SO_2 correlations greater than 0.75 (6 monitors). Using three exposure metrics, the authors did not observe an association between SO_2 and risk of hospital admission for cerebrovascular diseases. Contrary to other studies that reported associations between SO_2 concentrations and hospital admissions and ED visits for stroke in Canada (Chen et al., 2014b; Szyszkowicz et al., 2012a; Szyszkowicz, 2008), Villeneuve et al. (2012) reported null and/or imprecise associations between SO_2 and all stroke, ischemic stroke, and hemorrhagic stroke in Edmonton, AB. Studies in Hong Kong (Thach et al., 2010), Dijon, France (Henrotin et al., 2007), and Lyon, France (Mechtouff et al., 2012) also observed null associations between SO_2 concentrations and rates of hospital admission for stroke.

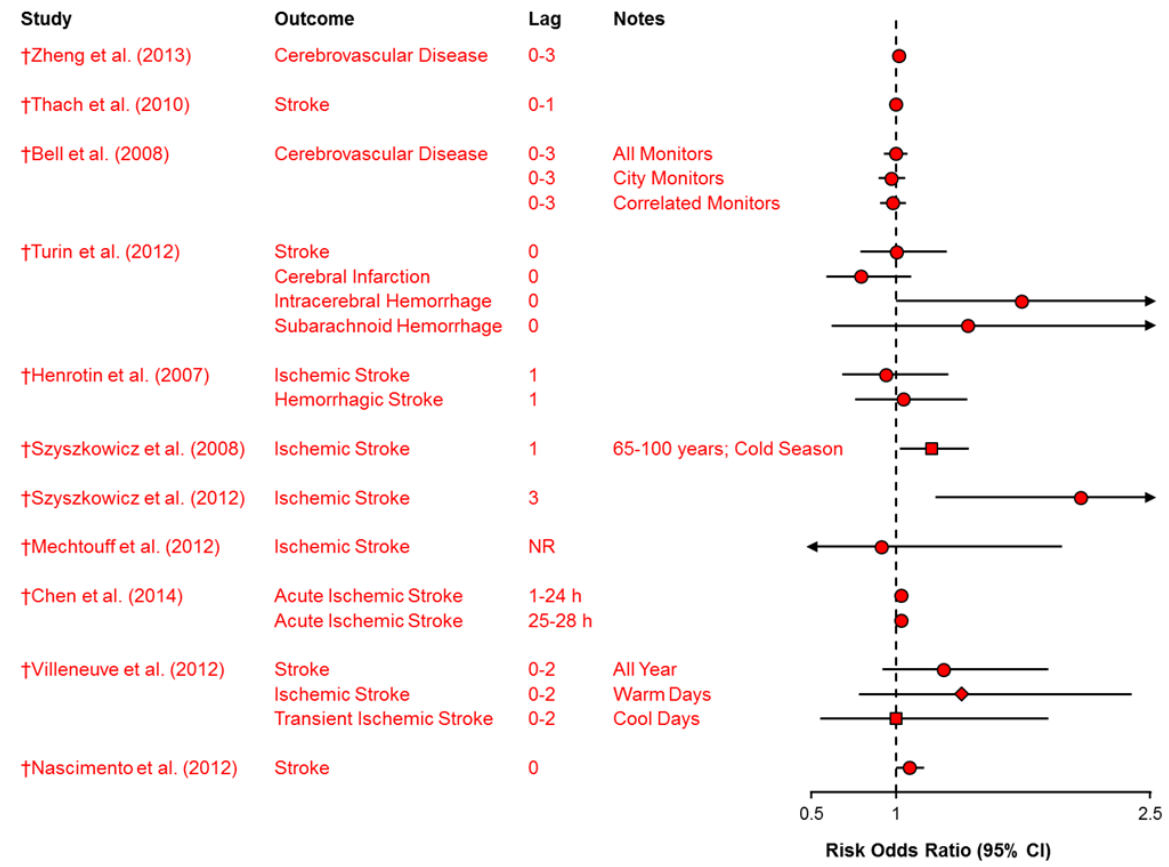
Thus, findings for the association between SO_2 and cerebrovascular diseases continue to be inconsistent across studies. As for other outcomes, associations reported from single pollutant models in some locations may be at least partly due to confounding by other pollutants.

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
†Zheng et al. (2013)	Lanzhou, China (2001−2005)	Average across four monitoring stations	24-h avg	Mean: 30.19	75th: 40.46 Max: 141.60
†Thach et al. (2010)	Hong Kong, China (1996−2002)	Average across eight monitoring stations	24-h avg	Mean: 6.79	NR
†Bell et al. (2008)	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
†Turin et al. (2012)	Takashima County, Japan (1988−2004)	Nearest monitor to Takashima county (20 km)	24-h avg	Mean: 3.9	75th: 4.8
Henrotin et al. (2007)	Dijon, France (1994−2004)	Central site monitor	24-h avg	Mean: 2.63	75th: 3.44 Max: 24.81
†Szyszkowicz (2008)	Edmonton, AB (1992−2002)	Average across three monitoring stations	24-h avg	Mean: 2.6	NR
†Szyszkowicz et al. (2012a)	Vancouver, BC (1999−2003)	Average across 11 monitoring stations	24-h avg	Mean: 2.5	NR
†Mechtouff et al. (2012)	Lyon, France (2006−2007)	Average across five monitoring stations	24-h avg	Mean: 2.02	75th: 2.67 Max: 22.52
†Chen et al. (2014b)	Edmonton, AB (1998−2002)	Average across three monitoring stations	1-h avg	Mean: 2.0	95th: 6.7
†Villeneuve et al. (2012)	Edmonton, AB (2003−2009)	Average across three monitoring stations	24-h avg	Mean: 1.5	75th: 1.9
†Costa Nascimento et al. (2012)	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.

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, but not standardized for other metrics [e.g., (Chen et al., 2014b)]. Lag times are reported in days, unless otherwise noted. Corresponding quantitative results are reported in Supplemental Table 5S-15 (U.S. EPA, 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

Based on the data available at the time, the 2008 ISA for Sulfur Oxides (U.S. EPA, 2008d) concluded that the overall evidence was insufficient to determine that SO_2 has an effect on blood pressure. Recent evidence provides limited and inconsistent evidence for changes in blood pressure associated with short-term exposure to SO_2.

Epidemiologic Studies

A number of longitudinal studies measured BP in subjects in Beijing before, during, and after the 2008 Beijing Olympics when citywide air pollution control measures substantially reduced ambient levels of most criteria pollutants. Huang et al. (2012) measured blood pressure repeatedly on up to four occasions in 40 participants with pre-existing cardiovascular disease in Beijing, including one measurement during the 2008 Beijing Olympics when citywide air pollution control measures reduced ambient SO_2 concentrations by up to 50%. Huang et al. (2012) found a small decrement in diastolic blood pressure per IQR (NR) increase in prior 30-minute exposure to SO_2 [−0.9 mm Hg (95% CI: −2.0, 0.2 mm Hg)], but observed a null association between ambient SO_2 and systolic blood pressure. Focusing on healthy young adults, Rich et al. (2012) and Zhang et al. (2013) observed associations between SO_2 and blood pressure in repeated-measures studies conducted before, during, and after the 2008 Beijing Olympics (no quantitative results; results presented graphically). Using the same protocol, Zhang et al. (2013) and Rich et al. (2012) observed a positive association between 24-h avg SO_2 and systolic blood pressure, but an inverse association between 24-h avg SO_2 and diastolic blood pressure. The negative association between SO_2 and diastolic blood pressure was relatively unchanged after adjustment for $PM_{2.5}$, EC, or sulfate, while the association between SO_2 and systolic blood pressure was also robust to sulfate, but attenuated, although still positive, after adjustment for $PM_{2.5}$ or EC (Zhang et al., 2013).

In another repeated measures study, Kim et al. (2016b) observed positive associations between short-term SO_2 concentrations and systolic blood pressure, diastolic blood pressure, and mean arterial pressure among 560 older adults living in Seoul, South Korea. A pair of cross-sectional studies reported conflicting evidence of an association. Examining data from 7,578 participants in the Taiwanese Survey on Prevalence of Hyperglycemia, Hyperlipidemia, and Hypertension, Chuang et al. (2010) concluded that there is “no significant association” between SO_2 concentrations and blood pressure (no quantitative results presented). However, in a cross-sectional analysis of data from 9,238 participants in the Taiwan Community-based Integrated Screening program, Chen et al. (2012d) found a 4.0 mm Hg (95% CI: 3.0 to 5.0 mm Hg) increase in diastolic blood pressure per 10-ppb increase in SO_2 concentrations 2 days earlier, and a 1.6 mm Hg (95% CI: 0.15, 3.1 mm Hg) decrease in systolic blood pressure related to SO_2 concentrations 3 days earlier.

In addition to longitudinal and cross-sectional studies, a few new studies examined ED visits for hypertension. In Beijing, Guo et al. (2010) observed a 10.0% (95% CI: 1.1, 19.7%) increase in risk of ED visits for hypertension per 10-ppb increase in 24-h avg SO_2 on the same day. The association was attenuated, but still positive, in a copollutant model

adjusting for PM_{10} [6.7% (95% CI: −3.4, 17.9%) increase at lag 0] and no longer present in a copollutant model adjusting for NO_2 [−0.8% (95% CI: −12.8, 13.0%) change at lag 0]. Inconsistent results were reported in two studies of ED visits for hypertension in Canada. In a case-crossover study in Calgary and Edmonton, Brook and Kousha (2015) reported positive associations between ED visits for hypertension and 24-h avg SO_2 concentrations for males [OR: 2.50 (95% CI: 1.00, 5.87) per 10-ppb increase] and females [OR: 2.59 (95% CI: 1.12, 5.61) per 10-ppb increase]. Conversely, in Edmonton, Szyszkowicz et al. (2012b) observed that ED visits for hypertension were both positively and negatively associated with SO_2 depending on the lag time examined.

Experimental Studies

Several experimental studies examined hypertension and blood pressure following SO_2 exposure. Study characteristics are summarized in Supplemental Table 5S-13 (U.S. EPA, 2016s). One controlled human exposure study reported no change in mean arterial pressure following SO_2 exposure (Routledge et al., 2006). Two animal toxicological studies have examined blood pressure following SO_2 exposure (Halinen et al., 2000b; Halinen et al., 2000a). In both studies, SO_2 was administered intratracheally to hyperventilated guinea pigs in cold, dry air. These studies reported increases in blood pressure following cold, dry air exposure with and without SO_2 and did not determine whether there were any effects on blood pressure caused by SO_2 that may not be attributable to cold, dry air exposure.

Summary of Blood Pressure

In summary, epidemiologic studies evaluating the association between ambient SO_2 concentrations and blood pressure remain inconsistent with most relying on central site monitors and few examining the potential for copollutant confounding. Experimental studies provide no additional evidence for SO_2-induced changes in blood pressure. The most informative studies to date found no evidence of within-person changes in blood pressure despite relatively large changes in SO_2 concentrations during the Beijing Olympics. Experimental studies do not demonstrate effects of SO_2 on blood pressure. As such, the current evidence does not support the presence of an association between ambient SO_2 and blood pressure.

5.3.1.6 Venous Thromboembolism

Venous thromboembolism (VTE) is a term that includes both deep vein thrombosis (DVT) and pulmonary embolism (PE). DVT occurs when a blood clot develops in the deep veins, most commonly in the lower extremities. A part of the clot can break off and travel to the lungs, causing a PE, which can be life threatening.

There were no epidemiologic studies of VTE available for the 2008 ISA for Sulfur Oxides. One recent study covering the metropolitan region of Santiago, Chile, found a 10.8% (95% CI: 3.3, 15.7%) and 8.5% (95% CI: 4.0, 13.2%) increased rate of hospital admission for venous thrombosis and pulmonary embolism, respectively, per 10-ppb increase in 24-h avg SO_2 concentrations (Dales et al., 2010). Copollutant models were not evaluated. Given the limited epidemiologic evidence, the association between ambient SO_2 concentrations and venous thromboembolism is unclear.

5.3.1.7 Heart Failure

Results among the studies reviewed in the 2008 ISA for Sulfur Oxides (U.S. EPA, 2008d) were inconsistent with regard to the association between ambient SO_2 concentrations and hospital admissions or ED visits for heart failure. A small number of additional studies are now available, including a multicity study of seven Canadian cities (Stieb et al., 2009). Stieb et al. (2009) observed an imprecise association (i.e., wide 95% CI) between 24-h avg SO_2 concentrations on the previous day and ED visits for heart failure [3.0% (95% CI: −1.9, 8.2%) increase in risk of ED visits per 10-ppb increase in SO_2]. Similarly, in Guangzhou, China, Yang et al. (2014a) observed a 14.5% increase (95% CI: 6.1, 23.2%) in emergency ambulance dispatches for heart failure per 10-ppb increase in 24-h avg SO_2 concentrations on the same day. This association was slightly attenuated, but still positive and statistically significant in copollutant models adjusting for PM_{10} [13.1% (95% CI: 3.3, 23.4%)] and NO_2 [11.3% (95% CI: 1.7, 21.5%)]. In contrast, Yang (2008) did not observe evidence of a positive association between ambient SO_2 exposure and heart failure in Taipei, Taiwan.

In summary, the available epidemiologic evidence is limited and inconsistent, and therefore does not support the presence of an association between ambient SO_2 concentrations and hospital admissions or ED visits for heart failure.

5.3.1.8 Aggregated Cardiovascular Disease

Many epidemiologic studies consider the composite endpoint of all cardiovascular diseases, which typically includes all diseases of the circulatory system (e.g., heart diseases and cerebrovascular diseases). This section summarizes the results of epidemiologic studies evaluating the association between ambient SO_2 concentrations and ED visits or hospitalizations for all cardiovascular diseases. Table 5-28 presents study details and air quality characteristics of the city, or across all cities, from the U.S. and Canadian cardiovascular-related hospital admission and ED visit studies evaluated in the 2008 ISA for Sulfur Oxides and those more recent.

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.

Study	Location (Years)	Type of Visit (ICD 9/10)	Metric	Mean Concentration ppb	Upper Percentile of Concentrations ppb
U.S.					
Gwynn et al. (2000)	Buffalo and Rochester, NY (1988−1990)	Hospital admissions: circulatory (401−405, 410−417)	24-h avg	12.2	Max: 37.7
†Ito et al. (2011)	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	
Koken et al. (2003)	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

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
Low et al. (2006)	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
Metzger et al. (2004)	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
Michaud et al. (2004)	Hilo, HI (1997−2001)	ED visits Heart (410−414, 425−429)	24-h avg	1.92 (all hourly measurements)	Max: 447 (all hourly measurements)
Moolgavkar (2003) Moolgavkar (2000)	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
Morris et al. (1995)	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
Peel et al. (2007)	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
†Rich et al. (2010)	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
Schwartz and Morris (1995)	Detroit, MI (1986−1989)	Hospital discharge: IHD (410−414), CHF (428), dysrhythmia (427)	24-h avg	25.4	90th: 44.0
Schwartz (1997)	Tuscon, AZ (1988−1990)	Hospital discharge: CVD (390−429)	24-h avg	4.6	90th: 10.1
Tolbert et al. (2007)	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
Ulirsch et al. (2007)	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)
Wellenius et al. (2005b)	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
Wellenius et al. (2005a)	Allegheny County, PA (1987−1999)	Hospital admissions: CHF (428)	24-h avg	14.78 (9.88)	95th: 33.93
Canada					
Burnett et al. (1997)	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
Burnett et al. (1999)	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
Fung et al. (2005)	Windsor, ON (1995−2000)	CHF (428), IHD (410−414), dysrhythmias (427) and all cardiac	1-h max	27.5 (16.5)	Max: 129
Stieb et al. (2000)	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
†Szyszkowicz (2008)	Edmonton, AB (1992−2002)	ED visits: acute ischemic stroke (434 and 436)	24-h avg	2.6	NR
†Szyszkowicz et al. (2012a)	Vancouver, BC (1999−2003)	ED visits (discharge diagnosis): transient ischemic attack, cerebrovascular incident, seizure	24-h avg	2.5	NR
†Szyszkowicz et al. (2012b)	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
Villeneuve et al. (2006a)	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_2 = sulfur dioxide.

†Studies published since the 2008 ISA for Sulfur Oxides.

The majority of epidemiologic studies reviewed in the 2008 ISA for Sulfur Oxides (U.S. EPA, 2008d) found a positive association between ambient SO_2 concentrations and rates of hospital admission or ED visits for all cardiovascular diseases. One prominent study from the previous ISA was a study conducted in 14 cities across Spain, which observed a 3.5% (95% CI: 0.5, 6.7%) increased risk of hospital admission for all cardiovascular diseases per 10-ppb increase in SO_2 at lag 0−1 [(Ballester et al., 2006) study details and results for this and other studies in this section are presented in Table 5-29, and Figure 5-14]. The authors indicate (results not reported) that the association with SO_2 was attenuated after adjustment for CO or NO_2 in copollutant models. Most studies published since the 2008 ISA for Sulfur Oxides also observed positive associations between SO_2 and ED visits or hospitalizations for all CVD, although only a few considered potential copollutant confounding. For example, a case-crossover study in Beijing found that SO_2 averaged over eight monitoring sites was associated with risk of ED visits for all cardiovascular diseases in a single-pollutant model [OR: 1.04 (95% CI: 1.01, 1.06) per 10-ppb increase in SO_2 on the same day] (Guo et al., 2009). The association remained comparable in copollutant models adjusting for either $PM_{2.5}$ [OR: 1.03 (95% CI: 0.99, 1.06)] or NO_2 [OR: 1.03 (95% CI: 1.00, 1.07)]. Similarly, in Shanghai, Chen et al. (2010b) reported a small, but precise increase in risk of hospital admissions for CVD per 10-ppb increase in 24-h avg SO_2 at lag 5 [1.7% (95% CI: 0.5, 3.0%)] and lag 0−6 [1.3% (5% CI: 0.0, 3.2%)]. The association at lag 5 was similar after adjusting for NO_2 or PM_{10}, 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.

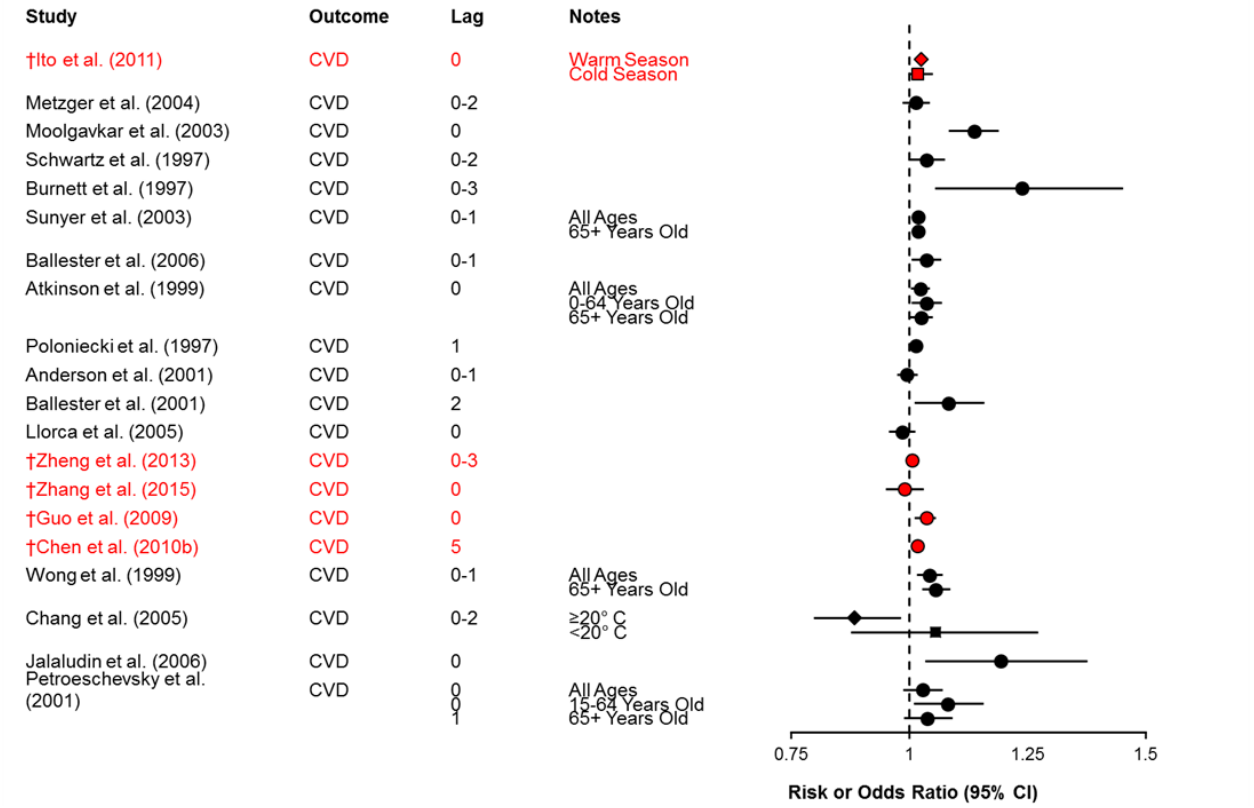
Study	Location (Years)	Exposure Assignment	Metric	Mean/Median Concentration ppb	Upper Percentile of Concentrations ppb
†Ito et al. (2011)	New York City, NY (2000−2006)	Average across five monitoring sites	24-h avg	Mean: 7.4	NR
Metzger et al. (2004)	Atlanta, GA (1993−2000)	Central site monitor	1-h max	Median: 11	90th: 39
Moolgavkar (2003)	Los Angeles, CA (1987−1995)	Central site monitor	24-h avg	NR	NR
Schwartz (1997)	Tuscon, AZ (1998−1990)	Central site monitor	24-h avg	Mean: 4.6	75th: 5.9 90th: 10.1
Burnett et al. (1997)	Toronto (summer 1992−1994)	Average across four to six monitoring sites	1-h max	Mean: 7.9	75th: 11 Max: 26
Sunyer et al. (2003)	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
Ballester et al. (2006)	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
Atkinson et al. (1999)	London, England (1992−1994)	Average across five monitoring sites	24-h avg	Mean: 8.1	90th: 11.8 Max: 31.4
Poloniecki et al. (1997)	London, England (1987−1994)	Central site monitor	24-h avg	Median: 6	90th: 21 Max: 114
Anderson et al. (2001)	Birmingham, England (1994−1996)	Average across five monitoring sites	24-h avg	Mean: 7.2	90th: 12.3 Max: 59.8
Ballester et al. (2001)	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
Llorca et al. (2005)	Torrelavega, Spain (1992−1995)	Average across three monitoring sites	24-h avg	Mean: 5.1	NR
†Filho et al. (2008)	São Paulo, Brazil (2001−2003)	Average across 13 monitoring sites	24-h avg	Mean: 5.3	Max: 16.4
†Martins et al. (2006)	São Paulo, Brazil (1996−2001)	Average across six monitoring sites	24-h avg	Mean: 6.5	Max: 28.7
†Zheng et al. (2013)	Lanzhou, China (2001−2005)	Average across four monitoring sites	24-h avg	Mean: 30.2	75th: 40.5 Max: 141.6
†Zhang et al. (2015b)	Beijing, China (2009−2011)	Average across 11 monitoring stations	24-h avg	Mean: 10.7	75th: 13.4 Max: 89.5
†Guo et al. (2009)	Beijing, China (2004−2006)	Average across eight monitoring sites	24-h avg	Mean: 18.8	75th: 23.7 Max: 111.8
†Chen et al. (2010b)	Shanghai, China (2005−2007)	Average across six monitoring sites	24-h avg	Mean: 21.4	75th: 27.5 Max: 89.7
Wong et al. (1999)	Hong Kong, China (1994−1995)	Average across seven monitoring sites	24-h avg	Median: 6.5	75th: 9.5 Max: 26.1
Chang et al. (2005)	Taipei, Taiwan (1997−2001)	Average across six monitoring sites	24-h avg	Mean: 4.3	75th: 5.5 Max: 14.6
Jalaludin et al. (2006)	Sydney, Australia (1997−2001)	Average across 14 monitoring sites	24-h avg	Mean: 1.07	75th: 1.39 Max: 3.94
Petroeschevsky et al. (2001)	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)cc All results are from single pollutant models.

Figure 5-14 Studies of hospital admissions and emergency department visits for all cardiovascular disease.

A number of other studies considering single-pollutant models also reported generally consistent associations between SO_2 concentrations and hospital admissions or ED visits for CVD. A study in New York City (Ito et al., 2011) observed an association between SO_2 concentrations that was stronger and more precise in the warm season [OR: 1.026 (95% CI: 1.021, 1.031) per 10-ppb increase in 24-h avg SO_2] than in the cold season [OR: 1.018 (95% CI: 0.998, 1.049)]. Two studies in São Paolo, Brazil (Filho et al., 2008; Martins et al., 2006) also found associations in single pollutant models (no quantitative results; results presented graphically). Another study found an increase in the risk of daily hospital admissions per IQR increase in 24-h avg SO_2 in the heavily polluted city of

Lanzhou, China (Zheng et al., 2013). However, this association was less clinically relevant when standardized to a 10-ppb increase in 24-h avg SO_2. In contrast, a large study in Beijing, China reported that CVD ED visits were not associated with SO_2 concentrations on the same day (Zhang et al., 2015b). The authors also examined a number of other single-day lags and cumulative lags and found little evidence of an association.

Overall, consistent associations between ambient SO_2 concentrations and rates of hospital admissions or ED visits for all cardiovascular diseases have been observed. Although associations are evident in single-pollutant models in many locations, there was limited assessment of potential copollutant confounding. Therefore, this association may at least partly be the result of confounding by correlated pollutants. Additionally, most studies examined 24-h avg exposure metrics for SO_2, which may not adequately capture the spatial and temporal variability in SO_2 concentrations (Section 5.2.1.2).

5.3.1.9 Cardiovascular Mortality

Studies evaluated in the 2008 SO_X ISA that examined the association between short-term SO_2 exposure and cause-specific mortality found consistent positive associations with cardiovascular mortality using a 24-h avg exposure metric. Across studies, there was evidence that the magnitude of the SO_2-cardiovascular mortality relationship was similar or slightly larger than total mortality. Recent multicity studies conducted in Asia (Chen et al., 2012b; Kan et al., 2010b) and Italy (Bellini et al., 2007), and a meta-analysis of studies conducted in Asia (Atkinson et al., 2012) provide evidence that is consistent with those studies evaluated in the 2008 SO_X ISA (Section 5.5.1.3, Figure 5-18).

The associations between short-term SO_2 concentrations and cardiovascular mortality are further supported by studies focusing on stroke mortality (Yang et al., 2014b; Chen et al., 2013). In a study conducted in eight of the CAPES cities, Chen et al. (2013) reported associations for SO_2 and stroke similar to those for all cardiovascular mortality across all of the CAPES cities (Section 5.5.1.3, Figure 5-18). The magnitude of the association for stroke mortality observed in Chen et al. (2013) is supported by multiple systematic reviews and meta-analyses of stroke mortality (Shah et al., 2015; Yang et al., 2014b). Both studies reported similar results, with Yang et al. (2014b) reporting a 2.5% increase in stroke mortality (95% CI: 1.8, 3.1) for a 10-ppb increase in 24-h avg SO_2 concentrations in a meta-analysis of mortality studies conducted in Asia, Europe, and North America and Shah et al. (2015) reporting a 2.2% increase in stroke mortality (95% CI: 1.4, 3.1) for a 10-ppb increase in SO_2 concentrations (averaging time was not reported) in a meta-analysis of studies conducted worldwide. However, when interpreting the results of Yang et al. (2014b), it is important to note that when examining regional

associations in SO_2-related stroke (i.e., Asia vs. Europe and North America), which combined both mortality and hospital admission outcomes, the magnitude of the association was much smaller, 0.8% (95% CI: −0.2, 1.7), than those observed in studies conducted in Asia, 2.1% (95% CI: 1.2, 3.2). This could be attributed to the relatively low variability and overall low SO_2 concentrations observed in both Europe and North America compared to Asia (Section 5.5.1.3, Table 5-39).

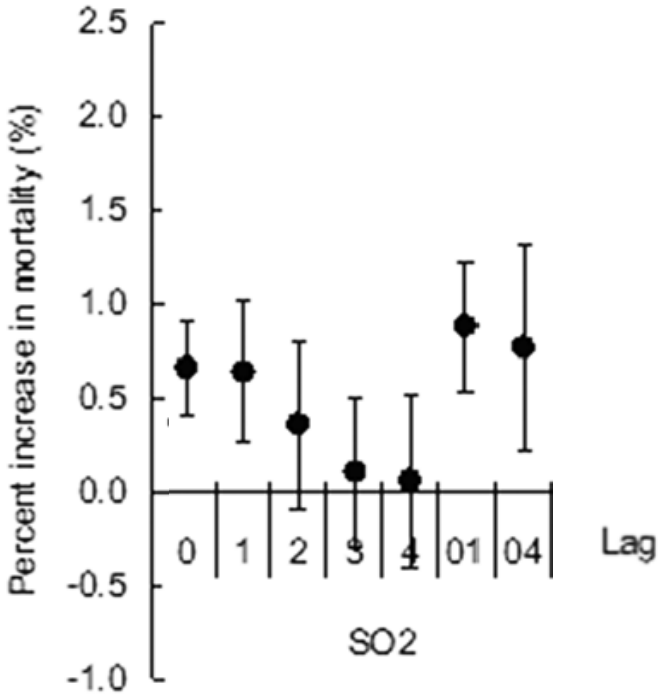
Previous studies evaluated in and prior to the 2008 SO_X ISA that examined the association between short-term SO_2 exposures and cardiovascular mortality focused exclusively on single-pollutant analyses. Therefore, questions arose with regard to the independent effect of SO_2 on cardiovascular mortality and whether associations remained robust in copollutant models. A few recent multicity studies conducted in China (Chen et al., 2012b) and across Asia (Kan et al., 2010b) examined both of these questions. Chen et al. (2012b) found that the SO_2-cardiovascular mortality association was attenuated, but remained positive in copollutant models with PM_{10} [1.0% (95% CI: 0.08, 1.9) for a 10-ppb increase in 24-h avg SO_2 concentrations at lag 0−1] and NO_2 [0.5% (95% CI: −0.5, 1.4)]. These results are similar to those reported by Chen et al. (2012b) when examining the SO_2-total mortality association in models with NO_2 (i.e., ~80% reduction), but a larger degree of attenuation was observed in models with PM_{10} for cardiovascular mortality (i.e., ~40% reduction for total mortality and 50% reduction for cardiovascular mortality) (Section 5.5.1.4). Kan et al. (2010b), as part of the PAPA study, also examined potential copollutant confounding (i.e., NO_2, PM_{10}, and O_3) but only in each city individually. The authors found that, although the SO_2-cardiovascular mortality association remained positive in copollutant models, there was evidence of an attenuation of the association in models with PM_{10} and NO_2 (Figure 5-19). In an analysis of stroke mortality in eight of the CAPES cities, Chen et al. (2013) reported pattern of associations similar to that of Chen et al. (2012b) and Kan et al. (2010b) in copollutant models with PM_{10} and NO_2. In single-pollutant models, the authors reported a 2.3% (95% CI: 1.4, 3.2) increase in stroke mortality for a 10 ppb increase in 24-h avg SO_2 concentrations at lag 0−1. However, in copollutant models, Chen et al. (2013) observed that SO_2-stroke mortality associations were attenuated in models with PM_{10}, ~40% reduction [1.9% (95% CI: 0.3, 3.5)] and NO_2, ~80% reduction [0.0% (95% CI: −1.8, 1.9)]. Overall, the studies that examined potential copollutant confounding on the SO_2-cardiovascular mortality relationship report results consistent with what was observed for total mortality. However, the overall assessment of copollutant confounding remains limited, and it is unclear how the results observed in Asia translate to other locations, specifically due to the unique air pollution mixture and higher concentrations observed in Asian cities.

Of the multicity studies evaluated, potential seasonal differences in SO_2-cardiovascular mortality associations were only assessed in a study conducted in Italy (Bellini et al.,

2007) with additional information from U.S.-based single-city studies conducted in Philadelphia (Sacks et al., 2012) and New York City (Ito et al., 2011). In a study of 15 Italian cities, Bellini et al. (2007) reported larger SO_2-cardiovascular mortality associations in the summer [9.4% increase (April−September)], compared to both winter [1.6% increase (October−March)] and all-year analyses (92.9% increase), which are consistent with the pattern of associations observed for total and respiratory mortality. These results are supported by Ito et al. (2011) in a study conducted in New York City that found that when examining single-day lags of 0 to 3 days, the SO_2-cardiovascular mortality association was consistently positive during the warm season, ranging from a 1.2 to 3.5% increase across lags. The authors reported no evidence of an association in winter and all-year analyses. Within this analysis, Ito et al. (2011) reported rather poor monitor-to-monitor temporal correlations for SO_2, which would indicate potential exposure error and subsequently attenuation and imprecision in the risk estimate (Section 3.4.2, Section 3.4.4). Sacks et al. (2012) provide additional support to the limited evidence indicating differences in the seasonal pattern of SO_2-cardiovascular mortality associations. However, as detailed in Section 5.5.1.4, Sacks et al. (2012) demonstrated that across models that use various approaches to control for seasonality and the potential confounding effects of weather, the magnitude of seasonal SO_2-cardiovascular mortality associations may vary depending on the modeling approach employed. Therefore, although Bellini et al. (2007) and Ito et al. (2011) provide initial evidence indicating potentially larger cardiovascular mortality associations in the summer, the results of Sacks et al. (2012) suggest that the evidence remains unclear whether the seasonal pattern of SO_2-cardiovascular mortality associations is consistent across statistical modeling choices and study locations.

An uncertainty that often arises when evaluating studies that examine the relationship between short-term air pollution exposures and cause-specific mortality is whether analyses of statistical modeling parameters, the lag structure of associations, and the C-R relationship provide results that are consistent with what is observed for total mortality. Chen et al. (2013) examined each of these issues in a study of stroke mortality, with additional supporting evidence from the full CAPES study (Chen et al., 2012b). When examining alternative approaches to controlling for seasonality, Chen et al. (2013) found that increasing the df employed from 4 to 10 df per year did not substantially change the SO_2-stroke mortality association. However, Chen et al. (2012b) when altering the lag structure of the temperature term included to control for the potential confounding effects of weather, reported an attenuation of the association, although it did remain positive. However, as detailed in Section 5.5.1.4, this could be the result of including only one temperature term in the model.

When examining the lag structure of associations, Chen et al. (2013) reported results for stroke mortality that are consistent with those observed for all cardiovascular mortality. As depicted in Figure 5-15 there is evidence of a steady decline in the SO_2-stroke mortality association at longer individual lag days, with the strongest association occurring for a moving average of lag 0−1 days. A similar pattern of associations was observed for cardiovascular mortality by Chen et al. (2012b) in the full CAPES study (Figure 5-20), as well as the PAPA study (Kan et al., 2010b) (Figure 5-20). These results are further confirmed in a systematic review and meta-analysis of studies of stroke mortality conducted by Yang et al. (2014b), which found the strongest associations at lag 0 and 1 in a subgroup analysis of single-day lags of 0 to 2 days.

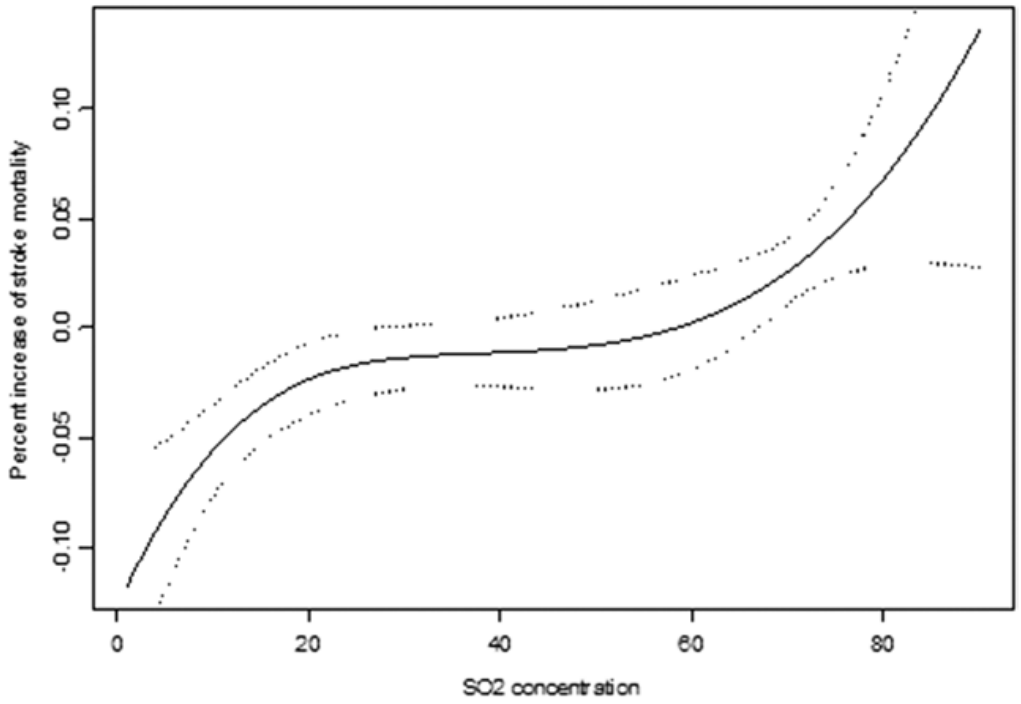


SO_2 = sulfur dioxide.
Source: Adapted from Chen et al. (2013).

Figure 5-15 Percent increase in stroke mortality associated with a 10 µg/m³ (3.62 ppb) increase in sulfur dioxide concentrations using different lag structures.

Chen et al. (2013) also examined the shape of the SO_2-stroke mortality C-R relationship. To examine the assumption of linearity, the authors fit both a linear and spline model to the SO_2-stroke mortality relationship. Chen et al. (2013) then computed the deviance

between the two models to determine any evidence of nonlinearity. An examination of the deviance did not indicate that the spline model improved the overall fit of the SO_2-stroke mortality relationship (Figure 5-16).



SO_2 = 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/m³ (3.62 ppb) increase in 24-h avg concentrations at lag 0−1 days.

Overall, recent multicity studies report evidence of consistent positive associations between short-term SO_2 concentrations and cardiovascular mortality, which is consistent with those studies evaluated in the 2008 SO_X ISA. Unlike studies evaluated in the 2008 SO_X ISA, recent studies examined whether copollutants confound the relationship between short-term SO_2 concentrations and cardiovascular mortality. Overall, these studies reported evidence that the SO_2-respiratory mortality association was attenuated in models with NO_2 and PM_{10}, but the analyses are limited to Asian cities where the air pollution mixture and concentrations are different than those reported in other areas of

the world. A few studies examined potential seasonal patterns in associations, and found initial evidence of larger SO_2-cardiovascular mortality associations in the summer/warm season. However, seasonal associations may be influenced by study location and the statistical modeling choice employed. Limited analyses of model specification, the lag structure of associations, and the C-R relationship suggest that: (1) associations remain robust when alternating the df used to control for seasonality; (2) associations are larger and more precise within the first few days after exposure in the range of 0 and 1 days; and (3) there is a linear, no threshold C-R relationship, respectively. However, for both total and cause-specific mortality, the overall assessment of linearity in the C-R relationship is based on a very limited exploration of alternatives.

5.3.1.10 Subclinical Effects Underlying Cardiovascular Effects

The following subsections review studies of subclinical effects that serve as useful measures of physiological and biochemical responses that could provide mechanistic evidence to describe a role for SO_2 in the manifestation of cardiovascular diseases. These subclinical effects are not widely validated markers of specific clinical cardiovascular outcomes, but could potentially underlie the development, progression, or indication of various clinical events and provide biological plausibility for multiple outcomes.

Heart Rate and Heart Rate Variability

The 2008 ISA for Sulfur Oxides concluded that the overall evidence available at the time was insufficient to conclude that SO_2 has an effect on cardiac autonomic control as assessed by indices of HRV. HRV provides a noninvasive marker of cardiac autonomic nervous system function. The rhythmic variation in the intervals between heart beats can be quantified in either the time domain or the frequency domain (TFESC and NASPE, 1996). Common time-domain measures of HRV include the standard deviation of all normal-to-normal intervals (SDNN, an index of total HRV) and the root-mean-square of successive differences (rMSSD, an index influenced mainly by the parasympathetic nervous system). In the frequency domain, HRV is usually divided into the high frequency (HF) and low frequency (LF) components, as well as the ratio of the LF to HF components (LF:HF) (TFESC and NASPE, 1996). Decreases in indices of HRV have been associated with increased risk of cardiovascular events in prospective cohort studies (La Rovere et al., 2003; Kikuya et al., 2000; Tsuji et al., 1996; Tsuji et al., 1994).

Epidemiology

A number of additional epidemiologic studies are now available for review. In a cross-sectional study in South Korea, Min et al. (2009) reported negative associations between ambient SO_2 concentrations and indices of HRV (SDNN, and the LF and HF components) among 256 smokers, but no association among the 767 nonsmokers (no quantitative results; result presented graphically). In another cross-sectional study, Min et al. (2008b) reported a −7.6% (95% CI: −14.7, 0.1%) change in SDNN and a −23.1% (95% CI: −35.4, −6.5%) change in LF per 10-ppb increase in 24-h avg SO_2 among 1,349 participants in South Korea. The amount of overlapping participants between these two studies is unclear.

The above studies are limited by their cross-sectional approach that compares measures of HRV across individuals assessed on different days. In contrast, longitudinal or repeated-measure study provide an estimate of the average association between SO_2 and measures of HRV within individuals. Huang et al. (2012) measured HRV repeatedly in 40 participants with pre-existing cardiovascular disease in Beijing in the summer of 2007 and again in the summer of 2008, including one measurement period during the 2008 Beijing Olympics when citywide air pollution control measures substantially reduced ambient concentrations of most criteria pollutants. In this study, SO_2 concentrations during the Olympics were reduced by nearly 30% versus the previous month and nearly 50% versus the same period the previous summer (Huang et al., 2012). Despite these large changes in SO_2 concentrations, overall only small associations were observed between SO_2 concentrations and HRV indices, limited to a 4.8% reduction (95% CI: −9.1, −0.3%) in the LF component and an unexpected 4.1% increase (95% CI: −2.2, 10.9%) in the HF component of HRV per interquartile range (NR) increase in SO_2 in the previous 12 hours (Huang et al., 2012). In subgroup analyses, SDNN was significantly positively associated with SO_2 concentrations among those with higher levels of C-reactive protein (CRP; a marker of inflammation), those with diabetes, and males. These results are difficult to understand given that a higher SDNN is generally thought to be associated with lower risk of cardiovascular events. The findings were also inconsistent with another study that observed a negative association between SDNN and ambient SO_2 concentrations. A repeated measure study in Shanghai, China reported a 4.36% reduction (95% CI: −5.85, −2.86%) in SDNN per IQR increase (NR) in 4-hour moving average exposure to SO_2 (Sun et al., 2015). This association was attenuated, but still statistically significant in copollutant models adjusting for BC [−2.91% (95% CI: −4.66, −1.13%)] and O_3 [−3.24% (95% CI: −4.83, −1.62%)], and attenuated and no longer statistically significant, but still negative in copollutant models adjusting for NO_2 [−0.56% (95% CI: −2.38, 1.30%)] and CO [−1.25% (95% CI: −3.02, 0.55%)]. In another study in Beijing before, during, and after the 2008 Olympics, Rich et al. (2012) observed

small but statistically significant increases in heart rate associated with ambient SO_2 concentrations on the previous day (no quantitative results; result presented graphically). In expanded results from the same protocol, Zhang et al. (2013) found that the association was similar in copollutants models adjusting for CO, NO_2, O_3, EC, or OC, but was attenuated and no longer positive after adjustment for $PM_{2.5}$ or SO_4^{2-}. Zhang et al. (2013) also reported a strong association between LF:HF and ambient SO_2 concentrations on the previous day. This association was relatively unchanged after adjustment for CO, NO_2, O_3, EC, OC, or $PM_{2.5}$ in copollutant models, and attenuated but still positive after adjustment for SO_4^{2-}. In contrast, a panel study in Taipei, Taiwan used Holter monitors to continuously monitor HRV in 46 participants, and observed no associations between ambient SO_2 and SDNN, r-MSSD, LF component, or HF component (quantitative results not reported) (Chuang et al., 2007). Although new studies are available, findings are mixed and they do not support the presence of an association between ambient SO_2 and measures of HRV.

Experimental Studies

Several experimental studies examined heart rate and HRV following SO_2 exposure. Study characteristics are summarized in Supplemental Table 5S-13. (U.S. EPA, 2016s) Animal studies have reported no changes in heart rate following SO_2 exposures of 1,000−5,000 ppb in guinea pigs and 1,200 ppb in rats (Nadziejko et al., 2004; Halinen et al., 2000b; Halinen et al., 2000a).

Controlled human exposure studies have reported changes in heart rate following SO_2 exposure but not during exposure. Tunnicliffe et al. (2001) reported no change in heart rate in healthy adults or adults with asthma during exposure to 200 ppb SO_2 for 1 hour at rest. However, in a similar study design, Routledge et al. (2006) reported a decrease in heart rate measured by the RR interval from electrocardiographic (ECG) recordings 4 hours after SO_2 exposure in healthy adults. This change in heart rate was not observed in SO_2-exposed older adults with stable angina and coronary artery disease during or immediately after exposure. Both studies found no change in heart rate during or immediately following similar exposure conditions. Tunnicliffe et al. (2001) did not obtain ECG measures following exposure and thus may have been unable to capture the decrease in heart rate reported by Routledge et al. (2006).

Tunnicliffe et al. (2001) and Routledge et al. (2006) reported changes in different measures of HRV in adults following SO_2 exposure. Tunnicliffe et al. (2001) reported that HF power, LF power, and total power were higher with SO_2 exposures compared to air exposure in the healthy subjects, but that these indices were reduced during SO_2 exposure in the subjects with asthma (statistical significance only in total power in healthy adults). The LF:HF ratios were unchanged in both groups. Routledge et al. (2006)

reported a reduction in SDNN, rMSSD, percentage of successive RR interval differences exceeding 50 ms (pNN_{50}), and HF power (not statistically significant) in healthy adults 4 hours after SO_2 exposure. Baroreflex sensitivity was also reduced 4 hours after SO_2 exposure determined by changes in α-HF and α-LF. There were no changes in HRV among the patients with coronary heart disease; however, this lack of response may be due to a drug treatment effect because a large portion of these patients were taking beta-blockers. The changes in HRV observed in Tunnicliffe et al. (2001) and Routledge et al. (2006) indicate the potential for SO_2 to affect the autonomic nervous system (see Section 4.3.1).

Summary of Heart Rate and Heart Rate Variability

The current epidemiologic evidence does not support the presence of an association between ambient SO_2 and measures of HRV. No changes in heart rate were observed in experimental animal studies while changes in HRV observed in human clinical studies may indicate the potential for SO_2 to affect the autonomic nervous system (see Section 4.3.1). Overall, studies evaluating the effect of ambient SO_2 concentrations and measures of HRV and heart rate remain limited.

QT Interval Duration

The QT interval provides an electrocardiographic marker of ventricular repolarization. Prolongation of the QT interval is associated with increased risk of life-threatening ventricular arrhythmias. In an analysis of data from the Boston-area Normative Aging Study, Baja et al. (2010) observed a small and imprecise (i.e., wide confidence intervals) association between heart-rate-corrected QT interval and 10-hour moving average of SO_2 concentrations among older, generally white men (no quantitative results; result presented graphically). The only prior study available for comparison from the 2008 ISA for Sulfur Oxides (U.S. EPA, 2008d) also found that SO_2 concentrations were positively associated with increased QT interval duration amongst a small sample of 56 men in Erfurt, Germany [3.75 ms increase (95% CI: 1.21, 6.28 ms) per 0.61-ppb increase in 24-h avg SO_2] (Henneberger et al., 2005). There was little variability between daily measured SO_2 concentrations, so the effect estimate is not standardized to prevent inflation of the confidence interval.

The two reviewed studies provide limited evidence of association between short-term SO_2 exposure and markers of ventricular repolarization. Neither of these studies evaluated potential copollutant confounding and coherence for an association between SO_2 exposure and arrhythmias is not provided by experimental studies (Section 5.5.1.3).

Insulin Resistance

There were no epidemiologic studies of diabetes or insulin deficiency available for the 2008 ISA for Sulfur Oxides. Recent studies reported contrasting findings regarding short-term associations between air pollutants and measures of insulin resistance and fasting glucose, which play key roles in the development of Type II diabetes mellitus. In a panel study of older adults in Korea, Kim and Hong (2012) observed 0.94 (95% CI: −0.02, 1.88) and 0.94 (95% CI: 0.01, 1.81) mean increases in the homeostatic model assessment index of insulin resistance [fasting insulin × (fasting glucose ÷ 22.5)] per 10-ppb increase in 24-h avg SO_2 at lags 3 and 4, respectively. There were imprecise (i.e., wide 95% CI) or null associations at all other individual lag days examined, from 0 to 10. Another panel study, conducted in the heavily polluted Tangshan, China, reported an association between 24-h avg SO_2 concentrations and fasting glucose levels (Chen et al., 2015b). However, this association is unlikely to be clinically relevant when standardized to a 10-ppb increase in 24-h avg SO_2 [0.045 mmol/L (95% CI: 0.039, 0.050 mmol/L) increase at lag 0−3]. Conversely, Kelishadi et al. (2009) reported the lack of an association between 24-h avg SO_2 and insulin resistance in a cross-sectional study of 374 Iranian children aged 10−18 years.

In summary, the available epidemiologic evidence is limited and inconsistent, and does not support the presence of an association between ambient SO_2 concentrations and measures of insulin resistance.

Biomarkers of Cardiovascular Risk

Several epidemiologic and toxicological studies have explored the potential relationship between SO_2 and biomarkers of cardiovascular risk. In particular, markers of inflammation have been evaluated in a number of epidemiologic and toxicological studies published since the 2008 ISA for Sulfur Oxides (U.S. EPA, 2008d) (Table 5-30). Relatively few studies have evaluated the potential link between SO_2 and other circulating markers of cardiovascular risk, including markers of coagulation, vascular 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_2 (ppb)	Exposure Assessment	Selected Effect Estimates[a] (95% CI)	
†Dubowsky et al. (2006)	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)	
†Steinvil et al. (2008)	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)
†Thompson et al. (2010)	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_2 concentrations. Null association between SO_2 and fibrinogen Correlations: CO: 0.43, NO_2: 0.44, O_3: −0.19, $PM_{2.5}$: 0.45	
†Gandhi et al. (2014)	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_2 (ppb)	Exposure Assessment	Selected Effect Estimates[a] (95% CI)
†Lee et al. (2011b)	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_2… associations (with CRP) were negligible for both the entire population and nonsmokers only."
†Hildebrandt et al. (2009)	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_2 and inflammatory (fibrinogen, E-selectin) or coagulation (D-dimer, prothrombin) markers.
Baccarelli et al. (2007a)	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_2 not correlated with anticoagulation proteins (plasma fibrinogen, functional AT, functional protein C, protein C antigen, functional protein S, or free protein S).
Baccarelli et al. (2007b)	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)
Wellenius et al. (2007)	Boston, MA 2002−2003 (n = 28)	24-h avg: 4.8	Citywide avg	No quantitative results presented. "No significant associations were observed between (NO_2) and B-type natriuretic peptide levels at any of the lags examined."
†Goldberg et al. (2008)	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)
†Brüske et al. (2011)	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_2 with Lp-PLA_2 at Lag days 2 and 3 and positive associations were estimated with Lp-PLA_2 Lag days 4 and 5. Correlations: PNC: 0.77, $PM_{2.5}$: 0.42, PM_{10}: 0.43, CO: 0.63, NO_2: 0.51, NO: 0.60, O_3: −0.45.

Table 5-30 (Continued): Epidemiologic studies of biomarkers of cardiovascular effects.

Study	Location and Years (Sample Size)	Mean and Upper Concentration SO_2 (ppb)	Exposure Assessment	Selected Effect Estimates[a] (95% CI)
†Zhang et al. (2013)	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_2 and fibrinogen (lag 6). Inverse association between SO_2 and WBC count (lag 5).
†Lin et al. (2015)	Beijing, China 2007−2008 (n = 36 school children)	NR	Monitor located nearby school	*Urinary 8-oxodG* (Geometric mean ratio by SO_2 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) *Urinary Malondialdehyde* <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)
†Khafaie et al. (2013)	Pune City, India 2005−2007 (n = 1,392)	24-h avg: 8.3	Citywide avg	No quantitative results; results presented graphically. SO_2 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_2 = lipoprotein-associated phospholipase A;2; n = sample size; NO = nitric oxide; NO_2 = nitrogen dioxide; NR = not reported; O_3 = ozone; $PM_{2.5}$ = particulate matter with a nominal aerodynamic diameter less than or equal to 2.5 μm; PM_{10} = particulate matter with a nominal aerodynamic diameter less than or equal to 10 μm; PNC = particle number concentration; SO_2 = 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.

[a]Effect estimates are standardized to a 10-ppb or 40-ppb increase in SO_2 concentration for 24-h avg and 1-h max metrics, respectively.

Epidemiologic Studies

The epidemiologic data available for review by the 2008 ISA for Sulfur Oxides (U.S. EPA, 2008d) did not suggest a consistent link between SO_2 and biomarkers of cardiovascular risk, including markers of inflammation and coagulation. Results from more recent studies continue to be inconsistent. Dubowsky et al. (2006) investigated

associations between ambient pollutants and markers of systemic inflammation in a panel (repeated-measures) study of 44 seniors in St. Louis, MO and found that higher ambient SO_2 concentrations were associated with lower levels of CRP and white blood cells, but not IL-6 (results for this study, and other studies in this section can be found in Table 5-30). Similarly, during the Beijing Olympics, SO_2 was inversely associated with white blood cell counts, although positively associated with fibrinogen (Zhang et al., 2013). The negative associations observed in these two studies are unexpected and difficult to explain. In contrast, among 45 nonsmoking adults, Thompson et al. (2010) found a positive association between SO_2 and IL-6, but not fibrinogen. In another panel study examining pollutant levels before, during, and after the Beijing Olympics, Lin et al. (2015) reported positive associations between SO_2 concentrations and urinary markers of oxidative stress, malondialdehyde and 8-oxodG, in children.

In a cross-sectional analysis of data from a panel study of 49 young adults in New Jersey, Gandhi et al. (2014) observed that plasma nitrite levels, a marker for endothelial dysfunction, were associated with an increase in 24-h avg SO_2 concentrations on the same day. Khafaie et al. (2013) observed a positive association between SO_2 and CRP in a cross-sectional study of Type II diabetes patients in Pune City, India, whereas a study of 1,696 pregnant women (Lee et al., 2011b), and one of 38 male patients with chronic pulmonary disease (Hildebrandt et al., 2009) observed null associations between SO_2 and CRP. In a cross-sectional analysis of 3,659 participants in Tel-Aviv, Steinvil et al. (2008) observed inconsistent and/or imprecise associations between SO_2 and CRP, white blood cells, or fibrinogen among men and women. Observed associations were both positive and negative depending on the length of the lags, making interpretation of the results difficult.

Ambient SO_2 concentrations are reportedly not associated with blood coagulation (Baccarelli et al., 2007a), plasma homocysteine (Baccarelli et al., 2007b), markers of vascular injury (Hildebrandt et al., 2009), or markers of functional status in patients with heart failure (Wellenius et al., 2007). Conversely, SO_2 concentrations were inversely associated with blood oxygen saturation in patients with heart failure (Goldberg et al., 2008) and positively associated with lipoprotein-associated phospholipase A2 (Lp-PLA2) in survivors of myocardial infarction (Brüske et al., 2011).

Experimental Studies

Several experimental studies examined biomarkers of cardiovascular risk following SO_2 exposure, including markers of inflammation, coagulation, and oxidative injury. A recent study examined the effect of exposure to SO_2 on the mitochondrial function of the heart. Study characteristics are summarized in Supplemental Table 5S-13 (U.S. EPA, 2016s).

No changes were reported in serum C-reactive protein or markers of coagulation (fibrinogen, D-dimer, platelet aggregation, blood count, or differential white cell count) in healthy humans and patients with stable angina and coronary artery disease exposed to SO_2 (Routledge et al., 2006). An animal toxicological study examined the hematological effects of short-term SO_2 exposure on blood biomarkers. Acute exposure of rats to 870 ppb SO_2 for 24 hours resulted in increased hematocrit, sulfhemoglobin, and osmotic fragility as well as decreased whole blood and packed cell viscosities (Baskurt, 1988). These results indicate a systemic effect of inhaled SO_2 and are consistent with an oxidative injury to red blood cells.

A recent study reported mitochondrial dysfunction in cardiac muscles following SO_2 inhalation in adult rats exposed to 1,340 ppb and greater concentrations (2,670 and 5,340 ppb) of SO_2 for 4 hours/day for 30 days (Qin et al., 2016). Inhalation of SO_2 (1,340 ppb) resulted in mitochondrial ultrastructural changes in cardiac myocytes, including swollen mitochondria and reduced amounts of cristae. In addition to the structural changes, SO_2 exposure decreased cytochrome c oxidase activity, mitochondrial membrane potential, ATP contents, mtDNA content, mRNA expression of subunits that are synthesized in the mitochondria (complex IV and V), and mitochondrial transcription factors (TFAM, NRF1, and PGC-1a). Mechanistic studies conducted in vitro suggest reactive oxygen species contribute to the mitochondrial dysfunction leading to the observed decrease in cardiomyocyte energy status and metabolic activity. In addition to this study in the heart, a study has reported similar changes in the brain (Qin et al., 2012). Further discussion of these mechanisms are found in Section 4.3.4.

Summary of Blood Markers of Cardiovascular Risk

There is inconsistent evidence regarding any potential link between SO_2 and other circulating markers of cardiovascular risk. Studies of markers of inflammation or oxidative stress in experimental animals are limited. Overall, evidence from available studies does not support an effect of ambient SO_2 concentrations and markers of cardiovascular disease including inflammation.

5.3.1.11 Summary and Causal Determination

Overall, the available evidence is inadequate to infer the presence or absence of a causal relationship between short-term exposure to SO_2 and cardiovascular health effects. Multiple epidemiologic studies report positive associations between short-term ambient SO_2 concentrations and cardiovascular outcomes; however, uncertainty remains regarding the biological plausibility of the effects observed in epidemiologic studies. The limited experimental evidence in humans or animals is not coherent with the positive associations

observed in the epidemiologic studies and fails to provide evidence to propose a potential mode of action. The observed associations in epidemiologic studies are generally attenuated after adjustment for copollutants, complicating the determination of an independent SO_2 effect.

This determination is consistent with that of the 2008 ISA for Sulfur Oxides (U.S. EPA, 2008d). The majority of epidemiologic studies reviewed in the 2008 ISA for Sulfur Oxides examined hospital admissions or ED visits for aggregated categories of cardiovascular disease or for mortality from cardiovascular causes. These studies generally reported positive associations in single pollutant models but analyses designed to assess copollutant confounding were limited. Relatively few studies evaluated specific cardiovascular outcomes such as MI, arrhythmia, cerebrovascular disease, and heart failure, and those that were available did not support an association with short-term SO_2 exposure. Controlled human exposure studies demonstrated the potential for SO_2 exposure to exert an effect on the autonomic nervous system but there was a lack of supporting animal toxicological data. The available animal toxicological studies did not report effects on HR, HRV, arrhythmia, or blood pressure following short-term SO_2 exposures [Table 5S-6 (U.S. EPA, 2016m)]. In addition, limited and inconsistent mechanistic evidence, including evidence pertaining to key events in a proposed mode of action, failed to describe a role for SO_2 in the triggering of cardiovascular diseases. Although multiple epidemiologic studies add to the evidence available for the current review, the additional studies do not substantially reduce uncertainties related to copollutant confounding. Moreover, there continues to be a lack of experimental evidence to provide biological plausibility to strengthen the inference of causality for SO_2-related cardiovascular effects.

The evidence for cardiovascular effects, with respect to the causal determination for short-term exposure to SO_2 is detailed below using the framework described in the Preamble to the ISAs [(U.S. EPA, 2015b), Table I and Table II]. The key evidence, supporting or contradicting, as it relates to the causal framework is summarized in 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[a]	Key Evidence[b]	Key References[b]	SO_2 Concentrations Associated with Effects[c]
Triggering a myocardial infarction			
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_2, or PM_{10}.	Section 5.3.1.2 Section 5.3.1.8 Supplemental figures 5S-3, 5S-4, and 5S-5 (U.S. EPA, 2016b, c, d)	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	Section 4.3	
	Limited and inconsistent evidence of increased systemic inflammation in epidemiologic studies	Section 5.3.1.10	
Other cardiovascular effects			
Inconclusive evidence from epidemiologic, controlled human exposure and toxicological studies	Epidemiologic studies report generally null associations between SO_2 and risk of cardiac arrest and arrhythmias. One experimental study provides no evidence of arrhythmia.	Section 5.3.1.3	
	Inconsistent epidemiologic evidence for an association between SO_2 and risk of cerebrovascular disease and stroke, and increased blood pressure and hypertension	Section 5.3.1.4 and Section 5.3.1.5	
	Insufficient quantity of studies evaluating decompensation of heart failure and venous thrombosis and pulmonary embolism	Section 5.3.1.6 and Section 5.3.1.7	

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[a]	Key Evidence[b]	Key References[b]	SO_2 Concentrations Associated with Effects[c]
	Changes in HR and HRV reported in controlled human exposure but coherence with animal toxicological and epidemiologic studies is lacking	Tunnicliffe et al. (2001) Routledge et al. (2006) Section 5.3.1.10	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 4.3.1 Figure 4–2	
Cardiovascular mortality			
Consistent epidemiologic evidence but uncertainty regarding SO_2 independent effect	Multicity studies consistently observe associations with cardiovascular mortality, including stroke with 24-h avg SO_2 at lags primarily of 0−1 d. Analysis of potential confounding by copollutants primarily limited to PM_{10} and NO_2 reported evidence of attenuation of associations. No studies included copollutant analyses with $PM_{2.5}$.	Section 5.3.1.9 Chen et al. (2012b) Chen et al. (2013) Kan et al. (2010b) Bellini et al. (2007) Atkinson et al. (2012)	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_2 = nitrogen dioxide; PM_{10} = particulate matter with a nominal aerodynamic diameter less than or equal to 10 µm; SO_2 = sulfur dioxide.

[a]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).

[b]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.

[c]Describes the SO_2 concentrations with which the evidence is substantiated.

Recent epidemiologic studies of specific cardiovascular outcomes add to the overall evidence for the effect of short-term SO_2 exposure on the cardiovascular system with a number of these studies evaluating effects related to triggering an MI (Section 5.3.1.2). Several recent epidemiologic studies of MI hospitalizations and ED visits consistently report associations in single pollutant models but associations are not always robust in copollutant models indicating that the associations may be due to confounding (Hsieh et al., 2010; Cheng et al., 2009; Ballester et al., 2006). The small number of studies based on clinical MI data, rather than hospitalizations, report inconsistent evidence regarding associations between ambient SO_2 concentrations and risk of MI (Milojevic et al., 2014; Turin et al., 2012; Bhaskaran et al., 2011). The only study that examined the association of hourly ambient SO_2 concentrations prior to MI onset reported no association, although there was some evidence of a positive association in a sensitivity analysis of older adults

(Bhaskaran et al., 2011). Although Chuang et al. (2008) reported an association between short-term SO_2 exposure and ST-segment changes, a nonspecific marker of myocardial ischemia, in patients with a history of coronary heart disease that generally remained unchanged after additional control for $PM_{2.5}$ and BC in copollutant models; the evidence overall, was not generally consistent.

Findings from recent studies of the association of short-term exposure to SO_2 with hospital admissions or ED visits for cerebrovascular diseases or stroke are inconsistent and, associations reported from single pollutant models in some locations may be due to confounding by copollutants (Section 5.3.1.4). Epidemiologic studies evaluating the association between ambient SO_2 concentrations and blood pressure remain inconsistent with most relying on centrally located monitors that do not capture the spatial variability of SO_2 and few examining the potential for copollutant confounding (Section 5.3.1.5). Although a small number of studies were conducted to examine the association of short-term SO_2 exposure with other clinical outcomes, including heart failure (Section 5.3.1.7) and VTE (Section 5.3.1.6), findings from these studies do not support an effect of short-term exposure to SO_2. There is also a lack of epidemiologic evidence supporting an effect of short-term SO_2 exposure on arrhythmia (Section 5.3.1.3), although associations between short-term SO_2 exposure and markers of ventricular repolarization abnormalities that are risk factors for arrhythmia have been observed (Baja et al., 2010; Henneberger et al., 2005) (Section 5.3.1.10).

Consistently positive associations have been reported in epidemiologic studies of short-term SO_2 exposure and cardiovascular mortality (Section 5.3.1.9). These include studies reviewed in the 2008 ISA for Sulfur Oxides and recent multicity studies that generally report an association similar or slightly larger in magnitude for cardiovascular mortality compared to total mortality. Studies that report results from copollutants models generally report attenuation of the association between short-term SO_2 exposure and cardiovascular mortality after adjustment for PM_{10} and NO_2.

Few experimental studies have evaluated the effects of SO_2 exposure on the cardiovascular system. There is some evidence from controlled human exposure studies, for which copollutant confounding is not a concern, that short-term exposure to SO_2 can affect the autonomic nervous system of healthy adults and adults with asthma (Routledge et al., 2006; Tunnicliffe et al., 2001) (Section 5.3.1.10). These studies report changes in HR and HRV following SO_2 exposure in adults. However, coherence with these findings is not provided by epidemiologic or experimental animal studies, which have not observed an effect of short-term SO_2 exposure on HR or HRV. In addition, uncertainty remains regarding a potentially biologically plausible mechanism for short-term exposure to SO_2 leading to cardiovascular disease. Cardiovascular effects following SO_2 exposure

could be mediated through activation of neural reflexes or oxidative stress; however, uncertainty remains (Section 4.3). Diffusion of sulfite into the circulation and tissues following exposure to SO_2 has been reported and could play a role in the induction of systemic effects; however, these studies generally involve prolonged exposure to SO_2 at concentrations higher than is typically found in ambient air (Section 4.3.4). Overall, the limited evidence available from these experimental studies in humans and animals are not coherent with the positive associations observed in the epidemiologic studies and do not support a potential mode of action.

Despite numerous additional epidemiologic studies reporting positive associations between short-term SO_2 exposure and cardiovascular effects, a key uncertainty that remains since the 2008 ISA for Sulfur Oxides is the potential for confounding by other pollutants, specifically those from a common source that are highly correlated with SO_2. The majority of hospital admission or ED visit studies have not evaluated whether the reported associations with SO_2 are robust to adjustment for other pollutants. Those studies that do examine associations with SO_2 adjusted for PM [Figure 5S-3, (U.S. EPA, 2016b) and Table 5S-17 (U.S. EPA, 2016v)], NO_2 [Figure 5S-4, (U.S. EPA, 2016c) and Table 5S-18 (U.S. EPA, 2015g)], or other correlated pollutants [Figure 5S-5; (U.S. EPA, 2016d) and Table 5S-19 (U.S. EPA, 2015h)] report that, in general, associations were either attenuated or no longer present after controlling for potential copollutant confounding (Hsieh et al., 2010; Cheng et al., 2009; Ballester et al., 2006). A limited number of studies examined copollutant confounding on the SO_2-cardiovascular mortality relationship, which included analyses on stroke mortality, and provided evidence that the SO_2 association was reduced in copollutant models with NO_2 and PM_{10} (Chen et al., 2013; Chen et al., 2012b; Kan et al., 2010b). Finally, while copollutant models are a common statistical tool used to evaluate the potential for copollutant confounding, their interpretation can be limited (Section 5.1.2). Without consistent and reproducible experimental evidence that is coherent with the effects observed in epidemiologic studies, uncertainty still exists concerning the role of correlated pollutants in the associations observed with SO_2. Thus, uncertainty remains regarding the extent to which SO_2 exposure is independently associated with cardiovascular outcomes or if SO_2 is a marker for the effects of another correlated pollutant or mix of pollutants.

In conclusion, the evidence overall is inadequate to infer the presence or absence of a causal relationship between short-term SO_2 exposure and cardiovascular health effects. This conclusion does not represent a change from the conclusion of the 2008 ISA for Sulfur Oxides (U.S. EPA, 2008d). Multiple epidemiologic studies report positive associations between short-term ambient SO_2 concentrations and cardiovascular outcomes, but these associations are generally attenuated after adjustment for copollutants. There is limited experimental evidence in humans or animals evaluating

exposure to SO_2 and the results of these studies do not provide coherence for the positive associations observed in the epidemiologic studies. Further, the available experimental studies do not provide evidence to propose a potential mode of action; consequently, uncertainty remains regarding the biological plausibility of effects observed in epidemiologic studies. The combined evidence from epidemiologic and experimental studies lacks coherence and is of insufficient consistency, and thus, is inadequate to infer the presence or absence of a causal relationship between short-term SO_2 exposure and cardiovascular effects.

5.3.2 Long-Term Exposure

5.3.2.1 Introduction

Studies of the effects of long-term exposure to SO_2 on the cardiovascular system were not available for inclusion in the 1982 AQCD (U.S. EPA, 1982a). The 2008 ISA for Sulfur Oxides (U.S. EPA, 2008d) reviewed a limited body of toxicological and epidemiologic studies published through 2006 and concluded that the available evidence was "too limited to make any conclusions" between the effects of long-term exposure to SO_2 and cardiovascular health.

The 2008 ISA for Sulfur Oxides included one epidemiologic study, which reported an increased risk of cardiovascular events in association with long-term exposure to SO_2 in post-menopausal women (50−79 years old) without previous CVD from 36 U.S. metropolitan areas. In this study, Miller et al. (2007) found that $PM_{2.5}$ was most strongly associated with cardiovascular events (MI, revascularization, angina, CHF, CHD death), compared to the other pollutants evaluated [hazard ratio (HR): 1.24 (95% CI: 1.04, 1.48) per 10 $\mu g/m^3$], followed by SO_2 [1.07 (95% CI: 0.95, 1.20) per 5 ppb]. Exposures to air pollution were estimated by assigning the annual (for the year 2000) mean air pollutant concentration measured at the monitor nearest to the subject's five-digit residential ZIP code centroid. The effect estimate for SO_2 was strengthened in a multipollutant model that was adjusted for several other pollutants including $PM_{2.5}$. However, correlations among pollutants were not described and exposure measurement error may have introduced a bias (Section 3.4.2). Consequently, the extent to which this study supports an independent effect of SO_2 on the cardiovascular system is limited. Several recent epidemiologic studies of the association of long term SO_2 exposure with subclinical and clinical cardiovascular outcomes add to the available body of evidence. These recent studies do not change the conclusion from the 2008 ISA for Sulfur Oxides (U.S. EPA, 2008d).

Experimental animal studies with long-term exposures below 2,000 ppb were not available for inclusion in the 2008 ISA for Sulfur Oxides. Although a small number of studies using exposures above 2,000 ppb were included, they did not contribute heavily to conclusions because the concentrations of SO_2 used in these studies were unlikely to be relevant to ambient concentrations of SO_2. No new toxicological studies in humans or animals have been published since the 2008 ISA for Sulfur Oxides. Overall, the biological plausibility and independence of the effects observed in epidemiologic studies remains an important uncertainty.

This section reviews the published studies of the cardiovascular effects of long-term exposure to SO_2 (i.e., longer than 1 month). To clearly characterize the evidence underlying causality, the discussion of the evidence is organized into groups of related outcomes [ischemic heart disease and myocardial infarction (Section 5.3.2.2), cerebrovascular disease and stroke (Section 5.3.2.3), hypertension (Section 5.3.2.4), other cardiovascular effects (Section 5.3.2.5), and cardiovascular mortality (Section 5.3.2.6)]. Evidence for subclinical effects (e.g., blood biomarkers of cardiovascular effects) of long-term exposure to SO_2 are discussed in Section 5.3.2.7 and serve to inform biological plausibility across multiple clinical cardiovascular events and outcomes.

Similar to Section 5.3.1, studies examining cardiovascular effects of sulfite exposure (via i.p., i.v., etc.) are not included in this section because these studies generally involve exposures to sulfite that are higher than what is expected to occur following inhalation of SO_2 at ambient relevant concentrations. Studies in humans and animals suggest that prolonged exposure to SO_2 may result in measurable changes in the concentrations of sulfite in plasma and tissues, but these changes would be expected to be far less following concentrations of SO_2 typically found in ambient air. The literature describing the distribution and metabolism of sulfite is discussed in Section 4.2.3 and Section 4.2.4. The potential role of sulfite in the induction of systemic effects, such as effects of the cardiovascular system, is discussed in Section 4.2.4.

5.3.2.2 Ischemic Heart Disease and Myocardial Infarction

IHD generally develops due to a buildup of plaques in the arterial walls (i.e., atherosclerosis) that impede the blood flow and oxygen delivery to the heart. This restricted oxygen delivery or ischemia from excess plaque, plaque rupture and clot formation can lead to an MI. Several epidemiologic studies provide evidence of a relationship between long-term exposure to SO_2 and ischemic heart disease and incident or fatal MI (Table 5-32). However, uncertainty remains regarding the influence of exposure measurement error on the effect estimates observed in epidemiologic studies

(Section 3.4.2) and the ability of these studies to distinguish the independent effect of long-term SO_2 exposure from the effect of correlated copollutant exposures (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)[a]
†Lipsett et al. (2011)	California Teachers Study Cohort N = 124,614 California Jun 1996−Dec 2005	SO_2 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_2 with: ozone, r = −0.17 $PM_{2.5}$, r = 0.02 PM_{10}, r = 0.54 NO_2, r = 0.67 CO, r = 0.80	MI incidence SO_2: 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
†Atkinson et al. (2013)	National GP Patient Cohort England 2003	IQR: 0,83 mean (SD): 1.47	Annual average SO_2 concentration for 2002 at a 1 by 1-km resolution derived from dispersion models and linked to residential post codes Correlation of SO_2 with: NO_2, 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)[a]
†Rosenlund et al. (2006)	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_2 from heating at residential address. Residential history available for 30 yr exposure estimate. Correlation of 30 yr SO_2 with: 30 yr NO_2, r = 0.73 30 yr CO, r = 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
†Ancona et al. (2015)	Rome, Italy (SO_X: 2001−2010; follow-up: 2001−2010)	2.5 µg/m^3 SO_X SD: 0.9	Lagrangian particle dispersion model (SPRAY Ver. 5) used SO_X as exposure marker for petrochemical refinery emissions PM_{10}: 0.81 H_2S: 0.78	IHD[b] HR men: 0.87 (0.74, 1.02) HR women: 0.83 (0.64,1.07) CVD[b] HR men: 1.01 (0.93, 1.0) HR women: 1.02 (0.92, 1.12)
Miller et al. (2007)	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 $PM_{2.5}$, $PM_{10-2.5}$, CO, NO_2, and O_3

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)[a]
†Qin et al. (2015)	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_2 concentration for each district NO_2, *r* = 0.38 O_3, *r* = 0.87 PM_{10}, *r* = 0.70	CVD BMI<25 kg/m^2 1. 11 (0.97, 1.27) BMI<25 kg/m^2 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
†Dong et al. (2013a)	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_2 concentration for each district NO_2, *r* = 0.38 O_3, *r* = 0.87 PM_{10}, *r* = 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_2 = nitrogen dioxide; NR = not reported; OR = odds ratio; O_3 = ozone; $PM_{2.5}$ = particulate matter with a nominal aerodynamic diameter less than or equal to 2.5 µm; PM_{10} = particulate matter with a nominal aerodynamic diameter less than or equal to 10 µm; $PM_{10-2.5}$ = 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_2 = sulfur dioxide; SO_X = sulfur oxides; WHI = Women's Health Initiative.

[a]Effect estimates are standardized per 5-ppb increase in SO_2 concentrations.

[b]Effect estimate per 2.88 µg/m^3 increase in SO_X concentration (as reported by author in original publication).

†Studies published since the 2008 ISA for Sulfur Oxides.

Lipsett et al. (2011) analyzed the association of incident MI with long-term exposure to SO_2, other gases (NO_2, CO, O_3), and PM. These authors studied a cohort of California public school teachers aged 20−80 years old (n = 124,614). Each participant's geocoded residential address was linked to pollutant surfaces that were determined by IDW

interpolation of pollutant concentrations measured at fixed site monitors during the period 1996−2005. The average of monthly SO_2 concentrations was modeled as a time-dependent function for subjects with at least 12 months of exposure. Those living outside the radial range for which the monitor was intended to provide representative data were excluded from the analysis. This "representative range" was 3 km for neighborhood SO_2 monitors and 5 km for the urban/regional SO_2. The association between SO_2 and incident MI was imprecise and standardization to an increase in SO_2 concentration of 5 ppb (as opposed to the IQR of 0.43) affected the stability of the estimate. An increased risk of 1.20 (1.02, 1.41) was observed per 10 $\mu g/m^3$ per $PM_{2.5}$. Fewer observations were available for the SO_2 compared to PM analyses because the requirements for the participants' proximity to the monitor were more stringent for SO_2 (residing within 5 km as opposed to 20 km for PM).

Atkinson et al. (2013) examined the association of incident cardiovascular disease with SO_2. These authors studied patients (aged 40−89 years) registered with 205 general practices across England. The authors report that approximately 98% of the population is registered with a general practitioner minimizing the potential for selective participation. Predicted annual average SO_2 concentrations within 1 × 1-km grids, estimated using dispersion models, were assigned to participants based on their residential postal code. Cardiovascular disease outcomes included in the analysis were MI, stroke, arrhythmias, and heart failure. Authors reported an association of SO_2 with MI in a fully adjusted model [HR: 1.34 (95% CI: 1.13, 1.50) per 5 ppb]. The performance of the dispersion model used to estimate SO_2 concentration was characterized as moderate to poor depending on the study year. Failure of the model to capture the spatial variability of SO_2 could lead to bias toward or away from the null (Section 3.4.4.2). Associations of other pollutants (i.e., PM_{10}, NO_2, ozone) with MI were also observed in this study.

Rosenlund et al. (2006) conducted a population case-control study to examine the association of first MI with long-term exposure to air pollution in Stockholm, Sweden. In this study residential histories were used to estimate 30-yr avg SO_2 concentration from residential heating sources using dispersion models. Although a positive association of SO_2 and other pollutants (NO_2, CO, PM_{10}) with fatal MI was observed in this study, no association between nonfatal MI and long-term SO_2 exposure was reported. Panasevich et al. (2013) reported higher tumor necrosis factor alpha (TNF-α) levels among those with a genetic polymorphism of a TNF-α gene (*TNF308G/A*) as well as an increased risk of MI in the same population (Section 5.3.2.5).

Weak or inverse associations of both cardiovascular and ischemic heart disease were reported in a study relying on a Lagrangian particle dispersion model (see Section 3.3.2.4) to estimate SO_X emissions (gaseous and particulate component) from a

refinery (Ancona et al., 2015). Exposure model performance statistics were not reported. Null associations of cardiovascular hospitalizations with PM_{10}, which was highly correlated with SO_X (r = 0.81) in this study, were observed. Because SO_X was used as a marker for refinery emissions, which contains multiple toxics including VOCs, the study was not designed to evaluate the independent effect of SO_2. In addition to the study by Miller et al. (2007), which was included in the previous review, two analyses examined the association of long-term SO_2 exposure with relatively broadly defined outcome that included several cardiovascular diseases (Qin et al., 2015; Dong et al., 2013a). These studies, which were conducted among Chinese adults, reported imprecise increases in the risk of cardiovascular disease and results suggest the potential for age and body weight to modify the association with long-term SO_2 exposure. Neither of these analyses adjusted for copollutant confounding, and the district-level SO_2 concentrations used to indicate exposure may not have adequately captured the spatial variability of long-term SO_2 exposure.

Overall, these epidemiologic data do not provide support for an association of long-term SO_2 exposure with IHD or more broadly defined categories of cardiovascular disease. There is uncertainty related the independent effect of SO_2 on the cardiovascular system. Comparable associations between concentrations of other pollutants (i.e. $PM_{2.5}$ and PM_{10}) and long-term SO_2 exposures were reported in most studies, which were generally not designed to evaluate copollutant confounding. Further, the exposure assessment techniques applied in the studies were subject to varying degrees of error depending on the method. The uncertainties stemming from exposure measurement error were potentially substantial (Section 3.4.2).

5.3.2.3 Cerebrovascular Diseases and Stroke

Lipsett et al. (2011) evaluated the association of incident stroke with long-term exposure to SO_2, other gases (NO_2, NO_X, CO, ozone), and PM (Table 5-33). The authors observed an imprecise, although positive association between SO_2 and incident stroke. Point estimates for the association of other pollutants (PM_{10}, $PM_{2.5}$, NO_2, NO_X, and ozone) with incident stroke were also increased. A positive association of SO_2 with incident stroke of 1.13 (95% CI: 1.00, 1.34) per 5 ppb was reported by Atkinson et al. (2013) in patients across England (study methods in Section 5.3.2.2). Null associations with other pollutants (PM_{10}, NO_2, and ozone) were observed.

Two analyses of a random selection of adults (n = 24,845) ranging from 18 to 74 years old from households in 33 Chinese communities were examined the association between long-term SO_2 exposure and stroke. Monitor concentrations within each district were

used to derive 3-yr avg concentrations that were assigned to participants. The mean concentration among study participants was 20 ppb. Dong et al. (2013a) reported an increased risk of stroke [OR: 1.09 (1.01, 1.18) per 5 ppb] with the strongest associations in males. Qin et al. (2015) further evaluated effect modification by obesity and reported an increased risk of stroke among participants with BMI greater or equal to 25 kg/m^2 [OR: 1.18 (1.05, 1.32) per 5 ppb]. Neither of these studies considered copollutants confounding and both reported associations with at least one of the other pollutants that were evaluated (PM_{10}, NO_2, or ozone). The district level SO_2 concentrations may not have adequately captured the spatial variability of SO_2.

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)
†Lipsett et al. (2011)	California Teachers Study Cohort N = 124,614 California Jun 1996−Dec 2005	SO_2 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_2 with: ozone, r = −0.17 $PM_{2.5}$, r = 0.02 PM_{10}, r = 0.54 NO_2, r = 0.67 CO, r = 0.80	Stroke incidence SO_2: 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
†Atkinson et al. (2013)	National GP Patient Cohort England 2003	IQR: 0,83 mean (SD): 1.47	Annual average SO_2 concentration for 2002 at a 1 by 1 km resolution derived from dispersion models and linked to residential post codes Correlation of SO_2 with: NO_2, 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)
†Dong et al. (2013a)	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_2 concentration for each district NO_2, *r* = 0.38 O_3, *r* = 0.87 PM_{10}, *r* = 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
†Qin et al. (2015)	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_2 concentration for each district NO_2, *r* = 0.38 O_3, *r* = 0.87 PM_{10}, *r* = 0.70	Stroke BMI <25 kg/m^2: OR: 1.03 (0.92, 1.14) BMI 25 kg/m^2: 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)
†Johnson et al. (2010)	Edmonton, Alberta Canada Jan 2003–Dec 2007	SO_2 mean: 1.3	IDW average monitor SO_2 concentration assigned at postal code centroid level Correlation of 5-yr avg SO_2 with: NO_2, r = 0.40 O_3, r = 0.41 CO, r = −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) [a]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_2 = nitrogen dioxide; non-HS = nonhemhorragic stroke; Q1 = 1st quartile; Q2 = 2nd quartile; Q3 = 3rd quartile; Q4 = 4th quartile; Q5 = 5th quartile; OR = odds ratio; O_3 = ozone; $PM_{2.5}$ = particulate matter with a nominal aerodynamic diameter less than or equal to 2.5 µm; PM_{10} = particulate matter with a nominal aerodynamic diameter less than or equal to 10 µm; r = correlation coefficient; RR = relative risk; SD = standard deviation; SO_2 = sulfur dioxide; TIA = transient ischemic attack.

[a]Effect estimates are standardized per 5-ppb increase in SO_2 concentrations.

†Studies published since the 2008 ISA for Sulfur Oxides.

An inverse association between SO_2 concentration and stroke incidence was observed in an ecological analysis of long-term exposure to ambient pollution conducted in Edmonton (Johnson et al., 2010) while an association of SO_2 with stroke prevalence was observed in a study of 33 Chinese communities [OR: 1.21 (95% CI 1.01, 1.46)] (Dong et al., 2013a).

In summary, the epidemiologic studies do not provide evidence in strong support of an effect of long-term SO_2 exposure on stroke morbidity. Findings are not generally consistent across studies and there are uncertainties related to the potential for exposure measurement error and confounding by copollutants.

5.3.2.4 Blood Pressure and Hypertension

Several analyses conducted in China where the mean long-term SO_2 concentration is 18.7 ppb report positive associations with hypertension and increased blood pressure. Dong et al. (2013d) found increased risk of hypertension [OR: 1.17 (95% CI: 1.06, 1.28) per 5-ppb increase in SO_2 concentration] among adults greater than 55 years of age in 33 Chinese communities. The absolute change in diastolic and systolic blood pressure in

the study population overall was 0.46 mmHg (95% CI: 0.15, 0.75) and 1.18 mmHg (95% CI: 0.68, 1.69) per 5-ppb increase in SO_2 concentration, respectively. Zhao et al. (2013) reported a greater effect of SO_2 on blood pressure among the overweight and obese in this population. A similar trend was also observed with other pollutants (i.e., ozone and NO_2). In a study of children 5−17 years old from elementary schools in seven Chinese cities, Dong et al. (2014) reported associations with arterial blood pressure hypertension in males [OR: 1.17 (95% CI 1.08, 1.27)] and females [OR 1.19 (95% CI 1.10, 1.28)] per 5-ppb increase in 4-yr avg SO_2 concentration. In an extended analysis of this cohort, Dong et al. (2015) reported large risks associated with SO_2 concentration in overweight and obese children. Although an array of risk factors were considered in the analysis as potential confounders (Table 5-34), no adjustment for copollutants was presented nor were copollutant correlations reported. Associations of hypertension with the other pollutants examined (i.e., PM_{10}, ozone, CO, NO_2) 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)
†Dong et al. (2013d)	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_2 concentration for each district NO_2, *r* = 0.38 O_3, *r* = 0.87 PM_{10}, *r* = 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
†Zhao et al. (2013)	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_2 concentration for each district NO_2, *r* = 0.38 O_3, *r* = 0.87 PM_{10}, *r* = 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)
†Dong et al. (2014)	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
†Dong et al. (2015)	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_2 = nitrogen dioxide; NR = not reported; O_3 = ozone; OR = odds ratio; PM_{10} = particulate matter with a nominal aerodynamic diameter less than or equal to 10 µm; *r* = correlation coefficient; SBP = systolic blood pressure; SO_2 = sulfur dioxide.

†Studies published since the 2008 ISA for Sulfur Oxides.

5.3.2.5 Other Cardiovascular Effects

Few studies have evaluated other cardiovascular effects associated with long-term SO_2 concentrations. Atkinson et al. (2013) examined the association of arrhythmias and heart failure with long-term SO_2 exposure. Study methods are described in Section 5.3.2.2. Authors reported a positive association of SO_2 with heart failure in a fully adjusted model [HR: 1.27 (95% CI: 1.06−1.59) per 5 ppb] and with arrhythmia [HR: 1.13 (95% CI 1.00, 1.27)]. A similar pattern of findings was observed for the associations of NO_2 and PM_{10} with which moderate correlations with SO_2 were reported. No association of annual SO_2 concentration with hospital admissions for heart failure was reported in a study of county-level air pollution indicator concentrations (Bennett et al., 2014).

5.3.2.6 Cardiovascular Mortality

The recent evidence for associations between long-term SO_2 exposure and total mortality (Section 5.5.2) is generally consistent with the evidence in the 2008 ISA for Sulfur Oxides. Several studies report associations between long-term SO_2 exposure and cardiovascular mortality (Figure 5-27); however, there is no consistent trend toward positive associations for cardiopulmonary or cardiovascular causes of death overall. Additionally, confounding by copollutants is not ruled out (Section 3.4.3) and uncertainties remain regarding the influence of exposure measurement error (Section 3.4.2). Together, these uncertainties limit the interpretation of the causal nature of the associations observed in the available epidemiologic studies of long-term mortality.

5.3.2.7 Subclinical Effects Underlying Cardiovascular Diseases

Carotid intima-media thickness (cIMT) is a measurement of thickness of the inner layers of the wall of the artery and can be used to indicate the presence of subclinical atherosclerosis. Other markers of preclinical atherosclerosis include pulse wave velocity and augmentation index, both of which indicate arterial stiffening. In an analysis of the Atherosclerosis Risk in Young Adults study, which is a prospective cohort study (Lenters et al., 2010), no association of SO_2 concentration with carotid intima-media thickness (cIMT) was observed; however, there was a weak imprecise increase in aortic pulse wave velocity reported. The other pollutants examined (NO_2, $PM_{2.5}$, black smoke) were also not associated cIMT although associations between NO_2 concentration and both pulse wave velocity and augmentation index were observed. SO_2 concentration at the home

address for the year 2000 was assigned to participants of this study. The correlations of SO_2 with NO_2, black smoke, and $PM_{2.5}$ reported in this study were low, ranging from $r = 0.09$ to 0.12. The correlation of SO_2 with metrics of traffic intensity were also low ($r = -0.06$ to 0.06). In another study, Weng et al. (2015) reported that annual average SO_2 concentration was correlated with brachial-ankle pulse wave velocity in univariate analyses but not after adjustment for PM_{10} and other potential confounders. This study was based on data from 127 heart disease patients undergoing hemodialysis in Taoyuan, Taiwan.

Inflammation and oxidative stress have been shown to play a role in the progression of chronic cardiovascular disease. Forbes et al. (2009b) examined the association of predicted annual average SO_2 concentration with CRP and fibrinogen among the English population. Multilevel linear regression models were used to determine pooled estimates across three cross-sectional surveys conducted during different years. Each participant's postal code of residence was linked to predicted annual average SO_2 concentration derived from dispersion models. SO_2, PM_{10}, O_3, and NO_2 were not associated with increased CRP or fibrinogen in these data. A study conducted among men and women (45−70 years) in Stockholm reported an association of 30-yr avg source-specific heating-related SO_2 concentration estimated using dispersion models with increases in IL-6; however, SO_2 was not associated with CRP, TNF-α, fibrinogen, or plasminogen activator inhibitor-1 in this study (Panasevich et al., 2009). Associations between long-term NO_2 concentration, which were moderately correlated with SO_2 ($r = 0.53$), and increased plasma IL-6 were also observed in this study. A study conducted among older adults in Taiwan reported no changes in blood pressure, total cholesterol, fasting glucose, hemoglobin A1c, IL-6 and neutrophils in association with increasing SO_2 concentration while associations between these endpoints and other pollutants were observed (Chuang et al., 2011).

Overall, the body of evidence is limited and there is no consistent positive trend in the associations observed between SO_2 and subclinical atherosclerosis or circulating markers of inflammation. These findings are consistent with the general lack of mechanistic evidence for key events in the proposed mode of action leading to extrapulmonary effects.

5.3.2.8 Summary and Causal Determination

Overall, the evidence is inadequate to infer the presence or absence of a causal relationship between long-term exposure to SO_2 and cardiovascular health effects.

Although a number of epidemiologic studies report positive associations between long-term exposure to SO_2 concentrations and cardiovascular disease and stroke (Section 5.3.2.3), the evidence for any one outcome is limited and inconsistent. As discussed in Section 3.4.2.2, centrally located monitors may not capture the spatial variability in SO_2 concentration. Dispersion models generally capture SO_2 variability on near-source spatial scales (up to tens of km) but exposure estimates from such models are subject to other uncertainties (Section 3.3.2.4). Bias stemming from exposure measurement error can be either direction (i.e. toward or away from the null) and no studies corrected for such error, complicating the interpretation of findings from studies of long-term exposure of SO_2 (Section 3.4.4.2). There is also uncertainty regarding the potential for copollutant confounding (Section 3.4.3). Primary pollutants such as NO_2 and CO typically show moderate to high correlations with SO_2 (Table 5-32, Table 5-33, and Table 5-34) and there is a lack of experimental evidence to provide coherence or biological plausibility for an independent effect of SO_2 on cardiovascular health. Several epidemiologic studies evaluated the association between SO_2 concentration and subclinical atherosclerosis or circulating markers of inflammation; however, there is no consistent positive trend in the associations observed between SO_2 and these potential key events in a mode of action.

The available evidence examining the relationship between long-term exposure to SO_2 and cardiovascular effects was evaluated using the framework described in Table I and Table II of the Preamble to the ISAs (U.S. EPA, 2015b). The key evidence, supporting or contradicting, as it relates to the causal framework is summarized in Table 5-35. In conclusion, the evidence lacks coherence and is of insufficient consistency, and thus, is inadequate to infer the presence or absence of a causal relationship between long-term exposure to SO_2 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[a]	Key Evidence[b]	Key References[b]	SO_2 Concentrations Associated with Effects[c]
Some epidemiologic studies report positive associations but results are not generally consistent.	Positive associations of SO_2 with MI, CVD events, or stroke events	Lipsett et al. (2011)	1.72 ppb (mean)
		Atkinson et al. (2013)	1.47 ppb (mean)
		Miller et al. (2007)	NR
	Null/inverse associations observed with MI and stroke	Rosenlund et al. (2006)	9.6 ppb (med)
		Johnson et al. (2010)	1.3 ppb (mean)
Limited coherence with evidence for cardiovascular mortality	No consistent positive trend observed in long term studies of cardiovascular mortality.	Section 5.3.2.4	
Uncertainty due to confounding by correlated pollutants	Correlations of SO_2 with CO and NO_2 vary by location but are generally moderate to high.	Table 5-32 Table 5-33 Table 5-34	
Uncertainty due to exposure measurement error	Centrally located monitors may not capture spatial variability of SO_2 concentrations.	Miller et al. (2007) Section 3.4.2	
	SO_2 estimates from dispersion model show poor to moderate agreement with measured concentrations.	Atkinson et al. (2013) Forbes et al. (2009a)	
	Exposure measurement error can introduce bias away from the null in studies of long-term exposure	Section 3.4.4.2	
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_2 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[a]	Key Evidence[b]	Key References[b]	SO_2 Concentrations Associated with Effects[c]
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	Section 4.3 Section 5.3.2.7	

CO = carbon monoxide; CRP = C-reactive protein; CVD = cardiovascular disease; IL-6 = interleukin-6; MI = myocardial infarction; NO_2 = nitrogen dioxide; NR = not reported; SO_2 = sulfur dioxide.

[a]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).

[b]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.

[c]Describes the SO_2 concentrations with which the evidence is substantiated.

5.4 Reproductive and Developmental Effects

5.4.1 Introduction

This section covers studies of health endpoints with exposures to SO_2 occurring during or around pregnancy and/or the first years of life. This includes not only pregnancy and birth outcomes (including infant mortality) occurring close in time to the exposure, but also developmental outcomes potentially occurring years later. Exposures occurring in pregnancy and early life may alter development, and have effects not immediately identifiable but evident at later points. These studies are characterized in this section as they contribute to the weight of evidence for effects of SO_2 on reproductive health and development. Evidence regarding fertility, reproduction, and pregnancy are discussed in Section 5.4.2, with a series of birth outcomes [fetal growth (Section 5.4.3.1), preterm birth (Section 5.4.3.2), birth weight (Section 5.4.3.3), birth defects (Section 5.4.3.4), fetal mortality (Section 5.4.3.5), and infant mortality (Section 5.4.3.6)] discussed in Section 5.4.3. Studies of developmental outcomes are discussed in Section 5.4.4, with a focus on respiratory developmental outcomes in Section 5.4.4.1.

Epidemiologic studies included in the 2008 SO_X ISA (U.S. EPA, 2008d) examined impacts on reproductive outcomes including preterm birth, birth weight, intra-uterine

growth retardation, birth defects, infant mortality, and neonatal respiratory hospitalizations. While positive associations were observed in the previous SO_X ISA (U.S. EPA, 2008d), there was little biologic plausibility for these associations provided by supporting toxicological literature. Interpretation of those results was also limited by the lack of control for potential confounding by copollutants, the small number of studies, and uncertainty regarding exposure. The 2008 SO_X ISA (U.S. EPA, 2008d) concluded the evidence was inadequate to infer the presence or absence of a causal relationship with reproductive and developmental effects.

The body of literature characterizing the reproductive health effects of exposure to SO_2 has grown considerably since the 2008 SO_X ISA (U.S. EPA, 2008d), with over 50 recent epidemiologic studies. However, the number of studies for any particular outcome remains relatively limited. Among the recent epidemiologic studies, birth outcomes (e.g., small for gestational age, preterm birth, and birth weight) predominate. Several new studies of congenital anomalies are now available in addition to the single study included in the 2008 SO_X ISA. Recent studies of other outcomes, such as fetal mortality, infant mortality, fertility, and conditions related to pregnancy have also been published. Key epidemiologic studies are summarized in Table 5-36. In toxicological research, a single study published at relevant exposure levels (1,500 ppb or lower) investigated reproductive and developmental changes in exposed female rats and their offspring, finding altered estrus cyclicity with fewer cycles over time, altered birth outcomes of increased litter size, and decreased postnatal body weight in offspring whose dams were exposed to SO_2. This study is summarized in Table 5-37. The majority of the remaining animal toxicological evidence for reproductive and development effects is for exposure at 5,000 ppb or greater, doses which are beyond the scope of this document.

Several recent articles have reviewed methodological issues relating to the study of outdoor air pollution and adverse birth outcomes (Chen et al., 2010a; Woodruff et al., 2009; Ritz and Wilhelm, 2008; Slama et al., 2008). Some of the key challenges to interpretation of birth outcome study results include: (1) the difficulty in assessing exposure as most studies use existing monitoring networks to estimate individual exposure to ambient air pollution; (2) the need for detailed exposure data and potential residential movement of mothers during pregnancy; (3) the inability to control for potential confounders such as other risk factors that affect birth outcomes (e.g., smoking), evaluating the exposure window (e.g., trimester) of importance; and (4) the limited evidence on the physiological modes of action for these effects (Ritz and Wilhelm, 2008; Slama et al., 2008). An additional limitation is the failure for many studies of reproductive and developmental outcomes to adjust for co-occurring air pollutants. As ozone, $PM_{2.5}$, and NO_X have all been associated with reproductive and developmental health outcomes, the lack of adjustment makes interpretation of isolated SO_2 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_2 have been reported from this collaboration.

Overall, the number of studies examining associations between exposure to ambient SO_2 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_2 ppb	Exposure Assessment	Selected Effect Estimates[a] 95% CI
Fetal growth				
Liu et al. (2003)	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)
Brauer et al. (2008)	Vancouver (n = 70,249)	2.2	Inverse distance weighting of three closest monitors within 50 km, 14 SO_2 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)
Rich et al. (2009)	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_2 ppb	Exposure Assessment	Selected Effect Estimates[a] 95% CI
†Le et al. (2012)	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_2, and PM_{10} 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_2, and PM_{10} 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_2, and PM_{10} Q1: ref Q2: 1.17 (0.94, 1.45) Q3: 1.24 (1.02, 1.50) Q4: 1.31 (1.06, 1.60)
Preterm birth				
Liu et al. (2003)	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)
Sagiv et al. (2005)	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)
†Zhao et al. (2011)	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)
†Mendola et al. (2016a)	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_2 ppb	Exposure Assessment	Selected Effect Estimates[a] 95% CI
Low birth weight				
Ha et al. (2001)	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)
Lee et al. (2003)	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)
Liu et al. (2003)	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)
Dugandzic et al. (2006)	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)
†Morello-Frosch et al. (2010)	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)
†Ebisu and Bell (2012)	Northeastern and mid-Atlantic U.S. (n = 1,207,800)	6.1	County average from monitors	EP: 1.05 (1.01, 1.09)
†Kumar (2012)	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)
Birth Weight				
†Darrow et al. (2011) Distributed lag, 1-h max SO_2	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)
†Geer et al. (2012)	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_2 ppb	Exposure Assessment	Selected Effect Estimates[a] 95% CI
Fetal and infant mortality				
†Hwang et al. (2011)	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)
†Faiz et al. (2012)	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)
†Faiz et al. (2013)	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 $PM_{2.5}$: 1.18 (1.00, 1.40) Adjusted NO_2: 1.15 (1.00, 1.32) Adjusted CO: 1.05 (0.93, 1.20)
Woodruff et al. (2008)	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_{10}, CO, O_3: 1.13 (0.79, 1.60) Adjusted $PM_{2.5}$, CO, O_3: 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_2 ppb	Exposure Assessment	Selected Effect Estimates[a] 95% CI
Developmental				
Dales et al. (2006)	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_3, NO_2, CO 1.95 (0.54, 3.68) Adjusted for O_3, NO_2, CO, PM_{10} 1.57 (0.25, 3.29)
†Clark et al. (2010)	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_2 = nitrogen dioxide; O_3 = ozone; $PM_{2.5}$ = particulate matter with a nominal aerodynamic diameter less than or equal to 2.5 µm; PM_{10} = particulate matter with a nominal aerodynamic diameter less than or equal to 10 µm; $PM_{10-2.5}$ = 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_2 = sulfur dioxide; T1 = 1st trimester; T2 = 2nd trimester; T3 = 3rd trimester; VSGA = very small for gestational age.

[a]Relative risk per 5-ppb change in SO_2, 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_2 Exposure	Measured Outcome(s)
Mamatsashvili (1970b) 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

Infertility affects approximately 11% of all women ages 15−44 in the U.S. (Chandra et al., 2013), and can have negative psychological impacts and affect quality of life;

infertility and subfertility may also potentially signal poorer physiological health. Those with fertility problems are at higher risk for adverse pregnancy and birth outcomes if they do become pregnant (Hansen et al., 2005; Helmerhorst et al., 2004; Jackson et al., 2004). Outcomes studied in this area include fecundity (the ability to conceive frequently, quantified as length of time to pregnancy) and fertility (the ability to have a live birth). Studies in this area frequently use populations undergoing assisted reproductive treatment, as these populations have a large amount of data collected on them during treatment and defined menstrual cycles and start points. In cohorts recruited from the general population, exact timing can be difficult to determine due to reliance on participant recall, particularly if they are surveyed well after initiation of pregnancy attempts. Many pregnancies are unplanned, which also adds a level of complication to quantifying fertility. Researchers may also investigate potential mechanistic links between pregnancy conditions and biomarkers and later birth outcomes; such as pregnancy-related hypertension, which is a leading cause of perinatal and maternal mortality and morbidity (Lee et al., 2012).

Four recent studies have examined the effects of SO_2 on measures of fertility; all use different populations and outcomes and observed mainly null effects for SO_2 exposures. Recent studies examined semen quality parameters in cohorts of men from Chongqing, China (Zhou et al., 2014) and Poland (Radwan et al., 2015) and observed decreases in normal morphology with increases in SO_2 exposure; however, all other quality metrics showed null associations. Slama et al. (2013) examined fecundity rate ratios (FRs) with SO_2 exposures before and after the initiation of unprotected intercourse in a Czech Republic population. Exposures prior to intercourse initiation (long-term, ~30 or 60 days) had slightly reduced FRs; however, SO_2 was highly correlated with $PM_{2.5}$ and NO_2 in this population and stronger reductions in fertility were observed with those pollutants. Legro et al. (2010) examined odds of live birth in a population undergoing in vitro fertilization and observed null associations for SO_2 with all exposure windows from medication start to birth (short-term windows during in vitro fertilization, long term from transfer to pregnancy).

Mixed effect estimates are observed with SO_2 exposure across other pregnancy-related outcomes. Recent studies examined increased blood pressure during pregnancy or pregnancy-related hypertensive disorders, including pre-eclampsia. Several studies observed no associations between SO_2 exposure during the first trimester and changes in late pregnancy blood pressure (Lee et al., 2012) or hypertensive disorders (Michikawa et al., 2015); however, a study in Florida observed increased hypertension with higher SO_2 exposure during the first trimester (Xu et al., 2014). Mendola et al. (2016b) observed a positive association between pre-eclampsia and SO_2 exposure among people with asthma, but not among people without asthmas; the interaction between exposure to SO_2 and

asthma was statistically significant for the first trimester exposure window. A small Iranian study found no association between pre-eclampsia and SO_2 above versus below median concentrations (Nahidi et al., 2014). Assibey-Mensah et al. (2015) observed no effect of SO_2 on hypertensive disorders in Beijing comparing 2008 Olympic period with same calendar days in 2009. In fact, there was an inverse relationship between SO_2 exposure in the third trimester and hypertensive disorders.

In other pregnancy-related outcomes, no associations were observed in the Allegheny County, PA population for short-term near-birth exposures and C-reactive protein, an inflammatory biomarker linked to increased risk of preterm birth (Lee et al., 2011b). Michikawa et al. (2016) observed positive associations with SO_2 exposure and placenta previa in a Japanese population, although the associations were smaller and less consistent than those observed for ozone or suspended particulate matter. Increases in SO_2 exposure during the preconception period and the first trimester were associated with increased odds of gestational diabetes mellitus (Robledo et al., 2015). Assibey-Mensah et al. (2015) examined other fetal-placental conditions, and observed no associations with SO_2 exposure in the first or second trimester, but reported a positive association with fetal-placental conditions and third trimester SO_2 exposures in Beijing comparing 2008 Olympic period with same calendar days in 2009. Wallace et al. (2016) observed positive associations between premature rupture of membranes and SO_2 exposure averaged over the whole pregnancy, but not for shorter exposure windows (i.e., days or hours before rupture).

No recent animal studies evaluating fertility and pregnancy were identified. An older study in laboratory animals exposed to SO_2 demonstrated reproductive toxicity in adult female rodents and their offspring. Adult female albino rats were exposed to either 0.057 ppm or 1.5 ppm SO_2 by inhalation for 72 days (Mamatsashvili, 1970b). During the first month of treatment at 1.5 ppm, substantial alterations in stages of the estrus cycle were seen including significant decreases in duration of diestrus and metastrus. During the 2nd and 3rd month of exposure, prolongation of estrus cyclicity was found with exposure to 1.5 ppm SO_2, leading to fewer estrus cycles during the study period. This change was not permanent as by 7 months after exposure ceased, estrus cyclicity returned to normal. Exposure of adult female rodents to SO_2 caused disruption of estrus cyclicity that was not permanent as it returned to normal after cessation of SO_2 exposure.

While studies of fertility, reproduction, and pregnancy are limited in number, generally, SO_2 exposures appear to have no association with these outcomes. A group of studies examining hypertensive disorders during pregnancy report inconsistent results, with the majority observing no association with SO_2 exposure. Similarly, studies examining endpoints related to fertility and other pregnancy conditions are generally inconsistent,

with the majority observing no association, and few studies examining any one specific outcome. Additionally, these studies do not provide evidence to help reduce uncertainty related to exposure measurement error, copollutant confounding, or biological mechanism by which SO_2 could cause these effects. These studies are summarized in Supplemental Table 5S-20 (U.S. EPA, 2015i).

5.4.3 Birth Outcomes

This section discusses several categories of birth outcomes, including fetal growth (Section 5.4.3.1), preterm birth (Section 5.4.3.2), birth weight (Section 5.4.3.3), birth defects (Section 5.4.3.4), fetal mortality (Section 5.4.3.5), and infant mortality (Section 5.4.3.6).

5.4.3.1 Fetal Growth

Fetal growth can be difficult to quantify; typically, small for gestational age (SGA) or intra-uterine growth restriction (IUGR) are used. These designations, often used interchangeably, are defined as infants with a birth weight below the 10th percentile for gestational age, usually with consideration for sex and race as well. There are a number of limitations in using SGA/IUGR as a metric of poor fetal growth. One is that a percentile-based measure will always quantify a certain percentage of the infant population as growth restricted whether or not this is truly the case (Wollmann, 1998). For example, in term infants, it is unlikely that 10% are actually growth restricted. Whereas in preterm infants, it is likely that more than 10% are growth restricted; therefore, SGA cases would be overestimated in term infants and underestimated in preterm infants. In addition, exact definitions shift between studies and some studies use alternate definitions of SGA/IUGR. For example, some studies use the birth weight distribution of their study population for defining SGA, which will naturally not be identical for every study population, and others use country standards, likely to be more stable over time (Le et al., 2012; Brauer et al., 2008; Liu et al., 2003). An alternate approach to categorizing growth restriction is to use ultrasound images during gestation (Woodruff et al., 2009). This approach has the benefit of examining all fetuses with ultrasounds, being less subjective to population definition, and distinguishing true growth restriction from merely small-sized infants. However, not all women receive prenatal care and ultrasounds, leading to the possibility of selection bias.

Several studies report positive associations between fetal growth and SO_2, although timing of exposure is inconsistent. A recent study conducted in Australia examined

ultrasound measures in midgestation in association with SO_2 exposures during early pregnancy (Hansen et al., 2008). Hansen et al. (2008) observed decreases in biparietal diameter and abdominal circumference with increases in SO_2 during the first 4 months of pregnancy [5-ppb SO_2 increase in 1st month: −4.25 mm (−6.81, −1.69) biparietal diameter; −9.31 mm (−19.31, 0.69) abdominal circumference]. Recent studies using the traditional definition of SGA/IUGR had mixed results. In Vancouver, increases in ORs for SGA were observed with entire pregnancy exposures (Brauer et al., 2008) and with 1st month and 1st trimester exposures (Liu et al., 2003). Rich et al. (2009) used an alternate definition of SGA—having a growth ratio (infant birth weight divided by median study cohort birth weight) below 0.75 for very SGA (VSGA), and between 0.75−0.85 for SGA—and observed elevated ORs with 1st trimester exposures for SGA, and 2nd and 3rd trimester exposures for VSGA. Other studies did not observe positive associations between fetal growth and SO_2. In a study conducted in Italy, (Capobussi et al., 2016) observe a null association for SGA when SO_2 exposure was estimated for the entire pregnancy, but modest positive associations when exposure was averaged across the first or second trimester. Whereas a study conducted in Calgary, Edmonton, and Montreal, Liu et al. (2007) found lowered ORs for IUGR with exposures in months 1 to 5 of pregnancy and no associations in months 6 to 9. Of the two recent studies in the U.S., Le et al. (2012) observed generally null associations for SGA and 1st and last month exposures; ORs with trimester exposure windows were null, although ORs became elevated for the 2nd and 3rd trimesters after adjustment for CO, NO_2, and PM_{10}.

No recent animal studies evaluating fetal growth were identified.

In summary, there is inconsistent evidence for increased odds of fetal growth restriction with exposure to SO_2 during pregnancy, and the evidence lacks consistency in fetal growth definition/metric and in exposure timing. Mean SO_2 exposures for these studies are generally low, although all studies examine average daily SO_2 concentrations. Additionally, these studies do not provide evidence to help reduce uncertainty related to exposure measurement error, copollutant confounding, or the biological mechanism by which SO_2 could cause these effects. Studies examining the association between SO_2 and fetal growth can be found in Supplemental Table 5S-21 (U.S. EPA, 2015j).

5.4.3.2 Preterm Birth

Preterm birth (PTB), delivery that occurs before 37 weeks of completed gestation, is a marker for fetal underdevelopment and a risk factor for further adverse health outcomes (e.g., infant mortality, neurodevelopmental problems, growth issues) (Mathews and MacDorman, 2010; Saigal and Doyle, 2008; IOM, 2007; Gilbert et al., 2003). PTB is

characterized by multiple etiologies (spontaneous, premature rupture of membranes, or medically induced), and identifying exact causes of PTB is difficult. It is likely that some mechanistic pathways are shared between the three groups; however, isolated causes are also likely to exist. Few, if any, studies distinguish between these three groups in examining associations between air pollution and PTB.

Given the uncertainty surrounding modes of action leading to PTB, many of the studies reviewed here consider both short- and long-term exposure periods. For example, exposure across all of gestation or during a particular trimester for long-term exposure windows, or weeks or days leading up to birth for short-term exposure windows. With near-birth exposure periods development will be at different points for term and preterm infants (e.g., exposure 2 weeks before birth is at 34 weeks for a 36-week PTB, and 38 weeks for a 40-week term birth), which suggests the possibility of different modes of action for increases in risk observed with near-birth exposures compared to exposures in specific periods of fetal development.

There is evidence supporting a relationship between SO_2 and preterm birth, primarily with exposure near-birth and including both older and newer studies. Among a U.S. birth cohort, Mendola et al. (2016a) examined PTB and exposure to SO_2 during different periods before and during pregnancy, observing generally null results among both women with and without asthma, except for when exposure was limited to weeks near birth (specifically weeks 34 and 36) for which positive associations were observed among women with asthma, but not for women without asthma. Studies in Europe and Asia report increased ORs/RRs of PTB with exposures across pregnancy, although not consistently between studies (Dibben and Clemens, 2015; Zhao et al., 2011; Leem et al., 2006; Bobak, 2000; Xu et al., 1995). In a recent time-series analysis, Zhao et al. (2011) found increased RRs with SO_2 exposure days 0−3 lagged from birth, but SO_2 was also highly correlated with PM_{10} (Pearson correlation coefficient = 0.75) and NO_2 (Pearson correlation coefficient = 0.84) in the study area. Dibben and Clemens (2015) used a pollution-climate model to assign SO_2 concentrations with high spatial resolution as well as incorporating daily activity data into the exposure and observed null associations with PTB and modest, positive associations with VPTB among births in Scotland. Qian et al. (2015) observed weak negative or null associations between SO_2 exposures and PTB across a range of different exposure windows among a birth cohort in Wuhan, China.

In the U.S. and Canada, studies of SO_2 and PTB in Pennsylvania (Sagiv et al., 2005) and Vancouver (Liu et al., 2003) found increased ORs with near-birth exposures [Sagiv et al. (2005): 6 week prebirth RR = 1.05 (1.00, 1.10); Liu et al. (2003): last month OR = 1.09 (1.01, 1.19) per 5-ppb increase]. More recently, in a Detroit, MI cohort, Le et al. (2012) found similar associations for exposures in the last month of pregnancy [OR 4th to 1st

quartile: 1.07 (1.01, 1.14)]. Another Vancouver cohort, examining entire pregnancy exposure, only observed increases [OR = 1.03 (0.93, 1.15) per 5-ppb SO_2 increase] with PTB <30 weeks (Brauer et al., 2008). Recent time-series and case-crossover studies in Atlanta, GA and Brisbane, Australia observed null associations for both 1st month and near-birth exposures using 1-h max SO_2 [exposure during last week of pregnancy RR per 5-ppb increase = 0.99 (0.98, 1.01)] (Darrow et al., 2009) and SO_2 concentrations 24−48 hours preceding the onset of labor (Li et al., 2016). Finally, a cross-sectional study of PTB across the U.S. reported that SO_2 showed "nonsignificant" effects with PTB for exposures during the month of birth (Trasande et al., 2013). In contrast, a recent study conducted in Italy observed negative associations between SO_2 exposure averaged across the entire pregnancy as well as each trimester and PTB, suggesting the SO_2 exposure was associated with longer gestation (Capobussi et al., 2016).

No recent animal studies evaluating preterm birth were identified.

In summary, there is some evidence for an association between exposure to SO_2 and preterm birth particularly with near-birth exposure windows. Studies examining PTB primarily used average daily SO_2. The one study that examined 1-h max SO_2 found no associations for PTB. Recent studies do not provide evidence to help reduce uncertainty related to exposure measurement error, copollutant confounding, or the biological mechanism by which SO_2 could cause preterm birth. Studies are characterized in Supplemental Table 5S-22 (U.S. EPA, 2015k).

5.4.3.3 Birth Weight

Birth weight is a measure of fetal growth and an important indicator of future infant and child health. Birth weight is determined by gestational age and intra-uterine growth, as well as maternal, placental, fetal, and environmental factors. Vulnerability to environmental insults affecting birth weight may occur throughout pregnancy. Implantation or formation of the placenta may be disrupted in the earliest weeks of pregnancy, leading to decreased fetal nutrition throughout pregnancy; or inflammation might result in constriction of the umbilical cord during the later trimesters resulting in poor fetal nutrition. As the largest gains in birth weight occur during the last weeks of gestation, this may be a particularly vulnerable period for birth weight outcomes. Information on birth weight is routinely collected for vital statistics; given that measures of birth weight do not suffer the same uncertainties as gestational age or growth restriction, it is one of the most studied outcomes within air pollution and reproductive health. Birth weight may be examined as a continuous outcome or dichotomous outcome as low birth weight (LBW) (less than 2,500 g or 5 lbs, 8 oz).

Studies examining LBW have found elevated ORs with exposures in the first trimester or first month (Dugandzic et al., 2006; Lee et al., 2003; Liu et al., 2003; Ha et al., 2001) and with entire pregnancy exposures (Capobussi et al., 2016; Dibben and Clemens, 2015; Yorifuji et al., 2015a; Ebisu and Bell, 2012; Kumar, 2012; Morello-Frosch et al., 2010). In the two studies that examined distance to monitor, using concentrations from closer monitors lead to stronger effect estimates (Kumar, 2012; Morello-Frosch et al., 2010). Some studies examining entire pregnancy exposure have also observed null associations between SO_2 and LBW (Brauer et al., 2008; Bell et al., 2007).

Studies examining continuous birth weight (Δg) have inconsistent results. In a northeast U.S. population, Bell et al. (2007) observed no association with change in birth weight for entire pregnancy exposure [−2.711 g (−13.253, 7.831) per 5 ppb SO_2], including in a stratified analysis of white and black mothers. Kumar (2012) reported results that shifted around the null based on distance from monitor in Chicago; some effects were positive, and some negative but all had wide confidence intervals. And, in a cross-sectional study across the county, Trasande et al. (2013) reported only "nonsignificant" effects for SO_2. One recent California cohort study reported increases in birth weight with increases in SO_2 exposure in entire pregnancy and first trimester, although effects were reduced with use of closer monitors (Morello-Frosch et al., 2010). A recent Texas study observed decreases in birth weight with county average SO_2 exposure for the entire pregnancy [−15.594 g (−25.344, −5.844)] (Geer et al., 2012). A study in Beijing during the summer Olympics of 2008 found increased SO_2 in the 8th month of pregnancy associated with decrements in birth weight; however, SO_2 was highly correlated with $PM_{2.5}$ and CO, which showed similar patterns of effect (Rich et al., 2015). Finally, a recent study in Atlanta found decreases in birth weight with increases in 3rd trimester 1-h max SO_2 (Darrow et al., 2011). This effect was stronger in non-Hispanic white and Hispanic mothers than non-Hispanic black mothers (Darrow et al., 2011).

No recent animal studies evaluating birth weight-related outcomes were identified. In laboratory animals from an older study, exposure to SO_2 affected birth outcomes in adult female rodents and their offspring. Adult female albino rats were exposed to either 0.057 ppm or 1.5 ppm SO_2 by inhalation for 72 days (Mamatsashvili, 1970b). At birth, litter sizes were significantly increased in number from dams that were exposed to SO_2 versus control dams (Table 5-37).

In summary, there is some evidence that LBW may be associated with SO_2, while evidence for an association with change in birth weight is inconsistent. Overall, the results of studies of LBW and birth weight remain inconsistent and these do not provide evidence to help reduce uncertainty related to exposure measurement error, copollutant confounding, or the biological mechanism by which SO_2 could cause these effects.

Studies for both LBW and change in birth weight can be found in Supplemental Table 5S-23 (U.S. EPA, 2015l).

5.4.3.4 Birth Defects

Birth defects are structural and functional abnormalities that can cause physical disability, intellectual disability, and other health problems. They are a leading cause of infant mortality and developmental disability in the U.S. (Mai et al., 2016). Since 2008, there have been several studies examining birth defects and SO_2 during pregnancy, particularly during weeks 3−8 of gestation, which is thought to be highly vulnerable to insults resulting in birth defects. Because birth defects as a whole are rare and specific birth defects are rarer, these studies often have effect estimates with very wide confidence intervals. Individual studies often look at different types of birth defects, meaning the body of work examining any one birth defect may still be limited. Cardiac birth defects and oral cleft defects are the most commonly studied anomalies. However, results (even for these defects) are inconsistent across studies. For example, odds of ventricular septal defects have been found to be increased (Gianicolo et al., 2014; Stingone et al., 2014; Agay-Shay et al., 2013; Gilboa et al., 2005), decreased (Hwang et al., 2015b; Dadvand et al., 2011a, b; Rankin et al., 2009), and null (Strickland et al., 2009) with increases in SO_2 exposure. Odds of cleft lip with or without cleft palate have been found to be increased (Zhu et al., 2015), decreased (Hwang and Jaakkola, 2008; Gilboa et al., 2005), or null (Dolk et al., 2010; Rankin et al., 2009) with increases in SO_2 exposure. A single study of limb deformities found increased odds with exposure to SO_2 during weeks 9−12 of pregnancy (Lin et al., 2014). Two studies examining repeating chromosomal defects found no association or correlation between trisomy 21 or any sperm disomy and SO_2 (Chung et al., 2014; Jurewicz et al., 2014). Studies of any congenital anomaly in Israel and China have reported inverse associations with increasing SO_2 (Farhi et al., 2014; Liang et al., 2014).

No recent animal studies evaluating birth defects were identified.

In summary, results for birth defects are either inconsistent across studies or limited in number of studies. Studies of birth defects and SO_2 are characterized in Supplemental Table 5S-24 (U.S. EPA, 2015m).

5.4.3.5 Fetal Mortality

Fetal mortality or stillbirth is the intra-uterine death of a fetus. In most areas fetal deaths are only reported after 20 weeks of completed gestation; this leads to potential bias, as the

population at risk of fetal death is any conception but the actual measured population is only those fetuses reaching at least 20 weeks gestational age. A single recent case-control study of spontaneous abortion occurring before 14 weeks of gestation found no associations with SO_2 exposures determined by time-weighted concentrations for residence and workplace (Moridi et al., 2014). A recent large California cohort found no associations between stillbirth and increasing SO_2 exposure (Green et al., 2015). In recent studies of a New Jersey population examining both long-term and short-term exposure windows, ORs for fetal death were elevated with a 2-day lag [OR per 5-ppb increase in SO_2: 1.12 (1.02, 1.24)] and with exposures across pregnancy and in each trimester, particularly the 3rd trimester [OR per 5-ppb increase in SO_2: 1.47 (1.05, 1.69)] (Faiz et al., 2013; Faiz et al., 2012). Hwang et al. (2011) examined fetal mortality among term and preterm deliveries in Taiwan, finding elevated associations for exposures during the 1st trimester only among preterm deliveries. Other studies have also found increased associations between SO_2 and fetal mortality, although mean SO_2 concentrations were higher in these studies (Hou et al., 2014; Pereira et al., 1998). Pereira et al. (1998) observed elevated RRs in a São Paulo, Brazil time series with short-term exposure. A recent study by Enkhmaa et al. (2014) found very strong correlations between seasonal SO_2 and fetal death, and Hou et al. (2014) found elevated ORs with long-term exposures around the time of conception. Although Hou et al. (2014)'s models were unadjusted for confounding factors and confidence intervals were very wide. In the study by Enkhmaa et al. (2014), other pollutants also showed very strong correlations and were highly correlated with one another.

No recent animal studies evaluating fetal mortality were identified.

In summary, although few in number, studies of fetal mortality and SO_2 show elevated associations for both short- and long-term exposures. However, these studies are limited by the uncertainties associated reproductive and developmental outcomes identified in the 2008 SO_X ISA. Studies are characterized in Supplemental Table 5S-25 (U.S. EPA, 2015n).

5.4.3.6 Infant Mortality

Studies of infant mortality and SO_2 are limited in number. In a U.S. study, Woodruff et al. (2008) observed increased ORs for respiratory-related post-neonatal infant mortality with long-term (2 months) exposure increases in county-level SO_2 concentrations [OR = 1.09 (0.89, 1.36) per 5-ppb increase]. This association remained after adjusting for other pollutants. A time-series study in Seoul, South Korea observed increased RRs for all cause post-neonatal infant mortality with short-term SO_2 exposure, although exact

timing of exposure was unclear (Son et al., 2008). No recent animal studies evaluating postnatal mortality were identified. Studies are characterized in Supplemental Table 5S-25 (U.S. EPA, 2015n).

5.4.4 Developmental Outcomes

5.4.4.1 Respiratory Outcomes

Recent studies examined asthma onset in association with early life exposure to SO_2. Clark et al. (2010), Liu et al. (2016), Deng et al. (2015b), and Deng et al. (2015a) observed elevated ORs for asthma with SO_2 exposure during pregnancy and the first year of life. Nishimura et al. (2013) observed elevated ORs for asthma with SO_2 exposure in the first 3 years of life, but not the first year of life alone. Asthma onset is covered in further detail in Section 5.2.1.2.

In a time-series study, Dales et al. (2006) investigated neonatal hospitalizations due to respiratory causes in Atlanta, GA; they observed elevated ORs with 2-day lagged SO_2 exposure. After adjustment for gaseous copollutants, confidence intervals for associations with gaseous pollutants and PM_{10} were very large, but effect estimates remained elevated. Hospitalizations due to respiratory causes are covered in Section 5.2.1.6.

In summary, there is some evidence for an association between gestational and early-life exposure to SO_2 and respiratory health effects later in life, although evidence is limited and exposure windows are uncertain. Key studies are summarized in Table 5-36.

5.4.4.2 Other Developmental Effects

Studies examining other developmental exposures are limited in number. A recent study examined SO_2 exposure with apnea and bradycardia in a subpopulation of infants in Atlanta, and observed no association for either health outcome (Peel et al., 2011). Huang et al. (2015a) observed no associations between prenatal and early life SO_2 exposures and atopic dermatitis among infants in Taiwan. Poursafa et al. (2016) examined the association between SO_2 exposure during pregnancy and markers of endothelial disfunction (i.e., ICAM-1, V-CAM-1, endothelin-1) in cord blood. They observed a positive association with endothelin-1, but not for other markers of endothelial disfunction. Among a Japanese cohort, prenatal exposure to SO_2 was associated with verbal and fine motor delays assessed at ages 2.5 and 5.5 years (Yorifuji et al., 2015b). In an older study from the animal toxicology literature, adult female albino rats were

exposed to either 0.057 ppm or 1.5 ppm SO_2 by inhalation, 12 hours/day for 72 days (Mamatsashvili, 1970b). Changes in offspring postnatal growth or body weight over time were reported with 1.5-ppm exposure.

Sulfur dioxide-dependent synaptic injury was measured in adolescent male rats exposed to 1.24 ppm SO_2 for 6 hours/day for 90 days (Yun et al., 2013). Nonsignificant morphological changes were seen in the hippocampal synaptic junctions using transmission electron microscopy. In the hippocampus, the synaptic vesicle membrane protein synaptophysin (SYP) was significantly downregulated as was ERK1/2 phosphorylation. Phosphorylation is an important contributor to synaptic plasticity. Thus, SO_2 exposure in the adolescent rat contributes to downregulation of synaptic vesicle protein SYP and decreased ERK1/2 phosphorylation, indicative of disruption at the hippocampal synapse.

5.4.5 Summary and Causal Determination

Overall the evidence is inadequate to infer a causal relationship between exposure to SO_2 and reproductive and developmental outcomes. This is consistent with the 2008 ISA for Sulfur Oxides, which also concluded the evidence was inadequate to infer the presence or absence of a causal relationship with reproductive and developmental effects. All available evidence, including more than 50 recent studies, examining the relationship between exposure to SO_2 and reproductive and developmental effects was evaluated using the framework described in the Preamble to the ISAs (U.S. EPA, 2015b). The key evidence as it relates to the causal framework is summarized in Table 5-38.

There are several well-designed, well-conducted epidemiologic studies, many described in papers published since the previous ISA, that indicate an association between SO_2 and reproductive and developmental health outcomes; the bulk of the evidence exists for adverse birth outcomes. For example, several high quality studies reported positive associations between SO_2 exposures during pregnancy and fetal growth metrics (Le et al., 2012; Rich et al., 2009; Brauer et al., 2008; Liu et al., 2003), preterm birth (Mendola et al., 2016a; Le et al., 2012; Zhao et al., 2011; Sagiv et al., 2005; Liu et al., 2003), birth weight (Ebisu and Bell, 2012; Darrow et al., 2011; Morello-Frosch et al., 2010; Liu et al., 2003), and fetal and infant mortality (Faiz et al., 2012; Hwang et al., 2011; Woodruff et al., 2008). However, the evidence is not entirely consistent, and has not substantially reduced any of the uncertainties connected with the associations observed between exposure to SO_2 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[a]	Key Evidence[b]	Key References[b]	SO_2 Concentrations Associated with Effects[c]
Overall reproductive and developmental effects—inadequate to infer a causal relationship			
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_2 and preterm birth after adjustment for common potential confounders. Associations not evaluated in copollutant models.	Liu et al. (2003) Sagiv et al. (2005) †Le et al. (2012) †Mendola et al. (2016a) Section 5.4.3.2	Mean: 4.9 ppb Mean: 7.9 ppb Mean: 5.8 ppb Mean: 4.0 ppb
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	Section 5.4.3.1	Means: 4.9−5.8 ppb
	Several high quality studies show associations between SO_2 exposure and low birth weight but not for change in birth weight. Timing of exposure is inconsistent across studies. Only one study uses 1-h max for exposure determination.	Section 5.4.3.3	Means: 2.1−13.2 ppb
	Limited and inconsistent epidemiologic evidence for associations with various birth defects	Section 5.4.3.4	Reported means: 1.9−6
	Limited number of studies of SO_2 and fetal death, positive associations observed across studies, although timing of exposure and outcome definitions are inconsistent Limited evidence for an association with SO_2 in respiratory related infant mortality	Section 5.4.3.6	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[a]	Key Evidence[b]	Key References[b]	SO_2 Concentrations Associated with Effects[c]
	Limited evidence for positive associations between prenatal/early life exposures and childhood respiratory outcomes	Section 5.4.4.1	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	Mamatsashvili (1970a)	57 or 1,427 ppb
Lack of evidence from epidemiologic studies to support an association of SO_2 exposure with detrimental effects on fertility or pregnancy	A limited number of studies on fertility and pregnancy outcomes show no associations with SO_2.	Section 5.4.4.1	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	†(Faiz et al. (2013); Slama et al. (2013); Le et al. (2012))	
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.	Chapter 3 Section 3.4.4.2	
Uncertainty regarding exposure timing for specific outcomes.	Associations of exposure to SO_2 at particular windows during pregnancy are inconsistent between studies and across outcomes.		

SO_2 = sulfur dioxide.

[a]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).

[b]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.

[c]Describes the SO_2 concentrations with which the evidence is substantiated (for experimental studies, below 2,000 ppb).

†Studies published since the 2008 ISA for Sulfur Oxides.

One uncertainty is timing of exposure, wherein associations remain inconsistent among studies and across outcomes. For example, some studies observe the strongest associations when exposure is averaged over the entire pregnancy, while others observe the strongest association when exposure is averaged over either the first, second, or third trimester. As an exception to this, studies of PTB generally observed positive associations between near-birth exposures (e.g., last month of gestation, same, or 3-day lag from birth) (Mendola et al., 2016a; Le et al., 2012; Zhao et al., 2011; Sagiv et al., 2005; Liu et al., 2003).

Another uncertainty centers on spatial and temporal variability in SO_2 exposures. SO_2 is a temporally and spatially heterogeneous pollutant; it is difficult to accurately estimate for "long-term" exposures, and there is the potential for exposure measurement error in long-term SO_2 exposures to bias estimates toward or away from the null (Section 3.5). None of the epidemiologic studies made corrections or adjustments for exposure measurement error or accounted for the potential for bias away from the null, the potential for which has been demonstrated in simulation studies (see Section 3.4.4.2). Current epidemiologic methods are not able to disentangle whether associations are due to extended exposure to moderate concentrations of SO_2 or repeated short-term exposure to peaks in SO_2 concentration.

Potential confounding by copollutants may explain some of the observed associations and cannot be ruled out. SO_2 is part of a mix of ambient air pollution; SO_2 shares sources with particulate matter and is chemically linked to sulfate. Few studies evaluate or provide information that would inform the independent effect of SO_2 in the context of the greater air pollution mixture, and of those that do, no clear trends for the effects of copollutant adjustment are apparent (Faiz et al., 2013; Slama et al., 2013; Le et al., 2012).

There is insufficient information on potential modes of action of SO_2 on reproductive outcomes at relevant exposure levels for this ISA (Chapter 4). In a single older study from Mamatsashvili (1970a), SO_2 inhalation exposure in laboratory rodents demonstrated reproductive changes in exposed females and their offspring, altered birth outcomes, and developmental effects. The specific outcomes affected after SO_2 exposure included altered estrus cycle length of F0 and F1 generations, decrements in offspring body weight gain or growth after in utero exposure, and changes in litter size. The majority of the remaining animal toxicological evidence for reproductive and developmental effects is for exposure at 5,000 ppb or greater, doses which are beyond the scope of this document.

Since the 2008 ISA for Sulfur Oxides, researchers have begun evaluating more health outcomes, including fertility, effects on pregnancy (e.g., pre-eclampsia, gestational diabetes), and developmental effects. For each of these individual outcomes the literature base is small, but new studies are quickly accumulating. However, at present there is little

coherence or consistency among epidemiologic and toxicological studies for these outcomes. In general, it is challenging to synthesize study findings on the wide variety of health outcomes collected under the reproductive and developmental effects heading. Given the wide variety of potential mechanisms or adverse outcome pathways that could affect this breadth of outcomes, coherence is unlikely to be reached given the limited literature base.

The state of California, under the auspices of Proposition 65, the California Safe Drinking Water and Toxic Enforcement Act of 1986, has listed sulfur dioxide as a chemical known to cause developmental toxicity based on evidence from laboratory animal studies and epidemiologic studies, with the strongest evidence from IUGR. SO_2 is not listed as a reproductive toxicant under Proposition 65; much of this evidence is from toxicological studies with exposure to SO_2 at 5,000 ppb or greater (beyond the scope of this ISA). Effects seen at the higher doses include male reproductive effects on sperm and fecundity, as well as oxidative damage to the male reproductive organs, changes in birth weight or litter size, delayed reflexes in early life, and aberrant behavior of pups after in utero exposure. Epidemiologic evidence used for this listing is also evaluated under differing criteria than are employed for the ISA.

Overall, many uncertainties remain when evaluating the evidence for these health endpoints; therefore, the evidence is inadequate to infer a causal relationship between exposure to SO_2 and reproductive and developmental outcomes.

5.5 Mortality

5.5.1 Short-Term Exposure

5.5.1.1 Introduction

Earlier studies that examined the association between short-term SO_X exposure, mainly SO_2, and total mortality were limited to historical data on high air pollution episodes (U.S. EPA, 1982a). These studies were unable to decipher whether the associations observed were due to particle pollution or SO_2. Additional studies evaluated in the 1986 Second Addendum to the 1982 AQCD (U.S. EPA, 1986b) further confirm the findings of these initial studies, but were still unable to address uncertainties and limitations related to examining the effect of SO_2 exposure on mortality, especially at lower concentrations.

In the 2008 SO_X ISA (U.S. EPA, 2008d), a larger body of literature was available to assess the relationship between short-term SO_2 exposures and mortality; however, these studies were still limited in that they primarily focused on PM, with SO_2 only being examined in single-pollutant models. These studies found that excess risk estimates for total mortality due to short-term SO_2 exposure from multicity studies and meta-analyses generally ranged from 0.4 to 2.0% for a 10-ppb increase in 24-h avg SO_2 concentrations. These associations were primarily observed at mean 24-h avg SO_2 concentrations <15 ppb. Studies that examined cause-specific mortality found evidence of risk estimates larger in magnitude for respiratory and cardiovascular mortality compared to total mortality with the largest associations for respiratory mortality. The larger SO_2-respiratory mortality associations observed in the epidemiologic literature were coherent with the scientific evidence providing stronger support for SO_2 effects on respiratory morbidity compared to cardiovascular morbidity (U.S. EPA, 2008d).

An examination of potential copollutant confounding of the SO_2-mortality relationship was sparse. Studies evaluated in the 2008 SO_X ISA found that SO_2-mortality risk estimates from copollutant models were robust, but imprecise. An additional study that examined the potential interaction between copollutants [i.e., SO_2 and black smoke (BS)] did not find evidence of interaction when stratifying days by high and low concentrations of BS (Katsouyanni et al., 1997). Of the studies evaluated only the Air Pollution and Health: A European Approach (APHEA) study examined seasonality and potential effect modifiers of the SO_2-mortality relationship, and provided initial evidence of mortality effects being larger during the warm season and that geographic location may influence city-specific SO_2-mortality risk estimates, respectively (Katsouyanni et al., 1997). The consistent, positive SO_2-mortality associations observed across studies were supported by an intervention study conducted in Hong Kong that examined the health impact of converting to fuel oil with low sulfur content and found evidence suggesting that a reduction in SO_2 concentrations leads to a reduction in mortality (Hedley et al., 2002). Overall, the relatively sparse number of studies that examined the relationship between short-term SO_2 exposure and mortality along with the limited data with regard to potential copollutant confounding resulted in the 2008 SO_X ISA concluding that the collective evidence is "suggestive" of a causal relationship between short-term SO_2 exposure and mortality.

Since the completion of the 2008 SO_X ISA (U.S. EPA, 2008d), there continues to be a growing body of epidemiologic literature that has examined the association between short-term SO_2 exposure and mortality. However, similar to the collection of studies evaluated in the 2008 SO_X ISA (U.S. EPA, 2008d), most of the recent studies do not focus specifically on the SO_2-mortality relationship, but instead on PM or O_3. Of the studies identified, a limited number have been conducted in the U.S., Canada, and

Europe, with the majority being conducted in Asia due to the increased focus on examining the effect of air pollution on health in developing countries. Although these studies are informative when evaluating the collective evidence, the interpretation of these studies in the context of results from studies conducted in the U.S., Canada, and Western Europe requires caution. This is because studies conducted in Asia encompass cities with meteorological, outdoor air pollution (e.g., concentrations, mixtures, and transport of pollutants), and sociodemographic (e.g., disease patterns, age structure, and socioeconomic variables) (Chen et al., 2012b; Kan et al., 2010a; Wong et al., 2008b) characteristics that differ from cities in North America and Europe, potentially limiting the generalizability of results from studies of Asian cities to other cities.

As detailed in previous ISAs [e.g., U.S. EPA (2013c)], this section focuses primarily on multicity studies because they examine the association between short-term SO_2 exposure and mortality over a large geographic area using a consistent statistical methodology, which avoids the potential publication bias often associated with single-city studies (U.S. EPA, 2008d). However, where applicable single-city studies are evaluated that encompass a long study-duration, provide additional evidence indicating that a specific population or lifestage is at increased risk of SO_2-related mortality, or address a limitation or uncertainty in the SO_2-mortality relationship not represented in multicity studies. The remaining studies identified are not evaluated in this section due to issues associated with study design or insufficient sample size, and are detailed in Supplemental Table 5S-26 (U.S. EPA, 2015o).

The organization of the material on short-term SO_2 exposure and mortality is as follows. Section 5.5.1.2 evaluates studies that examined the association between short-term SO_2 exposure and mortality, with the remaining sections addressing key limitations and uncertainties in the SO_2-mortality relationship that were evident at the completion of the 2008 SO_X ISA (U.S. EPA, 2008d). Subsequent sections evaluate whether there is evidence of: confounding (i.e., copollutants and seasonal/temporal) (Section 5.5.1.3), effect modification (i.e., sources of heterogeneity in risk estimates across cities or within a population) (Section 5.5.1.4), modification of the SO_2-mortality association including seasonal heterogeneity (Section 5.5.1.5), and the SO_2-mortality C-R relationship and related issues, such as the lag structure of associations (Section 5.5.1.5).

5.5.1.2 Associations between Short-Term Sulfur Dioxide Exposure and Mortality in All-Year Analyses

Multicity studies and meta-analyses evaluated in the 2008 SO_X ISA reported consistent, positive associations between short-term SO_2 exposure and total mortality in all-year analyses (U.S. EPA, 2008d). Although only a small number of multicity studies have

been conducted since the completion of the 2008 SO_X ISA, these studies, as well as a meta-analysis of studies conducted in Asia (Atkinson et al., 2012), build upon and provide additional evidence for an association between short-term SO_2 exposure and total mortality (Figure 5-17). Air quality characteristics and study specific details for the 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_X ISA and recently published multicity studies and meta-analyses.

Study	Location	Years	Mortality Outcome(s)	Averaging Time	Mean Concentration ppb	Upper Percentile Concentrations ppb
North America						
Dominici et al. (2003)	72 U.S. cities (NMMAPS)[a]	1987–1994	Total	24-h avg	0.4−14.2	---
Burnett et al. (2004)	12 Canadian cities	1981–1999	Total cardiovascular respiratory	24-h avg	0.9−9.6	---
†Moolgavkar et al. (2013)	85 U.S. cities (NMMAPS)[e]	1987–2000	Total	24-h avg	---	---
Europe						
Katsouyanni et al. (1997)	12 European cities (APHEA-1)	1980–1992	Total	24-h avg	5.0−28.2[b]	90th: 17.2−111.8
Biggeri et al. (2005)	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
Hoek (2003)	Netherlands	1986–1994	Total cardiovascular respiratory	24-h avg	3.5−5.6	---
†Berglind et al. (2009)	Five European cities[f]	1992–2002	Total	24-h avg	1.0−1.6[g]	---
†Bellini et al. (2007)	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_X ISA and recently published multicity studies and meta analyses.

Study	Location	Years	Mortality Outcome(s)	Averaging Time	Mean Concentration ppb	Upper Percentile Concentrations ppb
Asia						
†Kan et al. (2010b); Wong et al. (2008b); Wong et al. (2010)	Four Asian cities (PAPA)	1996–2004[h]	Total cardiovascular respiratory	24-h avg	5.0−17.1	75th: 6.0−21.5 Max: 23.4−71.7
†Chen et al. (2012b)	17 Chinese cities (CAPES)	1996–2010[i]	Total cardiovascular respiratory	24-h avg	6.1−38.2	75th: 6.5−56.1 Max: 25.2−298.5
†Chen et al. (2013)	Eight Chinese cities	1996–2008[i]	Stroke	24-h avg	6.1−32.1	---
†Meng et al. (2013)	Four Chinese cities	1996–2008[k]	COPD	24-h avg	6.8−19.1	---
Meta-analyses						
Stieb et al. (2003)	Meta-analysis	1958–1999[e]	Total	24-h avg	0.7−75.2	---
HEI (2004)	Meta-analysis (South Korea, China, Taiwan, India, Singapore, Thailand, Japan)	1980–2003[d]	Total	24-h avg	~10−>200	---
†Atkinson et al. (2012)	Meta-analysis (Asia)	1980–2007[j]	Total cardiovascular respiratory COPD	24-h avg	---	---
†Shah et al. (2015)	Meta-analysis	1948−Jan 2014	Stroke	NR	6.2[c]	Max: 30.2

Table 5-39 (Continued: Air quality characteristics of multicity studies and meta analyses evaluated in the 2008 SO_X ISA and recently published multicity studies and meta analyses.

Study	Location	Years	Mortality Outcome(s)	Averaging Time	Mean Concentration ppb	Upper Percentile Concentrations ppb
†Yang et al. (2014b)	Meta-analysis (Asia, Europe, and North America)	1996–2013	Stroke	24-h avg	Asia: 11.4[b] Europe: 5.2[b] North America: 4.2[b]	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_X = sulfur oxides.

[a]Of the 90 cities included in the NMMAPS analysis only 72 had SO_2 data.

[b]Median concentration.

[c]The mortality time series of studies included in the meta-analysis spanned these years.

[d]Studies included within this meta-analysis were published during this time period.

[e]Of the 108 cities included in the analyses using NMMAPS data, only 85 had SO_2 data.

[f]SO_2 data was not available for Barcelona; therefore, the SO_2 results only encompass four cities.

[g]Median concentrations.

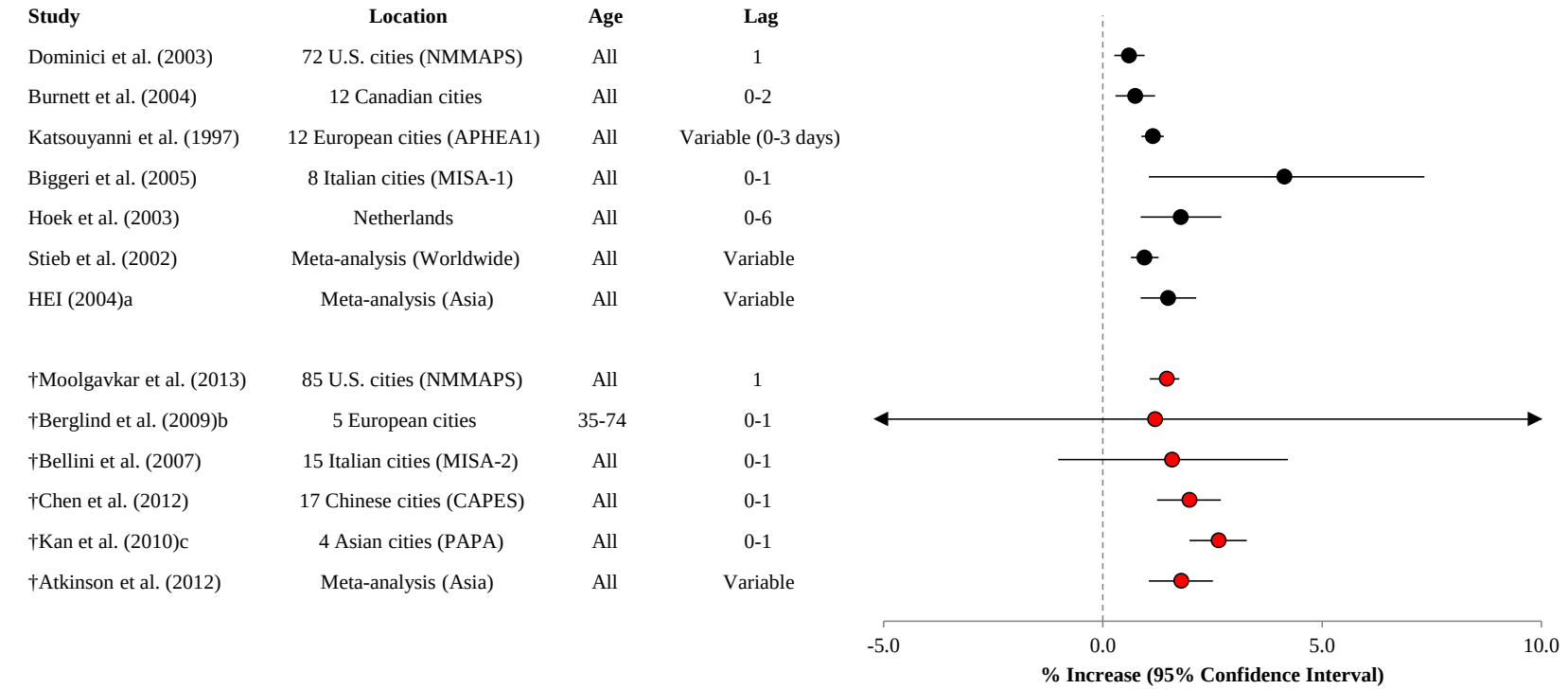
[h]The study period varied for each city, Bangkok: 1999−2003, Hong Kong: 1996−2002, and Shanghai and Wuhan: 2001−2004.

[i]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.

[j]Year defined represent the year in which studies were published that were included in the meta-analysis.

[k]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_X 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.

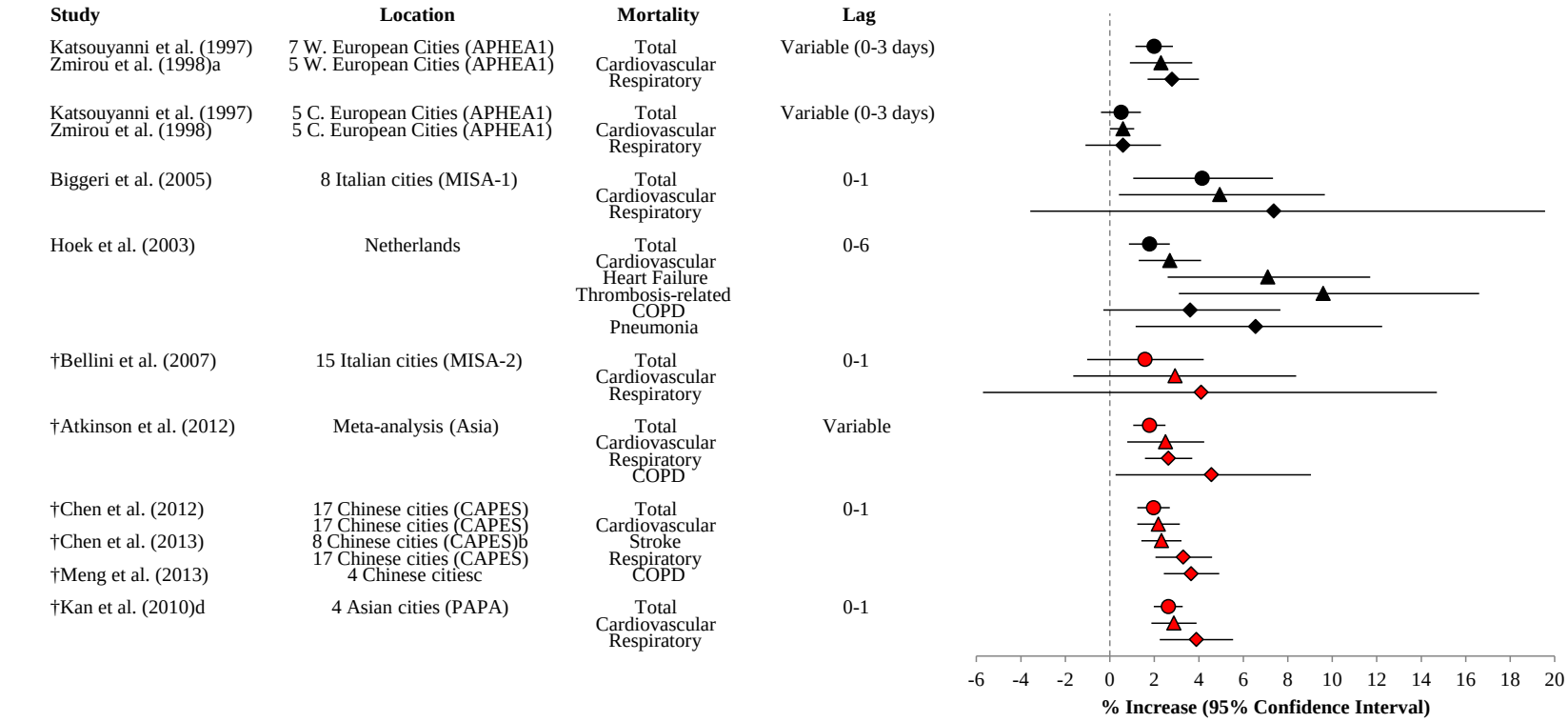
Note: † = studies published since the 2008 ISA for Sulfur Oxides;
a = Meta-analysis of Asian cities: South Korea, China, Hong Kong, Taipei, India, Singapore, Thailand, Japan (HEI, 2004);
b = Study was of myocardial infarction survivors therefore only included individuals 35+ (Berglind et al., 2009);
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, 2016l)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.

When focusing on specific causes of mortality, some studies evaluated in the 2008 SO_X ISA reported similar risk estimates across mortality outcomes [e.g., (Zmirou et al. (1998); Katsouyanni et al. (1997))], while others indicated larger risk estimates for respiratory mortality (Figure 5-18). However, a study conducted in the Netherlands by Hoek (2003) suggested that specific cardiovascular mortality outcomes have larger risk estimates compared to all cardiovascular, total, and respiratory-related mortality outcomes. Recent multicity mortality studies provide additional support indicating larger risk estimates for respiratory mortality compared to total and cardiovascular mortality. Additionally, the results from the studies depicted in Figure 5-18 lend additional support to the body of evidence indicating SO_2-induced respiratory effects presented in the 2008 SO_X ISA, as well as Section 5.2 of this ISA. Unlike the results reported in Hoek (2003), recent studies do not provide evidence indicating associations larger in magnitude for SO_2-related cardiovascular mortality compared to other mortality outcomes.

5.5.1.3 Potential Confounding of the Sulfur Dioxide-Mortality Relationship

A limitation of the studies evaluated in the 2008 SO_X ISA, was the relatively sparse analyses of the potential confounding effects of copollutants on the SO_2-mortality relationship (U.S. EPA, 2008d). The 2008 SO_X ISA specifically stated that the "potential confounding and lack of understanding regarding the interaction of SO_2 with copollutants" was one of the major limitations of the scientific literature that contributed to the conclusion that the evidence is "suggestive of a causal relationship" between short-term SO_2 exposures and mortality. Copollutant analyses conducted in recent studies further attempt to identify whether SO_2 has an independent effect on mortality. In addition to examining potential copollutant confounding, some studies have also examined whether the covariates included in statistical models employed to examine short-term SO_2 exposures and mortality adequately control for the potential confounding 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

In the 2008 SO_X ISA (U.S. EPA, 2008d), the analysis of potential copollutant confounding was limited to studies conducted by Dominici et al. (2003) within the U.S. as part of the National Morbidity Mortality Air Pollution Study (NMMAPS), Katsouyanni et al. (1997) in Europe as part of the Air Pollution and Health: A European Approach (APHEA-1) study, Hoek (2003) in the Netherlands, and Burnett et al. (2004) in 12 Canadian cities. Copollutant models in these studies focused on the effect of PM_{10}, BS or NO_2 on the SO_2-mortality relationship. The SO_2-mortality risk estimate was found to either increase (Hoek, 2003) or slightly attenuate (Dominici et al., 2003; Katsouyanni et al., 1997) in models with BS or PM_{10}; while risk estimates were reduced, but still remained positive in models with NO_2 (Burnett et al., 2004). Additionally, there was limited evidence from Burnett et al. (2000) of attenuation of the SO_2 association when $PM_{2.5}$ was included in the model. Recent multicity studies conducted in the U.S. and Asia have also examined whether there is evidence of copollutant confounding; however, similar to the literature base considered in the 2008 SO_X ISA (U.S. EPA, 2008d), the evaluation of copollutant confounding on the SO_2-mortality relationship has remained limited.

In a study of 108 U.S. cities using data from the NMMAPS for 1987−2000 (of which 85 had SO_2 data), Moolgavkar et al. (2013) used a subsampling approach where a random sample of 4 cities were removed from the 108 cities over 5,000 bootstrap cycles to examine associations between short-term air pollution concentrations and total mortality. This approach was used instead of the two-stage Bayesian hierarchical approach employed in the original NMMAPS analysis, which assumes that city-specific risk estimates are normally distributed around a national mean (Dominici et al., 2003). In a single-pollutant model using 100 df (~7 df/year, which is consistent with NMMAPS) to control for temporal trends, Moolgavkar et al. (2013) found a 1.5% (95% CI: 1.1, 1.7) increase in total (nonaccidental) mortality at lag 1 for a 10-ppb increase in 24-h avg SO_2 concentrations. In a copollutant analysis, the SO_2-mortality risk estimate remained robust and was similar in magnitude to the single pollutant result upon the inclusion of PM_{10} [1.3% (95% CI: 0.4, 2.0)]. An analysis of the influence of NO_2 on SO_2-mortality risk estimates was not conducted. The results of Moolgavkar et al. (2013) provide additional support for an SO_2-mortality association, as observed in Dominici et al. (2003), through an analysis that included more cities and used a different statistical approach than previously employed in multicity studies.

Additional multicity studies in Asia, conducted more extensive analyses of potential copollutant confounding by examining the effect of gaseous pollutants, in addition to

PM_{10}, on the SO_2-mortality relationship. In a study of 17 Chinese cities as part of the CAPES, (Chen et al., 2012b) examined associations between short-term SO_2 exposures and multiple mortality outcomes. The potential confounding effects of other pollutants on the SO_2-mortality relationship was assessed in copollutant models with PM_{10} and NO_2. Within the cities examined, SO_2 was found to be moderately correlated with PM_{10} (r = 0.49) and NO_2 (r = 0.65), respectively. The results from copollutant models (Table 5-40) indicate that although SO_2 risk estimates remained positive, they were attenuated by approximately 39−54% in models with PM_{10} and 65−79% in models with NO_2. These results are consistent with those observed in Chen et al. (2013), which focused on stroke mortality in a subset of the CAPES cities (i.e., eight cities) and also reported a similar reduction in SO_2 risk estimates in models with PM_{10} and NO_2.

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_2	---	1.98 (1.24, 2.69)	2.19 (1.24, 3.15)	3.31 (2.05, 4.59)
	+PM_{10}	1.10 (0.45, 1.76)	1.00 (0.08, 1.92)	2.03 (0.89, 3.17)
	+NO_2	0.42 (−1.56, 1.00)	0.47 (−0.47, 1.42)	1.16 (−0.03, 2.37)

CI = confidence interval; NO_2 = nitrogen dioxide; PM_{10} = particulate matter with a nominal aerodynamic diameter less than or equal to 10 µm.

Source: Adapted from Chen et al. (2012b).

Kan et al. (2010b) examined the association between short-term SO_2 exposures and mortality within four Asian cities as part of the PAPA study. Although the authors did not examine copollutant models in a combined four-city analysis, they did on a city-to-city basis. Similar to Chen et al. (2012b), in single pollutant models across cities and mortality outcomes, there was evidence of a consistent positive association (Figure 5-19). Of note is the highly imprecise estimate for Bangkok, but it is speculated that the variability in risk estimates for Bangkok could be attributed to the lack of variability in SO_2 concentrations in this city compared to the Chinese cities (standard deviation in SO_2 concentrations of 1.8 ppb; Chinese cities: 4.6−9.7 ppb) (Kan et al., 2010b). Across mortality outcomes and cities, SO_2-mortality risk estimates were attenuated, and in many cases null in copollutant models with NO_2. However, only in Shanghai and Wuhan were SO_2 correlations with NO_2 greater than 0.60 (r = 0.64 and 0.76, respectively). Similarly,

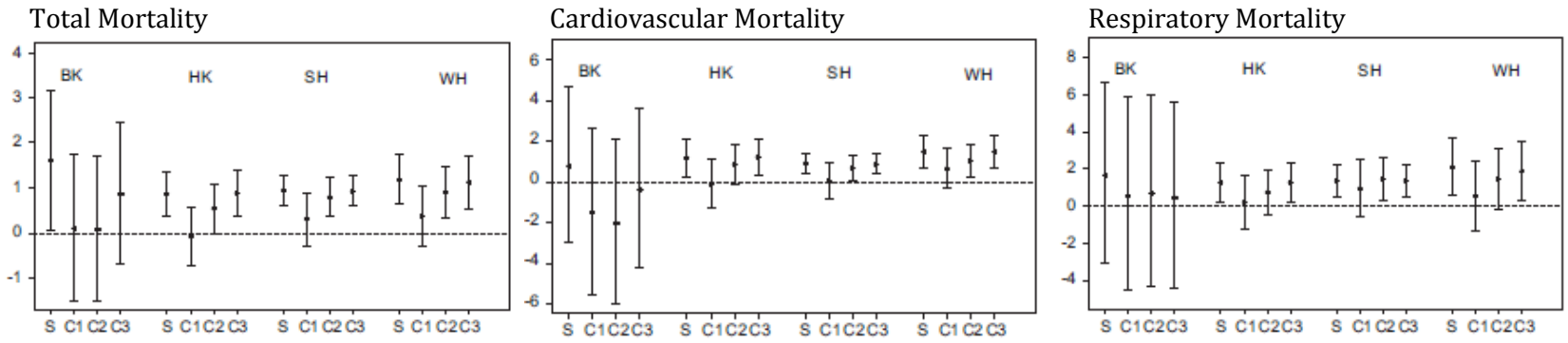
SO_2 was also found to be moderately correlated with PM_{10} in Shanghai (r = 0.67) and Wuhan (r = 0.65), but SO_2 mortality risk estimates, although attenuated, remained positive across cities. In copollutant models with O_3, SO_2 mortality risk estimates were almost unchanged compared to single-pollutant results.

Recent multicity studies add to the limited number of studies that have examined the potential confounding effects of copollutants on the SO_2-mortality relationship. Within the only recent U.S. study, Moolgavkar et al. (2013) reported that SO_2-mortality risk estimates remained robust in copollutant models with PM_{10}, which is consistent with Dominici et al. (2003), but these studies did not evaluate potential confounding by gaseous pollutants. Studies that examined gaseous pollutants, including Chen et al. (2012b) and Kan et al. (2010b) along with Burnett et al. (2004), found that in models with NO_2, SO_2 risk estimates were reduced to a large extent, but remained positive. However, the overall assessment of copollutant confounding remains limited, and it is unclear how the results observed in Asia translate to other locations, specifically due to the unique air pollution mixture and higher concentrations observed in Asian cities.

Modeling Approaches to Control for Weather and Temporal Confounding

Mortality risk estimates may be sensitive to model specification, which includes the selection of weather covariates to include in statistical models to account for the potential confounding effects of weather in short-term exposure studies. As such, some recent studies have conducted sensitivity analyses to examine the influence of alternative approaches to control for the potential confounding effects of weather on mortality risk estimates.

As part of the CAPES study, Chen et al. (2012b) examined the influence of alternative lag structures for controlling the potential confounding effects of temperature on the SO_2-mortality relationship by varying the lag structure of the temperature variable (i.e., lag 0, lag 0−3, or lag 0−7). The authors found that although the SO_2-mortality associations remained positive and statistically significant across alternative lag structures, risk estimates were attenuated as the number of lag days specified increased. The attenuation observed when using a temperature variable lagged from 0−3 to 0−7 days could be due to Chen et al. (2012b) only including one temperature term in the statistical model. This approach differs from that used in some of the seminal multicity studies (e.g., NMMAPS, APHEA) that include a temperature term averaged over multiple days (e.g., average of lag 1−3 days). A second temperature term is often included in models, in addition to a same-day temperature term, to account for (1) the potential delayed effects 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_{10}; C3 = sulfur dioxide + ozone.

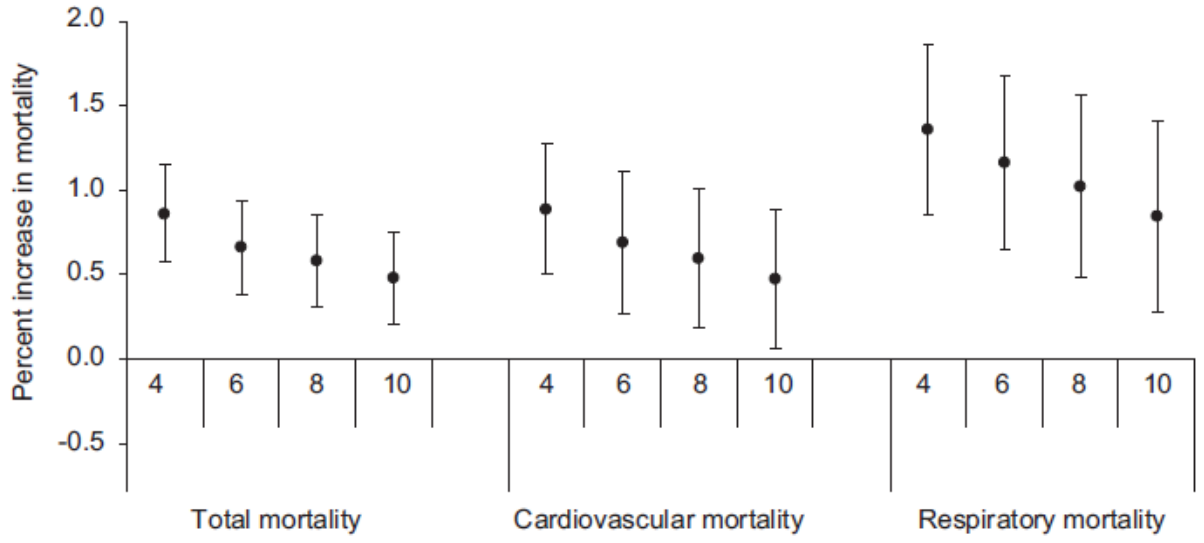
Source: Figure adapted from Kan et al. (2010b).

Figure 5-19 Percent increase in total, cardiovascular, and respiratory mortality associated with a 10 μg/m^3 (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_2-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_2 was slightly attenuated, but remained positive across the range of df examined (Figure 5-20.)

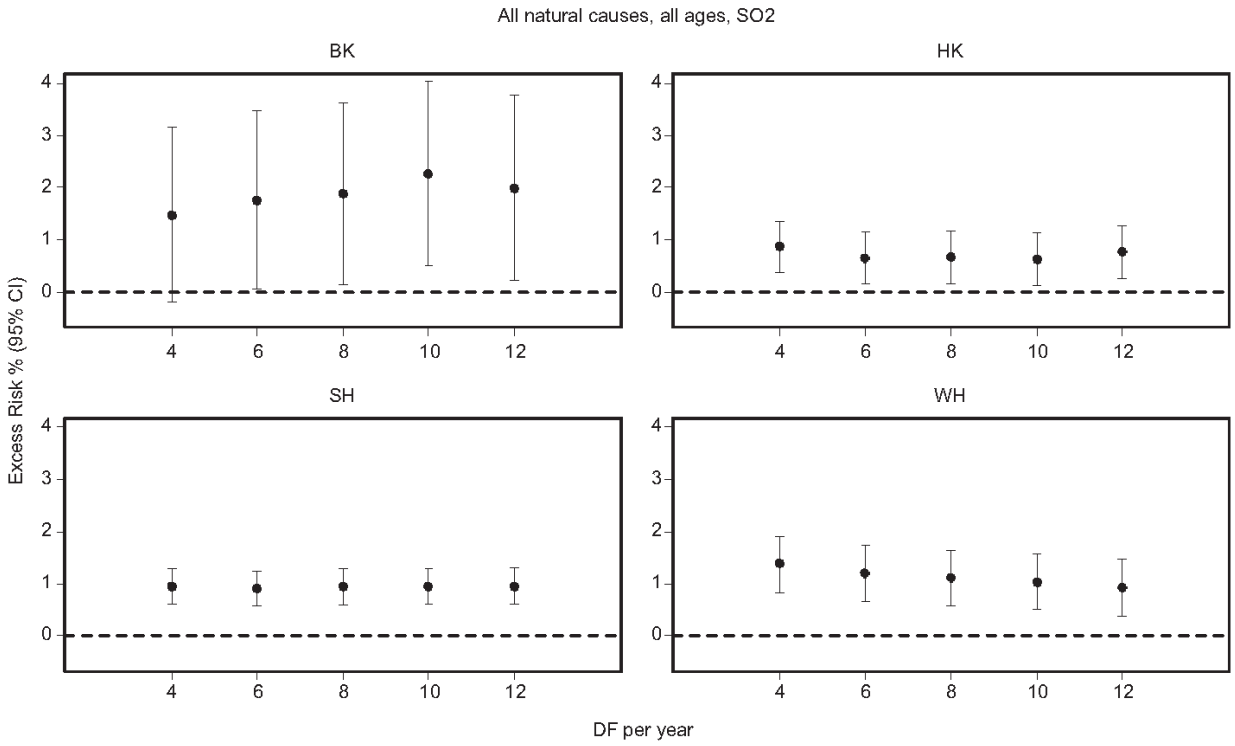


Source: (Chen et al., 2012b).

Figure 5-20 Percent increase in daily mortality associated with a 10 µg/m³ (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_2-mortality risk estimates

across cities. However, as depicted in Figure 5-20, and in some cities in Figure 5-21, using 4 df per year likely leads to inadequate control for temporal trends based on the 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^3 (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.

Unlike Chen et al. (2012b) and Kan et al. (2010b), which conducted a systematic analysis of the influence of increasing the df per year to control for temporal trends on the SO_2-mortality relationship, Moolgavkar et al. (2013) only compared models that used 50 df (~3.5 df per year) or 100 df (~7 df per year). Similar to both Chen et al. (2012b) and Kan et al. (2010b), the authors reported relatively similar SO_2-mortality risk estimates in both models [1.6% (95% CI: 0.9, 1.9) for a 10-ppb increase in 24-h avg SO_2 concentrations at lag 1 in the 50-df model and 1.5% (95% CI: 1.1, 1.7) in the 100 df model].

Overall, the studies that examined the effect of alternative approaches to control for the potentially confounding effects of weather and temporal trends report relatively consistent SO_2-mortality risk estimates across models. The results of these studies are further supported by an analysis conducted by Sacks et al. (2012), which examined whether the different modeling approaches (to control for both weather and temporal trends) used in a number of multicity studies (e.g., NMMAPS, APHEA) resulted in similar risk estimates when using the same data set. In all-year analyses focusing on cardiovascular mortality, SO_2-mortality risk estimates remained relatively stable across models using different weather covariates and a varying number of df per year (ranging from 4 to 8 df per year across models) to control for temporal trends. Although the results of Sacks et al. (2012) are consistent with Chen et al. (2012b), Kan et al. (2010b), and Moolgavkar et al. (2013) in all-year analyses, seasonal analyses indicate that differences in model specification may be more important when examining effects by season for some pollutants, such as SO_2.

5.5.1.4 Modification of the Sulfur Dioxide-Mortality Relationship

Individual- and Population-Level Factors

To date, a limited number of studies have examined potential factors that may increase the risk of SO_2-related mortality. In the 2008 SO_X ISA (U.S. EPA, 2008d), only Katsouyanni et al. (1997) examined potential effect measure modifiers and within the APHEA-2 study reported that geographic location may influence city-specific SO_2-mortality risk estimates. Similar to the 2008 SO_X ISA, only few recent multicity studies [i.e., (Chen et al. (2012b); Berglind et al. (2009); Wong et al. (2008b))] conducted extensive analyses of potential effect measure modifiers of the SO_2-mortality relationship as detailed in Chapter 6. These studies along with some single-city studies focusing on SO_2 and mortality provide limited evidence for potential differences in the risk of SO_2-related mortality by lifestage, sex, and socioeconomic status (SES).

Season and Weather

A limited number of studies have examined whether there is evidence of seasonal differences or that certain weather patterns modify in the SO_2-mortality relationship. In the 2008 SO_X ISA, only Zmirou et al. (1998) examined whether there are seasonal differences in SO_2-mortality risk associations in a subset of the APHEA-1 cities. The authors found some indication of larger associations in the summer months compared to the winter months.

Since the completion of the 2008 SO_X ISA, only a few recent studies have examined whether there are seasonal differences in SO_2-mortality associations, and these studies reported results consistent with Zmirou et al. (1998). In a study of 15 Italian cities (MISA-2), Bellini et al. (2007) is the only multicity study that examined whether there were seasonal differences in SO_2-mortality risk estimates. The authors found a similar pattern of associations across mortality outcomes with SO_2-mortality risk estimates being larger in the summer compared to the winter (total mortality: summer 3.2% vs. winter 1.4%; respiratory mortality: summer 12.0% vs. winter 4.1%; cardiovascular mortality: summer 9.4% vs. winter 1.6%). These results are consistent, with the only U.S.-based study that examined seasonal patterns in SO_2-mortality associations. In a study conducted in New York City focusing on cardiovascular mortality, Ito et al. (2011) reported larger risk estimates in the warm season [2.9% (95% CI: −1.2, 7.1)] compared to the cold season [0.0% (95% CI: −1.7, 1.8)] for a 10-ppb increase in 24-h avg SO_2 concentrations.

Instead of examining whether only specific seasons modify the SO_2-mortality association, Vanos et al. (2013) focused on weather patterns, referred to as synoptic weather types, in a study of 10 Canadian cities. Distinct weather types were identified by combining a number of variables including temperature, dew point temperature, sea level pressure, cloud cover, and wind velocity. Across the nine different synoptic weather types examined, for SO_2 Vanos et al. (2013) reported that mortality risk estimates in all age analyses tended to be larger in magnitude for dry versus moist weather types, particularly in warmer seasons.

Overall, the limited number of studies that conducted seasonal analyses reported initial evidence indicating larger SO_2-mortality associations during the summer season. Additionally, there is preliminary evidence that specific weather patterns in combination with certain seasons may modify the SO_2-mortality association.

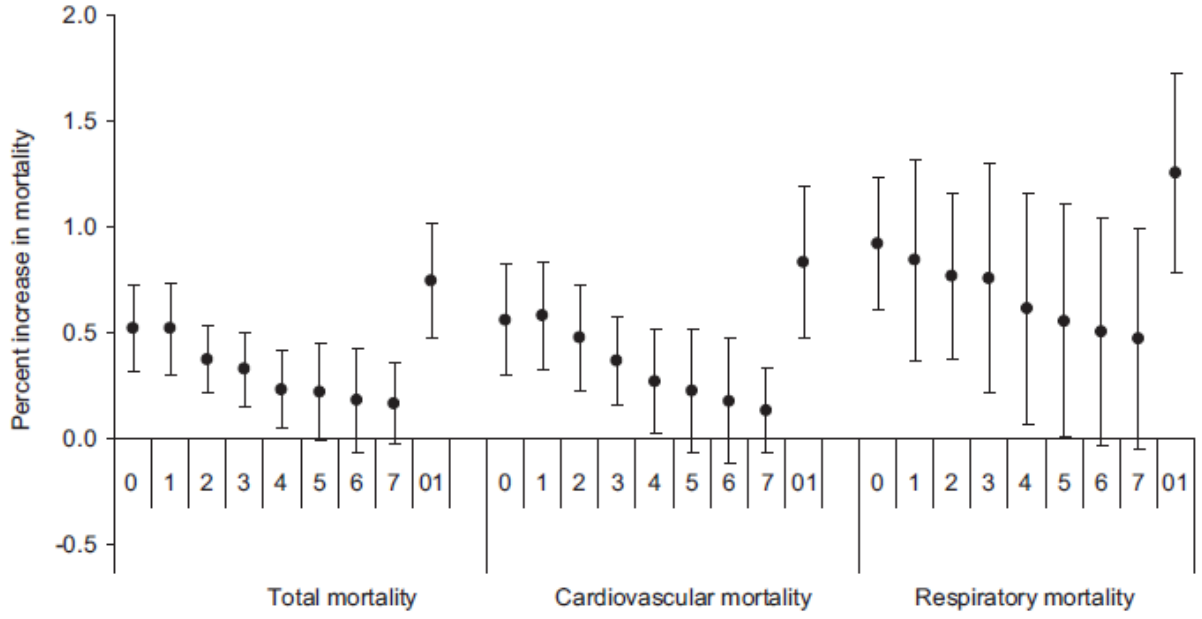
5.5.1.5 Sulfur Dioxide-Mortality Concentration-Response Relationship and Related Issues

Lag Structure of Associations

Of the studies evaluated in the 2008 SO_X ISA, the majority selected lag days a priori and did not extensively examine the lag structure of associations for short-term SO_2 exposures and mortality. These studies primarily focused on single- or multiday lags within the range of 0−3 days. However, in a study in the Netherlands, Hoek (2003) conducted more extensive analyses to examine whether there was evidence of immediate or delayed SO_2-mortality effects. The authors provided preliminary evidence of larger

SO_2-mortality risk estimates at a multiday lag of 0−6 days compared to a single-day lag (i.e., lag 1 day). Recent multicity studies have conducted additional analyses further examining the lag structure of associations for short-term SO_2 exposures and mortality.

Chen et al. (2012b), within the CAPES study, examined individual lag days (lag day 0 to 7) and a multiday lag of 0−1 days. As depicted in Figure 5-22, the authors found evidence of immediate SO_2 effects on mortality that slowly declined over time with the multiday lag of 0−1 days exhibiting the largest risk estimate across mortality outcomes.

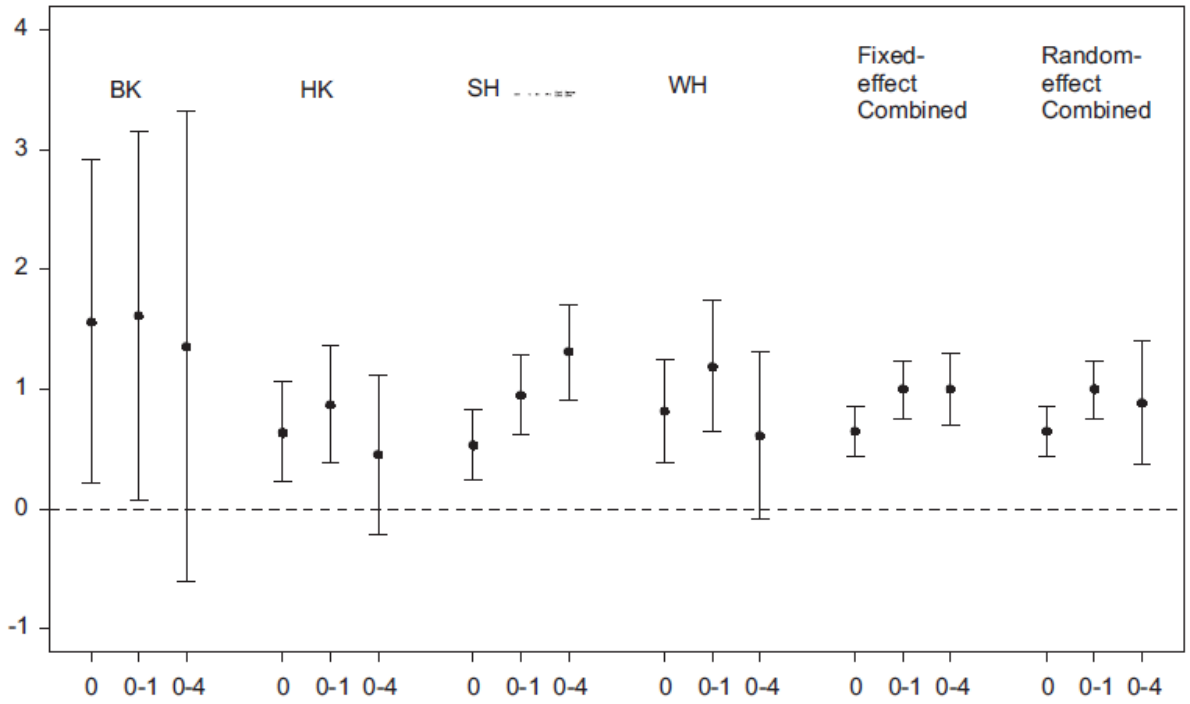


Source: (Chen et al., 2012b).

Figure 5-22 Percent increase in daily mortality associated with a 10 μg/m³ (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.

Kan et al. (2010b) also examined the lag structure of associations for the SO_2-mortality relationship within the PAPA study, but did not examine an extensive number of alternative lags, instead focusing on lag 0 and moving averages of 0−1 and 0−4 days (Figure 5-23). Unlike Chen et al. (2012b), which focused on the combined risk estimate across all cities, Kan et al. (2010b) examined the lag structure of associations both within individual cities and in a combined analyses across all PAPA cities. The results of both

the individual city and combined analyses are consistent with those observed by Chen et al. (2012b) in the CAPES study (i.e., the effect largest in magnitude across the lag days 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^3 (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.

Bellini et al. (2007) took a slightly different approach to examining the lag structure of associations in a study of 15 Italian cities (MISA-2) by focusing on whether there was evidence of mortality displacement. The authors reported larger SO_2-mortality effects at lag 0−15 days (3.8% for a 10-ppb increase in 24-h avg SO_2 concentrations) compared to a lag of 0−1 days (1.6%), which supports no evidence of mortality displacement. Additional information on the lag structure can be observed by examining the percent increase in mortality associated with short-term SO_2 exposures at each individual lag day of the lag 0−15-day model. The individual lag day results remained positive up to

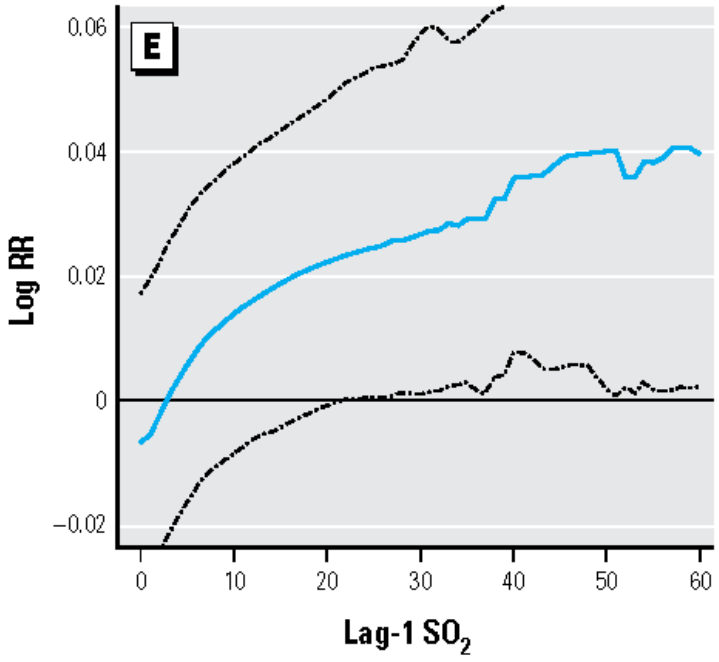
approximately lag day 10, which is consistent with the results from Chen et al. (2012b) (Figure 5-22). However, examining associations at single-day lags over a week, such as 10 days, may be uninformative due to potential inadequate control for weather variables at these longer durations. Additionally, these longer lags may not be biologically plausible due to controlled human exposure and animal toxicological studies demonstrating that effects attributed to SO_2 exposure are rather immediate (Section 5.2.1.2).

Overall, the limited analyses that have examined the lag structure of associations for short-term SO_2 exposures and mortality suggest that the greatest effects occur within the first few days after exposure (lag 0−1). However, the studies evaluated indicate that positive associations may persist longer although the magnitude of those effects diminishes over time.

Concentration-Response Relationship

The studies evaluated in the 2008 SO_X ISA (U.S. EPA, 2008d), as well as prior assessments, have not conducted formal analyses of the SO_2-mortality C-R relationship. Although limited in number, a few recent studies published since the completion of the 2008 SO_X ISA have conducted analyses to examine the shape of the SO_2-mortality C-R relationship and whether a threshold exists in the combined C-R relationship across multiple cities, or in an evaluation of single-city C-R relationships in the context of a multicity study. However, these studies have not conducted extensive analyses examining alternatives to linearity in the shape of the SO_2-mortality C-R relationship.

Using a subsampling approach, Moolgavkar et al. (2013) examined the shape of the C-R relationship between short-term air pollution exposures and mortality in the NMMAPS data set by applying a nonlinear function (i.e., natural splines with 6 df) to each pollutant. As demonstrated in Figure 5-24, the analysis conducted by Moolgavkar et al. (2013) provides support for a linear, no threshold relationship between short-term SO_2 exposures and total mortality.

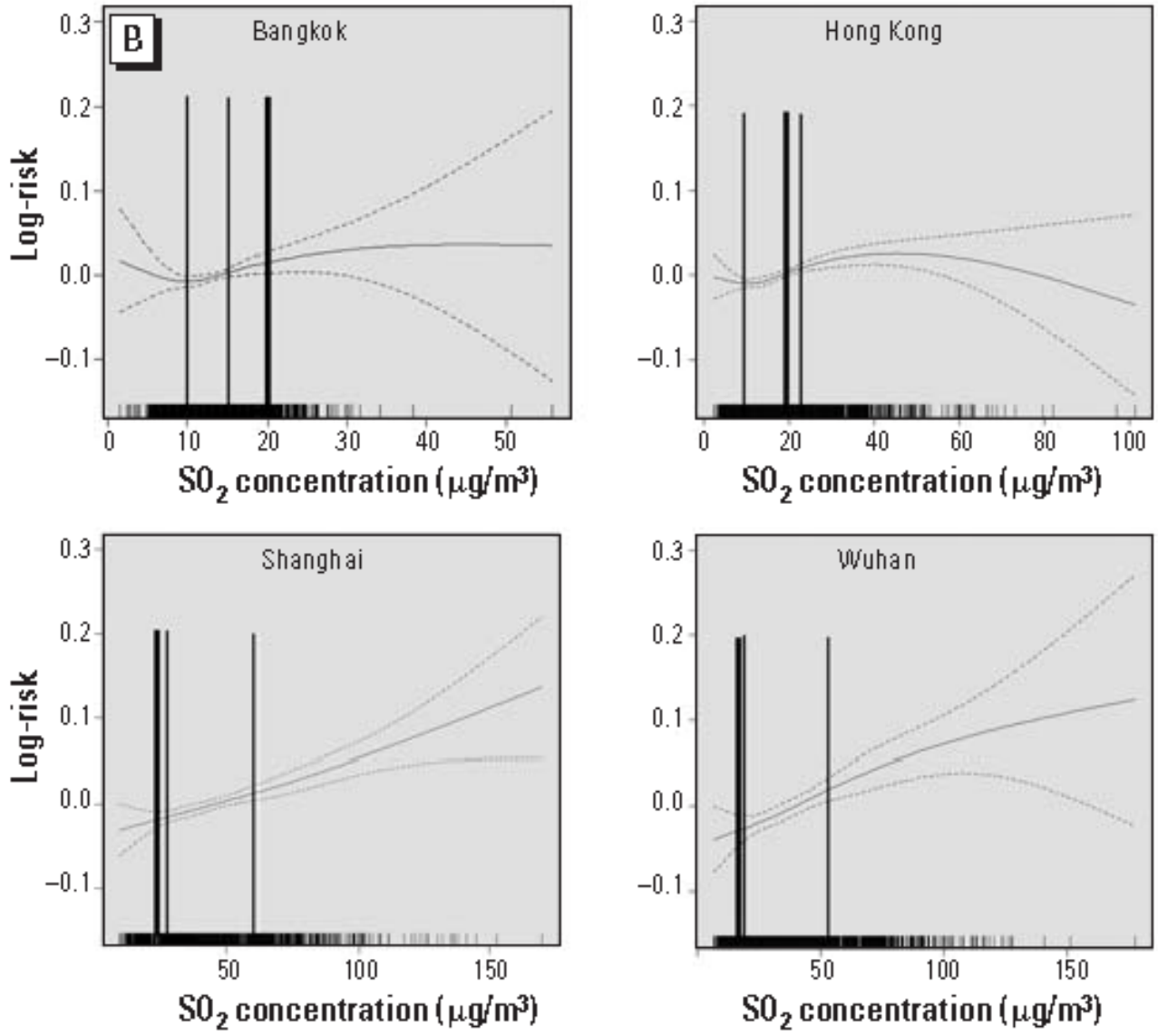


SO_2 = sulfur dioxide; RR = relative risk.
Note: Pointwise means and 95% confidence intervals adjusted for size of the bootstrap sample (d = 4).
Source: Reprinted from Environmental Health Perspectives; Moolgavkar et al. (2013).

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.

In the four-city PAPA study, Kan et al. (2010b) also examined the SO_2-mortality C-R relationship, but only focused on the shape of the C-R curve in each individual city. The C-R curve for the SO_2-mortality relationship was assessed by applying a natural spline smoother with 3 df to SO_2 concentrations. To examine whether the SO_2-mortality relationship deviates from linearity, the deviance between the smoothed (nonlinear) pollutant model and the unsmoothed (linear) pollutant model was examined. When examining the deviance, the authors only reported evidence for potential nonlinearity in Hong Kong. However, across the cities, there is evidence of a linear, no threshold, relationship within the range of SO_2 concentrations where the data density is the highest, specifically within the IQR (Figure 5-25). The linear relationship is most pronounced in Shanghai and Wuhan, with evidence of an inverted U-shape for Bangkok and Hong Kong. It should be noted, there is an overall lack of confidence in the shape of the C-R curve at the high end of the distribution of SO_2 concentrations in Bangkok and Shanghai due to the lower data density within this range of concentrations observed in both cities. A difficulty apparent in comparing the results across cities within Kan et al. (2010b) is

the drastically different range of SO_2 concentrations in Bangkok and Hong Kong compared Shanghai and Wuhan. However, the cities with similar distributions of SO_2 concentrations also have similar shapes to their respective SO_2-mortality C-R curves.



SO_2 = sulfur dioxide.

Note: *x*-axis is the average of lag 0−1 24-h avg SO_2 concentrations (μg/m^3). 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_2 concentrations within each city, while the thin vertical bar represents the World Health Organization guideline of 20 μg/m^3 for a 24-h avg time of SO_2.

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.

Both Moolgavkar et al. (2013) and Kan et al. (2010b) examined the shape of the SO_2-mortality C-R relationship by focusing on all-cause (total) mortality. Additional information on the shape of the C-R curve can be assessed in studies that focused on cause-specific mortality as discussed in Section 5.2.1.8 (respiratory mortality) and Section 5.3.1.9 (cardiovascular mortality). In studies of multiple Chinese cities, Meng et al. (2013) and Chen et al. (2013) examined the shape of the C-R relationship for mortality and short-term air pollution exposures on COPD and stroke mortality, respectively. In both studies the authors conducted similar analyses of linearity by examining the deviance between linear and spline models. Meng et al. (2013) and Chen et al. (2013) both found no evidence of a deviation in linearity in the SO_2-COPD mortality and SO_2-stroke mortality relationship, respectively (Figure 5-11 and Figure 5-16).

To date studies have conducted a rather limited exploration of potential alternatives to linearity when examining the shape of the C-R relationship, which in combination with the spatial and temporal variability in SO_2 concentrations, complicates the interpretation of the SO_2-mortality C-R relationship (Section 3.4.2.2. and Section 3.4.2.3.). With these limitations in mind, studies that examined the C-R relationship provide evidence that indicates a linear, no threshold relationship between short-term SO_2 concentrations and mortality, specifically within the range of SO_2 concentrations where the data density is highest. Some differences in the shape of the curve were observed on a city-to-city basis, which is consistent with the mortality C-R results that have been reported for other criteria air pollutants.

5.5.1.6 Summary and Causal Determination

Recent multicity studies evaluated since the completion of the 2008 SO_X ISA continue to provide consistent evidence of positive associations between short-term SO_2 exposures and total mortality. Although the body of evidence is larger, key uncertainties and data gaps still remain, which contribute to the conclusion that the evidence for short-term SO_2 exposures and total mortality is suggestive of, but not sufficient to infer, a causal relationship. This conclusion is consistent with that reached in the 2008 SO_X ISA (U.S. EPA, 2008d). Recent multicity studies evaluated have further informed key uncertainties and data gaps in the SO_2-mortality relationship identified in the 2008 SO_X ISA including confounding, modification of the SO_2-mortality relationship, potential seasonal differences in SO_2-mortality associations, and the shape of the SO_2-mortality C-R relationship. However, questions remain regarding whether SO_2 has an independent effect on mortality, which can be attributed to: (1) the limited number of studies that examined potential copollutant confounding, (2) the relative lack of copollutant analyses with $PM_{2.5}$, (3) and the evidence indicating attenuation of SO_2-mortality associations in

copollutant models with NO_2 and PM_{10}. Additionally, all of the studies evaluated averaged SO_2 concentrations over multiple monitors and used a 24-h avg exposure metric when assigning exposure, which may not adequately capture the spatial and temporal variability in SO_2 concentrations (Section 3.4.2.2. and Section 3.4.2.3). While correlations between 24-h avg and 1-h max SO_2 concentrations are high ($r > 0.75$) at most monitors, lower correlations may occur at some monitors and in individual studies which can add uncertainty to the ability of 24-h avg metrics to capture peak SO_2 concentrations. This section describes the evaluation of evidence for total mortality, with respect to the causal determination for short-term exposures to SO_2 using the framework described in Table II of the Preamble to the ISAs (U.S. EPA, 2015b). The key evidence, 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[a]	Key Evidence[b]	Key References[b]	SO_2 Concentrations Associated with Effects[c]
Consistent epidemiologic evidence from multiple, high quality studies at relevant SO_2 concentrations	Increases in mortality in multicity studies conducted in the U.S., Canada, Europe, and Asia	Section 5.5.1.2 Figure 5-15	Mean 24-h avg: U.S., Canada, South America, Europe: 0.4−28.2[e] ppb Asia: 0.7−>200 ppb Table 5-39
Uncertainty regarding potential confounding by copollutants	The magnitude of SO_2 associations remained positive, but were reduced in copollutant models with PM_{10} and NO_2. No studies examined copollutant models with $PM_{2.5}$. SO_2 generally exhibits low to moderate correlations with other NAAQS pollutants at collocated monitors, and attenuation of SO_2− mortality association may be a reflection of spatial variability among the pollutants.	Section 5.5.1.3 Section 3.4.3	
Uncertainty regarding exposure measurement error	U.S. studies that examine the association between short-term SO_2 exposures and mortality rely on single or the average of multiple monitors in an area and SO_2 generally has low to moderate spatial correlations across urban geographical scales.	Section 3.4.2.2	

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[a]	Key Evidence[b]	Key References[b]	SO_2 Concentrations Associated with Effects[c]
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_2 on cardiovascular effects contributing to limited coherence and biological plausibility for SO_2-related cardiovascular mortality, which comprises ~35% of total mortality.[d]	Section 5.3.1.11 Table 5-31	
	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_2 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_2-related respiratory mortality, which comprises ~8% of total mortality.[d]	Section 5.2.1.8 Table 5-21	

ED = emergency department; NAAQS = National Ambient Air Quality Standards; NO_2 = nitrogen dioxide; PM_{10} = particulate matter with a nominal aerodynamic diameter less than or equal to 10 μm; SO_2 = sulfur dioxide.

[a]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).

[b]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.

[c]Describes the SO_2 concentrations with which the evidence is substantiated.

[d]Statistics taken from American Heart Association (2011).

[e]The value of 28.2 represents the median concentration from Katsouyanni et al. (1997).

Collectively, the evidence from recent multicity studies of short-term SO_2 exposures and mortality consistently demonstrate positive SO_2-mortality associations in single-pollutant models. In the limited number studies that conducted copollutant analysis, correlations between SO_2 and other pollutants were low ($r < 0.4$) to moderate ($r = 0.4–0.7$). Although SO_2-mortality associations remain positive in copollutant models with PM_{10} and NO_2 they were often attenuated to a large degree, questioning the independent effect of SO_2 on mortality. However, SO_2 is more spatially variable than other pollutants as reflected in the generally low to moderate spatial correlations across urban geographical scales

(Section 3.4.2.2); therefore, the attenuation in SO_2 associations in copollutant models may be a reflection of the different degree of exposure error across pollutants (Section 3.4.3). It is important to note, the majority of recent studies that examined potential copollutant confounding have been conducted in Asian countries where correlations between pollutants may be higher, possibly limiting the generalizability of results to other study areas where SO_2 concentrations along with the concentrations of other air pollutants are much lower. This is reflected in the results of Moolgavkar et al. (2013) in a U.S. multicity study where there was very little evidence of attenuation of the SO_2-mortality association in copollutant models with PM_{10}; whereas, the multicity studies conducted in Asian cities showed a rather pronounced reduction in SO_2 associations. In addition to copollutant analyses, recent studies examined the influence of the extent of temporal adjustment and the lag structure for weather covariates on the SO_2-mortality association. When examining, the extent of temporal adjustment, multiple studies reported similar SO_2-mortality associations across a range of degrees of freedom per year. Only Chen et al. (2012b) examined the lag structure for weather covariates, specifically temperature, and found evidence of a difference in SO_2-mortality associations as the number of lag days increased, but this could be attributed to the analysis being based on only one covariate for temperature.

An examination of factors that may contribute to increased risk of SO_2-related mortality, as discussed in Chapter 6, found evidence indicating that older adults (≥65 years of age) may be at increased risk with very limited evidence of potential differences by sex and socioeconomic status. In the 2008 SO_X ISA, initial evidence suggested potential seasonal differences in SO_2-mortality associations, particularly in the summer months. A recent multicity study conducted in Italy along with single-city studies conducted in the U.S. add to this initial body of evidence suggesting larger associations during the summer or warm months. Preliminary evidence indicates that not only season, but season in combination with specific weather patterns may modify the SO_2-mortality association. Additionally, an examination of different modeling approaches provides evidence that the magnitude of the seasonal association may depend on the modeling approach employed to control for the potential confounding effects of weather (Sacks et al., 2012).

Those studies that examined the lag structure of associations for the SO_2-mortality relationship generally observed that there is evidence of an immediate effect (i.e., lag 0 to 1 days) of short-term SO_2 exposures on mortality. Multicity studies conducted in the U.S. and Asia have examined the shape of the C-R relationship and whether a threshold exists in both a multi- and single-city setting. These studies have used different statistical approaches and consistently demonstrated a linear relationship with no evidence of a threshold within the range of SO_2 concentrations where the data density is highest. The evidence of linearity in the SO_2-mortality C-R relationship is further supported by

studies of cause-specific mortality as detailed in Section 5.2.1.8 (respiratory mortality) and Section 5.3.1.9 (cardiovascular). However, to date, studies have not conducted extensive analyses exploring alternatives to linearity when examining the shape of the SO_2-mortality C-R relationship.

Overall, recent epidemiologic studies build upon and support the conclusions of the 2008 SO_X ISA for total mortality. However, the biological mechanism that could lead to mortality as a result of short-term SO_2 exposures has not been clearly characterized. This is evident when evaluating the underlying health effects (i.e., cardiovascular effects in Section 5.3 and respiratory effects in Section 5.2) that could lead to cardiovascular (~35% of total mortality) and respiratory (~9% of total mortality) mortality, the components of total mortality most thoroughly evaluated (Hoyert and Xu, 2012). For cardiovascular effects the evidence is "inadequate to infer a causal relationship" with exposure to short-term SO_2 concentrations. An evaluation of epidemiologic studies that examined the relationship between short-term SO_2 exposure and cardiovascular effects found a number positive associations but the evidence was not entirely consistent. Within the collective body of evidence for cardiovascular effects, important uncertainties remain especially regarding disentangling whether there is an independent effect of SO_2 on cardiovascular effects, which is the same uncertainty in total mortality studies. Overall, this evidence complicates the interpretation of the relationship between SO_2 and cardiovascular mortality." For respiratory effects the evidence indicates a causal relationship for short-term SO_2 exposures. The strongest evidence for respiratory effects is from studies examining SO_2-related asthma exacerbations, specifically controlled human exposure studies demonstrating respiratory effects (i.e., respiratory symptoms and decreased lung function) (Section 5.2.1.2) in people with asthma in response to short term, generally 5−10-minutes, SO_2 exposures. The results from controlled human exposure studies are generally supported by epidemiologic studies reporting respiratory-related morbidity including hospital admissions and ED visits, specifically for asthma. However, the biological mechanism that explains the continuum of effects that could lead to respiratory-related mortality remains unclear. Additionally, it is important to note epidemiologic studies that examine the association between short-term SO_2 exposures and mortality rely on single or the average of multiple monitors over an area to assign exposure. Therefore, the exposure assessment approach used in the mortality studies may contribute to exposure measurement error and underestimate associations observed due to the spatially heterogeneous distribution of SO_2 concentrations over a wide area (Section 3.4.2.2). In conclusion, the consistent positive associations observed across various multicity studies is limited by the uncertainty due to whether SO_2 is independently associated with total mortality, the representativeness of monitors and the 24-h avg SO_2 exposure metric in capturing the spatial and temporal variability in exposure to SO_2 (Section 3.4.2.2 and Section 3.4.2.3), and the uncertainty in the

biological mechanism that could lead to SO_2-induced mortality (Section 4.3). Collectively, this body of evidence is suggestive, but not sufficient to conclude there is a causal relationship between short-term SO_2 exposure and total mortality.

5.5.2 Long-Term Exposure

In past reviews, a limited number of epidemiologic studies have assessed the relationship between long-term exposure to SO_2 and mortality in adults. The 2008 SO_X ISA concluded that the scarce amount of evidence was "inadequate to infer a causal relationship" (U.S. EPA, 2008d). The 2008 SO_X ISA identified concerns as to whether the observed associations were due to SO_2 alone, or if sulfate or other particulate SO_X, such as H_2SO_4, or PM indices could have contributed to these associations. The possibility that the observed effects may not be due to SO_2, but other constituents that come from the same source as SO_2, or that PM may be more toxic in the presence of SO_2 or other components associated with SO_2, could not be ruled out. Overall, a lack of consistency across studies, inability to distinguish potential confounding by copollutants, and uncertainties regarding the geographic scale of analysis limited the interpretation of the causal relationship between long-term exposure to SO_2 and mortality.

This section includes a review of the evidence for an association between long-term exposure to SO_2 and mortality, integrating evidence presented in previous NAAQS reviews with evidence that is newly available to this review. The evidence in this section will focus on epidemiologic studies because experimental studies of long-term exposure and mortality are generally not conducted. However, this section will draw from the morbidity evidence presented for different health endpoints across the scientific disciplines (i.e., animal toxicological, controlled human exposure studies, and epidemiology) to support the association observed for cause-specific mortality. Studies are discussed by geographic region, with U.S. studies discussed in Section 5.5.2.1, European studies in Section 5.5.2.2, and Asian studies in Section 5.5.2.3. Section 5.5.2.4 describes studies that evaluated the SO_2-mortality relationship over small geographic scales. A brief summary of the studies included in these sections can be found in Table 5-42.

Table 5-42 Summary of studies of long-term exposure and mortality.

Study	Location Years	Mean SO_2 ppb	Exposure Assessment	Correlation with Other Pollutants	Selected Effect Estimates (95% CI)[a]
†Hart et al. (2011)	U.S. (SO_2: 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)
Krewski et al. (2000)	U.S. HSC: (SO_2: 1977−1985; follow-up: 1974−1991) ACS: (SO_2: 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: $PM_{2.5}$: 0.85 SO_4: 0.85 NO_2: 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)
Pope et al. (2002)	U.S. (SO_2: 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)
†Lipfert et al. (2009)	U.S. (SO_2: 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_X: 0.65 SO_4^{2-}: 0.79	All cause: 1.02 (1.01, 1.03)
†Krewski et al. (2009)	U.S. (SO_2: 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_2 ppb	Exposure Assessment	Correlation with Other Pollutants	Selected Effect Estimates (95% CI)[a]
Lipfert et al. (2006a)	U.S. (SO_2: 1999−2001; follow-up: 1997−2001)	16.3	County-level "peak" concentrations	Subject-weighted: $PM_{2.5}$: 0.71 NO_2: 0.41 Peak O_3: 0.21 Peak CO: 0.41 SO_4^{2-}: 0.77 OC: 0.34 EC: −0.13	All cause: 0.99 (0.97, 1.01)
Abbey et al. (1999)	U.S. (SO_2: 1966−1992; follow-up: 1977−1992)	5.6 IQR: 3.7	ZIP code-level mo averages cumulated and averaged over time	Mean concentration: PM_{10}: 0.31 O_3: 0.09 SO_4: 0.68 When exceeding 100 ppb (O_3) or 100 µg/m^3 (PM_{10}) PM_{10}: −0.05 O_3: 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)
Beelen et al. (2008b)	Netherlands (SO_2: 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)
Nafstad et al. (2004)	Norway (SO_2: 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)
Filleul et al. (2005)	France (SO_2: 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_2 −0.10	All cause: 1.01 (0.99, 1.04) Lung cancer: 0.99 (0.90, 1.09)
†Bentayeb et al. (2015)	France (SO_2: 1989−2008; follow-up: 1989−2013)	2.3	Annual concentrations from CHIMERE chemical-transport model	O_3: −0.13 $PM_{2.5}$: 0.58 PM_{10}: 0.57 $PM_{10-2.5}$: 0.30 NO_2: 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_2 ppb	Exposure Assessment	Correlation with Other Pollutants	Selected Effect Estimates (95% CI)[a]
†Hansell et al. (2016)	England (SO_2: 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)
†Carey et al. (2013)	England (SO_2: 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_2)	PM_{10}: 0.45 NO_2: 0.37 O_3: −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)
†Ancona et al. (2015)	Rome, Italy (SO_X: 2001−2010; follow-up: 2001−2010)	2.5 µg/m^3 SO_X SD: 0.9	Lagrangian particle dispersion model (SPRAY Ver. 5) used SO_X as exposure marker for petrochemical refinery emissions	PM_{10}: 0.81 H_2S: 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)
†Cao et al. (2011)	China (SO_2: 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_2 ppb	Exposure Assessment	Correlation with Other Pollutants	Selected Effect Estimates (95% CI)[a]
†Chen et al. (2016)	China (SO_2: 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)
†Dong et al. (2012)	China (SO_2: 1998−2009; follow-up: 1998−2009)	23.9 SD: 5.7	1-yr avg from five monitors		Respiratory: 1.05 (0.96, 1.16)
†Zhang et al. (2011)	Shenyang, China (SO_2: 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)
†Katanoda et al. (2011)	Japan (SO_2: 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)
Elliott et al. (2007)	Great Britain (SO_2: 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)
†Bennett et al. (2014)	Warwickshire, U.K. (SO_2: 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_2 ppb	Exposure Assessment	Correlation with Other Pollutants	Selected Effect Estimates (95% CI)[a]
†Wang et al. (2009)	Brisbane, Australia (SO_2: 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)
†Wang et al. (2014a)	China (SO_2: 2004−2010; life table: 2010)	46.31	Annual average across monitoring stations in 85 city regions		Life expectancy: 10-µg/m^3 increase in SO_2 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_2S = 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_2 = nitrogen dioxide; NO_X = the sum of NO and NO_2; NR = not reported; O_3 = ozone; OC = organic carbon; $PM_{2.5}$ = particulate matter with a nominal aerodynamic diameter less than or equal to 2.5 µm; PM_{10} = particulate matter with a nominal aerodynamic diameter less than or equal to 10 µm; $PM_{10-2.5}$ = 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_2 = sulfur dioxide; SO_4 = sulfate; SO_4^{2-} = sulfate; SO_X = oxides of sulfur; SPM = suspended particulate matter; TSP = total suspended solids.

[a]Effect estimates are standardized per 5-ppb increase in SO_2 concentrations.

†Studies published since the 2008 ISA for Sulfur Oxides.

5.5.2.1 U.S. Cohort Studies

A number of longitudinal cohort studies have been conducted in the U.S. and have found small, statistically significant positive associations between long-term exposure to SO_2 and total mortality (Hart et al., 2011; Lipfert et al., 2009; Pope et al., 2002; Krewski et al., 2000). The body of evidence is smaller and less consistent when these studies examine cause-specific mortality, although Hart et al. (2011) observed positive, yet imprecise associations with respiratory, lung cancer, and cardiovascular mortality. In the Trucking Industry Particle Study, Hart et al. (2011) used the work records for over 50,000 men employed in four U.S. trucking companies to identify all-cause and cause-specific mortality. Occupational exposures were assigned based on job title, while exposure to ambient air pollution (i.e., PM_{10}, SO_2, and NO_2 averaged over the study period) were determined using spatial smoothing and geographic information system (GIS)-based covariates based on residential address. All three pollutants were independently associated with all-cause mortality, with central estimates the highest for the association with NO_2 and lowest for the association with PM_{10}. Both NO_2 and SO_2

were positively associated with lung cancer, cardiovascular disease, and respiratory disease mortality, and negatively associated with COPD mortality. Correlation coefficients between SO_2 and other measured air pollutants were not reported, making it difficult to evaluate for the potential of copollutants confounding on the associations attributed to SO_2. There was no evidence of confounding by occupational exposures (based on job-title).

The Harvard Six Cities study is a prospective cohort study of the effects of air pollution with the main focus on PM components in six U.S. cities and provides limited evidence for an association between mortality and exposure to SO_2. Cox proportional hazards regression was conducted with data from a 14- to 16-year follow-up study of 8,111 adults in the six cities. Dockery et al. (1993) reported that lung cancer and cardiopulmonary mortality were more strongly associated with the concentrations of inhalable and fine PM and sulfate particles than with the levels of TSP, SO_2, NO_2, or acidity of the aerosol. Krewski et al. (2000) conducted a sensitivity analysis of the Harvard Six Cities study and examined associations between gaseous pollutants (i.e., O_3, NO_2, SO_2, and CO) and mortality, observing positive associations between SO_2 and total mortality and cardiopulmonary deaths. In this data set SO_2 was highly correlated with $PM_{2.5}$ (r = 0.85), sulfate (r = 0.85), and NO_2 (r = 0.84), making it difficult to attribute the observed associations to an independent effect of SO_2.

Pope et al. (1995) investigated associations between long-term exposure to PM and the mortality outcomes in the ACS cohort and provides limited evidence for an association between exposure to SO_2 and mortality. Ambient air pollution data from 151 U.S. metropolitan areas in 1981 were linked with individual risk factors in 552,138 adults who resided in these areas when enrolled in the prospective study in 1982. Death outcomes were ascertained through 1989. Gaseous pollutants were not analyzed in the original analysis. Extensive reanalysis of the ACS data, augmented with additional gaseous pollutants data, showed positive associations between mortality and SO_2, but not for the other gaseous pollutants (Jerrett et al., 2003; Krewski et al., 2000). Pope et al. (2002) extended analysis of the ACS cohort with double the follow-up time (to 1998) and triple the number of deaths compared to the original study (Pope et al., 1995). Both $PM_{2.5}$ and SO_2 were associated with all the mortality outcomes, although only SO_2 was associated with the deaths attributable to "all other causes." The association of SO_2 with mortality for "all other causes" makes it difficult to interpret the effect estimates due to a lack of biological plausibility for this association. More recently, Krewski et al. (2009) conducted an extended reanalysis of the study conducted by Pope et al. (2002), including examination of ecologic covariates (e.g., education attainment, housing characteristics, income) and evaluation of exposure windows. The inclusion of ecologic covariates generally resulted in increased risk estimates, with the greatest effect on mortality from

IHD. The authors also evaluated individual time-dependent exposure profiles to examine whether there is a critical exposure time window most strongly associated with mortality from ambient air pollution. The time window immediately preceding death (1−5 years) produced the strongest effects for mortality associated with exposure to SO_2, while later time windows (6−10 years and 11−15 years) generally showed null associations between SO_2 and mortality.

Lipfert et al. (2000a) conducted an analysis of a national cohort of ~70,000 male U.S. military veterans who were diagnosed as hypertensive in the mid-1970s and were followed up for about 21 years (up to 1996) and provides scant evidence for an association between exposure to SO_2 and mortality. This cohort was 35% black and 57% of the cohort were current smokers (81% of the cohort had been smokers at one time). $PM_{2.5}$, PM_{10}, $PM_{10-2.5}$, TSP, sulfate, CO, O_3, NO_2, SO_2, and lead (Pb) were examined in these analyses. The county of residence at the time of entry to the study was used to estimate exposures. Four exposure periods (from 1960 to 1996) were defined, and deaths during each of the three most recent exposure periods were considered. The results for SO_2 as part of their preliminary screening were generally null. Lipfert et al. (2000a) noted that Pb and SO_2 were not found to be associated with mortality, thus, were not considered further. They also noted that the pollution effect estimates were sensitive to the regression model specification, exposure periods, and the inclusion of ecological and individual variables. The authors reported that indications of concurrent mortality risks were found for NO_2 and peak O_3. In a subsequent analysis, Lipfert et al. (2006b) examined associations between traffic density and mortality in the same cohort, extending the follow-up period to 2001. As in their previous study (Lipfert et al., 2000a), four exposure periods were considered but included more recent years, and reported that traffic density was a better predictor of mortality than ambient air pollution variables with the possible exception of O_3. The log-transformed traffic density variable was only weakly correlated with SO_2 (r = 0.32) and $PM_{2.5}$ (r = 0.50) in this data set. Lipfert et al. (2006a) further extended analysis of the veterans' cohort data to include the U.S. EPA's Speciation Trends Network (STN) data, which collected chemical components of $PM_{2.5}$. They analyzed the STN data for 2002, again using county-level averages. $PM_{2.5}$ and gaseous pollutants data for 1999 through 2001 were also analyzed. As in the previous study (Lipfert et al., 2006b), traffic density was the most important predictor of mortality, but associations were also observed for elemental carbon, vanadium, nickel, and nitrate. Ozone, NO_2, and PM_{10} also showed positive but weaker associations. Once again, no associations were observed between long-term exposure to SO_2 and mortality. Lipfert et al. (2009) re-examined these associations, this time averaging the exposure variables over the entire follow-up period (1976−2001). For this exposure period, they observed positive associations between SO_2 and mortality. When the data set was stratified by county-level traffic density, the SO_2 association with mortality was stronger in the counties with high

density traffic, and attenuated to near null in the counties with lower traffic density. The fact that the association between long-term exposure to SO_2 and mortality is only observed in areas where traffic density has been characterized as high, along with the moderate to strong correlations between SO_2 and other traffic-related pollutants (e.g., $PM_{2.5}$, NO_2, NO_X, EC) in these analyses, makes it difficult to discern whether these associations are truly attributable to SO_2, or could be due to some other traffic-related pollutant or mixture of pollutants.

Abbey et al. (1999) investigated associations between long-term ambient concentrations of PM_{10}, sulfate, SO_2, O_3, and NO_2 and mortality in a cohort of 6,338 nonsmoking California Seventh-Day Adventists. Monthly indices of ambient air pollutant concentrations at 348 monitoring stations throughout California were interpolated to ZIP codes according to home or work location of study participants, cumulated, and then averaged over time. They reported associations between PM_{10} and total mortality for males and nonmalignant respiratory mortality for both sexes. SO_2 was positively associated with total mortality for males but not for females. Generally, null associations were observed for cardiopulmonary deaths and respiratory mortality for both males and females.

Overall, the majority of the limited evidence informing the association between long-term exposure to SO_2 and mortality from U.S. cohort studies was included in the 2008 SO_X ISA. A recent cohort study of male truck drivers (Hart et al., 2011) provided some additional evidence for an association between long-term exposure to SO_2 and both respiratory mortality and total mortality, while updates to the ACS (Krewski et al., 2009) and Veterans (Lipfert et al., 2009) cohort studies provides some limited evidence for an association with total mortality, although none of these recent studies help to resolve the uncertainties identified in the 2008 SO_X ISA related to copollutant confounding or the geographic scale of the analysis.

5.5.2.2 European Cohort Studies

A number of European cohort studies examined the association between both total mortality and cause-specific mortality and SO_2 concentrations, and found generally inconsistent results. Beelen et al. (2008b) analyzed data from the Netherlands Cohort Study on Diet and Cancer with 120,852 subjects. Traffic-related pollutants (BS, NO_2, SO_2, $PM_{2.5}$), and four types of traffic-exposure estimates were analyzed. While the local traffic component was estimated for BS, NO_2, and $PM_{2.5}$, no such attempt was made for SO_2 because there was "virtually no traffic contributions to this pollutant." Thus, only "background" SO_2 levels were reflected in the exposure estimates. Traffic intensity on the

nearest road was associated with all-cause mortality and a larger RR was observed for respiratory mortality. Results were similar for BS, NO_2 and $PM_{2.5}$, but no associations were observed for SO_2.

Several studies noting declining SO_2 concentrations during the follow-up period (from the mid-1970s through the mid-1990s) did not observe positive associations with mortality. Nafstad et al. (2004) linked data from 16,209 males (aged 0 to 49 years) living in Oslo, Norway with data from the Norwegian Death Register and with estimates of the average annual air pollution levels at the participants' home addresses. PM was not considered in this study because measurement methods changed during the study period. Exposure estimates for NO_X and SO_2 were constructed using models based on subject addresses, emission data for industry, heating, and traffic, and measured concentrations. While NO_X was associated with total, respiratory, lung cancer, and ischemic heart disease deaths, SO_2 did not show any associations with mortality. In this study, SO_2 levels were reduced by a factor of 7 during the study period (from 5.6 ppb in 1974 to 0.8 ppb in 1995), whereas NO_X did not show any clear downward trend. Filleul et al. (2005) linked daily measurements of SO_2, TSP, BS, NO_2, and NO with data on mortality for 14,284 adults who resided in 24 areas from seven French cities enrolled in the Air Pollution and Chronic Respiratory Diseases survey in 1974. Models were run before and after exclusion of six area monitors influenced by local traffic as determined by a NO:NO_2 ratio of >3. Before exclusion of the six areas, none of the air pollutants was associated with mortality outcomes. After exclusion of these areas, analyses showed associations between total mortality and TSP, BS, NO_2, and NO but not SO_2 or acidimetric measurements. In this study, SO_2 levels declined by a factor of two to three (depending on the city) between the 1974 through 1976 period and the 1990 through 1997 period. The changes in air pollution levels over the study period complicate interpretation of reported effect estimates.

Carey et al. (2013) examined the associations between long-term exposure to ambient air pollutants and total and cause-specific mortality in a national English cohort (n = 835,607). The authors used air dispersion models to estimate annual mean air pollution concentrations for 1-km grid cells for a single year prior to the follow-up period. Model validation using national air quality monitors and networks demonstrated good agreement for NO_2 and O_3, moderate agreement for PM_{10} and $PM_{2.5}$, but relatively poor agreement for SO_2 (R^2 = 0−0.39). The authors observed positive associations with total mortality for all of the air pollutants, and these associations were stronger for $PM_{2.5}$, NO_2, and SO_2 and respiratory and lung cancer mortality. Associations were generally not observed with cardiovascular mortality and any of the pollutants. Although the authors observed positive associations between SO_2 and mortality (especially respiratory mortality), these associations are difficult to interpret due to the poor validation of the

dispersion model for SO_2. Ancona et al. (2015) used a Lagrangian particle dispersion model (see Section 3.3.2.4 for details) to estimate annual means of SO_X (as an exposure marker for emissions from a petrochemical refinery) in Rome, Italy and associations with all-cause and cause-specific mortality among men and women. The authors did not present any validation results for their dispersion model. Predicted concentrations of SO_X were highly correlated with predicted concentrations of PM_{10} (r = 0.81), and because SO_X was used as an exposure marker for petrochemical refinery emissions, it would likely be correlated with other stack or fugitive refinery emissions, including $PM_{2.5}$ and VOCs. The authors observed associations for all-cause mortality and CVD mortality that were near the null value for both men and women. When restricted to IHD mortality, the association remained near the null value for men, but was elevated among women. Conversely, slightly increased risks were observed for respiratory mortality and mortality due to digestive diseases among men, while the risks for these were attenuated among women. Due to the unknown validity of the dispersion model and the high correlations with additional copollutants, it is difficult to interpret these associations.

Overall, the results of the European cohort studies provide very little evidence for an association between long-term exposure to SO_2 and mortality. The majority of these studies were included in the 2008 SO_X ISA (Beelen et al., 2008b; Filleul et al., 2005; Nafstad et al., 2004). Only the study by Carey et al. (2013) provided new evidence for this review. None of the studies used copollutant models or accounted for potential confounding or effect measure modification by other ambient air pollutants, including sulfate. The study by Carey et al. (2013) had the potential to inform uncertainties related to the geographic scale of the exposure assessment; however, the poor validation results of the dispersion model used to estimate the SO_2 concentrations for 1-km grid cells makes it difficult to interpret these results.

5.5.2.3 Asian Cohort Studies

Four recent cohort studies have been conducted in China to examine the association between long-term exposure to SO_2 and mortality (Chen et al., 2016; Dong et al., 2012; Cao et al., 2011; Zhang et al., 2011) and observed inconsistent results. Each of these studies used annual area-wide average concentrations from fixed site monitoring stations to assign exposure. Notably, the mean SO_2 concentrations in these study areas was much higher than concentrations observed in other locations (see Table 5-42). Cao et al. (2011) observed generally modest positive associations with all-cause, respiratory and lung cancer mortality. Chen et al. (2016) observed a positive association with lung cancer mortality, though the correlation between SO_2 and PM_{10} was high ($r > 0.94$), and it is possible that copollutant confounding could at least partially explain this relationship.

Dong et al. (2012) observed a modest, positive association with respiratory mortality, while Zhang et al. (2011) observed modest negative associations with all-cause mortality.

Katanoda et al. (2011) conducted a cohort study in Japan investigating the association between long-term exposure to $PM_{2.5}$, NO_2, and SO_2 and lung cancer and respiratory mortality. The authors used annual mean concentrations from fixed site monitoring stations near each of eight study areas. The authors observed positive associations between long-term exposure to $PM_{2.5}$, NO_2, and SO_2 and lung cancer and respiratory mortality, with the strongest effect observed for the SO_2 associations.

Overall, these recent Asian cohort studies provide some new evidence of an association between long-term exposure to SO_2 and mortality; however, they generally report similar associations for other ambient air pollutants, and do not evaluate for potential bias due to copollutant confounding (using copollutants models, reporting correlation coefficients between SO_2 and other measured pollutants, or other methods). Generally, these recent studies do not help to resolve the uncertainties identified in the 2008 SO_X ISA related to copollutant confounding or the geographic scale of the analysis.

5.5.2.4 Cross-Sectional Analysis Using Small Geographic Scale

Elliott et al. (2007) examined associations of BS and SO_2 with mortality in Great Britain using a cross-sectional analysis. However, unlike the earlier ecological cross-sectional mortality analyses in the U.S. in which mortality rates and air pollution levels were compared using large geographic boundaries (i.e., MSAs or counties), Elliott et al. (2007) compared the mortality rates and air pollution concentrations using a much smaller geographic unit, the electoral ward, with a mean area of 7.4 km^2 and a mean population of 5,301 per electoral ward. Of note, SO_2 levels declined from 41.4 ppb in the 1966 to 1970 period to 12.2 ppb in 1990 to 1994. This type of analysis does not allow adjustments for individual risk factors, but the study did adjust for socioeconomic status data available for each ward from the 1991 census. Social deprivation and air pollution were more highly correlated in the earlier exposure windows. They observed positive associations for both BS and SO_2 and mortality outcomes. The estimated effects were stronger for respiratory illness than other causes of mortality for the most recent exposure period and most recent mortality period (when pollution levels were lower).
The adjustment for social deprivation reduced the effect estimates for both pollutants. Simultaneous inclusion of BS and SO_2 reduced effect estimates for BS but not SO_2. Elliott et al. (2007) noted that the results were consistent with those reported in the Krewski et al. (2000) reanalysis of the ACS study. Similarly, Bennett et al. (2014) observed a positive association between ward-level SO_2 concentrations measured in 2010

and ward-level data on heart failure mortality from 2007−2012 in Warwickshire, U.K. Stronger associations were observed for estimated benzene exposure in this population, while estimated PM exposure was inversely associated with heart failure mortality. These analyses are ecological, but the exposure estimates in the smaller area compared to that in the U.S. cohort studies may have resulted in less exposure misclassification error, and the large underlying population appears to be reflected in the narrow confidence bands of effect estimates.

In a recent cross-sectional analysis, Wang et al. (2009) examined the long-term exposure to gaseous air pollutants (i.e., NO_2, O_3, and SO_2) and cardio-respiratory mortality in Brisbane, Australia. Pollutant concentrations were estimated for small geographic units, statistical local areas, using IDW. The authors observed a positive association between cardio-respiratory mortality and SO_2, but generally null associations for NO_2 and O_3.

The results of these cross-sectional studies are inconsistent, with much higher mortality effects attributed to SO_2 in Brisbane, Australia (Wang et al., 2009) and Warwickshire, U.K. (Bennett et al., 2014) than in Great Britain (Elliott et al., 2007). While each of these studies took a geospatial approach to their analyses, the cross-sectional nature of the study designs and the lack of control for potential bias due to copollutant confounding limit the interpretation of their results.

5.5.2.5 Summary and Causal Determination

Figure 5-26 presents total mortality effect estimates associated with long-term exposure to SO_2. The overall range of effects spans 0.93 to 1.26 per 5-ppb increase in the annual (or longer period) average SO_2 concentration. The analyses of the Harvard Six Cities and the ACS cohort data, which likely provide effect estimates that are most useful for evaluating possible health effects in the U.S., observed effect estimates of 1.02 to 1.06, while the effect estimate from the recent cohort study of truck drivers was 1.09. Note that each of the U.S. cohort studies has its own advantages and limitations. The Harvard Six Cities data have a small number of exposure estimates, but the study cities were carefully chosen to represent a range of air pollutant exposures. The ACS cohort had far more subjects, but the population was more highly educated than the representative U.S. population. Because educational status appeared to be an important effect modifier of air pollution effects in both studies, the overall effect estimate for the ACS cohort may underestimate the more general population. The evidence from the cohort studies conducted in Europe and Asia is generally similar to that observed from the U.S. cohort studies. That is, the magnitude of the effect estimates is generally similar, although there is greater inconsistency in the direction of the association. Also, the effect estimate

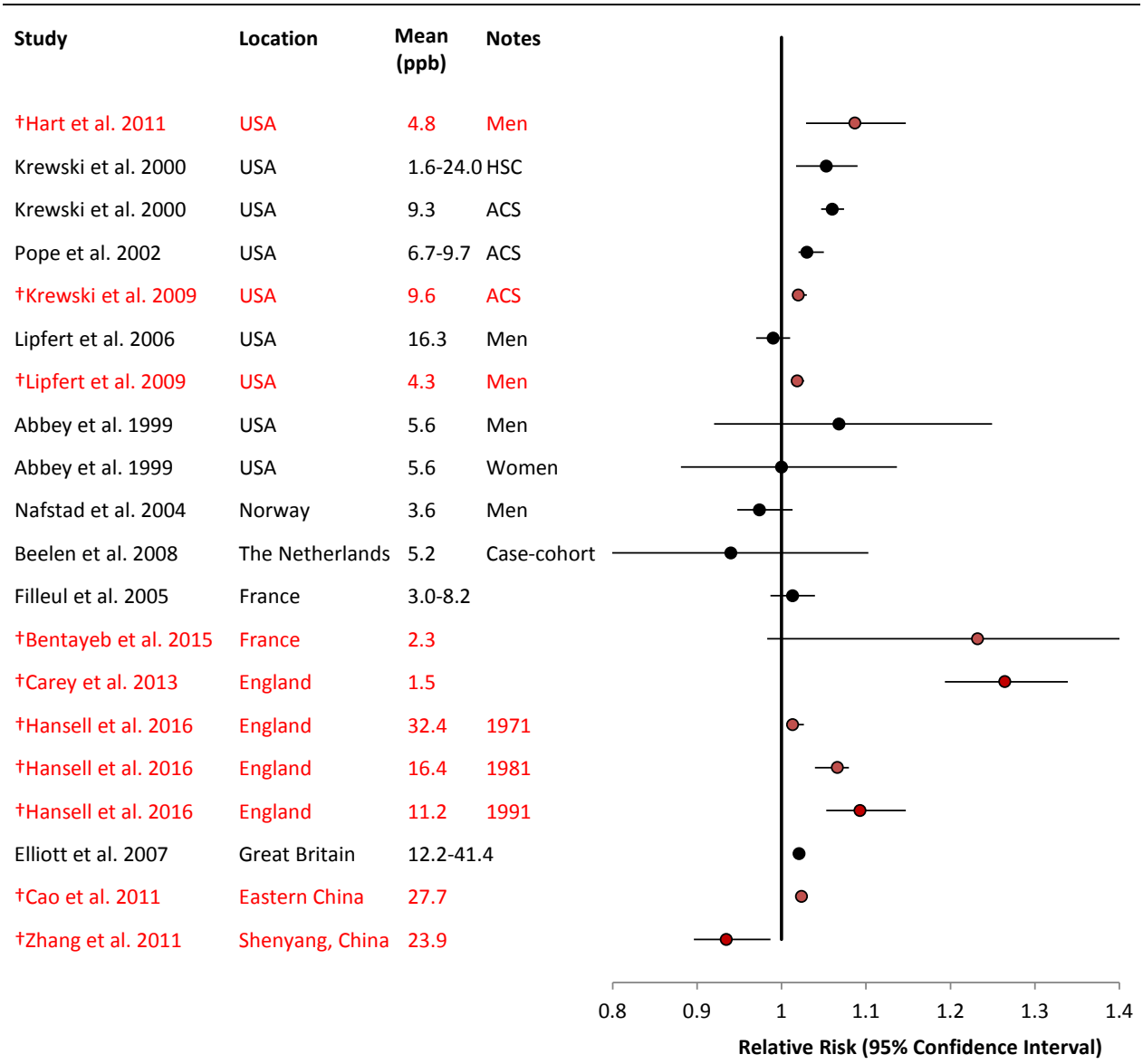
observed by Carey et al. (2013) is much higher than that observed in any of the other studies. Generally, these results are consistent with a recent study (Wang et al., 2014a) that evaluated the correlation between life expectancy and SO_2 concentrations in 85 major city regions in China. After accounting for a surrogate for socioeconomic status, they observed that city regions with higher SO_2 concentrations were correlated with lower life expectancies.

Figure 5-27 presents the cause-specific mortality effect estimates associated with long-term exposure to SO_2. The overall range of effects spans 0.93 to 4.40 per 5-ppb increase in the annual (or longer period) average SO_2 concentration. Generally, there was a trend toward more positive associations for respiratory and lung cancer mortality compared to cardiopulmonary, cardiovascular, and other causes of death. Specifically, recent studies examining respiratory mortality provide some evidence that this cause of death may be more consistently associated with long-term exposure to SO_2 than other causes of death. This is consistent with both the short- and long-term exposure to SO_2 that are associated with respiratory effects.

Overall, the majority of the limited evidence informing the association between long-term exposure to SO_2 and mortality was included in the 2008 SO_X ISA. The 2008 SO_X ISA identified concerns regarding the consistency of the observed associations, whether the observed associations were due to SO_2 alone, or if sulfate or other particulate SO_X or PM indices could have contributed to these associations, and the geographic scale of the exposure assessment. Specifically, the 2008 SO_X ISA noted the possibility that the observed effects may not be due to SO_2, but other co-occurring pollutants that come from the same source as SO_2, or that PM may be more toxic in the presence of SO_2 or other components associated with SO_2, could not be ruled out. None of the epidemiologic studies made corrections or adjustments for exposure measure measurement error, or accounted for the potential for bias away from the null, the potential for which has been demonstrated in simulation studies (see Section 3.4.4.2). Overall, a lack of consistency across studies, inability to distinguish potential confounding by copollutants, and uncertainties regarding the geographic scale of analysis limited the interpretation of the causal relationship between long-term exposure to SO_2 and mortality.

The recent evidence is generally consistent with the evidence in the 2008 SO_X ISA. The biggest notable difference is in the improved consistency in the association between long-term exposure to SO_2 and both respiratory and total mortality that comes from the inclusion of recent cohort studies. However, none of these recent studies help to resolve the uncertainties identified in the 2008 SO_X ISA related to copollutant confounding or the geographic scale of the analysis. All available evidence for mortality due to long-term exposure to SO_2 was evaluated using the framework described in Table II of the

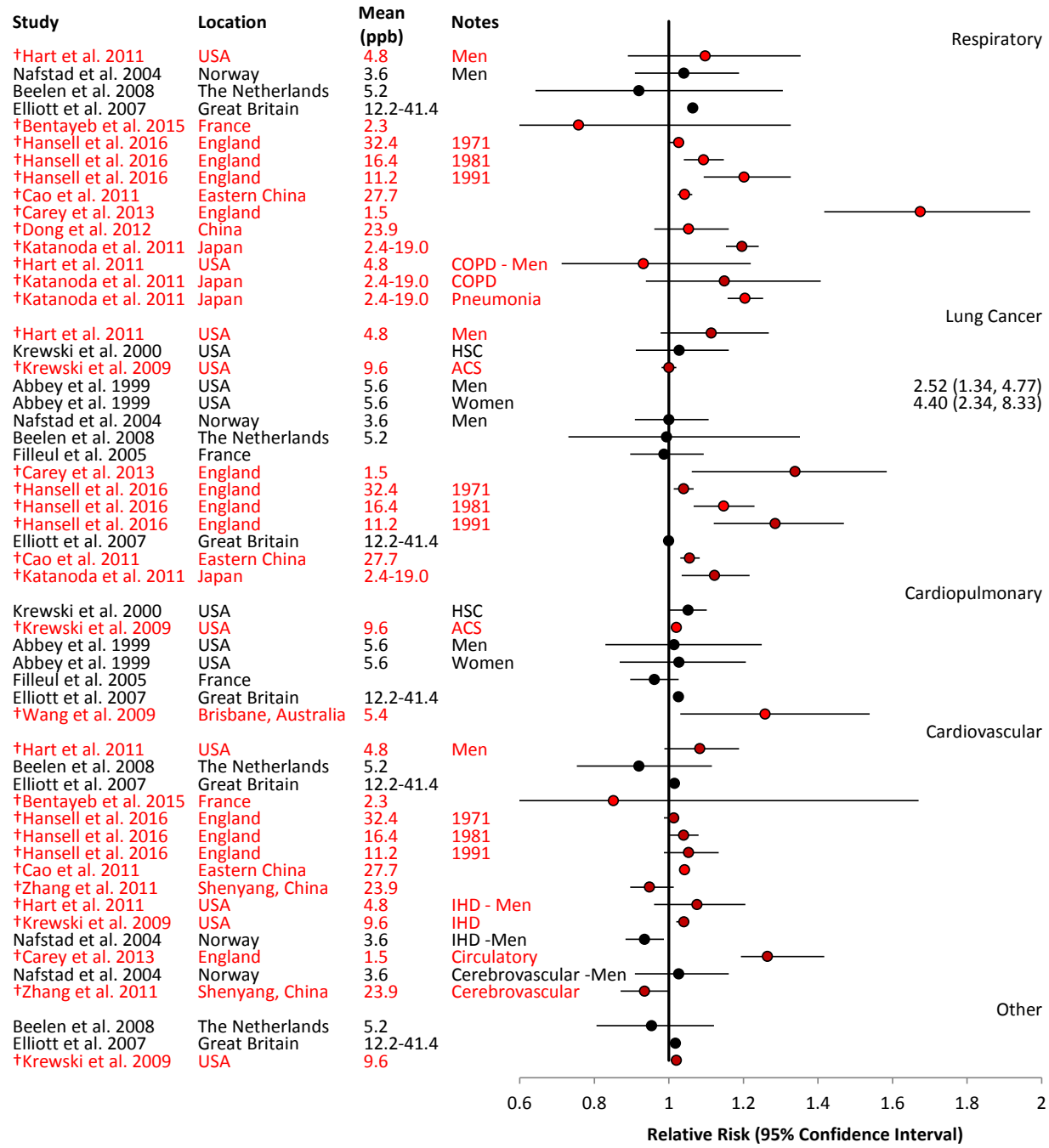
Preamble to the ISAs (U.S. EPA, 2015b). The key evidence as it relates to the causal framework is summarized in Table 5-43. The overall evidence is inadequate to infer a causal relationship between long-term exposure to SO_2 and total mortality among adults.



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, 2016y).

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[a]	Key Evidence[b]	Key References[b]	SO_2 Concentrations Associated with Effects[c]
Some epidemiologic studies report positive associations but results are not entirely consistent.	Small, positive associations between long-term exposure to SO_2 and mortality in the HSC cohort, the ACS cohort, and the Veterans cohort, even after adjustment for common potential confounders	Krewski et al. (2000)	Mean: 1.6−24.0 ppb
		†Krewski et al. (2009)	City-specific annual mean: 9.3−9.6 ppb
		Jerrett et al. (2003)	
		Krewski et al. (2000)	
		†Lipfert et al. (2009)	County-level mean from air quality model: 4.3 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_2.	†Hart et al. (2011)	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	Beelen et al. (2008b)	IDW to regional monitors: 5.2 ppb
		Nafstad et al. (2004)	Model/monitor hybrid: 3.6 ppb
		Filleul et al. (2005)	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.	Table 5-42	
Uncertainty regarding how exposure measurement error may influence the results	SO_2 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_2.	Section 3.4.2	
	Exposure measurement error in long-term SO_2 exposure can lead to bias toward or away from the null.	Section 3.4.4.2	
	No evidence for long-term exposure and respiratory health effects in adults to support the observed associations with respiratory mortality	Section 5.2.2.4	

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[a]	Key Evidence[b]	Key References[b]	SO_2 Concentrations Associated with Effects[c]
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	Section 5.3.2.4	

ACS = American Cancer Society; HSC = Harvard Six Cities; IDW = inverse distance weighting; SO_2 = sulfur dioxide.

[a]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).

[b]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.

[c]Describes the SO_2 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

The body of literature characterizing the carcinogenic, genotoxic, and mutagenic effects of exposure to SO_2 has grown since the 2008 SO_X ISA (U.S. EPA, 2008d). The cancer section of the ISA characterizes epidemiologic associations between SO_2 exposure and cancer incidence or cancer mortality, as well as the animal toxicology carcinogenicity studies (Section 5.6.2). Subsections discuss the evidence relating to lung cancer (Section 5.6.2.1), bladder cancer (Section 5.6.2.2), and other cancers (Section 5.6.2.3). Laboratory studies of mutagenicity or genotoxicity are discussed in Section 5.6.3.

The 2008 SO_X ISA summarized the literature on SO_2 concentrations and lung cancer as "inconclusive" (U.S. EPA, 2008d). Multiple studies across the U.S. and Europe investigated the relationship between SO_2 concentrations and lung cancer incidence and mortality. Many studies reported generally null associations, but some studies demonstrated positive associations. However, some studies were limited by a small number of cancer cases. The following summaries add to the previous knowledge on SO_2 concentrations and cancer incidence and mortality. The sections below describe studies investigating lung cancer, bladder cancer, and other cancers. Supplemental Tables provide detailed summaries of the respective new epidemiologic [Table 5S-31(U.S. EPA, 2016z)] and genotoxic/mutagenic [Table 5S-32 (U.S. EPA, 2016{)aa] literature.

The animal toxicology literature of SO_2 exposure is dominated by studies of SO_2 acting

as a cocarcinogen or tumor promoter, with one study of SO_2 inhalation associated with an increased rate of lung tumor formation in lung tumor-susceptible female rodents. Genotoxicity and mutagenicity studies show mixed results with null studies in a *Drosophila* model and positive micronuclei findings in a mouse inhalation model of SO_2 exposure.

5.6.2 Cancer Incidence and Mortality

5.6.2.1 Lung Cancer Incidence and Mortality

International studies exploring the associations between SO_2 concentrations and lung cancer incidence have provided inconsistent results. No recent studies on SO_2 concentration and lung cancer incidence in the U.S. have been published. Large studies conducted using the Netherlands Cohort Study on Diet and Cancer examined the association between SO_2 concentration and lung cancer incidence (Brunekreef et al., 2009; Beelen et al., 2008a). Null associations were reported in both analyses of the full cohort and a case-cohort design. None of the analyses adjusted for copollutants. An ecological study in Israel examining lung cancer incidence among men also reported null results for the association with SO_2 concentrations (Eitan et al., 2010). Results were relatively unchanged when adjusting for PM_{10}. No association was observed between SO_2 concentrations and lung cancer hospitalizations among men or women in southern France in an ecological study that did not control for copollutants (Pascal et al., 2013). However, an ecological analysis performed among women in Taiwan demonstrated a positive association between SO_2 concentration and lung cancer incidence (Tseng et al., 2012). This positive association remained in a regression model adjusted for other pollutants (CO, NO_2, NO, O_3, and PM_{10}; none of these air pollutants exhibited an association with lung cancer incidence). The association was present in analyses for both types of lung cancer examined, adenocarcinomas and squamous cell carcinomas. Thus, overall, multiple ecologic studies have been performed examining SO_2 concentrations and lung cancer incidence with inconsistent findings, and analyses using a large cohort study reported no association between SO_2 concentrations and lung cancer incidence but had no control of copollutant confounders. Each of these studies used SO_2 concentrations measured at central site monitors to assign exposure. Beelen et al. (2008a) and Brunekreef et al. (2009) used inverse distance weighting between the central site monitor location and residential address, and combined this with the output of land use regression (LUR) models for urban contributions. Eitan et al. (2010) generated spatially interpolated surfaces for a 7-year period, while the other ecological studies relied on annual averages

from the central site monitors. None of the studies corrected for exposure measurement error.

Studies in the U.S. have reported inconsistent findings for the association between SO_2 concentrations and lung cancer mortality (see Section 5.5.2 and Figure 5-27). No association between SO_2 concentrations and lung cancer mortality was present in a report by Health Effect Institute (Krewski et al., 2009). Estimates stratified by high school education (less than high school education, high school education, or greater) were also examined and no association was present in either subgroup. In addition to the entire time period of the study, the researchers also examined 5-year increments, none of which demonstrated an association. However, a recent study of men in the trucking industry found a slight positive association between SO_2 concentrations and lung cancer mortality (Hart et al., 2011). With the inclusion of PM_{10} and NO_2 in the model, the 95% CI included the null but the point estimate was in the positive direction and only slightly attenuated.

Recent studies have also been performed in Asia and Europe examining the relationship between SO_2 and lung cancer mortality. In China, a positive association was observed between SO_2 and lung cancer mortality (Chen et al., 2016; Cao et al., 2011). In the study by Cao et al. (2011), this association was relatively unchanged with adjustment of either TSP or NO_X. A study in Japan also reported a positive association between SO_2 and lung cancer mortality (Katanoda et al., 2011). However, the estimate was reduced when additional potential confounders (smoking of parents during subjects' childhood, consumption of nonyellow or nongreen vegetables, occupation, and health insurance) were controlled for and no copollutant assessment was performed. Positive associations were also observed for suspended PM, $PM_{2.5}$, and NO_2 concentrations. When examining subgroups, the association was highest among male smokers. The point estimate was similar to the overall estimate for male former smokers but the 95% confidence interval was wide due to the small size of the study population. The estimate was lowest among female never smokers. The number of male never smokers and female smokers were too small to assess individually. A study in the U.K. also demonstrated a positive association between SO_2 concentration and lung cancer mortality (Carey et al., 2013).
The association was slightly attenuated when education was included in the model instead of income. However, a large study using the Netherlands Cohort Study on Diet and Cancer reported no association between SO_2 concentration and lung cancer mortality (Brunekreef et al., 2009). This study was mentioned above and also did not demonstrate an association between SO_2 concentration and lung cancer incidence. No copollutant models were examined. In summary, consistent with studies conducted in the U.S. examining SO_2 concentrations and cancer mortality, recent studies performed in Asia and Europe also had inconsistent findings. Many of these studies used SO_2 concentrations

measured at central site monitors to assign exposure, and none of the studies corrected for exposure measurement error. Brunekreef et al. (2009) used inverse distance weighting between the central site monitor location and residential address, and combined this with the output of land use regression (LUR) models for urban contributions. Hart et al. (2011) used spatial smoothing, and Carey et al. (2013) used a dispersion model constructed with emissions data to assign exposure.

A study in Italy used a Lagrangian dispersion model to estimate SO_X concentrations as a marker for refinery plant emissions [exposure assessment technique summarized in Section 3.3.2.4 (Ancona et al., 2015)]. The relationship between these estimates and cancer mortality and hospitalizations were investigated. No association was observed for lung cancer among men or women; however, these results are difficult to interpret. The estimated SO_X concentrations were highly correlated with estimates of PM_{10}, which is expected as SO_X was being treated as a marker for petrochemical refinery emissions. This makes interpretation difficult as copollutant models were not shown for lung cancer and additionally the validity of the model is unknown.

A recent meta-analysis (Chen et al., 2015a) combined the results of five studies of SO_2 and lung cancer and found an overall OR of 1.03 (95% CI: 1.02, 1.05), although one of the five studies [(Cao et al., 2011); characterized above] accounted for nearly 80% of the weight contributing to the overall OR and was the only study of the five to observe a positive and statistically significant association between SO_2 exposure and lung cancer. Three of the remaining studies included in the meta-analysis observed null associations between SO_2 and lung cancer.

Sulfur Dioxide Lung Carcinogenesis, Cocarcinogenic Potential, and Tumor Promotion in Laboratory Animal Models

The toxicological evidence for effects of sulfur dioxide in carcinogenicity, mutagenicity, or genotoxicity is characterized below. Other regulatory agencies have characterized the carcinogenic potential of sulfur dioxide and its metabolites. The International Agency for Research on Cancer (IARC) has determined sulfur dioxide, sulfites, bisulfites, and metabisulfites are not classifiable as to their carcinogenicity to humans (Group 3) and the American Conference of Governmental Industrial Hygienists has rated sulfur dioxide as not classifiable as a human carcinogen (A4).

Direct evidence of carcinogenicity was studied evaluating incidence of lung tumors in a lung adenoma-susceptible mouse strain, (the LX mouse), with chronic exposure to sulfur dioxide at 500 ppm, 5 minutes/day, 5 days/week for 2 years (Peacock and Spence, 1967). SO_2-exposed female mice had an increase in the number of lung tumors subgrouped as (1) adenomas and (2) primary carcinomas versus controls. Males had a smaller increase

in adenomas versus controls and similar levels of primary carcinomas compared to controls.

Evidence exists for SO_2 to be a cocarcinogen (Pauluhn et al., 1985); SO_2 and benzo[a]pyrene, B[a]P, coexposure increased the incidence of lung tumor formation in rodents versus B[a]P exposure alone. Chronic coexposure to SO_2 and B[a]P resulted in increased incidence of upper respiratory tract neoplasia in rats (Laskin et al., 1976) and hamsters (Pauluhn et al., 1985) over B[a]P exposure alone. SO_2 exposure shortened the induction period for spontaneous squamous cell lung tumor formation after B[a]P exposure (Laskin et al., 1976); rats were exposed 5 days a week, 6 hours/day for their lifetime to 10 ppm SO_2 alone via inhalation or 4 ppm SO_2 + 10 mg/m^3 B[a]P (1 hour B[a]P/day). SO_2 exposure also shortened the induction time for methylcholanthrene-induced carcinogenesis.

Multiple studies explored SO_2 as a cocarcinogen or promoter after particulate-induced tumorigenesis. In a study of suspended particulate matter- (SPM-) induced tumorigenesis (proliferative lesions of pulmonary endocrine cells) in the rat, SO_2 did not exacerbate SPM-dependent hyperplasia when rats were exposed to the mixture of SPM and SO_2 (Ito et al., 1997). Adult male rats were exposed to SO_2 for 11 months, 16 hours/day ± SPM for 4 weeks, once/week by intratracheal injection. SO_2 did not act as a tumor promoter or cocarcinogen in this model. In a separate study of diesel exhaust particle- (DEP-) dependent lung tumorigenesis, SO_2 was able to promote DEP-dependent tumorigenesis (Ohyama et al., 1999). Adult male rats were intratracheally instilled with diesel exhaust particle extract-coated carbon black particles (DEcCBP) and exposed to 4 ppm SO_2 for 10 months. Eighteen months after starting the experiment, the animals were examined for respiratory tract tumors and DNA adducts were measured in lung tissue. Lung tumors and DNA adducts were seen in animals with coexposure to SO_2 and DEcCBP but not in animals only exposed to DEcCBP. SO_2 acted as a tumor promoter in animals exposed to DEcCBP. In a separate investigation, hamsters were exposed to diesel engine exhaust (separately with and without particles) and a mixture of SO_2 and NO_2 with or without exposure to the carcinogen diethyl-nitrosamine to investigate the potential cocarcinogenic effect of exposure to the dioxides mixture and diesel engine exhaust in the respiratory tract (Heinrich et al., 1989). These adult male hamster were exposed for 19 hours/day, 5 days/week for 6, 10.5, 15, or 18 months to diesel exhaust, filtered diesel exhaust (without particles), a dioxide mixture of NO_2 (5 ppm) and SO_2 (10 ppm), or clean air. Two exposure groups from each of the aforementioned test groups were also given a single subcutaneous injection of diethylnitrosamine (DEN) (3 mg or 6 mg/kg body weight). Exposure to the dioxide mixture by itself did not elevate tumor rate (tumor induction), nor did it exacerbate DEN-dependent effects (tumor promotion) in the hamster. In summary, a comparison of multiple studies of SO_2 coexposure with particles

reported mixed results in various models of carcinogenicity, cocarcinogenic potential, or tumor promotion.

Oncogene and tumor suppressor genes also appear to be affected by SO_2 exposure, especially with coexposure to benzo[a]pyrene, B[a]P. Synergistic expression of c-fos and c-jun with SO_2 and B[a]P coexposure was observed in rodent lungs (Qin and Meng, 2006). SO_2 and B[a]P coexposure in male Wistar rats (26.5 ppm SO_2 inhalation, 6 hours/day for 7 days; 3 mg B[a]P instilled) statistically significantly downregulated expression of tumor suppressor genes *p16* and *myc*, and increased expression of oncogenes *c-myc*, *H-ras*, and *p53*. Others have reported that SO_2 exposure alone could induce *p53* expression in rats (Bai and Meng, 2005).

5.6.2.2 Bladder Cancer Incidence and Mortality

Several studies on the relationship between SO_2 concentrations and bladder cancer incidence and mortality have been published since the 2008 SO_X ISA (U.S. EPA, 2008d). Positive associations were observed in studies of bladder cancer mortality but not bladder cancer incidence. An ecological study in southern France reported on the relationship between SO_2 concentrations and hospitalizations for bladder cancer without examination of copollutant models (Pascal et al., 2013). Null associations were observed for men and women. Another ecological study in Israel examining bladder cancer incidence also reported sex-stratified results (Eitan et al., 2010). Neither sex demonstrated an association between SO_2 concentrations and bladder cancer in models with and without adjustment for PM_{10}. However, an association was observed in a study examining the relationship between SO_2 and bladder cancer mortality (Liu et al., 2009a). Liu et al. (2009a) investigated the association between SO_2 and bladder cancer mortality using controls with mortality due to causes unrelated to neoplasm or genitourinary-related disease and matched by sex, year of birth, and year of death. A positive association was observed between SO_2 concentration in the second and third tertiles of exposure and bladder cancer mortality. For further investigations, the authors created a three-level exposure variable combining NO_2 and SO_2 concentrations: the lowest tertile of SO_2 and NO_2 concentrations ($\leq$4.32 ppb and $\leq$20.99 ppb, respectively), the highest tertile of SO_2 and NO_2 concentrations (>6.49 ppb and >27.33 ppb, respectively), and other categorizations/combinations. The ORs were 1.98 (95% CI 1.36, 2.88) for the highest level of NO_2 and SO_2 and 1.37 (95% CI 1.03, 1.82) for the middle level categorizations. Although the point estimates are higher than those observed for SO_2 alone (see Supplemental Table 5S-31, (U.S. EPA, 2016z), the 95% confidence intervals overlap, and therefore, conclusions that NO_2 and SO_2 combined contribute to higher odds of mortality than either alone cannot be drawn. Finally, a study using SO_X concentration

estimated using a Lagrangian dispersion model reported no association between SO_X concentration and bladder cancer mortality or hospitalizations among men or women (Ancona et al., 2015). However, results of this study are difficult to interpret because of unknown validity of the model (see Section 3.3.2.4) and high correlation with PM_{10} and H_2S.

5.6.2.3 Incidence of Other Cancers

Recent studies of SO_2 concentrations and other cancer types have been published since the 2008 ISA for Sulfur Oxides (U.S. EPA, 2008d), but provide limited information on associations with SO_2. An ecological study in southern France investigated the relationships between SO_2 and hospitalizations for breast cancer, acute leukemia, myeloma, and non-Hodgkin lymphoma (Pascal et al., 2013). Null associations were observed in sex-stratified analyses among men and women, with the exception of a positive association between SO_2 and acute leukemia among men. However, the authors urge caution when interpreting the results due to a small number of male acute leukemia cases. This study did not examine copollutant confounding. Another ecologic study used Surveillance, Epidemiology, and End Results data to examine the correlation between SO_2 concentrations and breast cancer incidence (Wei et al., 2012). A positive relationship was detected, but a there was no control for potential confounders of other air pollutants (of which CO, NO_X, and VOCs, but not PM_{10}, also demonstrated a positive correlation with breast cancer incidence). Both of these studies are limited by their ecologic nature and the lack of individual-level data. A cross-sectional study was conducted in South Korea that looked at the association between symptom scores for prostate cancer and emissions data for SO_X (measured in kg/year/person) and a number of other air pollutants (Shim et al., 2015). In logistic regression models adjusted for age, the authors observed positive associations between men living in areas with greater emissions of SO_X and symptom scores for prostate cancer. Similar results were observed for NO_X, CO, PM_{10}, VOCs and NH_3. The lack of control for potential confounding by other air pollutants or risk factors (e.g., smoking, SES) limit the interpretation of these results.

A cohort study examined the relationship between SO_X concentrations, estimated using a Lagrangian dispersion model, and hospitalizations and mortality for various cancer types (Ancona et al., 2015). No associations were found between SO_X concentrations and either hospitalizations or mortality due to cancers of the stomach, colon/rectum, liver, kidney, brain, or breast. Positive associations were observed for SO_X concentration and mortality due to pancreatic and larynx cancers among women but not men. The 95% confidence interval showed a large degree of imprecision in the estimates for cancer of the larynx. The association with pancreatic cancer was not robust to adjustment with H_2S or PM_{10}.

When examining the association between estimated SO_X concentration and hospitalizations, a positive, but imprecise, association was observed for cancer of the larynx among women and an inverse association was noted for cancers of lymphatic and hematopoietic tissue.

5.6.2.4 Summary of Cancer Incidence and Mortality

Similar to studies of SO_2 concentrations and lung cancer in the previous ISA (U.S. EPA, 2008d), recent studies of SO_2 concentrations and lung cancer have provided inconsistent results (Carey et al., 2013; Pascal et al., 2013; Tseng et al., 2012; Cao et al., 2011; Hart et al., 2011; Katanoda et al., 2011; Eitan et al., 2010; Brunekreef et al., 2009; Krewski et al., 2009; Beelen et al., 2008a). Studies of bladder cancer appear to find no association between SO_2 concentrations and bladder cancer incidence (Pascal et al., 2013; Eitan et al., 2010), but a study of SO_2 concentration and bladder cancer mortality reported a positive association (Liu et al., 2009a). Limited information is available regarding other cancers. Animal toxicology models of SO_2 inhalation exposure show SO_2 acting as a promoter or cocarcinogen, with one study showing increased lung tumor formation in a lung tumor-prone animal model.

5.6.3 Genotoxicity and Mutagenicity

Multiple studies of genotoxicity or mutagenesis with SO_2 in vivo or SO_2 in vitro exposure have been reported in the literature and are detailed below in Supplemental Table 5S-32 (U.S. EPA, 2016{)aa.

After inhalation exposure to SO_2, mouse bone marrow micronuclei formation (MN) was significantly elevated in both males and females after exposure to SO_2 (5.4, 10.7, 21.4, or 32.1 ppm SO_2, 4 hours/day for 7 days) (Meng et al., 2002). The polychromatophilic erythroblasts of the bone marrow (MNPCE) were formed in significantly increased numbers with SO_2 exposure. Another study recapitulated these findings; subacute exposure to SO_2 (10.7 ppm SO_2 for 5 day, 6 hours/days) induced a significant increase in MNPCE with this effect attenuated by exogenous antioxidant SSO pretreatment (Ruan et al., 2003).

The rate of DNA single strand breaks induced by B[a]P exposure in fetal hamster lung cells (50 ppm for 2 weeks) (Pool et al., 1988b) and rat liver cells (2.5, 5, 9.9, or 19.9 ppm, 4 hours/day for 7 days) (Pool et al., 1988a) was significantly attenuated by concomitant exposure to SO_2 (50 ppm for 2 weeks).

Genotoxicity testing of *Drosophila* sperm for sex-linked recessive lethals after feeding larvae 0.04 M or 0.08 M sodium sulfite in a 1% glucose solution was performed and no increase was found above background. One caveat is that sulfite can interact with glucose, making the exposure assessment more complicated.

Multiple studies of genotoxicity or mutagenesis with SO2 in vivo or in vitro exposure have been reported in the literature and are summarized in Supplemental Table 5S-32 (U.S. EPA, 2016{)aa. Mixed results of genotoxicity or mutagenicity have been reported after SO_2 exposure including positive associations with SO_2 inhalation exposure in the mouse MN assay.

5.6.4 Summary and Causal Determination

The overall evidence for long-term SO_2 exposure and cancer is inadequate to infer a causal relationship. This conclusion is based on the inconsistent evidence from epidemiologic studies, as well as mixed evidence within the animal toxicology and mode of action framework for mutagenesis and genotoxicity. In past reviews, a limited number of epidemiologic studies had assessed the relationship between long-term SO_2 concentrations and cancer incidence and mortality. The 2008 ISA for Sulfur Oxides concluded that the evidence was "inconclusive" (U.S. EPA, 2008d). Recent studies include evidence on lung cancer as well as new types of cancer, evaluating both incidence and mortality. However the additional recent evidence has not informed any of the uncertainties identified in the previous review, including uncertainties due to exposure measurement error, potential copollutant confounding, and limited mechanistic evidence or biological plausibility. All available evidence for cancer due to long-term SO_2 concentrations was evaluated using the framework described in Table II of the Preamble to the ISAs (U.S. EPA, 2015b). The key evidence as it relates to the causal framework is summarized in Table 5-44.

American Conference of Governmental Industrial Hygienists has rated sulfur dioxide as A4, not classifiable as a human carcinogen. The IARC has classified SO_2 as a Group 3 substance, not classifiable as to its carcinogenicity to humans. The Registry of Toxic Effects of Chemical Substances of National Institute for Occupational Safety and Health lists SO_2 as tumorigenic and cocarcinogenic by inhalation in rats and mice. The National Toxicology Program of the National Institutes of Health and the U.S. Environmental Protection Agency have not classified SO_2 for its potential carcinogenicity. Overall, there is inconsistent evidence for an association between long-term SO_2 exposure and cancer from epidemiologic and toxicological studies. Some of the epidemiologic studies observed positive associations while others did not. Some of these studies with positive

associations were relatively unchanged with the inclusion of various cofounders and copollutants, although many did not evaluate the potential for copollutant confounding. Cohort studies have reported null associations between SO_2 concentrations and lung cancer incidence. Similarly, some ecological studies also reported no associations; although, an ecological study in Taiwan among women did report an association between SO_2 concentrations and lung cancer incidence that was relatively unchanged when including other pollutants. Positive associations were also observed in a study of SO_2 concentrations and bladder cancer mortality but not in ecological studies of bladder cancer incidence. The study of bladder cancer mortality examined the relationship between bladder cancer mortality and joint exposure to high levels of NO_2 and SO_2, but no copollutant assessment was performed controlling for NO_2 or other air pollutants. None of the epidemiologic studies made corrections or adjustments for exposure measure measurement error, or accounted for the potential for bias away from the null, the potential for which has been demonstrated in simulation studies (see Section 3.4.4.2).

Animal toxicological studies employing SO_2 exposure with other known carcinogens provide some evidence, showing that inhaled SO_2 can increase tumor load in laboratory rodents. Toxicological data provided by a study in LX mice, lung adenoma susceptible animals, showed evidence of the direct carcinogenic potential of SO_2. Other studies in animal models show SO_2 as a cocarcinogen with B[a]P or as a tumor promoter with particulate-induced tumorigenesis. Nonetheless, toxicological data provide no clear evidence of SO_2 acting as a complete carcinogen and not all epidemiologic studies report positive associations.

Collectively, the inconsistent evidence from several toxicological and epidemiologic studies is inadequate to infer a causal relationship between long-term exposure to SO_2 and 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[a]	Key Evidence[b]	Key References[b]	SO_2 Concentrations Associated with Effects[c]
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	Section 5.6.2	Means varied across studies including areas estimating mean concentrations of SO_2 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[a]	Key Evidence[b]	Key References[b]	SO_2 Concentrations Associated with Effects[c]
Uncertainty due to exposure measurement error	Central site monitors used in cancer studies may not capture spatial variability of SO_2 concentrations.	Section 3.4.2.2	
	Exposure measure measurement error in long-term SO_2 exposure assessment can bias toward or away from the null.	Section 3.4.4.2	
Uncertainty due to confounding by correlated copollutants	Correlations of SO_2 with other pollutants vary by study or are not examined. Some pollutants are moderately to highly correlated with SO_2 but are not always taken into account as potential confounders.	Section 3.4.3	
Uncertainty due to limited coherence with toxicological evidence	Studies in a tumor-susceptible mouse model, females had increased numbers of lung adenomas and carcinomas.	Peacock and Spence (1967)	500,000 ppb
		Laskin et al. (1976)	10,000 ppb
	Studies of facilitation of metastasis and coexposures with known carcinogens show mixed SO_2 related effects.	Pauluhn et al. (1985)	172,000 ppb
		Ohyama et al. (1999)	4,000 ppb
		Heinrich et al. (1989)	5,000 or 10,000 ppb
		Ito et al. (1997)	4,000 ppb
		Section 5.6.2.1	
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_2	Meng et al. (2002), Ruan et al. (2003), Pool et al. (1988b) Section 5.6.3	5,000, 10,700, 21,400, 32,100 ppb

MOA = mode of action; SO_2 = sulfur dioxide.

[a]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).

[b]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.

[c]Describes the NO_2 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.

Evaluation Factors
Study Design
Controlled Human Exposure:
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.
Animal Toxicology:
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.
Epidemiology:
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.

Evaluation Factors
Study Population/Test Model
Controlled Human Exposure:
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.[a] 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.
Animal Toxicology:
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_2 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.
Epidemiology:
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.
Pollutant
Controlled Human Exposure:
The focus is on studies testing SO_2 exposure.
Animal Toxicology:
The focus is on studies testing SO_2 exposure.
Epidemiology:
The focus is on studies testing SO_2 exposure.

Table A-1 (Continued): Scientific considerations for evaluating the strength of inference from studies on the health effects of sulfur oxides.

Evaluation Factors
Exposure Assessment or Assignment
Controlled Human Exposure:
For this assessment, the focus will be on studies that use SO_2 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_2, were emphasized) (Section 1.2).
Animal Toxicology:
For this assessment, the focus will be on studies that use SO_2 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).
Epidemiology:
Of primary relevance are relationships of health effects with the ambient component of exposure to SO_2. 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_2 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_2 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_2 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_2 concentrations, which is particularly important for assessing exposure near large stationary sources. Alternatively, grid-scale models (e.g., CMAQ) that represent SO_2 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_2 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_2. 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.

Table A-1 (Continued): Scientific considerations for evaluating the strength of inference from studies on the health effects of sulfur oxides.

Evaluation Factors
Outcome Assessment/Evaluation
Controlled Human Exposure:
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.
Animal Toxicology:
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.
Epidemiology:
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.[a] 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,[b] 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.
Potential Copollutant Confounding
Controlled Human Exposure:
Exposure should be well characterized to evaluate independent effects of SO_2.
Animal Toxicology:
Exposure should be well characterized to evaluate independent effects of SO_2.

Table A-1 (Continued): Scientific considerations for evaluating the strength of inference from studies on the health effects of sulfur oxides.

Evaluation Factors
Epidemiology:
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_2 and copollutants and comparing health associations between SO_2 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_2 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_2 and other criteria pollutants at collocated monitors (Section 3.4.3), ranging from negative to strong correlations, making evaluation of copollutant confounding necessary on a study-specific, rather than a general, basis.
Other Potential Confounding Factors
Controlled Human Exposure:
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).
Animal Toxicology:
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).
Epidemiology:
Factors are considered to be potential confounders if demonstrated in the scientific literature to be related to health effects and correlated with SO_2. 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_2 and health effects, which can bias results toward the null. In the absence of information linking health risk factors to SO_2, 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: For time-series and panel studies of short-term exposure: • Respiratory effects—meteorology, day of week, season, medication use, allergen exposure (potential effect modifier) • Cardiovascular effects—meteorology, day of week, season, medication use • Total mortality—meteorology, day of week, season, long-term temporal trends For studies of long-term exposure: • Respiratory effects—socioeconomic status, race, age, medication use, smoking, stress • Cardiovascular, reproductive, and development effects—socioeconomic status, race, age, medication use, smoking, stress, noise • Total mortality—socioeconomic status, race, age, medication use, smoking, comorbid health conditions • Cancer—socioeconomic status, race, age, occupational exposure

Table A-1 (Continued): Scientific considerations for evaluating the strength of inference from studies on the health effects of sulfur oxides.

Evaluation Factors
Statistical Methodology
Controlled Human Exposure:
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.
Animal Toxicology:
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.
Epidemiology:
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 *t*-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.

AERMOD = American Meteorological Society/U.S. EPA Regulatory Model; CI = confidence interval; CMAQ = Community Multiscale Air Quality; SES = socioeconomic status; SO_2 = sulfur dioxide.

[a]Toren et al. (1993); (Murgia et al. (2014); Weakley et al. (2013); Yang et al. (2011); Heckbert et al. (2004); Barr et al. (2002); Muhajarine et al. (1997)).

[b]Burney et al. (1989).

[c]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_2 (comorbid health condition).

Chapter 6 Populations and Lifestages Potentially at Increased Risk for Health Effects Related to Sulfur Dioxide Exposure

6.1 Introduction

Interindividual variation in human responses to air pollution exposure can result in some groups or lifestages being at increased risk for health effects in response to ambient exposure to an air pollutant. The NAAQS are intended to protect public health with an adequate margin of safety. Protection is provided for both the population as a whole and those potentially at increased risk for health effects in response to exposure to a criteria air pollutant (e.g., SO_2) [see Preamble to the ISAs (U.S. EPA, 2015b)]. The scientific literature has used a variety of terms to identify factors and subsequently populations or lifestages that may be at increased risk of an air pollutant-related health effect, including *susceptible*, *vulnerable*, *sensitive*, and *at risk*, with recent literature introducing the term *response-modifying factor* (Vinikoor-Imler et al., 2014) [see Preamble to the ISAs (U.S. EPA, 2015b)]. Due to the inconsistency in definitions for these terms across the scientific literature and the lack of a consensus on terminology in the scientific community, as detailed in the Preamble to the ISAs (U.S. EPA, 2015b), this chapter focuses on identifying those populations or lifestages potentially "at risk" of an SO_2-related health effect. This leads to a focus on the identification, evaluation, and characterization of factors to address the main question of what populations and lifestages are at increased risk of an SO_2-related health effect. Some factors may lead to a reduction in risk, and these are recognized during the evaluation process, but for the purposes of identifying those populations or lifestages at greatest risk to inform decisions on the NAAQS, the focus of this chapter is on characterizing those factors that may increase risk.

Individuals, and ultimately populations, can be at increased risk of an air pollutant-related health effect in a number of ways. As discussed in the Preamble to the ISAs (U.S. EPA, 2015b), risk may be modified by intrinsic or extrinsic factors that act synergistically with SO_2 on a health endpoint (e.g., sociodemographic or behavioral factors), differences in internal dose (e.g., due to variability in ventilation rates or exercise behaviors), or differences in exposure to air pollutant concentrations (e.g., more time spent in areas with higher ambient concentrations). The objective of this chapter is to identify, evaluate, and characterize the evidence for factors that potentially increase the risk of health effects related to exposure to SO_2. Note also that although individual factors that may increase the risk of an SO_2-related health effect are discussed in this chapter, it is likely in many cases that portions of the population are at increased risk of an SO_2-related health effect

due to a combination of factors [e.g., residential location and socioeconomic status (SES)], but information on the interaction among factors remains limited. Thus, the following sections identify, evaluate, and characterize the overall confidence that individual factors potentially result in increased risk for SO_2-related health effects [see Preamble to the ISAs (U.S. EPA, 2015b)].

6.2 Approach to Evaluating and Characterizing the Evidence for At Risk Factors

The systematic approach used to evaluate factors that may increase the risk of a population or specific lifestage to an air pollutant-related health effect is described in more detail in the Preamble to the ISAs (U.S. EPA, 2015b). The evidence evaluated includes relevant studies discussed in Chapter 5 of this ISA and builds on the evidence presented in the 2008 ISA for Sulfur Oxides (U.S. EPA, 2008d). Based on the approach developed in previous ISAs (U.S. EPA, 2016e, 2013b, c) evidence is integrated across scientific disciplines, across health effects, and where available, with information on exposure and dosimetry (Chapter 3 and Chapter 4). Greater emphasis is placed on those health outcomes for which a "causal" relationship was concluded in Chapter 5 of this ISA, while information from studies of health outcomes for which the causal determination is "suggestive" is only used as supporting evidence where warranted. Studies examining health outcomes for which an "inadequate" relationship was concluded are not included in this chapter due to the uncertainty in the independent association between exposure to SO_2 and the health outcome; as a result, these studies are unable to provide information on whether certain populations are at increased risk of SO_2-related health effects. Conclusions are drawn based on the overall confidence that a specific factor may result in a population or lifestage being at increased risk of an SO_2-related health effect.

As discussed in the Preamble to the ISAs (U.S. EPA, 2015b), this evaluation includes evidence from epidemiologic, controlled human exposure, and toxicological studies in addition to considering relevant exposure-related information. With regard to epidemiologic studies, the evaluation focuses on those studies that include stratified analyses to compare populations or lifestages exposed to similar air pollutant concentrations within the same study design along with consideration of the strengths and limitations of each study. Other epidemiologic studies that do not stratify results but instead examine a specific population or lifestage can provide supporting evidence for the pattern of associations observed in studies that formally examine effect modification. Similar to the characterization of evidence in Chapter 5, statistical significance is not the sole criterion by which effect modification is determined; the greatest emphasis is placed

on patterns or trends in results across studies. Experimental studies in human subjects or animal models that focus on factors, such as genetic background or health status, are evaluated because they provide coherence and biological plausibility of effects observed in epidemiologic studies. Also evaluated are studies examining whether factors may result in differential exposure to SO_2 and subsequent increased risk of SO_2-related health effects.

The objective of this chapter is to identify, evaluate, and characterize the overall confidence that various factors may increase the risk of an SO_2-related health effect in a population or lifestage, building on the conclusions drawn in the ISA with respect to SO_2 exposure and health effects. The broad categories of factors evaluated in this chapter include pre-existing disease/condition (Section 6.3), genetic factors (Section 6.4), and sociodemographic and behavioral factors (Section 6.5). Formal conclusions are made with respect to whether a specific factor increases the risk of an SO_2-related health effect based on the characterization of evidence framework detailed in Table 6-1. A summary of the characterization of the evidence for each factor considered in this chapter is presented 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

Individuals with pre-existing disease may be considered at greater risk for some air pollution-related health effects because they are likely in a compromised biological state depending on the disease and severity. The 2008 ISA for Sulfur Oxides (U.S. EPA, 2008d) concluded that those with pre-existing pulmonary conditions were likely to be at greater risk for SO_2-related health effects, especially individuals with asthma. Of the recent epidemiologic studies evaluating effect modification of respiratory effects by pre-existing disease, most focused on asthma (Section 6.3.1). Table 6-2 presents the prevalence of asthma and other respiratory diseases according to the Centers for Disease Control and Prevention's (CDC's) National Center for Health Statistics (Schiller et al., 2012), including the proportion of adults with a current diagnosis categorized by age and geographic region. The large proportions of the U.S. population affected by many chronic diseases indicates the potential public health impact, and thus, the importance of characterizing the risk of SO_2-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.

	Adults (18+)	Age (%)[a]					Region (%)[b]			
Chronic Disease/Condition	N (in Thousands)	<18[c]	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
Selected respiratory diseases										
Asthma[d]	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.

[a]Percentage of individual adults and children within each age group with disease, based on N (at the top of each age column).

[b]Percentage of individual adults (18+) within each geographic region with disease, based on N (at the top of each region column).

[c]Statistics for <18 category from http://www.cdc.gov/asthma/most_recent_data.htm, last updated March 2016; accessed on July 28, 2016.

[d]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.

6.3.1 Asthma

Approximately 8.0% of adults and 8.6% of children (age <18 years) in the U.S. currently have asthma (Blackwell et al., 2014; Bloom et al., 2013), and it is the leading chronic illness affecting children (Bloom et al., 2013). Based on evidence from the 2008 ISA for Sulfur Oxides (U.S. EPA, 2008d) and recent studies, Chapter 5 concludes that a causal relationship exists between short-term SO_2 exposure and respiratory effects, based primarily on evidence from controlled human exposure studies demonstrating decrements in lung function in individuals with asthma (Section 5.2.1.2 and Section 5.2.1.9). This is nearly the same body of evidence evaluated in the 2008 ISA for Sulfur Oxides (U.S. EPA, 2008d), which also concluded that individuals with asthma are more sensitive to exposures to ambient SO_2. Children with asthma may be particularly at risk compared to adults with asthma due to (1) their increased responsiveness to methacholine, a potential surrogate for SO_2 (Section 5.2.1.2), relative to adults; (2) children's increased ventilation rates relative to body mass compared to adults; and (3) the increased proportion of oral breathing observed among children, particularly boys, relative to adults (Section 4.1.2). In addition, children tend to spend more time outdoors (where SO_2 levels are higher, compared to indoor levels), and have the potential to be exposed to higher levels of SO_2. Such oral breathing allows greater SO_2 penetration into the tracheobronchial region of the lower airways than nasal breathing (Section 4.2.2). This section briefly describes evidence from the experimental studies and supporting evidence from epidemiologic 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[a]	Outcome	Study Population[b]	Study Details	Study
Controlled human exposure						
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^3 NaCl droplet, 1 mg/m^3 NaCl droplet for 60 min at rest	Koenig et al. (1980)
		-	Decrements in sRaw and FEV_1			
Asthma (atopic)	Healthy	↑	Lung function (sRaw)	n = 4 normal adults, n = 21 atopic adults n = 16 adults with mild asthma n = 24 adults with moderate/ severe asthma	0.2, 0.4, 0.6 ppm SO_2 for 1 h with exercise; Exposures were repeated eight times	Linn et al. (1987)
Mild asthma		↑				
Moderate/ severe asthma		↑				
Asthma (atopic)	Healthy	↑	Lung function (FEV_1)			
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	Magnussen et al. (1990)

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[a]	Outcome	Study Population[b]	Study Details	Study
Asthma	Healthy	-	Lung function (FEV_1, FVC, MMEF)	n = 12 adults with asthma, 12 healthy adults	0.2 ppm SO_2 for 1 h at rest	Tunnicliffe et al. (2003)
Epidemiology						
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	Amadeo et al. (2015)
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	Lin et al. (2015)
Toxicology						
Rat asthma model (OVA sensitization)	Normal rats	↑	AHR (metha-choline)	Rats (Sprague-Dawley), n = 10 males/group (4 wk)	2 ppm SO_2 for 4 h/d for 4 wk beginning at 15 d	Song et al. (2012)
		↑	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_1 = 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_2 = sulfur dioxide; sRAW = specific airway resistance; V_{max50} = maximal expiratory flow rate at 50%; V_{max75} = maximal expiratory flow rate at 75%.

[a]Up facing arrow (↑) indicates that the effect of SO_2 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_2 is smaller in the group with the factor evaluated than in the reference group. A dash (-) indicates no substantial difference in SO_2-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_2 relative to exposure to filtered air.

[b]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.

Across experimental evidence, adults with asthma consistently have greater decrements in lung function with SO_2 exposure than those without asthma. Controlled human exposure studies have evaluated respiratory outcomes among adults at SO_2 concentrations ranging from 0.2 to 1 ppm and included exposures with and without exercise. Linn et al. (1987) conducted an extensive study examining several concentrations of SO_2 with repeated exposures in healthy individuals, individuals with mild asthma, individuals with atopic asthma, and individuals with moderate/severe asthma and reported respiratory effects (airway resistance, FEV_1, symptoms) with increasing SO_2 exposures according to clinical status, with individuals having moderate and severe asthma showing the greatest SO_2-dependent effects. In addition, subject-level characteristics other than clinical status did not influence response. Magnussen et al. (1990) also reported greater decrements in sRaw in subjects with asthma relative to healthy controls with SO_2 exposures incorporating exercise; however, consistent decrements in lung function were not observed in adults and adolescents with asthma relative to healthy controls when exposed at rest (Tunnicliffe et al., 2003; Koenig et al., 1980). It is important to note that these studies were limited by exposure design and small sample sizes. In addition to controlled human exposure studies, a long-term exposure study conducted in ovalbumin (OVA)-sensitized rats as an asthma model demonstrated that 4 weeks of exposure to 2 ppm SO_2 resulted in increased airway resistance compared to normal rats (Song et al., 2012).

Of the literature included in this ISA, two epidemiologic studies included stratification by asthma status and did not find differences for short-term exposure to ambient SO_2 with respiratory outcomes [Table 6-3; (Amadeo et al., 2015; Lin et al., 2015)]. However, evidence presented in Section 5.2.1.2 generally demonstrates consistent positive associations between ambient SO_2 concentrations and asthma-related hospitalizations and ED visits. In addition, some evidence from recent panel studies and studies reviewed in the 2008 ISA for Sulfur Oxides (U.S. EPA, 2008d) indicates that children with asthma experience respiratory symptoms associated with exposure to ambient SO_2.

In conclusion, evidence from controlled human exposure studies and animal toxicology studies is consistent in demonstrating decrements in lung function with SO_2 exposures. There is also clear biological plausibility, including key events contributing to the mode of action (Section 4.3), supporting the observed effects from experimental studies. Furthermore, epidemiologic studies report associations between SO_2 exposure and emergency department visits and hospital admissions due to asthma, and that individuals with asthma experience respiratory symptoms associated with exposure to ambient SO_2. Overall, there is adequate evidence from multiple, high-quality studies and coherence across scientific disciplines to conclude that people with pre-existing asthma are at increased risk of SO_2-induced respiratory effects.

6.4 Genetic Factors

Genetic variation in the human population is known to contribute to numerous diseases and differential physiologic responses. The 2008 ISA for Sulfur Oxides (U.S. EPA, 2008d) discussed the biological plausibility of individuals with certain genotypes known to result in reduced function in genes encoding antioxidant enzymes being at increased risk for respiratory effects related to ambient air pollution. However, the evidence base was limited to two studies demonstrating individuals with polymorphisms in *GSTP1* and tumor necrosis factor to be at increased risk for SO_2-related asthma and decrements in lung function. A recently conducted study reviewed in this ISA examined effect measure modification by genotype (Reddy et al., 2012) and reported inconsistent results across *GSTM1* and *GSTP1* genotypes in a relatively small sample of children in South Africa. The *GSTM1* null genotype and the *GSTP1 Ile105Ile* and *Ile105Val* genotypes are associated with reduced antioxidant enzyme function; however, effect measure modification of these genotypes on SO_2-associated intra-day variability of FEV_1 showed conflicting results. Despite biological plausibility, the limited and inconsistent evidence base is inadequate to determine whether genetic background contributes to increased risk for SO_2-related health effects.

6.5 Sociodemographic and Behavioral Factors

6.5.1 Lifestage

The 2008 ISA for Sulfur Oxides (U.S. EPA, 2008d) discussed some evidence for increased risk of health effects related to SO_2 exposure among different lifestages (i.e., children and older adults). Lifestage refers to a distinguishable time frame in an individual's life characterized by unique and relatively stable behavioral or physiological characteristics associated with development and growth (U.S. EPA, 2014b). Differential health effects of SO_2 across lifestages theoretically could be due to several factors. With regard to children, the human respiratory system is not fully developed until 18−20 years of age, and therefore, children could plausibly have intrinsic risk for respiratory effects due to potential perturbations in normal lung development (Finkelstein and Johnston, 2004). Older adults (typically considered those 65 years of age or greater) have weakened immune function, impaired healing, decrements in pulmonary and cardiovascular function, and greater prevalence of chronic disease [(Rosenthal and Kavic, 2004); Table 6-2], which may contribute to or worsen health effects related to SO_2 exposure. Also, exposure or internal dose of SO_2 may vary across lifestages due to varying ventilation rates, increased oronasal breathing at rest, and time-activity patterns.

The following sections present the evidence comparing lifestages from the recent literature, which builds on the evidence presented in the 2008 ISA for Sulfur Oxides (U.S. EPA, 2008d).

6.5.1.1 Children

According to the 2010 census, 24% of the U.S. population is less than 18 years of age, with 6.5% less than age 6 (Howden and Meyer, 2011). The large proportion of children within the U.S. demonstrates the public health importance of characterizing the risk of SO_2-related health effects among children. This is especially so because of the causal relationship between ambient SO_2 exposure and respiratory outcomes, with strong evidence demonstrating lung function decrements in individuals with asthma, which affects approximately 11% of children 5 years and older. The 2008 ISA for Sulfur Oxides (U.S. EPA, 2008d) presented evidence indicating an increased risk of SO_2-related respiratory outcomes in children compared to adults; however, recent evidence is not entirely consistent with the evidence considered previously (Table 6-4). Although Son et al. (2013) found children (0−14 years) to be at greater risk for SO_2-related asthma hospital admissions, neither Ko et al. (2007b) nor Alhanti et al. (2016) observed differences between children and adults when examining associations of ambient SO_2 and asthma hospitalizations or emergency department visits. When examining evidence for different age groups of children, Jalaludin et al. (2008) observed that associations for respiratory-related ED visits among children ages 1−4 years were greater than for children ages 10−14 years; however, Samoli et al. (2011) and Villeneuve et al. (2007) did not find stronger associations for asthma-related hospital admissions or ED visits among younger children. Similarly, Dong et al. (2013c) did not find age-related differences among children for SO_2-associated asthma, and Sahsuvaroglu et al. (2009) found children ages 6−7 years had smaller SO_2-associated nonallergic asthma compared to adolescents at 13−14 years.

Overall, the combined evidence from the previous and current ISA examining respiratory outcomes across lifestages is suggestive of increased risk in children, given the inconsistencies across epidemiologic studies and limited toxicological evidence to inform plausibility. There are biological factors (e.g., increased ventilation rates relative to body mass among children and increased oral breathing that lead to greater SO_2 penetration and bronchial surface doses) that could support increased risk to children. However, recent evidence, mainly from epidemiologic studies of respiratory ED visits and hospital 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[a]	Outcome	Study Population	Study Details	Study
Short-term exposure						
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	Wong et al. (2009)
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	Ko et al. (2007b)
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	Son et al. (2013)
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	Samoli et al. (2011)
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	Villeneuve et al. (2007)
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	Jalaludin et al. (2008)

Table 6-4 (Continued): Epidemiologic studies evaluating childhood lifestage and sulfur dioxide exposure.

Factor Evaluated	Reference Category	Direction of Effect Modification[a]	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)	Alhanti et al. (2016)
Long-term exposure						
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 Provence, northeast China 2008–2009	Dong et al. (2013c)
		↑	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	Sahsuvaroglu et al. (2009)

ED = emergency department; n = sample size.

[a]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

According to the 2008 National Population Projections issued by the U.S. Census Bureau, approximately 12.9% of the U.S. population is age 65 years or older, and by 2030, this fraction is estimated to grow to 20% (Vincent and Velkoff, 2010). Thus, this lifestage represents a substantial proportion of the U.S. population that is potentially at increased risk for health effects related to SO_2 exposure.

The 2008 ISA for Sulfur Oxides (U.S. EPA, 2008d) indicated that compared with younger adults, older adults (typically ages 65 years and older) may be at increased risk for SO_2-related respiratory emergency department visits and hospitalizations, but limited evidence was available to inform risk related to respiratory effects. Recently published studies evaluating risk in older adults compared to younger adults are characterized in Table 6-5 and generally support conclusions from the 2008 ISA for Sulfur Oxides (U.S. EPA, 2008d). Villeneuve et al. (2007) and Son et al. (2013) both reported that asthma-related ED visits and hospital admissions were more strongly associated with short-term ambient SO_2 exposure in individuals older than 75 years than adults 65−74 years or those younger than 65. However, the handful of recent studies evaluating asthma and nonasthma respiratory admissions or ED visits in adults greater than 65 years of age reported inconsistent results compared to the earlier literature (Alhanti et al., 2016; Son et al., 2013; Arbex et al., 2009; Wong et al., 2009; Ko et al., 2007b). In addition to these studies of short-term SO_2 exposure, Forbes et al. (2009c) found older adults (45−74 and older than 75 years) to have larger decrements in lung function compared to adults aged 16−44. Additionally, Bravo et al. (2015), Chen et al. (2012c), and Wong et al. (2008b) found evidence for increased risk of total mortality with short-term SO_2 exposures in adults older than 75 years compared to other age groups, which is consistent with age-specific evidence from respiratory studies. Evidence examining short-term SO_2 exposure and total mortality is suggestive of, but not sufficient to infer, a causal relationship (Section 5.5.1).

Taken together, the collective evidence builds on conclusions from the previous ISA and is suggestive that older adults may be at increased risk for SO_2-related health effects. The evidence from the current and previous ISA related to respiratory hospitalizations and ED visits indicates that older adults, particularly those older than 75 years, may be at increased risk for SO_2-related health effects, although this evidence is not entirely consistent. Evidence is much more consistent for total mortality, demonstrating that older adults (>65 or 75 years) are at greater risk than younger individuals, although there is uncertainty in the independent association between short-term SO_2 exposure and total mortality.

6.5.2 Sex

A vast number of health conditions and diseases have been shown to differ by sex, and there is some indication of differences by sex in the relationship between air pollution and health effects. The 2010 U.S. census indicates an approximately equal distribution of males and females in the U.S.: 49.2% male and 50.8% female (Howden and Meyer, 2011). However, the distribution varies by age, with a greater prevalence of females

above 65 years of age compared to males. Thus, the public health implications of potential sex-based differences in air pollution-related health effects may vary among age 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[a]	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	Ko et al. (2007b)
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	Villeneuve et al. (2007)
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)	Alhanti et al. (2016)
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	Arbex et al. (2009)
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	Son et al. (2013)

Table 6-5 (Continued): Epidemiologic studies evaluating older adult lifestage and sulfur dioxide exposure.

Factor Evaluated	Reference Category	Direction of Effect Modification[a]	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	Wong et al. (2009)
Older adulthood ages ≥65 yr n = 138.5	All ages n = 270.3	-	Respiratory disease hospital admissions			
Older adulthood ages ≥65 yr[b]	Adulthood, childhood ages 5−64 yr[b]	↑	Total mortality	Data from Municipal Centers for Disease Control and Prevention	17 Chinese cities	Chen et al. (2012c)
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	Wong et al. (2008b)
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	Bravo et al. (2015)
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.

[a]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.

[b]Sample size not reported.

There are a number of studies evaluating sex-based differences in SO_2-associated health effects, as detailed in Table 6-6. Studies of short-term SO_2 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_2 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_2-related COPD ED visits (Arbex et al., 2009). In children, SO_2-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_2 exposure and asthma hospital admissions. In a long-term SO_2 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_2-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_2-related health effects.

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_2-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_2 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[a]	Outcome	Study Population	Study Details	Study
Short-term exposure						
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	Ishigami et al. (2008)
Female n = 39	Male n = 114	-	Lung function (FEV_1)	Elementary school children with asthma (no cigarette smoking in home) n = 182 children (ages 9−14 yr)	Windsor, Canada October−December 2005	Dales et al. (2009)
Female n = 235	Male n = 229	-	Lung function (FEV_1, FVC, PEF, FEV_1/FVC)	Children recruited from two schools with different roadway proximity n = 464 (6−14 yr)	Salamanca, Mexico 2004−2005	Linares et al. (2010)
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	Arbex et al. (2009)
Female n = 7.4 admissions/d	Male n = 8 admissions/d	↓	Asthma hospital admissions		Eight South Korean cities 2003−2008	Son et al. (2013)

Table 6-6 (Continued): Epidemiologic studies evaluating effect modification by sex and sulfur dioxide exposure.

Factor Evaluated	Reference Category	Direction of Effect Modification[a]	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	Samoli et al. (2011)
Long-term exposure						
Female n = 1,153	Male n = 1,337	↓	Asthma incidence	Children from 36 different kindergartens n = 2,490	Changsha, China	Deng et al. (2015a)

COPD = chronic obstructive pulmonary disease; ED = emergency department; FEV_1 = forced expiratory volume in 1 sec; FVC = forced vital capacity; n = sample size; PEF = peak expiratory flow.

[a]Up facing arrow indicates that the effect of SO_2 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.

A single study (Cakmak et al., 2016) evaluated the potential for SES (income or education) to modify the effect of long-term exposure to SO_2 on respiratory effects, specifically measures of lung function. The authors observed greater decrements in lung function for those in the lowest income and education groups when compared to those in the highest. In addition, a study evaluated effect modification by education on SO_2-associated health outcomes. Chen et al. (2012c) found lower education to increase risk for mortality with short-term SO_2 exposure. Overall, the evidence for effect modification by SES on SO_2-related health outcomes is limited to a single study of respiratory health effects and one of mortality. Evidence examining short-term SO_2 exposure and total mortality is suggestive of, but not sufficient to infer, a causal relationship (Section 5.5.1). This limited evidence is inadequate to determine whether low SES increases risk for SO_2-related health effects.

6.5.4 Smoking

Smoking is a common behavior as indicated by the 2010 National Health Interview Survey, which estimated that approximately 19.2% of the U.S. adult population report being current smokers and 21.5% report being former smokers (Schiller et al., 2012). Smoking is a well-documented risk factor for many diseases, but it is unclear whether smoking exacerbates health effects associated with air pollutant exposures, including SO_2.

Dong et al. (2012), Forbes et al. (2009c), and Smith et al. (2016) investigated effect modification of the relationship between long-term exposure to SO_2 and respiratory endpoints by smoking status. Dong et al. (2012) found that among the few respiratory deaths included in their retrospective cohort study, associations with long-term ambient SO_2 were only present with current smoking. Smith et al. (2016) observed positive associations between long-term average SO_2 concentration and pulmonary tuberculosis among ever smokers, but not with never smokers. Forbes et al. (2009c), on the other hand, did not find current smoking to increase risk for lung function decrements with long-term SO_2 exposure compared to not smoking; however, former smoking did appear to increase risk in this study.

Overall, the inconsistent evidence is inadequate to determine whether smoking exacerbates SO_2-related health effects. A limited number of long-term exposure studies observed positive associations among current or former smokers, but not for never smokers for various respiratory health endpoints, including respiratory mortality. No studies evaluated smoking as an effect modifier of the relationship between short-term exposure to SO_2 and respiratory outcomes, for which there is the most confidence in the causal nature of the relationship.

6.6 Conclusions

This chapter characterized factors that may result in populations and lifestages being at increased risk for SO_2-related health effects; a summary of at-risk factors and resulting evidence classifications is included in Table 6-7. The evaluation of each factor focused on the consistency, coherence, and biological plausibility of evidence integrated across scientific disciplines: specifically, epidemiologic, controlled human exposure, and toxicological studies using the weight-of-evidence approach detailed in Table 6-1. In evaluating and integrating evidence related to at-risk factors, it is important to consider additional information including exposure concentrations, dosimetry, modes of action, and/or the independence of relationships of SO_2 exposure with health effects as detailed

in Chapter 5. For many potential at-risk factors summarized in Table 6-7, the evidence was limited with respect to ambient exposures to SO_2.

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 (Section 6.3.1)	Consistent evidence for increased risk for SO_2-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 (Section 6.5.1.1)	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 (Section 6.5.1.2)	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 (Section 6.4)	None identified	Epidemiologic findings inconsistently show differences in SO_2-related health effects, show no difference, or are limited in quantity Uncertainty in independent relationships with SO_2 provides limited basis for inferences about differential risk
	Sex (Section 6.5.2)	None identified	
	Socioeconomic status (Section 6.5.3)	None identified	
	Smoking (Section 6.5.4)	None identified	
Evidence of no effect	None		

ED = emergency department; ISA = Integrated Science Assessment; SO_2 = sulfur dioxide.

Consistent with observations made in the 2008 ISA for Sulfur Oxides (U.S. EPA, 2008d), the evidence is adequate to conclude that people with asthma are at increased risk for

SO_2-related health effects. Most of the evidence for this conclusion was presented in the previous ISA, but recent studies consistently indicate increased risk across studies. Furthermore, the evidence is based on findings for short-term SO_2 exposure and respiratory effects (specifically lung function decrements), for which a causal relationship exists (Section 5.2.1.9). There are a limited number of epidemiologic studies evaluating SO_2-related respiratory effects in people with asthma, but there is evidence for asthma-related hospital admissions and emergency department visits (Section 5.2.1.2). Further support for increased risk in individuals with asthma is provided by biological plausibility drawn from modes of action.

There is suggestive evidence of an increased risk of SO_2-related respiratory effects in children and older adults. Although the 2008 ISA for Sulfur Oxides (U.S. EPA, 2008d) discussed several studies indicating stronger associations between SO_2 and respiratory outcomes for these lifestages, the evidence in the current ISA is less consistent. For children, studies comparing SO_2-associated respiratory outcomes reported mixed results, but known age-related factors such as higher ventilation rates and time-activity patterns provide plausibility for higher SO_2 exposure and/or dose in children. For adults, recent research generally finds similar associations for SO_2-related respiratory outcomes or mortality across age groups, although individuals over 75 years were more consistently at increased risk. In addition, there was limited toxicological evidence to support observations made across epidemiologic studies.

For all other at-risk factors considered based on information available in the studies included in the current ISA, evidence was inadequate to determine whether those factors result in increased risk for SO_2-related health effects. Generally, there was a limited number of studies available evaluating SES, genetic background, race/ethnicity, and smoking. Many of these factors are interrelated and are known to impact health risks related to air pollution in general, but the scientific evidence available in the published literature specific to health effects associated with ambient SO_2 exposure is inadequate to determine whether these factors confer increased risk.

In conclusion, evidence is adequate to conclude that people with asthma are at increased risk for SO_2-related health effects. Asthma prevalence in the U.S. is approximately 8−11% across age groups (Blackwell et al., 2014; Bloom et al., 2013), and thus, represents a substantial fraction of the population that may be at risk for respiratory effects related to ambient SO_2 concentrations.

References

See Note below[1]

Abbey, DE; Nishino, N; McDonnell, WF; Burchette, RJ; Knutsen, SF; Beeson, WL; Yang, JX. (1999). Long-term inhalable particles and other air pollutants related to mortality in nonsmokers. Am J Respir Crit Care Med 159: 373-382. http://dx.doi.org/10.1164/ajrccm.159.2.9806020

Abdul-Wahab, SA; Ali, S; Sardar, S; Irfan, N; Al-Damkhi, A, li. (2011). Evaluating the performance of an integrated CALPUFF-MM5 modeling system for predicting SO2 emission from a refinery. Clean Tech Environ Pol 13: 841-854. http://dx.doi.org/10.1007/s10098-011-0360-6

Abe, M. (1967). Effects of mixed NO2-SO2 gas on human pulmonary functions: effects of air pollution on the human body. J Med Dent Sci 14: 415-433.

Abraham, WM; Oliver, W, Jr; Welker, MJ; King, MM; Wanner, A; Sackner, MA. (1981). Differences in airway reactivity in normal and allergic sheep after exposure to sulfur dioxide. J Appl Physiol 51: 1651-1656.

Ackermann-Liebrich, U; Leuenberger, P; Schwartz, J; Schindler, C; Monn, C; Bolognini, G; Bongard, JP; Brändli, O; Domenighetti, G; Elsasser, S; Grize, L; Karrer, W; Keller, R; Keller-Wossidlo, H; Künzli, N; Martin, BW; Medici, TC; Perruchoud, AP; Schöni, MH; Tschopp, JM; Villiger, B; Wüthrich, B; Zellweger, JP; Zemp, E. (1997). Lung function and long term exposure to air pollutants in Switzerland. Am J Respir Crit Care Med 155: 122-129. http://dx.doi.org/10.1164/ajrccm.155.1.9001300

Adamkiewicz, G; Ebelt, S; Syring, M; Slater, J; Speizer, FE; Schwartz, J; Suh, H; Gold, DR. (2004). Association between air pollution exposure and exhaled nitric oxide in an elderly population. Thorax 59: 204-209. http://dx.doi.org/10.1136/thorax.2003.006445

Adams, C; Riggs, P; Volckens, J. (2009). Development of a method for personal, spatiotemporal exposure assessment. J Environ Monit 11: 1331-1339. http://dx.doi.org/10.1039/b903841h

Agay-Shay, K; Friger, M; Linn, S; Peled, A; Amitai, Y; Peretz, C. (2013). Air pollution and congenital heart defects. Environ Res 124: 28-34. http://dx.doi.org/10.1016/j.envres.2013.03.005

Akinbami, LJ; Lynch, CD; Parker, JD; Woodruff, TJ. (2010). The association between childhood asthma prevalence and monitored air pollutants in metropolitan areas, United States, 2001-2004. Environ Res 110: 294-301. http://dx.doi.org/10.1016/j.envres.2010.01.001

Alarie, Y. (1973). Sensory irritation by airborne chemicals [Review]. CRC Crit Rev Toxicol 2: 299-363. http://dx.doi.org/10.3109/10408447309082020

Alarie, Y. (1981). Toxicological evaluation of airborne chemical irritants and allergens using respiratory reflex reactions. In BKJ Leong (Ed.), Inhalation toxicology and technology (pp. 207-231). Ann Arbor, MI: Ann Arbor Science Publishers, Inc.

Alarie, Y; Luo, JE. (1986). Sensory irritiation by airborne chemicals: A basis to establish acceptable levels of exposure. In CS Barrow (Ed.), Toxicology of the nasal passages (pp. 91-100). Washington, DC: Hemisphere Publishing Corporation.

Alexander, B; Park, RJ; Jacob, DJ; Gong, S. (2009). Transition metal-catalyzed oxidation of atmospheric sulfur: Global implications for the sulfur budget. J Geophys Res Atmos 114. http://dx.doi.org/10.1029/2008JD010486

[1] 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).

Alhanti, BA; Chang, HH; Winquist, A; Mulholland, JA; Darrow, LA; Sarnat, SE. (2016). Ambient air pollution and emergency department visits for asthma: A multi-city assessment of effect modification by age. J Expo Sci Environ Epidemiol 26: 180-188. http://dx.doi.org/10.1038/jes.2015.57

Allen, RW; Adar, SD; Avol, E; Cohen, M; Curl, CL; Larson, T; Liu, LJ; Sheppard, L; Kaufman, JD. (2012). Modeling the residential infiltration of outdoor PM(2.5) in the Multi-Ethnic Study of Atherosclerosis and Air Pollution (MESA Air). Environ Health Perspect 120: 824-830. http://dx.doi.org/10.1289/ehp.1104447

Almqvist, C; Worm, M; Leynaert, B. (2008). Impact of gender on asthma in childhood and adolescence: A GA2LEN review [Review]. Allergy 63: 47-57. http://dx.doi.org/10.1111/j.1398-9995.2007.01524.x

Altuğ, H; Gaga, EO; Döğeroğlu, T; Brunekreef, B; Hoek, G; Van Doorn, W. (2014). Effects of ambient air pollution on respiratory tract complaints and airway inflammation in primary school children. Sci Total Environ 479-480: 201-209. http://dx.doi.org/10.1016/j.scitotenv.2014.01.127

Altuğ, H; Gaga, EO; Döğeroğlu, T; Ozden, O; Ornektekin, S; Brunekreef, B; Meliefste, K; Hoek, G; Van Doorn, W. (2013). Effects of air pollution on lung function and symptoms of asthma, rhinitis and eczema in primary school children. Environ Sci Pollut Res Int 20: 6455-6467. http://dx.doi.org/10.1007/s11356-013-1674-1

Amadeo, B; Robert, C; Rondeau, V; Mounouchy, MA; Cordeau, L; Birembaux, X; Citadelle, E; Gotin, J; Gouranton, M; Marcin, G; Laurac, D; Raherison, C. (2015). Impact of close-proximity air pollution on lung function in schoolchildren in the French West Indies. BMC Public Health 15: 45. http://dx.doi.org/10.1186/s12889-015-1382-5

Amdur, MO; Chen, LC; Guty, J; Lam, HF; Miller, PD. (1988). Speciation and pulmonary effects of acidic SOx formed on the surface of ultrafine zinc oxide aerosols. Atmos Environ 22: 557-560. http://dx.doi.org/10.1016/0004-6981(88)90199-0

Amdur, MO; McCarthy, JF; Gill, MW. (1983). Effect of mixing conditions on irritant potency of zinc oxide and sulfur dioxide. Am Ind Hyg Assoc J 44: 7-13. http://dx.doi.org/10.1080/15298668391404284

Amdur, MO; Melvin, WW, Jr; Drinker, P. (1953). Effects of inhalation of sulphur dioxide by man. Lancet 265: 758-759. http://dx.doi.org/10.1016/S0140-6736(53)91455-X

American Heart Association. (2011). Cardiovascular disease statistics. Available online at http://web.archive.org/web/20110410093532/http://www.americanheart.org/presenter.jhtml?identifier=4478 (accessed April 12, 2011).

Ancona, C; Badaloni, C; Mataloni, F; Bolignano, A; Bucci, S; Cesaroni, G; Sozzi, R; Davoli, M; Forastiere, F. (2015). Mortality and morbidity in a population exposed to multiple sources of air pollution: A retrospective cohort study using air dispersion models. Environ Res 137: 467-474. http://dx.doi.org/10.1016/j.envres.2014.10.036

Andersen, I; Lundqvist, GR; Jensen, PL; Proctor, DF. (1974). Human response to controlled levels of sulfur dioxide. Arch Environ Occup Health 28: 31-39. http://dx.doi.org/10.1080/00039896.1974.10666429

Anderson, HR; Armstrong, B; Hajat, S; Harrison, R; Monk, V; Poloniecki, J; Timmis, A; Wilkinson, P. (2010). Air pollution and activation of implantable cardioverter defibrillators in London. Epidemiology 21: 405-413. http://dx.doi.org/10.1097/EDE.0b013e3181d61600

Anderson, HR; Bremner, SA; Atkinson, RW; Harrison, RM; Walters, S. (2001). Particulate matter and daily mortality and hospital admissions in the West Midlands conurbation of the United Kingdom: associations with fine and coarse particles, black smoke and sulphate. Occup Environ Med 58: 504-510. http://dx.doi.org/10.1136/oem.58.8.504

Andersson, E; Knutsson, A; Hagberg, S; Nilsson, T; Karlsson, B; Alfredsson, L; Toren, K. (2006). Incidence of asthma among workers exposed to sulphur dioxide and other irritant gases. Eur Respir J 27: 720-725. http://dx.doi.org/10.1183/09031936.06.00034305

Annesi-Maesano, I; Rouve, S; Desqueyroux, H; Jankovski, R; Klossek, JM; Thibaudon, M; Demoly, P; Didier, A. (2012). Grass pollen counts, air pollution levels and allergic rhinitis severity. Int Arch Allergy Immunol 158: 397-404. http://dx.doi.org/10.1159/000332964

Anyenda, EO; Higashi, T; Kambayashi, Y; Nguyen, TT; Michigami, Y; Fujimura, M; Hara, J; Tsujiguchi, H; Kitaoka, M; Asakura, H; Hori, D; Yamada, Y; Hayashi, K; Hayakawa, K; Nakamura, H. (2016). Associations of cough prevalence with ambient polycyclic aromatic hydrocarbons, nitrogen and sulphur dioxide: A longitudinal study. Int J Environ Res Public Health 13: 800. http://dx.doi.org/10.3390/ijerph13080800

Arbex, MA; de Souza Conceição, GM; Cendon, SP; Arbex, FF; Lopes, AC; Moysés, EP; Santiago, SL; Saldiva, PHN; Pereira, LAA; Braga, ALF. (2009). Urban air pollution and chronic obstructive pulmonary disease-related emergency department visits. J Epidemiol Community Health 63: 777-783. http://dx.doi.org/10.1136/jech.2008.078360

Armstrong, BK; White, E; Saracci, R. (1992). Principles of exposure measurement in epidemiology. New York, NY: Oxford University Press.

Arnedo-Pena, A; García-Marcos, L; Carvajal Urueña, I; Busquets Monge, R; Morales Suárez-Varela, M; Miner Canflanca, I; Batlles Garrido, J; Blanco Quirós, A; López-Silvarrey Varela, A; García Hernández, G; Aguinaga Ontoso, I; González Díaz, C. (2009). Air pollution and recent symptoms of asthma, allergic rhinitis, and atopic eczema in schoolchildren aged between 6 and 7 years. Arch Bronconeumol 45: 224-229. http://dx.doi.org/10.1016/S1579-2129(09)72152-4

Arts, JH; de Heer, C; Woutersen, RA. (2006). Local effects in the respiratory tract: relevance of subjectively measured irritation for setting occupational exposure limits [Review]. Int Arch Occup Environ Health 79: 283-298. http://dx.doi.org/10.1007/s00420-005-0044-9

Asgharian, B; Price, OT; Schroeter, JD; Kimbell, JS; Jones, L; Singal, M. (2011). Derivation of mass transfer coefficients for transient uptake and tissue disposition of soluble and reactive vapors in lung airways. Ann Biomed Eng 39: 1788-1804. http://dx.doi.org/10.1007/s10439-011-0274-9

Assibey-Mensah, V; Liu, K; Thurston, SW; Stevens, TP; Zhang, J; Zhang, J; Kane, C; Pan, Y; Weinberger, B; Ohman-Strickland, P; Woodruff, T; Rich, DQ. (2015). Impact of the 2008 Beijing Olympics on the risk of pregnancy complications. Arch Environ Occup Health 71: 208-215. http://dx.doi.org/10.1080/19338244.2015.1058236

Atabi, F; Jafarigol, F; Moattar, F; Nouri, J. (2016). Comparison of AERMOD and CALPUFF models for simulating SO2 concentrations in a gas refinery. Environ Monit Assess 188: 516. http://dx.doi.org/10.1007/s10661-016-5508-8

Atari, DO; Luginaah, I; Xu, X; Fung, K. (2008). Spatial variability of ambient nitrogen dioxide and sulfur dioxide in Sarnia, "Chemical Valley," Ontario, Canada. J Toxicol Environ Health A 71: 1572-1581. http://dx.doi.org/10.1080/15287390802414158

Atari, DO; Luginaah, IN; Fung, K. (2009). The relationship between odour annoyance scores and modelled ambient air pollution in Sarnia, "Chemical Valley", Ontario. Int J Environ Res Public Health 6: 2655-2675. http://dx.doi.org/10.3390/ijerph6102655

Atkinson, RW; Bremner, SA; Anderson, HR; Strachan, DP; Bland, JM; Ponce de Leon, A. (1999). Short-term associations between emergency hospital admissions for respiratory and cardiovascular disease and outdoor air pollution in London. Arch Environ Health 54: 398-411. http://dx.doi.org/10.1080/00039899909603371

Atkinson, RW; Carey, IM; Kent, AJ; van Staa, TP; Anderson, HR; Cook, DG. (2013). Long-term exposure to outdoor air pollution and incidence of cardiovascular diseases. Epidemiology 24: 44-53. http://dx.doi.org/10.1097/EDE.0b013e318276ccb8

Atkinson, RW; Carey, IM; Kent, AJ; van Staa, TP; Anderson, HR; Cook, DG. (2015). Long-term exposure to outdoor air pollution and the incidence of chronic obstructive pulmonary disease in a national English cohort. Occup Environ Med 72: 42-48. http://dx.doi.org/10.1136/oemed-2014-102266

Atkinson, RW; Cohen, A; Mehta, S; Anderson, HR. (2012). Systematic review and meta-analysis of epidemiological time-series studies on outdoor air pollution and health in Asia. Air Qual Atmos Health 5: 383-391. http://dx.doi.org/10.1007/s11869-010-0123-2

ATS (American Thoracic Society). (2000). What constitutes an adverse health effect of air pollution? Am J Respir Crit Care Med 161: 665-673. http://dx.doi.org/10.1164/ajrccm.161.2.ats4-00

ATSDR (Agency for Toxic Substances and Disease Registry). (2006). A study of ambient air contaminants and asthma in New York City: Part A and B. Atlanta, GA: U.S. Department of Health and Human Services. http://permanent.access.gpo.gov/lps88357/ASTHMA_BRONX_FINAL_REPORT.pdf

Atzori, L; Bannenberg, G; Corriga, AM; Lou, YP; Lundberg, JM; Ryrfeldt, A; Moldéus, P. (1992). Sulfur dioxide-induced bronchoconstriction via ruthenium red-sensitive activation of sensory nerves. Respiration 59: 272-278. http://dx.doi.org/10.1159/000196072

Avital, A; Noviski, N; Bar-Yishay, E; Springer, C; Levy, M; Godfrey, S. (1991). Nonspecific bronchial reactivity in asthmatic children depends on severity but not on age. Am Rev Respir Dis 144: 36-38. http://dx.doi.org/10.1164/ajrccm/144.1.36

Baccarelli, A; Zanobetti, A; Martinelli, I; Grillo, P; Hou, L; Giacomini, S; Bonzini, M; Lanzani, G; Mannucci, PM; Bertazzi, PA; Schwartz, J. (2007a). Effects of exposure to air pollution on blood coagulation. J Thromb Haemost 5: 252-260. http://dx.doi.org/10.1111/j.1538-7836.2007.02300.x

Baccarelli, A; Zanobetti, A; Martinelli, I; Grillo, P; Hou, L; Lanzani, G; Mannucci, PM; Bertazzi, PA; Schwartz, J. (2007b). Air pollution, smoking, and plasma homocysteine. Environ Health Perspect 115: 176-181. http://dx.doi.org/10.1289/ehp.9517

Bai, J; Meng, Z. (2005). Effects of sulfur dioxide on apoptosis-related gene expressions in lungs from rats. Regul Toxicol Pharmacol 43: 272-279. http://dx.doi.org/10.1016/j.yrtph.2005.09.002

Baja, ES; Schwartz, JD; Wellenius, GA; Coull, BA; Zanobetti, A; Vokonas, PS; Suh, HH. (2010). Traffic-related air pollution and QT interval: Modification by diabetes, obesity, and oxidative stress gene polymorphisms in the Normative Aging Study. Environ Health Perspect 118: 840-846. http://dx.doi.org/10.1289/ehp.0901396

Balazy, M; Abu-Yousef, IA; Harpp, DN; Park, J. (2003). Identification of carbonyl sulfide and sulfur dioxide in porcine coronary artery by gas chromatography/mass spectrometry, possible relevance to EDHF. Biochem Biophys Res Commun 311: 728-734. http://dx.doi.org/10.1016/j.bbrc.2003.10.055

Balchum, OJ; Dybicki, J; Meneely, GR. (1959). Absorption and distribution of S35O2 inhaled through the nose and mouth by dogs. Am J Physiol 197: 1317-1321.

Balchum, OJ; Dybicki, J; Meneely, GR. (1960). The dynamics of sulfur dioxide inhalation: Absorption, distribution, and retention. AMA Arch Ind Health 21: 564-569.

Baldasano, JM; Soret, A; Guevara, M; Martínez, F; Gassó, S. (2014). Integrated assessment of air pollution using observations and modelling in Santa Cruz de Tenerife (Canary Islands). Sci Total Environ 473-474: 576-588. http://dx.doi.org/10.1016/j.scitotenv.2013.12.062

Ballester, F; Rodriguez, P; Iniguez, C; Saez, M; Daponte, A; Galan, I; Taracido, M; Arribas, F; Bellido, J; Cirarda, FB; Canada, A; Guillen, JJ; Guillen-Grima, F; Lopez, E; Perez-Hoyos, S; Lertxundi, A; Toro, S. (2006). Air pollution and cardiovascular admisisons association in Spain: Results within the EMECAS project. J Epidemiol Community Health 60: 328-336. http://dx.doi.org/10.1136/jech.2005.037978

Ballester, F; Tenías, JM; Pérez-Hoyos, S. (2001). Air pollution and emergency hospital admissions for cardiovascular diseases in Valencia, Spain. J Epidemiol Community Health 55: 57-65. http://dx.doi.org/10.1136/jech.55.1.57

Balmes, JR; Fine, JM; Sheppard, D. (1987). Symptomatic bronchoconstriction after short-term inhalation of sulfur dioxide. Am J Respir Crit Care Med 136: 1117-1121. http://dx.doi.org/10.1164/ajrccm/136.5.1117

Banerjee, T; Singh, SB; Srivastava, RK. (2011). Development and performance evaluation of statistical models correlating air pollutants and meteorological variables at Pantnagar, India. Atmos Res 99: 505-517. http://dx.doi.org/10.1016/j.atmosres.2010.12.003

Bannenberg, G; Atzori, L; Xue, J; Auberson, S; Kimland, M; Ryrfeldt, A; Lundberg, JM; Moldeus, P. (1994). Sulfur dioxide and sodium metabisulfite induce bronchoconstriction in the isolated perfused and ventilated guinea pig lung via stimulation of capsaicin-sensitive sensory nerves. Respiration 61: 130-137. http://dx.doi.org/10.1159/000196324

Barr, RG; Herbstman, J; Speizer, FE; Camargo, CA, Jr. (2002). Validation of self-reported chronic obstructive pulmonary disease in a cohort study of nurses. Am J Epidemiol 155: 965-971. http://dx.doi.org/10.1093/aje/155.10.965

Barrett, EG; Day, KC; Gigliotti, AP; Reed, MD; McDonald, JD; Mauderly, JL; Seilkop, SK. (2011). Effects of simulated downwind coal combustion emissions on pre-existing allergic airway responses in mice. Inhal Toxicol 23: 792-804. http://dx.doi.org/10.3109/08958378.2011.609917

Barthelemy, P; Badier, M; Jammes, Y. (1988). Interaction between SO2 and cold-induced bronchospasm in anesthetized rabbits. Respir Physiol 71: 1-10. http://dx.doi.org/10.1016/0034-5687(88)90110-7

Baskurt, OK. (1988). Acute hematologic and hemorheologic effects of sulfur dioxide inhalation. Arch Environ Occup Health 43: 344-348. http://dx.doi.org/10.1080/00039896.1988.9934946

Bateson, TF; Coull, BA; Hubbell, B; Ito, K; Jerrett, M; Lumley, T; Thomas, D; Vedal, S; Ross, M. (2007). Panel discussion review: Session three - issues involved in interpretation of epidemiologic analyses - statistical modeling. J Expo Sci Environ Epidemiol 17: S90-S96. http://dx.doi.org/10.1038/sj.jes.7500631

Baur, X; Bakehe, P; Vellguth, H. (2012). Bronchial asthma and COPD due to irritants in the workplace - an evidence-based approach. J Occup Med Toxicol 7: 19. http://dx.doi.org/10.1186/1745-6673-7-19

Baxter, LK; Sacks, JD. (2014). Clustering cities with similar fine particulate matter exposure characteristics based on residential infiltration and in-vehicle commuting factors. Sci Total Environ 470-471: 631-638. http://dx.doi.org/10.1016/j.scitotenv.2013.10.019

Becquemin, MM; Bertholon, JF; Bouchikhi, A; Malarbet, JL; Roy, M. (1999). Oronasal ventilation partitioning in adults and children: Effect on aerosol deposition in airways. Radiat Prot Dosimetry 81: 221-228.

Bedi, JF; Folinsbee, LJ; Horvath, SM; Ebenstein, RS. (1979). Human exposure to sulfur dioxide and ozone: absence of a synergistic effect. Arch Environ Occup Health 34: 233-239. http://dx.doi.org/10.1080/00039896.1979.10667405

Beelen, R; Hoek, G; Fischer, P; van den Brandt, PA; Brunekreef, B. (2007). Estimated long-term outdoor air pollution concentrations in a cohort study. Atmos Environ 41: 13431358. http://dx.doi.org/10.1016/j.atmosenv.2006.10.020

Beelen, R; Hoek, G; van den Brandt, PA; Goldbohm, RA; Fischer, P; Schouten, LJ; Armstrong, B; Brunekreef, B. (2008a). Long-term exposure to traffic-related air pollution and lung cancer risk. Epidemiology 19: 702-710. http://dx.doi.org/10.1097/EDE.0b013e318181b3ca

Beelen, R; Hoek, G; van den Brandt, PA; Goldbohm, RA; Fischer, P; Schouten, LJ; Jerrett, M; Hughes, E; Armstrong, B; Brunekreef, B. (2008b). Long-term effects of traffic-related air pollution on mortality in a Dutch cohort (NLCS-AIR study). Environ Health Perspect 116: 196-202. http://dx.doi.org/10.1289/ehp.10767

Beirle, S; Hörmann, C; Penning de Vries, M; Dörner, S; Kern, C; Wagner, T. (2013). Estimating the volcanic emission rate and atmospheric lifetime of SO2 from space: a case study for Kīlauea volcano, Hawai'i. Atmos Chem Phys Discuss 13: 28695-28727. http://dx.doi.org/10.5194/acpd-13-28695-2013

Bell, ML; Ebisu, K; Belanger, K. (2007). Ambient air pollution and low birth weight in Connecticut and Massachusetts. Environ Health Perspect 115: 1118-1124. http://dx.doi.org/10.1289/ehp.9759

Bell, ML; Levy, JK; Lin, Z. (2008). The effect of sandstorms and air pollution on cause-specific hospital admissions in Taipei, Taiwan. Occup Environ Med 65: 104-111. http://dx.doi.org/10.1136/oem.2006.031500

Bellini, P; Baccini, M; Biggeri, A; Terracini, B. (2007). The meta-analysis of the Italian studies on short-term effects of air pollution (MISA): Old and new issues on the interpretation of the statistical evidences. Environmetrics 18: 219-229. http://dx.doi.org/10.1002/env.836

Bennett, O; Kandala, NB; Ji, C; Linnane, J; Clarke, A. (2014). Spatial variation of heart failure and air pollution in Warwickshire, UK: an investigation of small scale variation at the ward-level. BMJ Open 4: e006028. http://dx.doi.org/10.1136/bmjopen-2014-006028

Bennett, W; Zeman, K; Jarabek, A. (2003). Nasal contribution to breathing with exercise: Effect of race and gender. J Appl Physiol 95: 497-503. http://dx.doi.org/10.1152/japplphysiol.00718.2002

Bennett, WD; Zeman, KL; Jarabek, AM. (2008). Nasal contribution to breathing and fine particle deposition in children versus adults. J Toxicol Environ Health A 71: 227-237. http://dx.doi.org/10.1080/15287390701598200

Bentayeb, M; Wagner, V; Stempfelet, M; Zins, M; Goldberg, M; Pascal, M; Larrieu, S; Beaudeau, P; Cassadou, S; Eilstein, D; Filleul, L; Le Tertre, A; Medina, S; Pascal, L; Prouvost, H; Quénel, P; Zeghnoun, A; Lefranc, A. (2015). Association between long-term exposure to air pollution and mortality in France: A 25-year follow-up study. Environ Int 85: 5-14. http://dx.doi.org/10.1016/j.envint.2015.08.006

Bergen, S; Szpiro, AA. (2015). Mitigating the impact of measurement error when using penalized regression to model exposure in two-stage air pollution epidemiology studies. Environ Ecol Stat 22: 601-631. http://dx.doi.org/10.1007/s10651-015-0314-y

Berglind, N; Bellander, T; Forastiere, F; von Klot, S; Aalto, P; Elosua, R; Kulmala, M; Lanki, T; Löwel, H; Peters, A; Picciotto, S; Salomaa, V; Stafoggia, M; Sunyer, J; Nyberg, F. (2009). Ambient air pollution and daily mortality among survivors of myocardial infarction. Epidemiology 20: 110-118. http://dx.doi.org/10.1097/EDE.0b013e3181878b50

Berndt, T; Jokinen, T; Mauldin, R, III; Petaja, T; Herrmann, H; Junninen, H; Paasonen, P; Worsnop, DR; Sipila, M. (2012). Gas-phase ozonolysis of selected olefins: The yield of stabilized criegee intermediate and the reactivity toward SO2. J Phys Chem Lett 3: 2892-2896. http://dx.doi.org/10.1021/jz301158u

Bethel, RA; Epstein, J; Sheppard, D; Nadel, JA; Boushey, HA. (1983). Sulfur dioxide-induced bronchoconstriction in freely breathing, exercising, asthmatic subjects. Am Rev Respir Dis 128: 987-990.

Bethel, RA; Sheppard, D; Epstein, J; Tam, E; Nadel, JA; Boushey, HA. (1984). Interaction of sulfur dioxide and dry cold air in causing bronchoconstriction in asthmatic subjects. J Appl Physiol 57: 419-423.

Bethel, RA; Sheppard, D; Geffroy, B; Tam, E; Nadel, JA; Boushey, HA. (1985). Effect of 0.25 ppm sulfur dioxide on airway resistance in freely breathing, heavily exercising, asthmatic subjects. Am Rev Respir Dis 131: 659-661.

Bhaskaran, K; Hajat, S; Armstrong, B; Haines, A; Herrett, E; Wilkinson, P; Smeeth, L. (2011). The effects of hourly differences in air pollution on the risk of myocardial infarction: case crossover analysis of the MINAP database. B M J 343: d5531. http://dx.doi.org/10.1136/bmj.d5531

Bhattacharyya, N; Shapiro, NL. (2010). Air quality improvement and the prevalence of frequent ear infections in children. Otolaryngol Head Neck Surg 142: 242-246. http://dx.doi.org/10.1016/j.otohns.2009.10.052

Bigby, B; Boushey, H. (1993). Effects of nedocromil sodium on the bronchomotor response to sulfur dioxide in asthmatic patients. J Allergy Clin Immunol 92: 195-197. http://dx.doi.org/10.1016/0091-6749(93)90106-P

Biggeri, A; Baccini, M; Bellini, P; Terracini, B. (2005). Meta-analysis of the Italian studies of short-term effects of air pollution (MISA), 1990-1999. Int J Occup Environ Health 11: 107-122. http://dx.doi.org/10.1179/oeh.2005.11.1.107

Bishaw, A. (2012). Poverty: 2010 and 2011. American community survey briefs. Washington, DC: U.S. Department of Commerce, U.S. Census Bureau. http://www.census.gov/prod/2012pubs/acsbr11-01.pdf

Blackwell, DL; Lucas, JW; Clarke, TC. (2014). Summary health statistics for U.S. adults: National health interview survey, 2012. In Vital and health statistics. Hyattsville, MD: National Center for Health Statistics, U.S Department of Health and Human Services. http://www.cdc.gov/nchs/data/series/sr_10/sr10_260.pdf

Blanchard, CL; Hidy, GM; Tanenbaum, S; Edgerton, ES; Hartsell, BE. (2013). The Southeastern Aerosol Research and Characterization (SEARCH) study: Temporal trends in gas and PM concentrations and composition, 1999-2010. J Air Waste Manag Assoc 63: 247-259. http://dx.doi.org/10.1080/10962247.2012.748523

Bloom, B; Jones, LI; Freeman, G. (2013). Summary health statistics for U.S. children: National health interview survey, 2012. In Vital and health statistics. Hyattsville, MD: National Center for Health Statistics, U.S Department of Health and Human Services. http://www.cdc.gov/nchs/data/series/sr_10/sr10_258.pdf

Bluett, J; Gimson, N; Fisher, G; Heydenrych, C; Freeman, T; Godfrey, J. (2004). Good practice guide for atmospheric dispersion modelling: 2. Which dispersion model to use? In E New Zealand Ministry for the (Ed.), Good practice guide for atmospheric dispersion modelling (pp. 8-21). Wellington, New Zealand: Ministry for the Environment. http://www.mfe.govt.nz/publications/air/atmospheric-dispersion-modelling-jun04/html/page5.html

Bobak, M. (2000). Outdoor air pollution, low birth weight, and prematurity. Environ Health Perspect 108: 173-176. http://dx.doi.org/10.2307/3454517

Bobrowski, N; Kern, C; Platt, U; Hörmann, C; Wagner, T. (2010). Novel SO2 spectral evaluation scheme using the 360390 nm wavelength range. Atmos Meas Tech 3: 879-891. http://dx.doi.org/10.5194/amt-3-879-2010

Boezen, HM; Van Der Zee, SC; Postma, DS; Vonk, JM; Gerritsen, J; Hoek, G; Brunekreef, B; Rijcken, B; Schouten, JP. (1999). Effects of ambient air pollution on upper and lower respiratory symptoms and peak expiratory flow in children [Comment]. Lancet 353: 874-878. http://dx.doi.org/10.1016/S0140-6736(98)06311-9

Boezen, HM; Vonk, JM; Van Der Zee, SC; Gerritsen, J; Hoek, G; Brunekreef, B; Schouten, JP; Postma, DS. (2005). Susceptibility to air pollution in elderly males and females. Eur Respir J 25: 1018-1024. http://dx.doi.org/10.1183/09031936.05.00076104

Bogumil, K; Orphal, J; Homann, T; Voigt, S; Spietz, P; Fleischmann, OC; Vogel, A; Hartmann, M; Kromminga, H; Bovensmann, H; Frerick, J; Burrows, JP. (2003). Measurements of molecular absorption spectra with the SCIAMACHY pre-flight model: instrument characterization and reference data for atmospheric remote-sensing in the 230-2380 nm region. J Photochem Photobiol A 157: 167-184. http://dx.doi.org/10.1016/S1010-6030(03)00062-5

Borrell, LN; Nguyen, EA; Roth, LA; Oh, SS; Tcheurekdjian, H; Sen, S; Davis, A; Farber, HJ; Avila, PC; Brigino-Buenaventura, E; Lenoir, MA; Lurmann, F; Meade, K; Serebrisky, D; Rodriguez-Cintron, W; Kumar, R; Rodriguez-Santana, JR; Thyne, SM; Burchard, EG. (2013). Childhood obesity and asthma control in the GALA II and SAGE II studies. Am J Respir Crit Care Med 187: 697-702. http://dx.doi.org/10.1164/rccm.201211-2116OC

Boynard, A; Clerbaux, C; Clarisse, L; Safieddine, S; Pommier, M; Van Damme, M; Bauduin, S; Oudot, C; Hadji-Lazaro, J; Hurtmans, D; Coheur, PF. (2014). First simultaneous space measurements of atmospheric pollutants in the boundary layer from IASI: A case study in the North China Plain. Geophys Res Lett 41: 645-651. http://dx.doi.org/10.1002/2013GL058333

Brain, JD. (1970). The uptake of inhaled gases by the nose. Ann Otol Rhinol Laryngol 79: 529-539. http://dx.doi.org/10.1177/000348947007900315

Brauer, M; Koutrakis, P; Spengler, J. (1989). Personal exposures to acidic aerosols and gases. Environ Sci Technol 23: 1408-1412. http://dx.doi.org/10.1021/es00069a013

Brauer, M; Lencar, C; Tamburic, L; Koehoorn, M; Demers, P; Karr, C. (2008). A cohort study of traffic-related air pollution impacts on birth outcomes. Environ Health Perspect 116: 680-686. http://dx.doi.org/10.1289/ehp.10952

Bravo, MA; Son, J; de Freitas, CU; Gouveia, N; Bell, ML. (2015). Air pollution and mortality in São Paulo, Brazil: Effects of multiple pollutants and analysis of susceptible populations. J Expo Sci Environ Epidemiol 26: 150-161. http://dx.doi.org/10.1038/jes.2014.90

Breen, MS; Long, TC; Schultz, BD; Crooks, J; Breen, M; Langstaff, JE; Isaacs, KK; Tan, YM; Williams, RW; Cao, Y; Geller, AM; Devlin, RB; Batterman, SA; Buckley, TJ. (2014a). GPS-based microenvironment tracker (MicroTrac) model to estimate time-location of individuals for air pollution exposure assessments: Model evaluation in central North Carolina. J Expo Sci Environ Epidemiol 24: 412-420. http://dx.doi.org/10.1038/jes.2014.13

Breen, MS; Schultz, BD; Sohn, MD; Long, T; Langstaff, J; Williams, R; Isaacs, K; Meng, QY; Stallings, C; Smith, L. (2014b). A review of air exchange rate models for air pollution exposure assessments [Review]. J Expo Sci Environ Epidemiol 24: 555-563. http://dx.doi.org/10.1038/jes.2013.30

Briggs, GA. (1993). Plume dispersion in the convective boundary layer. Part II: Analysis of CONDORS field experiment data. J Appl Meteorol 32: 1388-1425. http://dx.doi.org/10.1175/1520-0450(1993)032<1388:PDITCB>2.0.CO;2

Brimblecombe, P. (2003). The global sulfur cycle. In HD Holland; KK Turekian (Eds.), Treatise on geochemistry (Second editions) (2nd ed., pp. 559-591). Amsterdam, The Netherlands: Elsevier Inc. http://dx.doi.org/10.1016/B978-0-08-095975-7.00814-7

Brochu, P; Bouchard, M; Haddad, S. (2014). Physiological daily inhalation rates for health risk assessment in overweight/obese children, adults, and elderly. Risk Anal 34: 567-582. http://dx.doi.org/10.1111/risa.12125

Brochu, P; Brodeur, J; Krishnan, K. (2011). Derivation of physiological inhalation rates in children, adults, and elderly based on nighttime and daytime respiratory parameters. Inhal Toxicol 23: 74-94. http://dx.doi.org/10.3109/08958378.2010.543439

Brody, DJ; Zhang, X; Kit, BK; Dillon, CF. (2013). Reference values and factors associated with exhaled nitric oxide: U.S. youth and adults. Respir Med 107: 1682-1691. http://dx.doi.org/10.1016/j.rmed.2013.07.006

Brook, RD; Kousha, T. (2015). Air pollution and emergency department visits for hypertension in Edmonton and Calgary, Canada: A case-crossover study. Am J Hypertens 28: 1121-1126. http://dx.doi.org/10.1093/ajh/hpu302

Brown, KW; Sarnat, JA; Suh, HH; Coull, BA; Koutrakis, P. (2009). Factors influencing relationships between personal and ambient concentrations of gaseous and particulate pollutants. Sci Total Environ 407: 3754-3765. http://dx.doi.org/10.1016/j.scitotenv.2009.02.016

Brunekreef, B; Beelen, R; Hoek, G; Schouten, L; Bausch-Goldbohm, S; Fischer, P; Armstrong, B; Hughes, E; Jerrett, M; van den Brandt, P. (2009). Effects of long-term exposure to traffic-related air pollution on respiratory and cardiovascular mortality in the Netherlands: The NLCS-AIR Study. (139). Boston, MA: Health Effects Institute. http://www.n65.nl/NCLS-AIR-Study-2009.pdf

Brüske, I; Hampel, R; Baumgärtner, Z; Rückerl, R; Greven, S; Koenig, W; Peters, A; Schneider, A. (2011). Ambient air pollution and lipoprotein-associated phospholipase A2 in survivors of myocardial infarction. Environ Health Perspect 119: 921-926. http://dx.doi.org/10.1289/ehp.1002681

Burke, JM; Zufall, MJ; Ozkaynak, H. (2001). A population exposure model for particulate matter: Case study results for PM2.5 in Philadelphia, PA. J Expo Anal Environ Epidemiol 11: 470-489. http://dx.doi.org/10.1038/sj.jea.7500188

Burnett, RT; Brook, J; Dann, T; Delocla, C; Philips, O; Cakmak, S; Vincent, R; Goldberg, MS; Krewski, D. (2000). Association between particulate- and gas-phase components of urban air pollution and daily mortality in eight Canadian cities. Inhal Toxicol 12: 15-39. http://dx.doi.org/10.1080/08958370050164851

Burnett, RT; Cakmak, S; Brook, JR; Krewski, D. (1997). The role of particulate size and chemistry in the association between summertime ambient air pollution and hospitalization for cardiorespiratory diseases. Environ Health Perspect 105: 614-620. http://dx.doi.org/10.1289/ehp.97105614

Burnett, RT; Smith-Doiron, M; Stieb, D; Cakmak, S; Brook, JR. (1999). Effects of particulate and gaseous air pollution on cardiorespiratory hospitalizations. Arch Environ Health 54: 130-139. http://dx.doi.org/10.1080/00039899909602248

Burnett, RT; Stieb, D; Brook, JR; Cakmak, S; Dales, R; Raizenne, M; Vincent, R; Dann, T. (2004). Associations between short-term changes in nitrogen dioxide and mortality in Canadian cities. Arch Environ Occup Health 59: 228-236. http://dx.doi.org/10.3200/AEOH.59.5.228-236

Burney, PG; Laitinen, LA; Perdrizet, S; Huckauf, H; Tattersfield, AE; Chinn, S; Poisson, N; Heeren, A; Britton, JR; Jones, T. (1989). Validity and repeatability of the IUATLD (1984) Bronchial Symptoms Questionnaire: an international comparison. Eur Respir J 2: 940-945.

Burr, ML. (1992). Diagnosing asthma by questionnaire in epidemiological surveys [Editorial]. Clin Exp Allergy 22: 509-510. http://dx.doi.org/10.1111/j.1365-2222.1992.tb00158.x

Burra, TA; Moineddin, R; Agha, MM; Glazier, RH. (2009). Social disadvantage, air pollution, and asthma physician visits in Toronto, Canada. Environ Res 109: 567-574. http://dx.doi.org/10.1016/j.envres.2009.03.004

Burrows, B; Sears, MR; Flannery, EM; Herbison, GP; Holdaway, MD; Silva, PA. (1995). Relation of the course of bronchial responsiveness from age 9 to age 15 to allergy. Am J Respir Crit Care Med 152: 1302-1308. http://dx.doi.org/10.1164/ajrccm.152.4.7551386

Burstyn, I; Cherry, NM; Yasui, Y; Kim, HM. (2008). Relative performance of different exposure modeling approaches for sulfur dioxide concentrations in the air in rural western Canada. BMC Med Res Methodol 8: 43. http://dx.doi.org/10.1186/1471-2288-8-43

Byers, N; Ritchey, M; Vaidyanathan, A; Brandt, AJ; Yip, F. (2015). Short-term effects of ambient air pollutants on asthma-related emergency department visits in Indianapolis, Indiana, 2007-2011. J Asthma 53: 1-8. http://dx.doi.org/10.3109/02770903.2015.1091006

Byun, D; Schere, KL. (2006). Review of the governing equations, computational algorithms, and other components of the models-3 community multiscale air quality (CMAQ) modeling system [Review]. Appl Mech Rev 59: 51-77. http://dx.doi.org/10.1115/1.2128636

CAA. Clean Air Act, as amended by Pub. L. No. 101-549, section 108: Air quality criteria and control techniques, 42 USC 7408, 42 USC (1990a). http://www.law.cornell.edu/uscode/text/42/7408

CAA (Clean Air Act). (1990b). Clean Air Act, as amended by Pub. L. No. 101-549, section 109: National primary and secondary ambient air quality standards, 42 USC 7409. http://www.epa.gov/air/caa/title1.html#ia

CAA. Clean Air Act, section 302: Definitions, 42 USC 7602, 42 USC (2005). http://www.gpo.gov/fdsys/pkg/USCODE-2005-title42/pdf/USCODE-2005-title42-chap85-subchapIII-sec7602.pdf

Cakmak, S; Dales, RE; Judek, S. (2006). Respiratory health effects of air pollution gases: Modification by education and income. Arch Environ Occup Health 61: 5-10. http://dx.doi.org/10.3200/AEOH.61.1.5-10

Cakmak, S; Hebbern, C; Cakmak, JD; Vanos, J. (2016). The modifying effect of socioeconomic status on the relationship between traffic, air pollution and respiratory health in elementary schoolchildren. J Environ Manage 177: 1-8. http://dx.doi.org/10.1016/j.jenvman.2016.03.051

Calkins, WH. (1994). The chemical forms of sulfur in coal - a review. Fuel 73: 475-484. http://dx.doi.org/10.1016/0016-2361(94)90028-0

Cambra, K; Martinez-Rueda, T; Alonso-Fustel, E; Cirarda, FB; Ibanez, B; Esnaola, S; Calvo, M; Aldasoro, E; Montoya, I. (2011). Mortality in small geographical areas and proximity to air polluting industries in the Basque Country (Spain). Occup Environ Med 68: 140-147. http://dx.doi.org/10.1136/oem.2009.048215

CAMP Research Group (Childhood Asthma Management Program Research Group). (1999). Recruitment of participants in the childhood Asthma Management Program (CAMP). I. Description of methods. J Asthma 36: 217-237. http://dx.doi.org/10.3109/02770909909075406

Canova, C; Torresan, S; Simonato, L; Scapellato, ML; Tessari, R; Visentin, A; Lotti, M; Maestrelli, P. (2010). Carbon monoxide pollution is associated with decreased lung function in asthmatic adults. Eur Respir J 35: 266-272. http://dx.doi.org/10.1183/09031936.00043709

Cao, J; Yang, C; Li, J; Chen, R; Chen, B; Gu, B; Kan, H. (2011). Association between long-term exposure to outdoor air pollution and mortality in China: A cohort study. J Hazard Mater 186: 1594-1600. http://dx.doi.org/10.1016/j.jhazmat.2010.12.036

Capobussi, M; Tettamanti, R; Marcolin, L; Piovesan, L; Bronzin, S; Gattoni, ME; Polloni, I; Sabatino, G; Tersalvi, CA; Auxilia, F; Castaldi, S. (2016). Air pollution impact on pregnancy outcomes in Como, Italy. J Occup Environ Med 58: 47-52. http://dx.doi.org/10.1097/JOM.0000000000000630

Carey, IM; Atkinson, RW; Kent, AJ; van Staa, T; Cook, DG; Anderson, HR. (2013). Mortality associations with long-term exposure to outdoor air pollution in a national English cohort. Am J Respir Crit Care Med 187: 1226-1233. http://dx.doi.org/10.1164/rccm.201210-1758OC

Carn, SA; Krueger, AJ; Krotkov, NA; Yang, K; Levelt, PF. (2007). Sulfur dioxide emissions from Peruvian copper smelters detected by the Ozone Monitoring Instrument. Geophys Res Lett 34: L09801. http://dx.doi.org/10.1029/2006gl029020

Carraro, S; Gottardi, G; Bonetto, G; Baraldi, E. (2007). Exhaled nitric oxide in children with asthma and sinusitis [Review]. Pediatric Allergy and Immunology 18: 28-30. http://dx.doi.org/10.1111/j.1399-3038.2007.00629.x

Carruthers, DJ; Davies, BM; Edmunds, HA; Ellis, KL; McHugh, CA; Thomson, DJ. (1995). The Atmospheric Dispersion Modelling System (ADMS): Comparisons with data from the Kincaid experiment. Int J Environ Pollut 5: 382-400. http://dx.doi.org/10.1504/IJEP.1995.028385

Carson, JL; Brighton, LE; Collier, AM; Bromberg, PA. (2013). Correlative ultrastructural investigations of airway epithelium following experimental exposure to defined air pollutants and lifestyle exposure to tobacco smoke. Inhal Toxicol 25: 134-140. http://dx.doi.org/10.3109/08958378.2013.763314

Castro, HA; Cunha, MF; Mendonça, GA; Junger, WL; Cunha-Cruz, J; Leon, AP. (2009). Effect of air pollution on lung function in schoolchildren in Rio de Janeiro, Brazil. Rev Saude Publica 43: 26-34. http://dx.doi.org/10.1590/S0034-89102009000100004

Cendon, S; Pereira, LA; Braga, AL; Conceição, GM; Cury Junior, A; Romaldini, H; Lopes, AC; Saldiva, PH. (2006). Air pollution effects on myocardial infarction. Rev Saude Publica 40: 414-419. http://dx.doi.org/10.1590/S0034-89102006000300008

Chadha, TS; Birch, S; Sackner, MA. (1987). Oronasal distribution of ventilation during exercise in normal subjects and patients with asthma and rhinitis. Chest 92: 1037-1041. http://dx.doi.org/10.1378/chest.92.6.1037

Chambers, JM; Cleveland, WS; Kleiner, B; Tukey, JA. (1983). Comparing data distributions. In Graphical methods for data analysis. Belmont, California; Boston, Massachusetts: Wadsworth international Group, Duxbury Press.

Chan, L; QiHong, D; CuiYun, O; WeiWei, L; Sundell, J, an. (2013). Effects of ambient air pollution on allergic rhinitis among preschool children in Changsha, China. Chin Sci Bull 58: 4252-4258. http://dx.doi.org/10.1007/s11434-013-5725-2

Chandra, A; Copen, CE; Stephen, EH. (2013). Infertility and impaired fecundity in the United States, 1982-2010: data from the National Survey of Family Growth. Atlanta, GA: Centers for Disease Control. http://www.cdc.gov/nchs/data/nhsr/nhsr067.pdf

Chang, CC; Tsai, SS; Ho, SC; Yang, CY. (2005). Air pollution and hospital admissions for cardiovascular disease in Taipei, Taiwan. Environ Res 98: 114-119. http://dx.doi.org/10.1016/j.envres.2004.07.005

Chang, HH; Fuentes, M; Frey, HC. (2012a). Time series analysis of personal exposure to ambient air pollution and mortality using an exposure simulator. J Expo Sci Environ Epidemiol 22: 483-488. http://dx.doi.org/10.1038/jes.2012.53

Chang, JC; Hanna, SR. (2004). Air quality model performance evaluation. Meteorol Atmos Phys 87: 167-196. http://dx.doi.org/10.1007/s00703-003-0070-7

Chang, JC; Hanna, SR. (2005). Technical descriptions and users guide for the BOOT statistical model evaluation software package, Version 2.0. Available online at http://www.harmo.org/kit/Download/BOOT_UG.pdf

Chang, LT; Koutrakis, P; Catalano, PJ; Suh, HH. (2000). Hourly personal exposures to fine particles and gaseous pollutants--Results from Baltimore, Maryland. J Air Waste Manag Assoc 50: 1223-1235. http://dx.doi.org/10.1080/10473289.2000.10464151

Chang, YK; Wu, CC; Lee, LT; Lin, RS; Yu, YH; Chen, YC. (2012b). The short-term effects of air pollution on adolescent lung function in Taiwan. Chemosphere 87: 26-30. http://dx.doi.org/10.1016/j.chemosphere.2011.11.048

Chapman, RS; Calafiore, DC; Hasselblad, V. (1985). Prevalence of persistent cough and phlegm in young adults in relation to long-term ambient sulfur oxide exposure. Am Rev Respir Dis 132: 261-267.

Che, WW; Frey, HC; Lau, AK. (2014). Assessment of the effect of population and diary sampling methods on estimation of school-age children exposure to fine particles. Risk Anal 34: 2066-2079. http://dx.doi.org/10.1111/risa.12238

Chen, BY; Chan, CC; Lee, CT; Cheng, TJ; Huang, WC; Jhou, JC; Han, YY; Chen, CC; Guo, YL. (2012a). The association of ambient air pollution with airway inflammation in schoolchildren. Am J Epidemiol 175: 764-774. http://dx.doi.org/10.1093/aje/kwr380

Chen, G; Li, J; Ying, Q; Sherman, S; Perkins, N; Rajeshwari, S; Mendola, P. (2014a). Evaluation of observation-fused regional air quality model results for population air pollution exposure estimation. Sci Total Environ 485-486: 563-574. http://dx.doi.org/10.1016/j.scitotenv.2014.03.107

Chen, G; Wan, X, ia; Yang, G; Zou, X. (2015a). Traffic-related air pollution and lung cancer: A meta-analysis. 6: 307-318. http://dx.doi.org/10.1111/1759-7714.12185

Chen, L; Bell, EM; Caton, AR; Druschel, CM; Lin, S. (2010a). Residential mobility during pregnancy and the potential for ambient air pollution exposure misclassification. Environ Res 110: 162-168. http://dx.doi.org/10.1016/j.envres.2009.11.001

Chen, L; Villeneuve, PJ; Rowe, BH; Liu, L; Stieb, DM. (2014b). The Air Quality Health Index as a predictor of emergency department visits for ischemic stroke in Edmonton, Canada. J Expo Sci Environ Epidemiol 24: 358-364. http://dx.doi.org/10.1038/jes.2013.82

Chen, L; Zhou, Y; Li, S; Williams, G; Kan, H; Marks, GB; Morawska, L; Abramson, MJ; Chen, S; Yao, T; Qin, T; Wu, S; Guo, Y. (2015b). Air pollution and fasting blood glucose: A longitudinal study in China. Sci Total Environ 541: 750-755. http://dx.doi.org/10.1016/j.scitotenv.2015.09.132

Chen, R; Chu, C; Tan, J; Cao, J; Song, W; Xu, X; Jiang, C; Ma, W; Yang, C; Chen, B; Gui, Y; Kan, H. (2010b). Ambient air pollution and hospital admission in Shanghai, China. J Hazard Mater 181: 234-240. http://dx.doi.org/10.1016/j.jhazmat.2010.05.002

Chen, R; Huang, W; Wong, CM; Wang, Z; Thach, TQ; Chen, B; Kan, H. (2012b). Short-term exposure to sulfur dioxide and daily mortality in 17 Chinese cities: The China air pollution and health effects study (CAPES). Environ Res 118: 101-106. http://dx.doi.org/10.1016/j.envres.2012.07.003

Chen, R; Samoli, E; Wong, CM; Huang, W; Wang, Z; Chen, B; Kan, H. (2012c). Associations between short-term exposure to nitrogen dioxide and mortality in 17 Chinese cities: The China Air Pollution and Health Effects Study (CAPES). Environ Int 45: 32-38. http://dx.doi.org/10.1016/j.envint.2012.04.008

Chen, R; Zhang, Y; Yang, C; Zhao, Z; Xu, X; Kan, H. (2013). Acute effect of ambient air pollution on stroke mortality in the china air pollution and health effects study. Stroke 44: 954-960. http://dx.doi.org/10.1161/STROKEAHA.111.673442

Chen, SY; Su, TC; Lin, YL; Chan, CC. (2012d). Short-term effects of air pollution on pulse pressure among nonsmoking adults. Epidemiology 23: 341-348. http://dx.doi.org/10.1097/EDE.0b013e3182452f1d

Chen, X; Zhang, LW; Huang, JJ; Song, FJ; Zhang, LP; Qian, ZM; Trevathan, E; Mao, HJ; Han, B; Vaughn, M; Chen, KX; Liu, YM; Chen, J; Zhao, BX; Jiang, GH; Gu, Q; Bai, ZP; Dong, GH; Tang, NJ. (2016). Long-term exposure to urban air pollution and lung cancer mortality: A 12-year cohort study in Northern China. Sci Total Environ 571: 855-861. http://dx.doi.org/10.1016/j.scitotenv.2016.07.064

Cheng, MF; Tsai, SS; Yang, CY. (2009). Air pollution and hospital admissions for myocardial infarction in a tropical city: Kaohsiung, Taiwan. J Toxicol Environ Health A 72: 1135-1140. http://dx.doi.org/10.1080/15287390903091756

Cherniack, R; Adkinson, NF; Strunk, R; Szefler, S; Tonascia, J; Weiss, S. (1999). The Childhood Asthma Management Program (CAMP): Design, rationale, and methods. Childhood Asthma Management Program Research Group. Contr Clin Trials 20: 91-120. http://dx.doi.org/10.1016/S0197-2456(98)00044-0

Chiang, TY; Yuan, TH; Shie, RH; Chen, CF; Chan, CC. (2016a). Increased incidence of allergic rhinitis, bronchitis and asthma, in children living near a petrochemical complex with SO2 pollution. Environ Int 96: 1-7. http://dx.doi.org/10.1016/j.envint.2016.08.009

Chiang, TY; Yuan, TH; Shie, RH; Chen, CF; Chan, CC. (2016b). Increased incidence of allergic rhinitis, bronchitis and asthma, in children living near a petrochemical complex with SO2 pollution - Supplementary data [Supplemental Data]. Environ Int 96.

Chin, M; Savoie, DL; Huebert, BJ; Bandy, AR; Thornton, DC; Bates, TS; Quinn, PK; Saltzman, ES; De Bruyn, WJ. (2000). Atmospheric sulfur cycle simulated in the global model GOCART: Comparison with field observations and regional budgets. J Geophys Res Atmos 105: 24689-24712. http://dx.doi.org/10.1029/2000JD900385

Ching, J; Herwehe, J; Swall, J. (2006). On joint deterministic grid modeling and sub-grid variability conceptual framework for model evaluation. Atmos Environ 40: 4935-4945. http://dx.doi.org/10.1016/j.atmonsenv.2006.01.021

Chowdhury, B; Sykes, I; Henn, D; Knipping, E; Karamchandani, P. (2012). Summary of updates to SCICHEM-2012 model: comparison of results with observations and previous version results. Presentation presented at 11th Annual CMAS Conference, October 15-17, 2012, UNC-Chapel Hill.

Chuang, KJ; Chan, CC; Su, TC; Lin, LY; Lee, CT. (2007). Associations between particulate sulfate and organic carbon exposures and heart rate variability in patients with or at risk for cardiovascular diseases. J Occup Environ Med 49: 610-617. http://dx.doi.org/10.1097/JOM.0b013e318058205b

Chuang, KJ; Coull, BA; Zanobetti, A; Suh, H; Schwartz, J; Stone, PH; Litonjua, A; Speizer, FE; Gold, DR. (2008). Particulate air pollution as a risk factor for ST-segment depression in patients with coronary artery disease. Circulation 118: 1314-1320. http://dx.doi.org/10.1161/CIRCULATIONAHA.108.765669

Chuang, KJ; Yan, YH; Cheng, TJ. (2010). Effect of air pollution on blood pressure, blood lipids, and blood sugar: A population-based approach. J Occup Environ Med 52: 258-262. http://dx.doi.org/10.1097/JOM.0b013e3181ceff7a

Chuang, KJ; Yan, YH; Chiu, SY; Cheng, TJ. (2011). Long-term air pollution exposure and risk factors for cardiovascular diseases among the elderly in Taiwan. Occup Environ Med 68: 64-68. http://dx.doi.org/10.1136/oem.2009.052704

Chung, MK; Lao, TT; Ting, YH; Wong, TW; Leung, TY. (2014). Seasonality of fetal trisomy 21 - Have ambient air pollutants played a role? J Matern Fetal Neonatal Med 28: 552-557. http://dx.doi.org/10.3109/14767058.2014.924104

Cimorelli, AJ; Perry, SG; Venkatram, A; Weil, JC; Paine, R; Wilson, RB; Lee, RF; Peters, WD; Brode, RW. (2005). AERMOD: A dispersion model for industrial source applications. Part I: General model formulation and boundary layer characterization. J Appl Meteorol 44: 682-693. http://dx.doi.org/10.1175/JAM2227.1

Clarisse, L; Fromm, M; Ngadi, Y; Emmons, L; Clerbaux, C; Hurtmans, D; Coheur, PF. (2011). Intercontinental transport of anthropogenic sulfur dioxide and other pollutants: An infrared remote sensing case study. Geophys Res Lett 38: L19806. http://dx.doi.org/10.1029/2011GL048976

Clarisse, L; Hurtmans, D; Clerbaux, C; Hadji-Lazaro, J; Ngadi, Y; Coheur, PF. (2012). Retrieval of sulphur dioxide from the infrared atmospheric sounding interferometer (IASI). Atmos Meas Tech 5: 581-594. http://dx.doi.org/10.5194/amt-5-581-2012

Clark, NA; Demers, PA; Karr, CJ; Koehoorn, M; Lencar, C; Tamburic, L; Brauer, M. (2010). Effect of early life exposure to air pollution on development of childhood asthma. Environ Health Perspect 118: 284-290. http://dx.doi.org/10.1289/ehp.0900916

Clarke, JF; Edgerton, ES; Martin, BE. (1997). Dry deposition calculations for the clean air status and trends network. Atmos Environ 31: 3667-3678. http://dx.doi.org/10.1016/S1352-2310(97)00141-6

Clougherty, JE; Kheirbek, I; Eisl, HM; Ross, Z; Pezeshki, G; Gorczynski, JE; Johnson, S; Markowitz, S; Kass, D; Matte, T. (2013). Intra-urban spatial variability in wintertime street-level concentrations of multiple combustion-related air pollutants: The New York City Community Air Survey (NYCCAS). J Expo Sci Environ Epidemiol 23: 232-240. http://dx.doi.org/10.1038/jes.2012.125

Coletta, C; Papapetropoulos, A; Erdelyi, K; Olah, G; Modis, K; Panopoulos, P; Asimakopoulou, A; Geroe, D; Sharina, I; Martin, E; Szabo, C. (2012). Hydrogen sulfide and nitric oxide are mutually dependent in the regulation of angiogenesis and endothelium-dependent vasorelaxation. Proc Natl Acad Sci USA 109: 9161-9166. http://dx.doi.org/10.1073/pnas.1202916109

Collaco, CR; Hochman, DJ; Goldblum, RM; Brooks, EG. (2006). Effect of sodium sulfite on mast cell degranulation and oxidant stress. Ann Allergy Asthma Immunol 96: 550-556. http://dx.doi.org/10.1016/S1081-1206(10)63549-1

Conner, MW; Flood, WH; Rogers, AE; Amdur, MO. (1989). Changes in pulmonary lavage fluid of guinea pigs exposed to ultrafine zinc oxide with adsorbed sulfuric acid. J Toxicol Environ Health 26: 223-234. http://dx.doi.org/10.1080/15287398909531247

Conner, MW; Lam, HF; Rogers, AE; Fitzgerald, S; Amdur, MO. (1985). Lung injury in guinea pigs caused by multiple exposures to submicron zinc oxide mixed with sulfur dioxide in a humidified furnace. J Toxicol Environ Health 16: 101-114. http://dx.doi.org/10.1080/15287398509530722

Correia-Deur, J; Claudio, L; Imazawa, AT; Eluf-Neto, J. (2012). Variations in peak expiratory flow measurements associated to air pollution and allergic sensitization in children in Sao Paulo, Brazil. Am J Ind Med 55: 1087-1098. http://dx.doi.org/10.1002/ajim.22060

Costa Nascimento, LF; Francisco, JB; Patto, MBR; Antunes, AM. (2012). Environmental pollutants and stroke-related hospital admissions. Cad Saude Publica 28: 1319-1324. http://dx.doi.org/10.1590/S0102-311X2012000700010

Cox, WM; Tikvart, JA. (1990). A statistical procedure for determining the best performing air quality simulation model. Atmos Environ A 24: 2387-2395. http://dx.doi.org/10.1016/0960-1686(90)90331-G

Crouse, U; Laine-Alava, MT. (1999). Effects of age, body mass index, and gender on nasal airflow rate and pressures. Laryngoscope 109: 1503-1508. http://dx.doi.org/10.1097/00005537-199909000-00027

Dabberdt, WF; Miller, E. (2000). Uncertainty, ensembles and air quality dispersion modeling: applications and challenges. Atmos Environ 34: 4667-4673. http://dx.doi.org/10.1016/S1352-2310(00)00141-2

Dadvand, P; Rankin, J; Rushton, S; Pless-Mulloli, T. (2011a). Ambient air pollution and congenital heart disease: A register-based study. Environ Res 111: 435-441. http://dx.doi.org/10.1016/j.envres.2011.01.022

Dadvand, P; Rankin, J; Rushton, S; Pless-Mulloli, T. (2011b). Association between maternal exposure to ambient air pollution and congenital heart disease: A register-based spatiotemporal analysis. Am J Epidemiol 173: 171-182. http://dx.doi.org/10.1093/aje/kwq342

Dales, R; Chen, L; Frescura, AM; Liu, L; Villeneuve, PJ. (2009). Acute effects of outdoor air pollution on forced expiratory volume in 1 s: A panel study of schoolchildren with asthma. Eur Respir J 34: 316-323. http://dx.doi.org/10.1183/09031936.00138908

Dales, R; Kauri, LM; Cakmak, S; Mahmud, M; Weichenthal, SA; Van Ryswyk, K; Kumarathasan, P; Thomson, E; Vincent, R; Broad, G; Liu, L. (2013). Acute changes in lung function associated with proximity to a steel plant: A randomized study. Environ Int 55: 15-19. http://dx.doi.org/10.1016/j.envint.2013.01.014

Dales, R; Wheeler, A; Mahmud, M; Frescura, AM; Smith-Doiron, M; Nethery, E; Liu, L. (2008). The influence of living near roadways on spirometry and exhaled nitric oxide in elementary schoolchildren. Environ Health Perspect 116: 1423-1427. http://dx.doi.org/10.1289/ehp.10943

Dales, RE; Cakmak, S; Doiron, MS. (2006). Gaseous air pollutants and hospitalization for respiratory disease in the neonatal period. Environ Health Perspect 114: 1751-1754.

Dales, RE; Cakmak, S; Vidal, CB. (2010). Air pollution and hospitalization for venous thromboembolic disease in Chile. J Thromb Haemost 8: 669-674. http://dx.doi.org/10.1111/j.1538-7836.2010.03760.x

Darrow, LA; Klein, M; Flanders, WD; Waller, LA; Correa, A; Marcus, M; Mulholland, JA; Russell, AG; Tolbert, PE. (2009). Ambient air pollution and preterm birth: A time-series analysis. Epidemiology 20: 689-698. http://dx.doi.org/10.1097/EDE.0b013e3181a7128f

Darrow, LA; Klein, M; Strickland, MJ; Mulholland, JA; Tolbert, PE. (2011). Ambient air pollution and birth weight in full-term infants in Atlanta, 1994-2004. Environ Health Perspect 119: 731-737. http://dx.doi.org/10.1289/ehp.1002785

Deger, L; Plante, C; Jacques, L; Goudreau, S; Perron, S; Hicks, J; Kosatsky, T; Smargiassi, A. (2012). Active and uncontrolled asthma among children exposed to air stack emissions of sulphur dioxide from petroleum refineries in Montreal, Quebec: A cross-sectional study. Can Respir J 19: 97-102.

Delfino, RJ; Coate, BD; Zeiger, RS; Seltzer, JM; Street, DH; Koutrakis, P. (1996). Daily asthma severity in relation to personal ozone exposure and outdoor fungal spores. Am J Respir Crit Care Med 154: 633-641. http://dx.doi.org/10.1164/ajrccm.154.3.8810598

Delfino, RJ; Gone, H; Linn, WS; Pellizzari, ED; Hu, Y. (2003a). Asthma symptoms in Hispanic children and daily ambient exposures to toxic and criteria air pollutants. Environ Health Perspect 111: 647-656.

Delfino, RJ; Gong, H; Linn, WS; Hu, Y; Pellizzari, ED. (2003b). Respiratory symptoms and peak expiratory flow in children with asthma in relation to volatile organic compounds in exhaled breath and ambient air. J Expo Anal Environ Epidemiol 13: 348-363. http://dx.doi.org/10.1038/sj.jea.7500287

Demokritou, P; Kavouras, IG; Ferguson, ST; Koutrakis, P. (2001). Development and laboratory performance evaluation of a personal multipollutant sampler for simultaneous measurements for particulate and gaseous pollutants. Aerosol Sci Technol 35: 741-752. http://dx.doi.org/10.1080/02786820152546789

Deng, Q; Lu, C; Norbäck, D; Bornehag, CG; Zhang, Y; Liu, W; Yuan, H; Sundell, J. (2015a). Early life exposure to ambient air pollution and childhood asthma in China. Environ Res 143: 83-92. http://dx.doi.org/10.1016/j.envres.2015.09.032

Deng, Q; Lu, C; Ou, C; Liu, W. (2015b). Effects of early life exposure to outdoor air pollution and indoor renovation on childhood asthma in China. Build Environ 93: 84-91. http://dx.doi.org/10.1016/j.buildenv.2015.01.019

Dennekamp, M; Akram, M; Abramson, MJ; Tonkin, A; Sim, MR; Fridman, M; Erbas, B. (2010). Outdoor air pollution as a trigger for out-of-hospital cardiac arrests. Epidemiology 21: 494-500. http://dx.doi.org/10.1097/EDE.0b013e3181e093db

Devalia, JL; Rusznak, C; Herdman, MJ; Trigg, CJ; Tarraf, H; Davies, RJ. (1994). Effect of nitrogen-dioxide and sulfur-dioxide on airway response of mild asthmatic-patients to allergen inhalation. Lancet 344: 1668-1671. http://dx.doi.org/10.1016/S0140-6736(94)90458-8

Dibben, C; Clemens, T. (2015). Place of work and residential exposure to ambient air pollution and birth outcomes in Scotland, using geographically fine pollution climate mapping estimates. Environ Res 140: 535-541. http://dx.doi.org/10.1016/j.envres.2015.05.010

Dionisio, KL; Baxter, LK; Chang, HH. (2014). An empirical assessment of exposure measurement error and effect attenuation in bipollutant epidemiologic models. Environ Health Perspect 122: 1216-1224. http://dx.doi.org/10.1289/ehp.1307772

Dockery, DW; Pope, CA, III; Xu, X; Spengler, JD; Ware, JH; Fay, ME; Ferris, BG, Jr; Speizer, FE. (1993). An association between air pollution and mortality in six US cities. N Engl J Med 329: 1753-1759. http://dx.doi.org/10.1056/NEJM199312093292401

Dockery, DW; Speizer, FE; Stram, DO; Ware, JH; Spengler, JD; Ferris, BG, Jr. (1989). Effects of inhalable particles on respiratory health of children. Am J Respir Crit Care Med 139: 587-594. http://dx.doi.org/10.1164/ajrccm/139.3.587

Dodge, R; Solomon, P; Moyers, J; Hayes, C. (1985). A longitudinal study of children exposed to sulfur oxides. Am J Epidemiol 121: 720-736. http://dx.doi.org/10.1093/aje/121.5.720

Dolk, H; Armstrong, B; Lachowycz, K; Vrijheid, M; Rankin, J; Abramsky, L; Boyd, PA; Wellesley, D. (2010). Ambient air pollution and risk of congenital anomalies in England, 1991-1999. Occup Environ Med 67: 223-227. http://dx.doi.org/10.1136/oem.2009.045997

Dollard, GJ; Unsworth, MH; Harve, MJ. (1983). Pollutant transfer in upland regions by occult precipitation. Nature 302: 241-243. http://dx.doi.org/10.1038/302241a0

Dominici, F; McDermott, A; Daniels, M; Zeger, SL; Samet, JM. (2003). Mortality among residents of 90 cities [HEI]. In Revised analyses of time-series studies of air pollution and health (pp. 9-24). Boston, MA: Health Effects Institute. http://pubs.healtheffects.org/view.php?id=4

Dong, G; Qian, Z; Wang, J; Chen, W; Ma, W; Trevathan, E; Xaverius, PK; DeClue, R; Wiese, A; Langston, M; Liu, MM; Wang, D; Ren, W. (2013a). Associations between ambient air pollution and prevalence of stroke and cardiovascular diseases in 33 Chinese communities. Atmos Environ 77: 968-973. http://dx.doi.org/10.1016/j.atmosenv.2013.06.034

Dong, GH; Qian, Z; Liu, MM; Wang, D; Ren, WH; Fu, Q; Wang, J; Simckes, M; Ferguson, TF; Trevathan, E. (2013b). Obesity enhanced respiratory health effects of ambient air pollution in Chinese children: the Seven Northeastern Cities study. Int J Obes (Lond) 37: 94-100. http://dx.doi.org/10.1038/ijo.2012.125

Dong, GH; Qian, ZM; Liu, MM; Wang, D; Ren, WH; Bawa, S; Fu, J; Wang, J; Lewis, R; Zelicoff, A; Simckes, M; Trevathan, E. (2013c). Breastfeeding as a modifier of the respiratory effects of air pollution in children. Epidemiology 24: 387-394. http://dx.doi.org/10.1097/EDE.0b013e3182877eb8

Dong, GH; Qian, ZM; Trevathan, E; Zeng, XW; Vaughn, MG; Wang, J; Zhao, Y; Liu, YQ; Ren, WH; Qin, XD. (2014). Air pollution associated hypertension and increased blood pressure may be reduced by breastfeeding in Chinese children: the Seven Northeastern Cities Chinese Children's Study. Int J Cardiol 176: 956-961. http://dx.doi.org/10.1016/j.ijcard.2014.08.099

Dong, GH; Qian, ZM; Xaverius, PK; Trevathan, E; Maalouf, S; Parker, J; Yang, L; Liu, MM; Wang, D; Ren, WH; Ma, W; Wang, J; Zelicoff, A; Fu, Q; Simckes, M. (2013d). Association between long-term air pollution and increased blood pressure and hypertension in China. Hypertension 61: 578-584. http://dx.doi.org/10.1161/HYPERTENSIONAHA.111.00003

Dong, GH; Wang, J; Zeng, XW; Chen, L; Qin, XD; Zhou, Y; Li, M; Yang, M; Zhao, Y; Ren, WH; Hu, QS. (2015). Interactions between air pollution and obesity on blood pressure and hypertension in Chinese children. Epidemiology 26: 740-747. http://dx.doi.org/10.1097/EDE.0000000000000336

Dong, GH; Zhang, P; Sun, B; Zhang, L; Chen, X; Ma, N; Yu, F; Guo, H; Huang, H; Lee, YL; Tang, N; Chen, J. (2012). Long-term exposure to ambient air pollution and respiratory disease mortality in Shenyang, China: A 12-year population-based retrospective cohort study. Respiration 84: 360-368. http://dx.doi.org/10.1159/000332930

Dourado, H; Santos, J; Reis, N, Jr; Melo, AMV. (2012). The effects of atmospheric turbulence on peak-to-mean concentration ratio and its consequence on the odour impact assessment using dispersion models. Chemical Engineering Transactions 30: 163-168. http://dx.doi.org/10.3303/CET1230028

Draxler, RR. (1999). HYSPLIT_4 user's guide. Available online at http://ready.arl.noaa.gov/HYSPLIT.php

Dubowsky, SD; Suh, H; Schwartz, J; Coull, BA; Gold, DR. (2006). Diabetes, obesity, and hypertension may enhance associations between air pollution and markers of systemic inflammation. Environ Health Perspect 114: 992-998. http://dx.doi.org/10.1289/ehp.8469

Dugandzic, R; Dodds, L; Stieb, D; Smith-Doiron, M. (2006). The association between low level exposures to ambient air pollution and term low birth weight: A retrospective cohort study. Environ Health 5: 3. http://dx.doi.org/10.1186/1476-069X-5-3

Eatough, DJ; Arthur, RJ; Eatough, NL; Hill, MW; Mangelson, NF; Richter, BE; Hansen, LD; Cooper, JA. (1984). Rapid conversion of SO2(g) to sulfate in a fog bank. Environ Sci Technol 18: 855-859.

Ebisu, K; Bell, ML. (2012). Airborne PM2.5 chemical components and low birth weight in the Northeastern and Mid-Atlantic regions of the United States. Environ Health Perspect 120: 1746-1752. http://dx.doi.org/10.1289/ehp.1104763

Eitan, O; Yuval, O; Barchana, M; Dubnov, J; Linn, S; Carmel, Y; Broday, DM. (2010). Spatial analysis of air pollution and cancer incidence rates in Haifa Bay, Israel. Sci Total Environ 408: 4429-4439. http://dx.doi.org/10.1016/j.scitotenv.2010.06.031

Elgethun, K; Yost, MG; Fitzpatrick, CTE; Nyerges, TL; Fenske, RA. (2007). Comparison of global positioning system (GPS) tracking and parent-report diaries to characterize children's time-location patterns. J Expo Sci Environ Epidemiol 17: 196-206. http://dx.doi.org/10.1038/sj.jes.7500496

Elliott, P; Shaddick, G; Wakefield, JC; de Hoogh, C; Briggs, DJ. (2007). Long-term associations of outdoor air pollution with mortality in Great Britain. Thorax 62: 1088-1094. http://dx.doi.org/10.1136/thx.2006.076851

Enkhmaa, D; Warburton, N; Javzandulam, B; Uyanga, J; Khishigsuren, Y; Lodoysamba, S; Enkhtur, S; Warburton, D. (2014). Seasonal ambient air pollution correlates strongly with spontaneous abortion in Mongolia. BMC Pregnancy Childbirth 14: 146. http://dx.doi.org/10.1186/1471-2393-14-146

Etlik, O; Tomur, A; Kutman, MN; Yorukan, S; Duman, O. (1995). The effects of sulfur dioxide inhalation and antioxidant vitamins on red blood cell lipoperoxidation. Environ Res 71: 25-28. http://dx.doi.org/10.1006/enrs.1995.1063

Faiz, AS; Rhoads, GG; Demissie, K; Kruse, L; Lin, Y; Rich, DQ. (2012). Ambient air pollution and the risk of stillbirth. Am J Epidemiol 176: 308-316. http://dx.doi.org/10.1093/aje/kws029

Faiz, AS; Rhoads, GG; Demissie, K; Lin, Y; Kruse, L; Rich, DQ. (2013). Does ambient air pollution trigger stillbirth? Epidemiology 24: 538-544. http://dx.doi.org/10.1097/EDE.0b013e3182949ce5

Farhi, A; Boyko, V; Almagor, J; Benenson, I; Segre, E; Rudich, Y; Stern, E; Lerner-Geva, L. (2014). The possible association between exposure to air pollution and the risk for congenital malformations. Environ Res 135C: 173-180. http://dx.doi.org/10.1016/j.envres.2014.08.024

Fattore, E; Davoli, E; Castiglioni, S; Bosetti, C; Re Depaolini, A; Marzona, I; Zuccato, E; Fanelli, R. (2016). Wastewater-based epidemiological evaluation of the effect of air pollution on short-acting beta-agonist consumption for acute asthma treatment. Environ Res 150: 106-111. http://dx.doi.org/10.1016/j.envres.2016.05.051

Feichter, J; Kjellstrom, E; Rodhe, H; Dentener, F; Lelieveld, J; Roelofs, GJ. (1996). Simulation of the tropospheric sulfur cycle in a global climate model. Atmos Environ 30: 1693-1707. http://dx.doi.org/10.1016/1352-2310(95)00394-0

Ferek, RJ; Covert, PA; Luke, W. (1997). Intercomparison of measurements of sulfur dioxide in ambient air by carbonate-impregnated filters and Teco pulsed-fluorescence analyzers. J Geophys Res Atmos 102: 1626716272. http://dx.doi.org/10.1029/96JD03587

Ferris, BG. (1978). Epidemiology standardization project II: Recommended respiratory disease questionnaires for use with adults and children in epidemiological research. Am J Respir Crit Care Med 118: 7-53.

Field, PI; Simmul, R; Bell, SC; Allen, DH; Berend, N. (1996). Evidence for opioid modulation and generation of prostaglandins in sulphur dioxide (SO)2-induced bronchoconstriction. Thorax 51: 159-163.

Filho, MAP; Pereira, LAA; Arbex, FF; Arbex, M; Conceição, GM; Santos, UP; Lopes, AC; Saldiva, PHN; Braga, ALF; Cendon, S. (2008). Effect of air pollution on diabetes and cardiovascular diseases in São Paulo, Brazil. Braz J Med Biol Res 41: 526-532. http://dx.doi.org/10.1590/S0100-879X2008005000020

Filipovic, MR; Miljkovic, J; Nauser, T; Royzen, M; Klos, K; Shubina, T; Koppenol, WH; Lippard, SJ; Ivanovic-Burmazovic, I. (2012). Chemical characterization of the smallest S-nitrosothiol, HSNO; cellular cross-talk of H2S and S-nitrosothiols. J Am Chem Soc 134: 12016-12027. http://dx.doi.org/10.1021/ja3009693

Filleul, L; Rondeau, V; Vandentorren, S; Le Moual, N; Cantagrel, A; Annesi-Maesano, I; Charpin, D; Declercq, C; Neukirch, F; Paris, C; Vervloet, D; Brochard, P; Tessier, JF; Kauffmann, F; Baldi, I. (2005). Twenty five year mortality and air pollution: Results from the French PAARC survey. Occup Environ Med 62: 453-460. http://dx.doi.org/10.1136/oem.2004.014746

Finkelstein, JN; Johnston, CJ. (2004). Enhanced sensitivity of the postnatal lung to environmental insults and oxidant stress [Review]. Pediatrics 113: 1092-1096. http://dx.doi.org/10.1542/peds.113.4.S1.1092

Finlayson-Pitts, BJ; Pitts, JN, Jr. (2000). Chemistry of the upper and lower atmosphere: Theory, experiments and applications. San Diego, CA: Academic Press. http://www.sciencedirect.com/science/book/9780122570605

Fioletov, VE; McLinden, CA; Krotkov, N; Moran, MD; Yang, K. (2011). Estimation of SO2 emissions using OMI retrievals. Geophys Res Lett 38: 1-5. http://dx.doi.org/10.1029/2011GL049402

Fioletov, VE; McLinden, CA; Krotkov, N; Yang, K; Loyola, DG; Valks, P; Theys, N; Van Roozendael, M; Nowlan, CR; Chance, K; Liu, X; Lee, C; Martin, RV. (2013). Application of OMI, SCIAMACHY, and GOME-2 satellite SO2 retrievals for detection of large emission sources. J Geophys Res Atmos 118: 11399-11418. http://dx.doi.org/10.1002/jgrd.50826

Forbes, LJ; Patel, MD; Rudnicka, AR; Cook, DG; Bush, T; Stedman, JR; Whincup, PH; Strachan, DP; Anderson, HR. (2009a). Chronic exposure to outdoor air pollution and diagnosed cardiovascular disease: meta-analysis of three large cross-sectional surveys. Environ Health 8: 30. http://dx.doi.org/10.1186/1476-069X-8-30

Forbes, LJ; Patel, MD; Rudnicka, AR; Cook, DG; Bush, T; Stedman, JR; Whincup, PH; Strachan, DP; Anderson, RH. (2009b). Chronic exposure to outdoor air pollution and markers of systemic inflammation. Epidemiology 20: 245-253. http://dx.doi.org/10.1097/EDE.0b013e318190ea3f

Forbes, LJL; Kapetanakis, V; Rudnicka, AR; Cook, DG; Bush, T; Stedman, JR; Whincup, PH; Strachan, DP; Anderson, HR. (2009c). Chronic exposure to outdoor air pollution and lung function in adults. Thorax 64: 657-663. http://dx.doi.org/10.1136/thx.2008.109389

Frank, NR; Amdur, MO; Worcester, J; Whittenberger, JL. (1962). Effects of acute controlled exposure to SO2 on respiratory mechanics in healthy male adults. J Appl Physiol 17: 252-258.

Frank, NR; Yoder, RE; Brain, JD; Yokoyama, E. (1969). SO2 (35S labeled) absorption by the nose and mouth under conditions of varying concentration and flow. Arch Environ Occup Health 18: 315-322.

Frank, NR; Yoder, RE; Yokoyama, E; Speizer, FE. (1967). The diffusion of 35SO2 from tissue fluids into the lungs following exposure of dogs to 35SO2. Health Phys 13: 31-38.

Friedman, B; Brophy, P; Brune, WH; Farmer, DK. (2016). Anthropogenic sulfur perturbations on biogenic oxidation: SO2 additions impact gas-phase OH oxidation products of α- and β-pinene. Environ Sci Technol 50: 1269-1279. http://dx.doi.org/10.1021/acs.est.5b05010

Frischer, T; Studnicka, M; Gartner, C; Tauber, E; Horak, F; Veiter, A; Spengler, J; Kuhr, J; Urbanek, R. (1999). Lung function growth and ambient ozone: A three-year population study in school children. Am J Respir Crit Care Med 160: 390-396. http://dx.doi.org/10.1164/ajrccm.160.2.9809075

Frost, KD. (2014). AERMOD performance evaluation for three coal-fired electrical generating units in Southwest Indiana. J Air Waste Manag Assoc 64: 280-290. http://dx.doi.org/10.1080/10962247.2013.858651

Fruin, SA; Hudda, N; Sioutas, C; Defino, RJ. (2011). Predictive model for vehicle air exchange rates based on a large, representative sample. Environ Sci Technol 45: 3569-3575. http://dx.doi.org/10.1021/es103897u

Frye, C; Hoelscher, B; Cyrys, J; Wjst, M; Wichmann, HE; Heinrich, J. (2003). Association of lung function with declining ambient air pollution. Environ Health Perspect 111: 383-387. http://dx.doi.org/10.1289/ehp.5355

Fung, KY; Khan, S; Krewski, D; Chen, Y. (2006). Association between air pollution and multiple respiratory hospitalizations among the elderly in Vancouver, Canada. Inhal Toxicol 18: 1005-1011. http://dx.doi.org/10.1080/08958370600904538

Fung, KY; Luginaah, I; Gorey, KM; Webster, G. (2005). Air pollution and daily hospital admissions for cardiovascular diseases in Windsor, Ontario. Can J Public Health 96: 29-33.

Gandhi, SK; Rich, DQ; Ohman-Strickland, PA; Kipen, HM; Gow, A. (2014). Plasma nitrite is an indicator of acute changes in ambient air pollutant concentrations. Inhal Toxicol 26: 426-434. http://dx.doi.org/10.3109/08958378.2014.913216

Ganguly, R; Batterman, S; Isakov, V; Snyder, M; Breen, M; Brakefield-Caldwell, W. (2015). Effect of geocoding errors on traffic-related air pollutant exposure and concentration estimates. J Expo Sci Environ Epidemiol 25: 490-498. http://dx.doi.org/10.1038/jes.2015.1

Gariazzo, C; Pelliccioni, A; Bogliolo, M; Scalisi, G. (2004). Evaluation of a Lagrangian particle model (SPRAY) to assess environmental impact of an industrial facility in complex terrain. Water Air Soil Pollut 155: 137-158. http://dx.doi.org/10.1023/B:WATE.0000026525.82039.ef

Geer, LA; Weedon, J; Bell, ML. (2012). Ambient air pollution and term birth weight in Texas from 1998 to 2004. J Air Waste Manag Assoc 62: 1285-1295. http://dx.doi.org/10.1080/10962247.2012.707632

Gehring, U; Wijga, AH; Brauer, M; Fischer, P; de Jongste, JC; Kerkhof, M; Oldenwening, M; Smit, HA; Brunekreef, B. (2010). Traffic-related air pollution and the development of asthma and allergies during the first 8 years of life. Am J Respir Crit Care Med 181: 596-603. http://dx.doi.org/10.1164/rccm.200906-0858OC

Gent, JF; Koutrakis, P; Belanger, K; Triche, E; Holford, TR; Bracken, MB; Leaderer, BP. (2009). Symptoms and medication use in children with asthma and traffic-related sources of fine particle pollution. Environ Health Perspect 117: 1168-1174. http://dx.doi.org/10.1289/ehp.0800335

Geyh, AS; Xue, J; Ozkaynak, H; Spengler, JD. (2000). The Harvard Southern California chronic ozone exposure study: Assessing ozone exposure of grade-school-age children in two southern California communities. Environ Health Perspect 108: 265-270. http://dx.doi.org/10.1289/ehp.00108265

Gianicolo, EAL; Mangia, C; Cervino, M; Bruni, A; Andreassi, MG; Latini, G. (2014). Congenital anomalies among live births in a high environmental risk area-A case-control study in Brindisi (southern Italy). Environ Res 128: 9-14. http://dx.doi.org/10.1016/j.envres.2013.11.002

Gifford, F. (1960). Peak to average concentration ratios according to a fluctuating plume dispersion model. Int J Air Pollut 3: 253-260.

Gilbert, WM; Nesbitt, TS; Danielsen, B. (2003). The cost of prematurity: Quantification by gestational age and birth weight. Obstet Gynecol 102: 488-492.

Gilboa, SM; Mendola, P; Olshan, AF; Langlois, PH; Savitz, DA; Loomis, D; Herring, AH; Fixler, DE. (2005). Relation between ambient air quality and selected birth defects, seven county study, Texas, 1997-2000. Am J Epidemiol 162: 238-252. http://dx.doi.org/10.1093/aje/kwi189

Gilliland, FD; Berhane, K; Islam, T; Mcconnell, R; Gauderman, WJ; Gilliland, SS; Avol, E; Peters, JM. (2003). Obesity and the risk of newly diagnosed asthma in school-age children. Am J Epidemiol 158: 406-415. http://dx.doi.org/10.1093/aje/kwg175

Giordano, L; Brunner, D; Flemming, J; Hogrefe, C; Im, U; Bianconi, R; Badia, A; Balzarini, A; Baro, R; Chemel, C; Curci, G; Forkel, R; Jimenez-Guerrero, P; Hirtl, M; Hodzic, A; Honzak, L; Jorba, O; Knote, C; Kuenen, JJP; Makar, PA; Manders-Groot, A; Neal, L; Perez, JL; Pirovano, G; Pouliot, G; San Jose, R; Savage, N; Schroeder, W; Sokhi, RS; Syrakov, D; Torian, A; Tuccella, P; Werhahn, J; Wolke, R; Yahya, K; Zabkar, R; Zhang, Y; Galmarini, S. (2015). Assessment of the MACC reanalysis and its influence as chemical boundary conditions for regional air quality modeling in AQMEII-2. Atmos Environ 115: 371-388. http://dx.doi.org/10.1016/j.atmosenv.2015.02.034

Glasgow, ML; Rudra, CB; Yoo, EH; Demirbas, M; Merriman, J; Nayak, P; Crabtree-Ide, C; Szpiro, AA; Rudra, A; Wactawski-Wende, J; Mu, L. (2014). Using smartphones to collect time-activity data for long-term personal-level air pollution exposure assessment. J Expo Sci Environ Epidemiol 26: 356-364. http://dx.doi.org/10.1038/jes.2014.78

Godoi, RH; Godoi, AF; Gonçalves Junior, SJ; Paralovo, SL; Borillo, GC; Gonçalves Gregório Barbosa, C; Arantes, MG; Charello, RC; Rosário Filho, NA; Grassi, MT; Yamamoto, CI; Potgieter-Vermaak, S; Rotondo, GG; De Wael, K; van Grieken, R. (2013). Healthy environment - indoor air quality of Brazilian elementary schools nearby petrochemical industry. Sci Total Environ 463-464: 639-646. http://dx.doi.org/10.1016/j.scitotenv.2013.06.043

Gold, DR; Damokosh, AI; Dockery, DW; Berkey, CS. (2003). Body-mass index as a predictor of incident asthma in a prospective cohort of children. Pediatr Pulmonol 36: 514-521. http://dx.doi.org/10.1002/ppul.10376

Goldberg, MS; Giannetti, N; Burnett, RT; Mayo, NE; Valois, MF; Brophy, JM. (2008). A panel study in congestive heart failure to estimate the short-term effects from personal factors and environmental conditions on oxygen saturation and pulse rate. Occup Environ Med 65: 659-666. http://dx.doi.org/10.1136/oem.2007.034934

Goldman, GT; Mulholland, JA; Russell, AG; Gass, K; Strickland, MJ; Tolbert, PE. (2012). Characterization of ambient air pollution measurement error in a time-series health study using a geostatistical simulation approach. Atmos Environ 57: 101-108. http://dx.doi.org/10.1016/j.atmosenv.2012.04.045

Goldman, GT; Mulholland, JA; Russell, AG; Srivastava, A; Strickland, MJ; Klein, M; Waller, LA; Tolbert, PE; Edgerton, ES. (2010). Ambient air pollutant measurement error: characterization and impacts in a time-series epidemiologic study in Atlanta. Environ Sci Technol 44: 7692-7698. http://dx.doi.org/10.1021/es101386r

Goldman, GT; Mulholland, JA; Russell, AG; Strickland, MJ; Klein, M; Waller, LA; Tolbert, PE. (2011). Impact of exposure measurement error in air pollution epidemiology: Effect of error type in time-series studies. Environ Health 10: 61. http://dx.doi.org/10.1186/1476-069X-10-61

Gong, H, Jr; Lachenbruch, PA; Harber, P; Linn, WS. (1995). Comparative short-term health responses to sulfur dioxide exposure and other common stresses in a panel of asthmatics. Toxicol Ind Health 11: 467-487.

Gong, H, Jr; Linn, WS; Shamoo, DA; Anderson, KR; Nugent, CA; Clark, KW; Lin, AE. (1996). Effect of inhaled salmeterol on sulfur dioxide-induced bronchoconstriction in asthmatic subjects. Chest 110: 1229-1235.

Gong, H, Jr; Linn, WS; Terrell, SL; Anderson, KR; Clark, KW. (2001). Anti-inflammatory and lung function effects of montelukast in asthmatic volunteers exposed to sulfur dioxide. Chest 119: 402-408. http://dx.doi.org/10.1378/chest.119.2.402

Gong, J; Hu, Y; Liu, M; Bu, R; Chang, Y, u; Bilal, M; Li, C; Wu, W, en; Ren, B. (2016). Land use regression models using satellite aerosol optical depth observations and 3D building data from the central cities of Liaoning Province, China. Pol J Environ Stud 25: 1015-1026. http://dx.doi.org/10.15244/pjoes/61261

Goodman, JE; Seeley, M; Mattuck, R; Thakali, S. (2015). Do group responses mask the effects of air pollutants on potentially sensitive individuals in controlled human exposure studies? [Review]. Regul Toxicol Pharmacol 71: 552-564. http://dx.doi.org/10.1016/j.yrtph.2015.02.002

Gorai, AK; Tuluri, F; Tchounwou, PB. (2014). A GIS based approach for assessing the association between air pollution and asthma in New York State, USA. Int J Environ Res Public Health 11: 4845-4869. http://dx.doi.org/10.3390/ijerph110504845

Green, R; Sarovar, V; Malig, B; Basu, R. (2015). Association of stillbirth with ambient air pollution in a California cohort study. Am J Epidemiol 181: 874-882. http://dx.doi.org/10.1093/aje/kwu460

Greenberg, N; Carel, RS; Derazne, E; Bibi, H; Shpriz, M; Tzur, D; Portnov, BA. (2016). Different effects of long-term exposures to SO2 and NO2 air pollutants on asthma severity in young adults. J Toxicol Environ Health A 79: 1-10. http://dx.doi.org/10.1080/15287394.2016.1153548

Greenwald, R; Sarnat, SE; Raysoni, AU; Li, WW; Johnson, BA; Stock, TH; Holguin, F; Sosa, T; Sarnat, JA. (2013). Associations between source-indicative pollution metrics and increases in pulmonary inflammation and reduced lung function in a panel of asthmatic children. Air Qual Atmos Health 6: 487-499. http://dx.doi.org/10.1007/s11869-012-0186-3

Gregory, RE; Gunnison, AF. (1984). Identification of plasma-proteins containing sulfite-reactive disulfide bonds. Chem Biol Interact 49: 55-69. http://dx.doi.org/10.1016/0009-2797(84)90052-8

Groneberg, DA; Quarcoo, D; Frossard, N; Fischer, A. (2004). Neurogenic mechanisms in bronchial inflammatory diseases [Review]. Allergy 59: 1139-1152. http://dx.doi.org/10.1111/j.1398-9995.2004.00665.x

Grontoft, T; Raychaudhuri, MR. (2004). Compilation of tables of surface deposition velocities for O3, NO2 and SO2 to a range of indoor surfaces. Atmos Environ 38: 533-544. http://dx.doi.org/10.1016/j.atmosenv.2003.10.010

Grunstein, MM; Hazucha, M; Sorli, J; Milic-Emili, J. (1977). Effect of SO2 on control of breathing in anesthetized cats. J Appl Physiol 43: 844-851.

Gryparis, A; Coull, BA; Schwartz, J. (2007). Controlling for confounding in the presence of measurement error in hierarchical models: A Bayesian approach. J Expo Sci Environ Epidemiol 17: S20-S28. http://dx.doi.org/10.1038/sj.jes.7500624

Guay, M; Stieb, DM; Smith-Doiron, M. (2011). Assessment of long-term exposure to air pollution in a longitudinal national health survey. J Expo Sci Environ Epidemiol 21: 337-342. http://dx.doi.org/10.1038/jes.2010.37

Gunnison, AF. (1981). Sulfite toxicity - a critical-review of invitro and invivo data. Food Cosmet Toxicol 19: 667-682. http://dx.doi.org/10.1016/0015-6264(81)90519-8

Gunnison, AF; Benton, AW. (1971). Sulfur dioxide: sulfite interaction with mammalian serum and plasma. Arch Environ Occup Health 22: 381-388.

Gunnison, AF; Jacobsen, DW; Schwartz, HJ. (1987a). Sulfite hypersensitivity: A critical review [Review]. CRC Crit Rev Toxicol 17: 185-214. http://dx.doi.org/10.3109/10408448709071208

Gunnison, AF; Palmes, ED. (1973). Persistence of plasma S-sulfonates following exposure of rabbits to sulfite and sulfur dioxide. Toxicol Appl Pharmacol 24: 266-278.

Gunnison, AF; Palmes, ED. (1974). S-sulfonates in human plasma following inhalation of sulfur dioxide. Am Ind Hyg Assoc J 35: 288-291. http://dx.doi.org/10.1080/0002889748507036

Gunnison, AF; Sellakumar, A; Currie, D; Snyder, EA. (1987b). Distribution, metabolism and toxicity of inhaled sulfur dioxide and endogenously generated sulfite in the respiratory tract of normal and sulfite oxidase-deficient rats. J Toxicol Environ Health 21: 141-162. http://dx.doi.org/10.1080/15287398709531008

Gunnison, AF; Zaccardi, J; Dulak, L; Chiang, G. (1981). Tissue distribution of s-sulfonate metabolites following exposure to sulfur-dioxide. Environ Res 24: 432-443.

Guo, Y; Jia, Y; Pan, X; Liu, L; Wichmann, HE. (2009). The association between fine particulate air pollution and hospital emergency room visits for cardiovascular diseases in Beijing, China. Sci Total Environ 407: 4826-4830. http://dx.doi.org/10.1016/j.scitotenv.2009.05.022

Guo, Y; Tong, S; Li, S; Barnett, AG; Yu, W; Zhang, Y; Pan, X. (2010). Gaseous air pollution and emergency hospital visits for hypertension in Beijing, China: a time-stratified case-crossover study. Environ Health 9: 57. http://dx.doi.org/10.1186/1476-069X-9-57

Gwynn, RC; Burnett, RT; Thurston, GD. (2000). A time-series analysis of acidic particulate matter and daily mortality and morbidity in the Buffalo, New York, region. Environ Health Perspect 108: 125-133.

Ha, EH; Hong, YC; Lee, BE; Woo, BH; Schwartz, J; Christiani, DC. (2001). Is air pollution a risk factor for low birth weight in Seoul? Epidemiology 12: 643-648.

Haider, SS; Hasan, M; Khan, NH. (1982). Air pollutant sulfur dioxide-induced alterations on the levels of lipids, lipid peroxidation and lipase activity in various regions of the rat brain. Basic Clin Pharmacol Toxicol 51: 45-50. http://dx.doi.org/10.1111/j.1600-0773.1982.tb01061.x

Hajj, AM; Burki, NK; Lee, LY. (1996). Role of tachykinins in sulfur dioxide-induced bronchoconstriction in anesthetized guinea pigs. J Appl Physiol 80: 2044-2050.

Hales, JM; Sutter, SL. (1973). Solubility of sulfur dioxide in water at low concentrations. Atmos Environ 7: 997-1001. http://dx.doi.org/10.1016/0004-6981(73)90049-8

Halinen, AI; Salonen, RO; Pennanen, AS. (2000a). Combined respiratory effects of cold air with SO2 or NO2 in single 1-hour exposures of hyperventilating guinea pigs. Inhal Toxicol 12: 693-713. http://dx.doi.org/10.1080/08958370050085147

Halinen, AI; Salonen, RO; Pennanen, AS; Kosma, VM. (2000b). Combined respiratory effects of cold air with SO2 or NO2 in repeated 10-minute exposures of hyperventilating guinea pigs. Inhal Toxicol 12: 671-691. http://dx.doi.org/10.1080/08958370050085138

Halios, CC; Helmis, CG; Eleftheriadis, K; Flocas, HA; Assimakopoulos, VD. (2009). A Comparative Study of the Main Mechanisms Controlling Indoor Air Pollution in Residential Flats. Water Air Soil Pollut 204: 333-350. http://dx.doi.org/10.1007/s11270-009-0048-2

Hand, JL; Schichtel, BA; Malm, WC; Pitchford, ML. (2012). Particulate sulfate ion concentration and SO2 emission trends in the United States from the early 1990s through 2010. Atmos Chem Phys 12: 10353-10365. http://dx.doi.org/10.5194/acp-12-10353-2012

Hanna, SR. (2007). Chapter 4.0. A review of uncertainty and sensitivity analyses of atmospheric transport and dispersion models. In Developments in environmental science: Air pollution modeling and its application XVIII. Boston, Massachusetts: Elsevier Publishing Co. http://dx.doi.org/10.1016/S1474-8177(07)06040-8

Hanna, SR; Briggs, GA; Hosker, RP. (1982). Handbook on atmospheric diffusion. (DOE/TIC-11223; DE82002045). Springfield, VA: U.S. Department of Energy.

Hanna, SR; Brown, MJ; Camelli, FE; Chan, ST; Coirier, WJ; Hansen, OR; Huber, AH; Kim, S; Reynolds, RM. (2006). Detailed simulations of atmospheric flow and dispersion in downtown Manhattan: An application of five computational fluid dynamics models. Bull Am Meteorol Soc 87: 1713-1726. http://dx.doi.org/10.1175/BAMS-87-12-1713

Hanna, SR; Chang, JC. (1993). Hybrid plume dispersion model (HPDM) improvements and testing at three field sites. Atmos Environ A 27: 1491-1508. http://dx.doi.org/10.1016/0960-1686(93)90135-L

Hanna, SR; Chang, JC; Strimaitis, DG. (1993). Hazardous gas model evaluation with field observations. Atmos Environ A 27: 2265-2285. http://dx.doi.org/10.1016/0960-1686(93)90397-H

Hanna, SR; Egan, BA; Purdum, J; Wagler, J. (2001). Evaluation of the ADMS, AERMOD, and ISC3 dispersion models with the OPTEX, Duke Forest, Kincaid, Indianapolis and Lovett field datasets. Int J Environ Pollut 16: 301-314. http://dx.doi.org/10.1504/IJEP.2001.000626

Hansell, A; Ghosh, RE; Blangiardo, M; Perkins, C; Vienneau, D; Goffe, K; Briggs, D; Gulliver, J. (2016). Historic air pollution exposure and long-term mortality risks in England and Wales: prospective longitudinal cohort study. Thorax 71: 330-338. http://dx.doi.org/10.1136/thoraxjnl-2015-207111

Hansen, CA; Barnett, AG; Pritchard, G. (2008). The effect of ambient air pollution during early pregnancy on fetal ultrasonic measurements during mid-pregnancy. Environ Health Perspect 116: 362-369. http://dx.doi.org/10.1289/ehp.10720

Hansen, M; Bower, C; Milne, E; de Klerk, N; Kurinczuk, JJ. (2005). Assisted reproductive technologies and the risk of birth defects--a systematic review [Review]. Hum Reprod 20: 328-338. http://dx.doi.org/10.1093/humrep/deh593

Harre, ESM; Price, PD; Ayrey, RB; Toop, LJ; Martin, IR; Town, GI. (1997). Respiratory effects of air pollution in chronic obstructive pulmonary disease: A three month prospective study. Thorax 52: 1040-1044. http://dx.doi.org/10.1136/thx.52.12.1040

Harries, MG; Parkes, PEG; Lessof, MH; Orr, TSC. (1981). Role of bronchial irritant receptors in asthma. Lancet 317: 5-7. http://dx.doi.org/10.1016/S0140-6736(81)90113-6

Hart, JE; Garshick, E; Dockery, DW; Smith, TJ; Ryan, L; Laden, F. (2011). Long-term ambient multi-pollutant exposures and mortality. Am J Respir Crit Care Med 183: 73-78. http://dx.doi.org/10.1164/rccm.200912-1903OC

Hazucha, M; Bates, DV. (1975). Combined effect of ozone and sulphur dioxide on human pulmonary function. Nature 257: 50-51. http://dx.doi.org/10.1038/257050a0

Heckbert, SR; Kooperberg, C; Safford, MM; Psaty, BM; Hsia, J; McTiernan, A; Gaziano, JM; Frishman, WH; Curb, JD. (2004). Comparison of self-report, hospital discharge codes, and adjudication of cardiovascular events in the Women's Health Initiative. Am J Epidemiol 160: 1152-1158. http://dx.doi.org/10.1093/aje/kwh314

Hedley, AJ; Wong, CM; Thach, TQ; Ma, S; Lam, TH; Anderson, HR. (2002). Cardiorespiratory and all-cause mortality after restrictions on sulphur content of fuel in Hong Kong: an intervention study. Lancet 360: 1646-1652.

HEI (Health Effects Institute). (2004). Health effects of outdoor air pollution in developing countries of Asia: a literature review. (Special report 15). Boston, MA: Health Effects Institute (HEI). https://ntrl.ntis.gov/NTRL/dashboard/searchResults.xhtml?searchQuery=PB2005103805

HEI (Health Effects Institute). (2012). Effects of short-term exposure to air pollution on hospital admissions of young children for acute lower respiratory infections in Ho Chi Minh City, Vietnam. (Research Report 169). Boston, MA: Health Effects Institute, HEI Collaborative Working Group on Air Pollution, Poverty, and Health in Ho Chi Minh City. https://www.healtheffects.org/publication/effects-short-term-exposure-air-pollution-hospital-admissions-young-children-acute-lower

Heinrich, U; Mohr, U; Fuhst, R; Brockmeyer, C. (1989). Investigation of a potential cotumorigenic effect of the dioxides of nitrogen and sulfur, and of diesel-engine exhaust, on the respiratory tract of Syrian golden hamsters (pp. 1-27). (Research report number26). Boston, MA: Health Effects Institute. http://pubs.healtheffects.org/getfile.php?u=769

Helmerhorst, FM; Perquin, DA; Donker, D; Keirse, MJ. (2004). Perinatal outcome of singletons and twins after assisted conception: a systematic review of controlled studies [Review]. B M J (Online) 328: 261-265. http://dx.doi.org/10.1136/bmj.37957.560278.EE

Henneberger, A; Zareba, W; Ibald-Mulli, A; Rückerl, R; Cyrys, J; Couderc, JP; Mykins, B; Woelke, G; Wichmann, HE; Peters, A. (2005). Repolarization changes induced by air pollution in ischemic heart disease patients. Environ Health Perspect 113: 440-446. http://dx.doi.org/10.1289/ehp.7579

Henrotin, JB; Besancenot, JP; Bejot, Y; Giroud, M. (2007). Short-term effects of ozone air pollution on ischaemic stroke occurrence: A case-crossover analysis from a 10-year population-based study in Dijon, France. Occup Environ Med 64: 439-445. http://dx.doi.org/10.1136/oem.2006.029306

Hertz-Picciotto, I; Cassady, D; Lee, K; Bennett, DH; Ritz, B; Vogt, R. (2010). Study of Use of Products and Exposure-Related Behaviors (SUPERB): study design, methods, and demographic characteristics of cohorts. Environ Health 9. http://dx.doi.org/10.1186/1476-069X-9-54

HEW (U.S. Department of Health, Education and Welfare). (1969). Air quality criteria for sulfur oxides. Washington, DC: National Air Pollution Control Administration.

Hidy, GM. (1994). Atmospheric sulfur and nitrogen oxides: Eastern North American source-receptor relationships. In Atmospheric sulfur and nitrogen oxides: Eastern North American source-receptor relationships. San Diego: Academic Press.

Hildebrandt, K; Rückerl, R; Koenig, W; Schneider, A; Pitz, M; Heinrich, J; Marder, V; Frampton, M; Oberdörster, G; Wichmann, HE; Peters, A. (2009). Short-term effects of air pollution: A panel study of blood markers in patients with chronic pulmonary disease. Part Fibre Toxicol 6: 25. http://dx.doi.org/10.1186/1743-8977-6-25

Hirsch, JA; Swenson, EW; Wanner, A. (1975). Tracheal mucous transport in beagles after long-term exposure to 1 ppm sulfur dioxide. Arch Environ Health 30: 249-253.

Hoek, G. (2003). Daily mortality and air pollution in The Netherlands [HEI]. In Revised analyses of time-series studies of air pollution and health (pp. 133-141). Boston, MA: Health Effects Institute. http://pubs.healtheffects.org/getfile.php?u=21

Holnicki, P; Kaluszko, A; Trapp, W. (2016). An urban scale application and validation of the CALPUFF model. Atmos Pollut Res 7: 393-402. http://dx.doi.org/10.1016/j.apr.2015.10.016

Honninger, G; von Friedeburg, C; Platt, U. (2004). Multi axis differential optical absorption spectroscopy (MAX-DOAS). Atmos Chem Phys 4: 231-254.

Hopp, RJ; Bewtra, A; Nair, NM; Townley, RG. (1985). The effect of age on methacholine response. J Allergy Clin Immunol 76: 609-613. http://dx.doi.org/10.1016/0091-6749(85)90783-3

Hopp, RJ; Bewtra, AK; Nair, NM; Watt, GD; Townley, RG. (1986). Methacholine inhalation challenge studies in a selected pediatric population. Am Rev Respir Dis 134: 994-998. http://dx.doi.org/10.1164/arrd.1986.134.5.994

Hoppel, WA; Caffrey, PF. (2005). Oxidation of S(IV) in sea-salt aerosol at high pH: ozone versus aerobic reaction. J Geophys Res 110: D23202. http://dx.doi.org/10.1029/2005JD006239

Horowitz, LW; Walters, S; Mauzerall, DL; Emmons, LK; Rasch, PJ; Granier, C; Tie, X; Lamarque, J, -F; Schultz, MG; Tyndall, GS; Orlando, JJ; Brasseur, GP. (2003). A global simulation of tropospheric ozone and related tracers: Description and evaluation of MOZART, version 2. J Geophys Res 108. http://dx.doi.org/10.1029/2002JD002853

Horstman, D; Roger, LJ; Kehrl, H; Hazucha, M. (1986). Airway sensitivity of asthmatics to sulfur dioxide. Toxicol Ind Health 2: 289-298.

Horstman, DH; Seal, E, Jr; Folinsbee, LJ; Ives, P; Roger, LJ. (1988). The relationship between exposure duration and sulfur dioxide-induced bronchoconstriction in asthmatic subjects. AIHA J 49: 38-47. http://dx.doi.org/10.1080/15298668891379341

Hou, HY; Wang, D; Zou, XP; Yang, ZH; Li, TC; Chen, YQ. (2014). Does ambient air pollutants increase the risk of fetal loss? A case-control study. Arch Gynecol Obstet 289: 285-291. http://dx.doi.org/10.1007/s00404-013-2962-1

Howden, LM; Meyer, JA. (2011). Age and sex composition: 2010. (2010 Census Briefs, C2010BR-03). Washington, DC: U.S. Department of Commerce, Economics and Statistics Administration, U.S. Census Bureau. http://www.census.gov/prod/cen2010/briefs/c2010br-03.pdf

Hoyert, DL; Xu, J. (2012). Deaths: Preliminary data for 2011. National Vital Statistics Reports 61: 1-51.

Hsieh, YL; Yang, YH; Wu, TN; Yang, CY. (2010). Air pollution and hospital admissions for myocardial infarction in a subtropical city: Taipei, Taiwan. J Toxicol Environ Health A 73: 757-765. http://dx.doi.org/10.1080/15287391003684789

Huang, CC; Wen, HJ; Chen, PC; Chiang, TL; Lin, SJ; Guo, YL. (2015a). Prenatal air pollutant exposure and occurrence of atopic dermatitis. Br J Dermatol 173: 981-988. http://dx.doi.org/10.1111/bjd.14039

Huang, L; Zhao, Y; Li, H; Chen, Z. (2015b). Kinetics of heterogeneous reaction of sulfur dioxide on authentic mineral dust: Effects of relative humidity and hydrogen peroxide. Environ Sci Technol 49: 10797-10805. http://dx.doi.org/10.1021/acs.est.5b03930

Huang, W; Zhu, T; Pan, X; Hu, M; Lu, SE; Lin, Y; Wang, T; Zhang, Y; Tang, X. (2012). Air pollution and autonomic and vascular dysfunction in patients with cardiovascular disease: Interactions of systemic inflammation, overweight, and gender. Am J Epidemiol 176: 117-126. http://dx.doi.org/10.1093/aje/kwr511

Hudda, N; Kostenidou, E; Sioutas, C; Delfino, RJ; Fruin, SA. (2011). Vehicle and driving characteristics that influence in-cabin particle number concentrations. Environ Sci Technol 45: 8691-8697. http://dx.doi.org/10.1021/es202025m

Hung, HM; Hoffmann, MR. (2015). Oxidation of gas-phase SO2 on the surfaces of acidic microdroplets: Implications for sulfate and sulfate radical anion formation in the atmospheric liquid phase. Environ Sci Technol 49: 13768-13776. http://dx.doi.org/10.1021/acs.est.5b01658

Hurley, PJ. (2006). An evaluation and inter-comparison of AUSPLUME, AERMOD and TAPM for seven field datasets of point source dispersion. Clean Air Environ Qual 40: 45-50.

Hwang, BF; Chen, YH; Lin, YT; Wu, XT; Leo Lee, Y. (2015a). Relationship between exposure to fine particulates and ozone and reduced lung function in children. Environ Res 137: 382-390. http://dx.doi.org/10.1016/j.envres.2015.01.009

Hwang, BF; Jaakkola, JJ. (2008). Ozone and other air pollutants and the risk of oral clefts. Environ Health Perspect 116: 1411-1415. http://dx.doi.org/10.1289/ehp.11311

Hwang, BF; Lee, YL; Jaakkola, JJ. (2011). Air pollution and stillbirth: A population-based case-control study in Taiwan. Environ Health Perspect 119: 1345-1349. http://dx.doi.org/10.1289/ehp.1003056

Hwang, BF; Lee, YL; Jaakkola, JJ. (2015b). Air Pollution and the Risk of Cardiac Defects: A Population-Based Case-Control Study. Medicine (Baltimore) 94: e1883. http://dx.doi.org/10.1097/MD.0000000000001883

Hwang, SS; Kang, S; Lee, JY; Lee, JS; Kim, HJ; Han, SK; Yim, JJ. (2014). Impact of outdoor air pollution on the incidence of tuberculosis in the Seoul metropolitan area, South Korea. Korean J Intern Med 29: 183-190. http://dx.doi.org/10.3904/kjim.2014.29.2.183

ICRP (International Commission on Radiological Protection). (1994). Human respiratory tract model for radiological protection: A report of a task group of the International Commission on Radiological Protection. ICRP Publication 66. New York, NY: Pergamon Press.

ICRP (International Commission on Radiological Protection). (2002). Basic anatomical and physiological data for use in radiological protection: Reference values (pp. 1-277). (ICRP Publication 89). New York, NY: Pergamon Press. http://dx.doi.org/10.1016/S0146-6453(03)00002-2

Ierodiakonou, D; Zanobetti, A; Coull, BA; Melly, S; Postma, DS; Boezen, HM; Vonk, JM; Williams, PV; Shapiro, GG; Mckone, EF; Hallstrand, TS; Koenig, JQ; Schildcrout, JS; Lumley, T; Fuhlbrigge, AN; Koutrakis, P; Schwartz, J; Weiss, ST; Gold, DR; Group, CAMPR. (2015). Ambient air pollution, lung function, and airway responsiveness in asthmatic children. J Allergy Clin Immunol 137: 390-399. http://dx.doi.org/10.1016/j.jaci.2015.05.028

IOM (Institute of Medicine). (2005). DRI, dietary reference intakes for water, potassium, sodium, chloride, and sulfate. Washington, DC: National Academies Press. https://www.nap.edu/read/10925/chapter/1#ii

IOM (Institute of Medicine). (2007). Preterm birth: Causes, consequences, and prevention. In Preterm birth: Causes, consequences, and prevention. Washington, DC: National Academies Press (US). http://dx.doi.org/10.17226/11622

Irwin, JS. (2014). A suggested method for dispersion model evaluation. J Air Waste Manag Assoc 64: 255-264. http://dx.doi.org/10.1080/10962247.2013.833147

Isaacs, K. (2014). The consolidated human activity database - master version (CHAD-Master) technical memorandum. Washington, DC: U.S. Environmental Protection Agency, National Exposure Research Laboratory. https://www.epa.gov/sites/production/files/2015-02/documents/chadmaster_091814_1.pdf

Isaacs, K; McCurdy, T; Glen, G; Nysewander, M; Errickson, A; Forbes, S; Graham, S; McCurdy, L; Smith, L; Tulve, N; Vallero, D. (2013). Statistical properties of longitudinal time-activity data for use in human exposure modeling. J Expo Sci Environ Epidemiol 23: 328-336. http://dx.doi.org/10.1038/jes.2012.94

Isakov, V; Venkatram, A; Touma, JS; Koracin, D; Otte, TL. (2007). Evaluating the use of outputs from comprehensive meteorological models in air quality modeling applications. Atmos Environ 41: 1689-1705. http://dx.doi.org/10.1016/j.atmosenv.2006.10.043

Ishigami, A; Kikuchi, Y; Iwasawa, S; Nishiwaki, Y; Takebayashi, T; Tanaka, S; Omae, K. (2008). Volcanic sulfur dioxide and acute respiratory symptoms on Miyakejima island. Occup Environ Med 65: 701-707. http://dx.doi.org/10.1136/oem.2007.033456

Ito, K; Mathes, R; Ross, Z; Nádas, A; Thurston, G; Matte, T. (2011). Fine particulate matter constituents associated with cardiovascular hospitalizations and mortality in New York City. Environ Health Perspect 119: 467-473. http://dx.doi.org/10.1289/ehp.1002667

Ito, K; Thurston, GD; Silverman, RA. (2007). Characterization of PM2.5, gaseous pollutants, and meteorological interactions in the context of time-series health effects models. J Expo Sci Environ Epidemiol 17: S45-S60. http://dx.doi.org/10.1038/sj.jes.7500627

Ito, T; Ohyama, KI; Kusano, T; Usuda, Y; Nozawa, A; Hayashi, H; Ohji, H; Kitamura, H; Kanisawa, M. (1997). Pulmonary endocrine cell hyperplasia and papilloma in rats induced by intratracheal injections of extract from particulate air pollutants. Exp Toxicol Pathol 49: 65-70. http://dx.doi.org/10.1016/S0940-2993(97)80066-8

Iwasawa, S; Kikuchi, Y; Nishiwaki, Y; Nakano, M; Michikawa, T; Tsuboi, T; Tanaka, S; Uemura, T; Ishigami, A; Nakashima, H; Takebayashi, T; Adachi, M; Morikawa, A; Maruyama, K; Kudo, S; Uchiyama, I; Omae, K. (2009). Effects of SO2 on respiratory system of adult Miyakejima resident 2 years after returning to the island. J Occup Health 51: 38-47. http://dx.doi.org/10.1539/joh.L8075

Iwasawa, S; Nakano, M; Tsuboi, T; Kochi, T; Tanaka, S; Katsunuma, T; Morikawa, A; Omae, K. (2015). Effects of sulfur dioxide on the respiratory system of Miyakejima child residents 6years after returning to the island. Int Arch Occup Environ Health 88: 1111-1118. http://dx.doi.org/10.1007/s00420-015-1037-y

Jackson, RA; Gibson, KA; Wu, YW; Croughan, MS. (2004). Perinatal outcomes in singletons following in vitro fertilization: a meta-analysis. Obstet Gynecol 103: 551-563. http://dx.doi.org/10.1097/01.AOG.0000114989.84822.51

Jacob, DJ. (1999). Introduction to atmospheric chemistry. Princeton, NJ: Princeton University Press. http://press.princeton.edu/titles/6767.html

Jacobson, MZ. (2002). Atmospheric pollution: History, science, and regulation. In Atmospheric Pollution: History, Science, and Regulation. New York: Cambridge University Press. http://www.cambridge.org/us/academic/subjects/earth-and-environmental-science/atmospheric-science-and-meteorology/atmospheric-pollution-history-science-and-regulation

Jaffe, DH; Singer, ME; Rimm, AA. (2003). Air pollution and emergency department visits for asthma among Ohio Medicaid recipients, 1991-1996. Environ Res 91: 21-28. http://dx.doi.org/10.1016/S0013-9351(02)00004-X

Jalaludin, B; Khalaj, B; Sheppeard, V; Morgan, G. (2008). Air pollution and ED visits for asthma in Australian children: A case-crossover analysis. Int Arch Occup Environ Health 81: 967-974. http://dx.doi.org/10.1007/s00420-007-0290-0

Jalaludin, B; Mannes, T; Morgan, G; Lincoln, D; Sheppeard, V; Corbett, S. (2007). Impact of ambient air pollution on gestational age is modified by season in Sydney, Australia. Environ Health 6: 16. http://dx.doi.org/10.1186/1476-069X-6-16

Jalaludin, B; Morgan, G; Lincoln, D; Sheppeard, V; Simpson, R; Corbett, S. (2006). Associations between ambient air pollution and daily emergency department attendances for cardiovascular disease in the elderly (65+ years), Sydney, Australia. J Expo Sci Environ Epidemiol 16: 225-237. http://dx.doi.org/10.1038/sj.jea.7500451

James, DS; Stidley, CA; Lambert, WE; Chick, TW; Mermier, CM; Samet, JM. (1997). Oronasal distribution of ventilation at different ages. Arch Environ Occup Health 52: 118-123. http://dx.doi.org/10.1080/00039899709602874

Jedrychowski, W; Flak, E; Mroz, E. (1999). The adverse effect of low levels of ambient air pollutants on lung function growth in preadolescent children. Environ Health Perspect 107: 669-674.

Jerrett, M; Burnett, RT; Pope, CA, III; Ito, K; Thurston, G; Krewski, D; Shi, Y; Calle, E; Thun, M. (2009). Long-term ozone exposure and mortality. N Engl J Med 360: 1085-1095. http://dx.doi.org/10.1056/NEJMoa0803894

Jerrett, M; Burnett, RT; Willis, A; Krewski, D; Goldberg, MS; Deluca, P; Finkelstein, N. (2003). Spatial analysis of the air pollution-mortality relationship in the context of ecologic confounders. J Toxicol Environ Health A 66: 1735-1777. http://dx.doi.org/10.1080/15287390306438

Johns, DO; Svendsgaard, D; Linn, WS. (2010). Analysis of the concentration-respiratory response among asthmatics following controlled short-term exposures to sulfur dioxide. Inhal Toxicol 22: 1184-1193. http://dx.doi.org/10.3109/08958378.2010.535220

Johnson-Winters, K; Tollin, G; Enemark, JH. (2010). Elucidating the catalytic mechanism of sulfite oxidizing enzymes using structural, spectroscopic, and kinetic analyses [Review]. Biochemistry 49: 7242-7254. http://dx.doi.org/10.1021/bi1008485

Johnson, D; Lewin, AG; Marston, G. (2001). The effect of Criegee-intermediate scavengers on the OH yield from the reaction of ozone with 2-methylbut-2-ene. J Phys Chem A 105: 2933-2935. http://dx.doi.org/10.1021/jp003975e

Johnson, JY; Rowe, BH; Villeneuve, PJ. (2010). Ecological analysis of long-term exposure to ambient air pollution and the incidence of stroke in Edmonton, Alberta, Canada. Stroke 41: 1319-1325. http://dx.doi.org/10.1161/STROKEAHA.110.580571

Jones, SL; Kittelson, J; Cowan, JO; Flannery, EM; Hancox, RJ; McLachlan, CR; Taylor, DR. (2001). The predictive value of exhaled nitric oxide measurements in assessing changes in asthma control. Am J Respir Crit Care Med 164: 738-743. http://dx.doi.org/10.1164/ajrccm.164.5.2012125

Jörres, R; Magnussen, H. (1990). Airways response of asthmatics after a 30 min exposure, at resting ventilation, to 0.25 ppm NO2 or 0.5 ppm SO2. Eur Respir J 3: 132-137.

Jurewicz, J; Radwan, M; Sobala, W; Polańska, K; Radwan, P; Jakubowski, L; Ulańska, A; Hanke, W. (2014). The relationship between exposure to air pollution and sperm disomy. Environ Mol Mutagen 56: 50-59. http://dx.doi.org/10.1002/em.21883

Kan, H; Chen, B; Zhao, N; London, SJ; Song, G; Chen, G; Zhang, Y; Jiang, L. (2010a). Part 1. A time-series study of ambient air pollution and daily mortality in Shanghai, China. In Public Health and Air Pollution in Asia (PAPA): Coordinated studies of short-term exposure to air pollution and daily mortality in four cities (pp. 17-78). Boston, MA: Health Effects Institute. https://www.healtheffects.org/system/files/PAPA_154_Part1_Kan.pdf

Kan, H; Wong, CM; Vichit-Vadakan, N; Qian, Z. (2010b). Short-term association between sulfur dioxide and daily mortality: The Public Health and Air Pollution in Asia (PAPA) study. Environ Res 110: 258-264. http://dx.doi.org/10.1016/j.envres.2010.01.006

Kanaroglou, PS; Adams, MD; De Luca, PF; Corr, D; Sohel, N. (2013). Estimation of sulfur dioxide air pollution concentrations with a spatial autoregressive model. Atmos Environ 79: 421-427. http://dx.doi.org/10.1016/j.atmosenv.2013.07.014

Kane, LE; Barrow, CS; Alarie, Y. (1979). A short-term test to predict acceptable levels of exposure to airborne sensory irritants. Am Ind Hyg Assoc J 40: 207-229. http://dx.doi.org/10.1080/15298667991429516

Kang, SH; Heo, J; Oh, IY; Kim, J; Lim, WH; Cho, Y; Choi, EK; Yi, SM; Do Shin, S; Kim, H; Oh, S. (2016). Ambient air pollution and out-of-hospital cardiac arrest. Int J Cardiol 203: 1086-1092. http://dx.doi.org/10.1016/j.ijcard.2015.11.100

Kara, E; Özdilek, HG; Kara, EE. (2013). Ambient air quality and asthma cases in Niğde, Turkey. Environ Sci Pollut Res Int 20: 4225-4234. http://dx.doi.org/10.1007/s11356-012-1376-0

Karamchandani, P; Vijayaraghavan, K; Chen, S; Balmori-Bronson, R; Knipping, EM. (2010). Development and application of a parallelized version of the advanced modeling system for transport, emissions, reactions and deposition of atmospheric matter (AMSTERDAM): 1. Model performance evaluation and impacts of plume-in-grid treatment. Atmos Pollut Res 1SI: 260-270. http://dx.doi.org/10.5094/APR.2010.033

Karr, CJ; Demers, PA; Koehoorn, MW; Lencar, CC; Tamburic, L; Brauer, M. (2009). Influence of ambient air pollutant sources on clinical encounters for infant bronchiolitis. Am J Respir Crit Care Med 180: 995-1001. http://dx.doi.org/10.1164/rccm.200901-0117OC

Katanoda, K; Sobue, T; Satoh, H; Tajima, K; Suzuki, T; Nakatsuka, H; Takezaki, T; Nakayama, T; Nitta, H; Tanabe, K; Tominaga, S. (2011). An association between long-term exposure to ambient air pollution and mortality from lung cancer and respiratory diseases in Japan. J Epidemiol 21: 132-143. http://dx.doi.org/10.2188/jea.JE20100098

Katsouyanni, K; Touloumi, G; Spix, C; Schwartz, J; Balducci, F; Medina, S; Rossi, G; Wojtyniak, B; Sunyer, J; Bacharova, L; Schouten, JP; Ponka, A; Anderson, HR. (1997). Short term effects of ambient sulphur dioxide and particulate matter on mortality in 12 European cities: Results from time series data from the APHEA project. BMJ 314: 1658-1663. http://dx.doi.org/10.1136/bmj.314.7095.1658

Kehrl, HR; Roger, LJ; Hazucha, MJ; Horstman, DH. (1987). Differing response of asthmatics to sulfur dioxide exposure with continuous and intermittent exercise. Am J Respir Crit Care Med 135: 350-355.

Kelishadi, R; Mirghaffari, N; Poursafa, P; Gidding, SS. (2009). Lifestyle and environmental factors associated with inflammation, oxidative stress and insulin resistance in children. Atherosclerosis 203: 311-319. http://dx.doi.org/10.1016/j.atherosclerosis.2008.06.022

Kerr, WJ; McWilliam, JS; Linder-Aronson, S. (1989). Mandibular form and position related to changed mode of breathing--a five-year longitudinal study. Angle Orthod 59: 91-96.

Khafaie, MA; Salvi, SS; Ojha, A; Khafaie, B; Gore, SS; Yajnik, CS. (2013). Systemic inflammation (C-reactive protein) in type 2 diabetic patients is associated with ambient air pollution in Pune City, India. Diabetes Care 36: 625-630. http://dx.doi.org/10.2337/dc12-0388

Kharitonov, SA; Barnes, PJ. (2000). Clinical aspects of exhaled nitric oxide [Review]. Eur Respir J 16: 781-792.

Khoder, MI. (2002). Atmospheric conversion of sulfur dioxide to particulate sulfat and nitrogen dioxide to particulate nitrate and gaseous nitric acid in an urban area. Chemosphere 49: 675-684. http://dx.doi.org/10.1016/S0045-6535(02)00391-0

Khokhar, MF; Platt, U; Wagner, T. (2008). Temporal trends of anthropogenic SO2 emitted by non-ferrous metal smelters in Peru and Russia estimated from Satellite observations. Atmos Chem Phys Discuss 8: 17393-17422. http://dx.doi.org/10.5194/acpd-8-17393-2008

Kikuya, M; Hozawa, A; Ohokubo, T; Tsuji, I; Michimata, M; Matsubara, M; Ota, M; Nagai, K; Araki, T; Satoh, H; Ito, S; Hisamichi, S; Imai, Y. (2000). Prognostic significance of blood pressure and heart rate variabilities: the Ohasama study. Hypertension 36: 901-906. http://dx.doi.org/10.1161/01.HYP.36.5.901

Kilkenny, C; Browne, WJ; Cuthill, IC; Emerson, M; Altman, DG. (2010). Improving bioscience research reporting: The ARRIVE guidelines for reporting animal research [Review]. PLoS Biol 8: e1000412. http://dx.doi.org/10.1371/journal.pbio.1000412

Kim, H; Park, Y; Park, K; Yoo, B. (2016a). Association between pollen risk indexes, air pollutants, and allergic diseases in Korea. Osong Public Health Res Perspect 7: 172-179. http://dx.doi.org/10.1016/j.phrp.2016.04.003

Kim, JH; Hong, YC. (2012). GSTM1, GSTT1, and GSTP1 polymorphisms and associations between air pollutants and markers of insulin resistance in elderly Koreans. Environ Health Perspect 120: 1378-1384. http://dx.doi.org/10.1289/ehp.1104406

Kim, KH; Kim, MY. (2001). Comparison of an open path differential optical absorption spectroscopy system and a conventional in situ monitoring system on the basis of long-term measurements of SO2, NO2, and O3. Atmos Environ 35: 4059-4072. http://dx.doi.org/10.1016/S1352-2310(01)00216-3

Kim, KN; Kim, JH; Jung, K; Hong, YC. (2016b). Associations of air pollution exposure with blood pressure and heart rate variability are modified by oxidative stress genes: A repeated-measures panel among elderly urban residents. Environ Health 15: 47. http://dx.doi.org/10.1186/s12940-016-0130-3

Kim, PS; Jacob, DJ; Fisher, JA; Travis, K; Yu, K; Zhu, L; Yantosca, RM; Sulprizio, MP; Jimenez, JL; Campuzano-Jost, P; Froyd, KD; Liao, J; Hair, JW; Fenn, MA; Butler, CF; Wagner, NL; Gordon, TD; Welti, A; Wennberg, PO; Crounse, JD; St. Clair, JM; Teng, AP; Millet, DB; Schwarz, JP; Markovic, MZ; Perring, AE. (2015). Sources, seasonality, and trends of southeast US aerosol: An integrated analysis of surface, aircraft, and satellite observations with the GEOS-Chem chemical transport model. Atmos Chem Phys 15: 10411-10433. http://dx.doi.org/10.5194/acp-15-10411-2015

Kim, T; Lee, K; Yang, W; Yu, SD. (2012). A new analytical method for the classification of time-location data obtained from the global positioning system (GPS). J Environ Monit 14: 2270-2274. http://dx.doi.org/10.1039/c2em30190c

Kimbell, JS; Miller, FJ. (1999). Regional respiratory-tract absorption of inhaled reactive gases: A modeling approach. In DE Gardner; JD Crapo; RO McClellan (Eds.), Toxicology of the lung (3rd ed ed., pp. 557-598). New York, NY: Taylor and Francis.

Klepeis, NE. (1999). An introduction to the indirect exposure assessment approach: Modeling human exposure using microenvironmental measurements and the recent National Human Activity Pattern Survey [Review]. Environ Health Perspect 107: 365-374. http://dx.doi.org/10.2307/3434429

Klepeis, NE; Nelson, WC; Ott, WR; Robinson, JP; Tsang, AM; Switzer, P; Behar, JV; Hern, SC; Engelmann, WH. (2001). The National Human Activity Pattern Survey (NHAPS): A resource for assessing exposure to environmental pollutants. J Expo Anal Environ Epidemiol 11: 231-252. http://dx.doi.org/10.1038/sj.jea.7500165

Klepeis, NE; Tsang, AM; Behar, JV. (1996). Analysis of the national human activity pattern survey (NHAPS) respondents from a standpoint of exposure assessment [EPA Report]. (EPA/600/R-96/074). Washington, DC: U.S. Environmental Protection Agency. http://exposurescience.org/pub/reports/NHAPS_Report1.pdf#....Local SettingsTemporary Internet FilesContent.Outlook3JQ221FPB_Approaches_Population_Tables.docx

Klimisch, HJ; Andreae, M; Tillmann, U. (1997). A systematic approach for evaluating the quality of experimental toxicological and ecotoxicological data. Regul Toxicol Pharmacol 25: 1-5. http://dx.doi.org/10.1006/rtph.1996.1076

Kloster, S; Six, KD; Feichter, J; Maier-Reimer, E; Roeckner, E; Wetzel, P; Stier, P; Esch, M. (2007). Response of dimethylsulfide (DMS) in the ocean and atmosphere to global warming. J Geophys Res 112: G03005. http://dx.doi.org/10.1029/2006JG000224

Knowledge Networks. (2009). Field report: National-scale activity survey (NSAS). Research Triangle Park, NC: Research Triangle Institute.

Ko, FW; Tam, W; Wong, TW; Chan, DP; Tung, AH; Lai, CKW; Hui, DSC. (2007a). Temporal relationship between air pollutants and hospital admissions for chronic obstructive pulmonary disease in Hong Kong. Thorax 62: 780-785. http://dx.doi.org/10.1136/thx.2006.076166

Ko, FWS; Tam, W; Wong, TW; Lai, CKW; Wong, GWK; Leung, TF; Ng, SSS; Hui, DSC. (2007b). Effects of air pollution on asthma hospitalization rates in different age groups in Hong Kong. Clin Exp Allergy 37: 1312-1319. http://dx.doi.org/10.1111/j.1365-2222.2007.02791.x

Koenig, JQ; Covert, DS; Hanley, QS; Van Belle, G; Pierson, WE. (1990). Prior exposure to ozone potentiates subsequent response to sulfur dioxide in adolescent asthmatic subjects. Am J Respir Crit Care Med 141: 377-380. http://dx.doi.org/10.1164/ajrccm/141.2.377

Koenig, JQ; Dumler, K; Rebolledo, V; Williams, PV; Pierson, WE. (1992). Theophylline mitigates the bronchoconstrictor effects of sulfur dioxide in subjects with asthma. J Allergy Clin Immunol 89: 789-794. http://dx.doi.org/10.1016/0091-6749(92)90432-2

Koenig, JQ; Marshall, SG; Horike, M; Shapiro, GG; Furukawa, CT; Bierman, CW; Pierson, WE. (1987). The effects of albuterol on sulfur dioxide-induced bronchoconstriction in allergic adolescents. J Allergy Clin Immunol 79: 54-58. http://dx.doi.org/10.1016/S0091-6749(87)80016-7

Koenig, JQ; Marshall, SG; van Belle, G; McManus, MS; Bierman, CW; Shapiro, GG; Furukawa, CT; Pierson, WE. (1988). Therapeutic range cromolyn dose-response inhibition and complete obliteration of SO2-induced bronchoconstriction in atopic adolescents. J Allergy Clin Immunol 81: 897-901.

Koenig, JQ; Pierson, WE; Frank, R. (1980). Acute effects of inhaled SO2 plus NaCl droplet aerosol on pulmonary function in asthmatic adolescents. Environ Res 22: 145-153.

Koenig, JQ; Pierson, WE; Horike, M; Frank, R. (1981). Effects of SO2 plus NaCl aerosol combined with moderate exercise on pulmonary function in asthmatic adolescents. Environ Res 25: 340-348.

Koenig, JQ; Pierson, WE; Horike, M; Frank, R. (1983). A comparison of the pulmonary effects of 0.5 ppm versus 1.0 ppm sulfur dioxide plus sodium chloride droplets in asthmatic adolescents. J Toxicol Environ Health 11: 129-139. http://dx.doi.org/10.1080/15287398309530327

Koken, PJM; Piver, WT; Ye, F; Elixhauser, A; Olsen, LM; Portier, CJ. (2003). Temperature, air pollution, and hospitalization for cardiovascular diseases among elderly people in Denver. Environ Health Perspect 111: 1312-1317.

Koutrakis, P; Wolfson, JM; Slater, JL; Brauer, M; Spengler, JD; Stevens, RK; Stone, CL. (1988). Evaluation of an annular denuder/filter pack system to collect acidic aerosols and gases. Environ Sci Technol 22: 1463-1468. http://dx.doi.org/10.1021/es00177a013

Krewski, D; Burnett, RT; Goldberg, MS; Hoover, K; Siemiatycki, J; Jerrett, M; Abrahamowicz, M; White, WH. (2000). Reanalysis of the Harvard Six Cities study and the American Cancer Society study of particulate air pollution and mortality. Cambridge, MA: Health Effects Institute. http://pubs.healtheffects.org/view.php?id=6

Krewski, D; Jerrett, M; Burnett, RT; Ma, R; Hughes, E; Shi, Y; Turner, MC; Pope, CA, III; Thurston, G; Calle, EE; Thun, MJ; Beckerman, B; Deluca, P; Finkelstein, N; Ito, K; Moore, DK; Newbold, KB; Ramsay, T; Ross, Z; Shin, H; Tempalski, B. (2009). Extended follow-up and spatial analysis of the American Cancer Society study linking particulate air pollution and mortality (pp. 5-114; discussion 115-136). (ISSN 1041-5505, HEI Research Report 140). Boston, MA: Health Effects Institute. http://pubs.healtheffects.org/view.php?id=315

Kumar, N. (2012). Uncertainty in the relationship between criteria pollutants and low birth weight in Chicago. Atmos Environ 49: 171-179. http://dx.doi.org/10.1016/j.atmosenv.2011.12.001

La Rovere, MT; Pinna, GD; Maestri, R; Mortara, A; Capomolla, S; Febo, O; Ferrari, R; Franchini, M; Gnemmi, M; Opasich, C; Riccardi, PG; Traversi, E; Cobelli, F. (2003). Short-term heart rate variability strongly predicts sudden cardiac death in chronic heart failure patients. Circulation 107: 565-570. http://dx.doi.org/10.1161/01.CIR.0000047275.25795.17

Lane, KJ; Scammell, MK; Levy, JI; Fuller, CH; Parambi, R, on; Zamore, W, ig; Mwamburi, M; Brugge, D. (2013). Positional error and time-activity patterns in near-highway proximity studies: an exposure misclassification analysis. Environ Health 12: 75. http://dx.doi.org/10.1186/1476-069X-12-75

Langner, J; Rodhe, H. (1991). A global three-dimensional model of the tropospheric sulfur cycle. J Atmos Chem 13: 225-263.

Laskin, S; Kuschner, M; Sellakumar, A; Katz, GV. (1976). Combined carcinogen-irritant animal inhalation studies. In EF Aharonson; A Ben-David; MA Klingberg (Eds.), Air pollution and the lung: proceedings of the twentieth annual (pp. 190-213). New York, NY: John Wiley & Sons.

Lawther, PJ. (1955). Effect of inhalation of sulphur dioxide on respiration and pulse-rate in normal subjects. Lancet 269: 745-748.

Lawther, PJ; MacFarlane, AJ; Waller, RE; Brooks, AGF. (1975). Pulmonary function and sulphur dioxide, some preliminary findings. Environ Res 10: 355-367. http://dx.doi.org/10.1016/0013-9351(75)90031-6

Lazarus, SC; Boushey, HA; Fahy, JV; Chinchilli, VM; Lemanske, RF; Sorkness, CA; Kraft, M; Fish, JE; Peters, SP; Craig, T; Drazen, JM; Ford, JG; Israel, E; Martin, RJ; Mauger, EA; Nachman, SA; Spahn, JD; Szefler, SJ; Asthma Clinical Research Network for the National Heart, L. (2001). Long-acting beta2-agonist monotherapy vs continued therapy with inhaled corticosteroids in patients with persistent asthma: a randomized controlled trial. JAMA 285: 2583-2593. http://dx.doi.org/10.1001/jama.285.20.2583

Lazarus, SC; Wong, HH; Watts, MJ; Boushey, HA; Lavins, BJ; Minkwitz, MC. (1997). The leukotriene receptor antagonist zafirlukast inhibits sulfur dioxide-induced bronchoconstriction in patients with asthma. Am J Respir Crit Care Med 156: 1725-1730. http://dx.doi.org/10.1164/ajrccm.156.6.9608006

Le, HQ; Batterman, SA; Wirth, JJ; Wahl, RL; Hoggatt, KJ; Sadeghnejad, A; Hultin, ML; Depa, M. (2012). Air pollutant exposure and preterm and term small-for-gestational-age births in Detroit, Michigan: Long-term trends and associations. Environ Int 44: 7-17. http://dx.doi.org/10.1016/j.envint.2012.01.003

Le Souëf, PN; Sears, MR; Sherrill, D. (1995). The effect of size and age of subject on airway responsiveness in children. Am J Respir Crit Care Med 152: 576-579. http://dx.doi.org/10.1164/ajrccm.152.2.7633710

Lee, BE; Ha, EH; Park, HS; Kim, YJ; Hong, YC; Kim, H; Lee, JT. (2003). Exposure to air pollution during different gestational phases contributes to risks of low birth weight. Hum Reprod 18: 638-643. http://dx.doi.org/10.1093/humrep/deg102

Lee, C; Martin, RV; van Donkelaar, A; Lee, H; Dickerson, RR; Hains, JC; Krotkov, N; Richter, A; Vinnikov, K; Schwab, JJ. (2011a). SO2 emissions and lifetimes: Estimates from inverse modeling using in situ and global, space-based (SCIAMACHY and OMI) observations. J Geophys Res 116: D06304. http://dx.doi.org/10.1029/2010JD014758

Lee, CL; Brimblecombe, P. (2016). Anthropogenic contributions to global carbonyl sulfide, carbon disulfide and organosulfides fluxes. Earth Sci Rev 160: 1-18. http://dx.doi.org/10.1016/j.earscirev.2016.06.005

Lee, HD, on; Yoo, JW, oo; Kang, M, inK; Kang, J, iS; Jung, JH; Oh, KJ. (2014). Evaluation of concentrations and source contribution of PM10 and SO2 emitted from industrial complexes in Ulsan, Korea: Interfacing of the WRF-CALPUFF modeling tools. Atmos Pollut Res 5: 664-676. http://dx.doi.org/10.5094/APR.2014.076

Lee, LY; Widdicombe, JG. (2001). Modulation of airway sensitivity to inhaled irritants: role of inflammatory mediators [Review]. Environ Health Perspect 4: 585-589.

Lee, PC; Talbott, EO; Roberts, JM; Catov, JM; Bilonick, RA; Stone, RA; Sharma, RK; Ritz, B. (2012). Ambient air pollution exposure and blood pressure changes during pregnancy. Environ Res 117: 46-53. http://dx.doi.org/10.1016/j.envres.2012.05.011

Lee, PC; Talbott, EO; Roberts, JM; Catov, JM; Sharma, RK; Ritz, B. (2011b). Particulate air pollution exposure and C-reactive protein during early pregnancy. Epidemiology 22: 524-531. http://dx.doi.org/10.1097/EDE.0b013e31821c6c58

Lee, YL; Wang, WH; Lu, CW; Lin, YH; Hwang, BF. (2011c). Effects of ambient air pollution on pulmonary function among schoolchildren. Int J Hyg Environ Health 214: 369-375. http://dx.doi.org/10.1016/j.ijheh.2011.05.004

Lee, YP. (2015). Perspective: Spectroscopy and kinetics of small gaseous Criegee intermediates. J Chem Phys 143: 020901. http://dx.doi.org/10.1063/1.4923165

Leem, JH; Kaplan, BM; Shim, YK; Pohl, HR; Gotway, CA; Bullard, SM; Rogers, JF; Smith, MM; Tylenda, CA. (2006). Exposures to air pollutants during pregnancy and preterm delivery. Environ Health Perspect 114: 905-910. http://dx.doi.org/10.1289/ehp.8733

Legro, RS; Sauer, MV; Mottla, GL; Richter, KS; Li, X; Dodson, WC; Liao, D. (2010). Effect of air quality on assisted human reproduction. Hum Reprod 25: 1317-1324. http://dx.doi.org/10.1093/humrep/deq021

Leiberman, A; Ohki, M; Forte, V; Fraschetti, J; Cole, P. (1990). Nose/mouth distribution of respiratory airflow in 'mouth breathing' children. Acta Otolaryngol 109: 454-460. http://dx.doi.org/10.3109/00016489009125169

Leidos Inc. (2016). Air quality monitoring program at the port of Los Angeles. Year eleven data summary, May 2015 - April 2016. San Pedro, CA: Port of Los Angeles, Environmental Planning Division.

Leiter, JC; Baker, GL. (1989). Partitioning of ventilation between nose and mouth: The role of nasal resistance. Am J Orthod Dentofacial Orthop 95: 432-438. http://dx.doi.org/10.1016/0889-5406(89)90305-3

Lenters, V; Uiterwaal, CS; Beelen, R; Bots, ML; Fischer, P; Brunekreef, B; Hoek, G. (2010). Long-term exposure to air pollution and vascular damage in young adults. Epidemiology 21: 512-520. http://dx.doi.org/10.1097/EDE.0b013e3181dec3a7

Leppänen, S; Anttila, P; Lättilä, H; Makkonen, U. (2005). Long-term comparison of filter method and sensitive analyser in monitoring of sulphur dioxide. Atmos Environ 39: 2683-2693. http://dx.doi.org/10.1016/j.atmosenv.2005.02.002

Levy, D; Sheppard, L; Checkoway, H; Kaufman, J; Lumley, T; Koenig, J; Siscovick, D. (2001). A case-crossover analysis of particulate matter air pollution and out-of-hospital primary cardiac arrest. Epidemiology 12: 193-199.

Li, C; Zhang, Q; Krotkov, NA; Streets, DG; He, K; Tsay, SC; Gleason, JF. (2010). Recent large reduction in sulfur dioxide emissions from Chinese power plants observed by the Ozone Monitoring Instrument. Geophys Res Lett 37: L08807. http://dx.doi.org/10.1029/2010GL042594

Li, R; Kou, X; Tian, J; Meng, Z; Cai, Z; Cheng, F; Dong, C. (2014). Effect of sulfur dioxide on inflammatory and immune regulation in asthmatic rats. Chemosphere 112: 296-304. http://dx.doi.org/10.1016/j.chemosphere.2014.04.065

Li, R; Meng, Z; Xie, J. (2007). Effects of sulfur dioxide on the expressions of MUC5AC and ICAM-1 in airway of asthmatic rats. Regul Toxicol Pharmacol 48: 284-291. http://dx.doi.org/10.1016/j.yrtph.2007.04.009

Li, R; Meng, Z; Xie, J. (2008). Effects of sulfur dioxide on the expressions of EGF, EGFR, and COX-2 in airway of asthmatic rats. Arch Environ Contam Toxicol 54: 748-757. http://dx.doi.org/10.1007/s00244-007-9054-9

Li, S; Batterman, S; Wasilevich, E; Wahl, R; Wirth, J; Su, FC; Mukherjee, B. (2011). Association of daily asthma emergency department visits and hospital admissions with ambient air pollutants among the pediatric Medicaid population in Detroit: Time-series and time-stratified case-crossover analyses with threshold effects. Environ Res 111: 1137-1147. http://dx.doi.org/10.1016/j.envres.2011.06.002

Li, S; Guo, Y; Williams, G. (2016). Acute impact of hourly ambient air pollution on preterm birth. Environ Health Perspect 124: 1623-1629. http://dx.doi.org/10.1289/EHP200

Li, X; Bazer, FW; Gao, H; Jobgen, W; Johnson, GA; Li, P; McKnight, JR; Satterfield, MC; Spencer, TE; Wu, G. (2009). Amino acids and gaseous signaling [Review]. Amino Acids 37: 65-78. http://dx.doi.org/10.1007/s00726-009-0264-5

Liang, Z; Wu, L; Fan, L; Zhao, Q. (2014). Ambient air pollution and birth defects in Haikou city, Hainan province. BMC Pediatr 14: 283. http://dx.doi.org/10.1186/s12887-014-0283-6

Liao, CM; Hsieh, NH; Chio, CP. (2011). Fluctuation analysis-based risk assessment for respiratory virus activity and air pollution associated asthma incidence. Sci Total Environ 409: 3325-3333. http://dx.doi.org/10.1016/j.scitotenv.2011.04.056

Lillis, D; Cruz, CN; Collett, J, Jr; Richards, LW; Pandis, SN. (1999). Production and removal of aerosol in a polluted fog layer: Model evaluation and fog effect on PM. Atmos Environ 33: 4797-4816. http://dx.doi.org/10.1016/S1352-2310(99)00264-2

Lin, HK; Tsai, JJ; Wen, MC; Tsai, MC; Chen, CJ; Fu, LS. (2011a). Sodium sulfite aggravated allergic sensitization and airway inflammation in mite allergen sensitized BALB/c mice. Hum Exp Toxicol 30: 1682-1689. http://dx.doi.org/10.1177/0960327111398673

Lin, LC; Takahashi, K. (2016). Will (CH3)(2)COO survive in humid conditions? J Chin Chem Soc 63: 472-479. http://dx.doi.org/10.1002/jccs.201500518

Lin, S; Hwang, SA; Pantea, C; Kielb, C; Fitzgerald, E. (2004). Childhood asthma hospitalizations and ambient air sulfur dioxide concentrations in Bronx County, New York. Arch Environ Occup Health 59: 266-275. http://dx.doi.org/10.3200/AEOH.59.5.266-275

Lin, W; Huang, W; Zhu, T; Hu, M; Brunekreef, B; Zhang, Y; Liu, X; Cheng, H; Gehring, U; Li, C; Tang, X. (2011b). Acute respiratory inflammation in children and black carbon in ambient air before and during the 2008 Beijing Olympics. Environ Health Perspect 119: 1507-1512. http://dx.doi.org/10.1289/ehp.1103461

Lin, W; Zhu, T; Xue, T; Peng, W; Brunekreef, B; Gehring, U; Huang, W; Hu, M; Zhang, Y; Tang, X. (2015). Association between changes in exposure to air pollution and biomarkers of oxidative stress in children before and during the Beijing olympics. Am J Epidemiol 181: 575-583. http://dx.doi.org/10.1093/aje/kwu327

Lin, YT; Lee, YL; Jung, CR; Jaakkola, JJ; Hwang, BF. (2014). Air pollution and limb defects: A matched-pairs case-control study in Taiwan. Environ Res 132: 273-280. http://dx.doi.org/10.1016/j.envres.2014.04.028

Linares, B; Guizar, JM; Amador, N; Garcia, A; Miranda, V; Perez, JR; Chapela, R. (2010). Impact of air pollution on pulmonary function and respiratory symptoms in children. Longitudinal repeated-measures study. BMC Pulm Med 10: 62. http://dx.doi.org/10.1186/1471-2466-10-62

Link, MS; Luttmann-Gibson, H; Schwartz, J; Mittleman, MA; Wessler, B; Gold, DR; Dockery, DW; Laden, F. (2013). Acute exposure to air pollution triggers atrial fibrillation. J Am Coll Cardiol 62: 816-825. http://dx.doi.org/10.1016/j.jacc.2013.05.043

Linn, WS; Avol, EL; Peng, RC; Shamoo, DA; Hackney, JD. (1987). Replicated dose-response study of sulfur dioxide effects in normal, atopic, and asthmatic volunteers. Am Rev Respir Dis 136: 1127-1134. http://dx.doi.org/10.1164/ajrccm/136.5.1127

Linn, WS; Avol, EL; Shamoo, DA; Peng, RC; Spier, CE; Smith, MN; Hackney, JD. (1988). Effect of metaproterenol sulfate on mild asthmatics' response to sulfur dioxide exposure and exercise. Arch Environ Occup Health 43: 399-406. http://dx.doi.org/10.1080/00039896.1988.9935858

Linn, WS; Avol, EL; Shamoo, DA; Venet, TG; Anderson, KR; Whynot, JD; Hackney, JD. (1984a). Asthmatics' responses to 6-hr sulfur dioxide exposures on two successive days. Arch Environ Health 39: 313-319. http://dx.doi.org/10.1080/00039896.1984.10545856

Linn, WS; Fischer, DA; Shamoo, DA; Spier, CE; Valencia, LM; Anzar, UT; Hackney, JD. (1985a). Controlled exposures of volunteers with chronic obstructive pulmonary disease to sulfur dioxide. Environ Res 37: 445-451. http://dx.doi.org/10.1016/0013-9351(85)90126-4

Linn, WS; Shamoo, DA; Anderson, KR; Whynot, JD; Avol, EL; Hackney, JD. (1985b). Effects of heat and humidity on the responses of exercising asthmatics to sulfur dioxide exposure. Am Rev Respir Dis 131: 221-225.

Linn, WS; Shamoo, DA; Peng, RC; Clark, KW; Avol, EL; Hackney, JD. (1990). Responses to sulfur dioxide and exercise by medication-dependent asthmatics: Effect of varying medication levels. Arch Environ Occup Health 45: 24-30. http://dx.doi.org/10.1080/00039896.1990.9935920

Linn, WS; Shamoo, DA; Spier, CE; Valencia, LM; Anzar, UT; Venet, TG; Hackney, JD. (1983a). Respiratory effects of 0.75 ppm sulfur dioxide in exercising asthmatics: Influence of upper-respiratory defenses. Environ Res 30: 340-348. http://dx.doi.org/10.1016/0013-9351(83)90219-0

Linn, WS; Shamoo, DA; Venet, TG; Bailey, RM; Wightman, LH; Hackney, JD. (1984b). Comparative effects of sulfur dioxide exposures at 5 degrees C and 22 degrees C in exercising asthmatics. Am Rev Respir Dis 129: 234-239.

Linn, WS; Shamoo, DA; Vinet, TG; Spier, CE; Valencia, LM; Anzar, UT; Hackney, JD. (1984c). Combined effect of sulfur dioxide and cold in exercising asthmatics. Arch Environ Occup Health 39: 339-346. http://dx.doi.org/10.1080/00039896.1984.10545860

Linn, WS; Venet, TG; Shamoo, DA; Valencia, LM; Anzar, UT; Spier, CE; Hackney, JD. (1983b). Respiratory effects of sulfur dioxide in heavily exercising asthmatics: A dose-response study. Am Rev Respir Dis 127: 278-283.

Lipfert, FW; Baty, JD; Miller, JP; Wyzga, RE. (2006a). PM2.5 constituents and related air quality variables as predictors of survival in a cohort of U.S. military veterans. Inhal Toxicol 18: 645-657. http://dx.doi.org/10.1080/08958370600742946

Lipfert, FW; Perry, HM, Jr; Miller, JP; Baty, JD; Wyzga, RE; Carmody, SE. (2000a). The Washington University-EPRI veterans' cohort mortality study: Preliminary results. Inhal Toxicol 12: 41-73. http://dx.doi.org/10.1080/713856640

Lipfert, FW; Wyzga, RE. (1996). The effects of exposure error on environmental epidemiology. In RF Phalen; RC Mannix; MC Tonini (Eds.), The second colloquium on particulate air pollution & human mortality & morbidity (pp. 4-295-294-302). Sacramento, CA: California Air Resources Board.

Lipfert, FW; Wyzga, RE; Baty, JD; Miller, JP. (2006b). Traffic density as a surrogate measure of environmental exposures in studies of air pollution health effects: Long-term mortality in a cohort of US veterans. Atmos Environ 40: 154-169. http://dx.doi.org/10.1016/j.atmosenv.2005.09.027

Lipfert, FW; Wyzga, RE; Baty, JD; Miller, JP. (2009). Air pollution and survival within the Washington University-EPRI veterans cohort: Risks based on modeled estimates of ambient levels of hazardous and criteria air pollutants. J Air Waste Manag Assoc 59: 473-489.

Lipfert, FW; Zhang, J; Wyzga, RE. (2000b). Infant mortality and air pollution: A comprehensive analysis of US data for 1990. J Air Waste Manag Assoc 50: 1350-1366. http://dx.doi.org/10.1080/10473289.2000.10464168

Lipsett, MJ; Ostro, BD; Reynolds, P; Goldberg, D; Hertz, A; Jerrett, M; Smith, DF; Garcia, C; Chang, ET; Bernstein, L. (2011). Long-term exposure to air pollution and cardiorespiratory disease in the California teachers study cohort. Am J Respir Crit Care Med 184: 828-835. http://dx.doi.org/10.1164/rccm.201012-2082OC

Liu, CC; Tsai, SS; Chiu, HF; Wu, TN; Chen, CC; Yang, CY. (2009a). Ambient exposure to criteria air pollutants and risk of death from bladder cancer in Taiwan. Inhal Toxicol 21: 48-54. http://dx.doi.org/10.1080/08958370802207326

Liu, D; Jin, H; Tang, C; Du, J. (2010). Sulfur dioxide: A novel gaseous signal in the regulation of cardiovascular functions [Review]. Mini Rev Med Chem 10: 1039-1045. http://dx.doi.org/10.2174/1389557511009011039

Liu, F; Zhao, Y; Liu, YQ; Liu, Y; Sun, J; Huang, MM; Liu, Y; Dong, GH. (2014a). Asthma and asthma related symptoms in 23,326 Chinese children in relation to indoor and outdoor environmental factors: The Seven Northeastern Cities (SNEC) Study. Sci Total Environ 497-498: 10-17. http://dx.doi.org/10.1016/j.scitotenv.2014.07.096

Liu, L. (2013). Email from Dr. Liu to Dr. Patel; Response to data request. Available online at http://www.regulations.gov/#!documentDetail;D=EPA-HQ-ORD-2013-0232-0013

Liu, L; Poon, R; Chen, L; Frescura, AM; Montuschi, P; Ciabattoni, G; Wheeler, A; Dales, R. (2009b). Acute effects of air pollution on pulmonary function, airway inflammation, and oxidative stress in asthmatic children. Environ Health Perspect 117: 668-674. http://dx.doi.org/10.1289/ehp11813

Liu, S; Krewski, D; Shi, Y; Chen, Y; Burnett, R. (2007). Association between maternal exposure to ambient air pollutants during pregnancy and fetal growth restriction. J Expo Sci Environ Epidemiol 17: 426-432. http://dx.doi.org/10.1038/sj.jes.7500503

Liu, S; Krewski, D; Shi, Y; Chen, Y; Burnett, RT. (2003). Association between gaseous ambient air pollutants and adverse pregnancy outcomes in Vancouver, Canada. Environ Health Perspect 111: 1773-1778.

Liu, W; Huang, C; Hu, Y; Fu, Q; Zou, Z; Sun, C; Shen, L; Wang, X; Cai, J; Pan, J; Huang, Y; Chang, J; Sun, Y; Sundell, J. (2016). Associations of gestational and early life exposures to ambient air pollution with childhood respiratory diseases in Shanghai, China: A retrospective cohort study. Environ Int 92-93: 284-293. http://dx.doi.org/10.1016/j.envint.2016.04.019

Liu, X; Easter, RC; Ghan, SJ; Zaveri, R; Rasch, P; Shi, X; Lamarque, JF; Gettelman, A; Morrison, H; Vitt, F; Conley, A; Park, S; Neale, R; Hannay, C; Ekman, AML; Hess, P; Mahowald, N; Collins, W; Iacono, MJ; Bretherton, CS; Flanner, MG; Mitchell, D. (2012a). Toward a minimal representation of aerosols in climate models: Description and evaluation in the Community Atmosphere Model CAM5. Geosci Model Dev 5: 709-739. http://dx.doi.org/10.5194/gmd-5-709-2012

Liu, X; Lessner, L; Carpenter, DO. (2012b). Association between residential proximity to fuel-fired power plants and hospitalization rate for respiratory diseases. Environ Health Perspect 120: 807-810. http://dx.doi.org/10.1289/ehp.1104146

Liu, XH; Penner, JE; Herzog, M. (2005). Global modeling of aerosol dynamics: Model description, evaluation, and interactions between sulfate and nonsulfate aerosols. J Geophys Res 110: D18206. http://dx.doi.org/10.1029/2004JD005674

Liu, Y; Bayes, KD; Sander, SP. (2014b). Measuring rate constants for reactions of the simplest Criegee intermediate (CH2OO) by monitoring the OH radical. J Phys Chem A 118: 741-747. http://dx.doi.org/10.1021/jp407058b

Llorca, J; Salas, A; Prieto-Salceda, D; Chinchon-Bengoechea, V; Delgado-Rodriguez, M. (2005). Nitrogen dioxide increases cardiorespiratory admissions in Torrelavega (Spain). J Environ Health 68: 30-35.

Loerting, T; Liedl, KR. (2000). Toward elimination of discrepancies between theory and experiment: The rate constant of the atmospheric conversion of SO3 to H2SO4. Proc Natl Acad Sci USA 97: 8874-8878. http://dx.doi.org/10.1073/pnas.97.16.8874

Long, MS; Keene, WC; Easter, RC; Sander, R; Liu, X; Kerkweg, A; Erickson, D. (2013). Sensitivity of tropospheric chemical composition to halogen-radical chemistry using a fully coupled size-resolved multiphase chemistry/global climate system Part 1: Halogen distributions, aerosol composition, and sensitivity of climate-relevant gases. Atmos Chem Phys Discuss 13: 6067-6129. http://dx.doi.org/10.5194/acpd-13-6067-2013

Longo, BM. (2009). The Kilauea Volcano adult health study. Nurs Res 58: 23-31. http://dx.doi.org/10.1097/NNR.0b013e3181900cc5

Longo, BM; Rossignol, A; Green, JB. (2008). Cardiorespiratory health effects associated with sulphurous volcanic air pollution. Public Health 122: 809-820. http://dx.doi.org/10.1016/j.puhe.2007.09.017

Longo, BM; Yang, W. (2008). Acute bronchitis and volcanic air pollution: A community-based cohort study at Kilauea Volcano, Hawai'i, USA. J Toxicol Environ Health A 71: 1565-1571. http://dx.doi.org/10.1080/15287390802414117

Longo, BM; Yang, W; Green, JB; Crosby, FL; Crosby, VL. (2010). Acute health effects associated with exposure to volcanic air pollution (vog) from increased activity at Kilauea Volcano in 2008. J Toxicol Environ Health A 73: 1370-1381. http://dx.doi.org/10.1080/15287394.2010.497440

López-Aparicio, S; Smolík, J; Mašková, L; Součková, M; Grøntoft, T; Ondráčková, L; Stankiewicz, J. (2011). Relationship of indoor and outdoor air pollutants in a naturally ventilated historical building envelope. Build Environ 46: 1460-1468. http://dx.doi.org/10.1016/j.buildenv.2011.01.013

Low, RB; Bielory, L; Qureshi, AI; Dunn, V; Stuhlmiller, DF; Dickey, DA. (2006). The relation of stroke admissions to recent weather, airborne allergens, air pollution, seasons, upper respiratory infections, and asthma incidence, September 11, 2001, and day of the week. Stroke 37: 951-957. http://dx.doi.org/10.1161/01.STR.0000214681.94680.66

Lu, C; Deng, Q; Yu, CWF; Sundell, J; Ou, C. (2014). Effects of ambient air pollution on the prevalence of pneumonia in children: Implication for National Ambient Air Quality Standards in China. Indoor Built Environ 23: 259-269. http://dx.doi.org/10.1177/1420326X13504423

Lu, R; Turco, RP; Jacobson, MZ. (1997a). An integrated air pollution modeling system for urban and regional scales: 1. Structure and performance. J Geophys Res 102: 6063-6079. http://dx.doi.org/10.1029/96JD03501

Lu, R; Turco, RP; Jacobson, MZ. (1997b). An integrated air pollution modeling system for urban and regional scales: 2. Simulations for SCAQS 1987. J Geophys Res Atmos 102: 6081-6098. http://dx.doi.org/10.1029/96JD03502

Luke, WT. (1997). Evaluation of a commercial pulsed fluorescence detector for the measurement of low-level SO2 concentrations during the gas-phase sulfur intercomparison experiment. J Geophys Res 102: 16255-16265. http://dx.doi.org/10.1029/96JD03347

Luo, L; Chen, S; Jin, H; Tang, C; Du, J. (2011). Endogenous generation of sulfur dioxide in rat tissues. Biochem Biophys Res Commun 415: 61-67. http://dx.doi.org/10.1016/j.bbrc.2011.10.012

MacIntyre, EA; Karr, CJ; Koehoorn, M; Demers, PA; Tamburic, L; Lencar, C; Brauer, M. (2011). Residential air pollution and otitis media during the first two years of life. Epidemiology 22: 81-89. http://dx.doi.org/10.1097/EDE.0b013e3181fdb60f

Madigan, MT; Martinko, JM; Brock, TD. (2006). Brock biology of microorganisms. In MT Madigan; JM Martinko; TD Brock (Eds.), Brock biology of microorganisms (11th ed.). Upper Saddle River, NJ: Pearson Prentice Hall.

Maestrelli, P; Canova, C; Scapellato, ML; Visentin, A; Tessari, R; Bartolucci, GB; Simonato, L; Lotti, M. (2011). Personal exposure to particulate matter is associated with worse health perception in adult asthma. J Investig Allergol Clin Immunol 21: 120-128.

Magnussen, H; Jorres, R; Wagner, HM; von Nieding, G. (1990). Relationship between the airway response to inhaled sulfur dioxide, isocapnic hyperventilation, and histamine in asthmatic subjects. Int Arch Occup Environ Health 62: 485-491. http://dx.doi.org/10.1007/BF00381178

Mai, CT; Kirby, RS; Correa, A; Rosenberg, D; Petros, M; Fagen, MC. (2016). Public health practice of population-based birth defects surveillance programs in the United States. J Public Health Manag Pract 22: E1-E8. http://dx.doi.org/10.1097/PHH.0000000000000221

Maier, KL; Wippermann, U; Leuschel, L; Josten, M; Pflugmacher, S; Schröder, P; Sandermann, H; Takenaka, S; Ziesenis, A; Heyder, J. (1999). Xenobiotic-metabolizing enzymes in the canine respiratory tract. Inhal Toxicol 11: 19-35. http://dx.doi.org/10.1080/089583799197249

Makamure, MT; Reddy, P; Chuturgoon, A; Naidoo, RN; Mentz, G; Batterman, S; Robins, TG. (2016a). Interaction between ambient pollutant exposure, CD14 (-159) polymorphism and respiratory outcomes among children in Kwazulu-Natal, Durban. Hum Exp Toxicol. http://dx.doi.org/10.1177/0960327116646620

Makamure, MT; Reddy, P; Chuturgoon, A; Naidoo, RN; Mentz, G; Batterman, S; Robins, TG. (2016b). Tumour necrosis factor α polymorphism (TNF-308α G/A) in association with asthma related phenotypes and air pollutants among children in KwaZulu-Natal. Asian Pac J Allergy Immunol. http://dx.doi.org/10.12932/AP0677

Mamatsashvili, MI. (1970a). Detrimental effects of carbon monoxide and sulfur dioxide on fertility of female rats. Hyg Sanit 35: 277-279.

Mamatsashvili, MI. (1970b). [Toxic effect of carbon monoxide, sulfur dioxide and their combinations on the fertility of female rats]. Gig Sanit 35: 100-101.

Mannshardt, E; Sucic, K; Jiao, W; Dominici, F; Frey, HC; Reich, B; Fuentes, M. (2013). Comparing exposure metrics for the effects of fine particulate matter on emergency hospital admissions. J Expo Sci Environ Epidemiol 23: 627-636. http://dx.doi.org/10.1038/jes.2013.39

Marshall, JD; Nethery, E; Brauer, M. (2008). Within-urban variability in ambient air pollution: Comparison of estimation methods. Atmos Environ 42: 1359-1369. http://dx.doi.org/10.1016/j.atmosenv.2007.08.012

Martins, LC; Pereira, LAA; Lin, CA; Santos, UP; Prioli, G; do Carmo Luiz, O; Saldiva, PHN; Braga, ALF. (2006). The effects of air pollution on cardiovascular diseases: Lag structures. Rev Saude Publica 40: 677-683. http://dx.doi.org/10.1590/S0034-89102006000500018

Mathews, TJ; MacDorman, MF. (2010). Infant mortality statistics from the 2006 period linked birth/infant death data set. Atlanta, GA: Centers for Disease Control. http://www.cdc.gov/nchs/data/nvsr/nvsr58/nvsr58_17.pdf

Matsumi, Y; Shigemori, H; Takahashi, K. (2005). Laser-induced fluorescence instrument for measuring atmospheric SO2. Atmos Environ 39: 3177-3185. http://dx.doi.org/10.1016/j.atmosenv.2005.02.023

Mauldin, RL, III; Berndt, T; Sipilä, M; Paasonen, P; Petäjä, T; Kim, S; Kurtén, T; Stratmann, F; Kerminen, VM; Kulmala, M. (2012). A new atmospherically relevant oxidant of sulphur dioxide. Nature 488: 193-196. http://dx.doi.org/10.1038/nature11278

McAdam, K; Steer, P; Perrotta, K. (2011). Using continuous sampling to examine the distribution of traffic related air pollution in proximity to a major road. Atmos Environ 45: 2080-2086. http://dx.doi.org/10.1016/j.atmosenv.2011.01.050

McCormick, BT; Herzog, M; Yang, J; Edmonds, M; Mather, TA; Carn, SA; Hidalgo, S; Langmann, B. (2014). A comparison of satellite- and ground-based measurements of SO 2 emissions from Tungurahua volcano, Ecuador. J Geophys Res Atmos 119: 42644285. http://dx.doi.org/10.1002/2013JD019771

McCurdy, T; Glen, G; Smith, L; Lakkadi, Y. (2000). The National Exposure Research Laboratory's consolidated human activity database. J Expo Anal Environ Epidemiol 10: 566-578. http://dx.doi.org/10.1038/sj.jea.7500114

McLinden, CA; Fioletov, V; Boersma, KF; Krotkov, N; Sioris, CE; Veefkind, JP; Yang, K. (2012). Air quality over the Canadian oil sands: A first assessment using satellite observations. Geophys Res Lett 39: L04804. http://dx.doi.org/10.1029/2011GL050273

Mechtouff, L; Canoui-Poitrine, F; Schott, AM; Nighoghossian, N; Trouillas, P; Termoz, A; Porthault-Chatard, S; David, JS; Chasles, V; Derex, L. (2012). Lack of association between air pollutant exposure and short-term risk of ischaemic stroke in Lyon, France. Int J Stroke 7: 669-674. http://dx.doi.org/10.1111/j.1747-4949.2011.00737.x

Medina, DS; Liu, YD; Wang, LM; Zhang, JS. (2011). Detection of sulfur dioxide by cavity ring-down spectroscopy. Environ Sci Technol 45: 1926-1931. http://dx.doi.org/10.1021/es103739r

Mehta, S; Ngo, LH; Dzung, DV; Cohen, A; Thach, TQ; Dan, VX; Tuan, ND; Giang, LT. (2013). Air pollution and admissions for acute lower respiratory infections in young children of Ho Chi Minh City. Air Qual Atmos Health 6: 167-179. http://dx.doi.org/10.1007/s11869-011-0158-z

Melville, GN. (1970). Changes in specific airway conductance in healthy volunteers following nasal and oral inhalation of SO2. West Indian Med J 19: 231-235.

Mendola, P; Wallace, M; Hwang, BS; Liu, D; Robledo, C; Männistö, T; Sundaram, R; Sherman, S; Ying, Q; Grantz, KL. (2016a). Preterm birth and air pollution: Critical windows of exposure for women with asthma. J Allergy Clin Immunol 138: 432-440.e435. http://dx.doi.org/10.1016/j.jaci.2015.12.1309

Mendola, P; Wallace, M; Liu, D; Robledo, C; Männistö, T; Grantz, KL. (2016b). Air pollution exposure and preeclampsia among US women with and without asthma. Environ Res 148: 248-255. http://dx.doi.org/10.1016/j.envres.2016.04.004

Meng, X; Wang, C; Cao, D; Wong, CM; Kan, H. (2013). Short-term effect of ambient air pollution on COPD mortality in four Chinese cities. Atmos Environ 77: 149-154. http://dx.doi.org/10.1016/j.atmosenv.2013.05.001

Meng, Z; Li, R; Zhang, X. (2005a). Levels of sulfite in three organs from mice exposed to sulfur [corrected] dioxide. Inhal Toxicol 17: 309-313. http://dx.doi.org/10.1080/08958370590922634

Meng, Z; Li, R; Zhang, X. (2005b). Levels of sulfite in three organs from mice exposed to sulfur dioxide [Erratum]. Inhal Toxicol 17: 495. http://dx.doi.org/10.1080/08958370591001671

Meng, Z; Zhang, B; Ruan, A; Sang, N; Zhang, J. (2002). Micronuclei induced by sulfur dioxide inhalation in mouse bone-marrow cells in vivo. Inhal Toxicol 14: 303-309. http://dx.doi.org/10.1080/08958370252809077

Metzger, KB; Klein, M; Flanders, WD; Peel, JL; Mulholland, JA; Langberg, JJ; Tolbert, PE. (2007). Ambient air pollution and cardiac arrhythmias in patients with implantable defibrillators. Epidemiology 18: 585-592. http://dx.doi.org/10.1097/EDE.0b013e318124ff0e

Metzger, KB; Tolbert, PE; Klein, M; Peel, JL; Flanders, WD; Todd, KH; Mulholland, JA; Ryan, PB; Frumkin, H. (2004). Ambient air pollution and cardiovascular emergency department visits. Epidemiology 15: 46-56. http://dx.doi.org/10.1097/01.EDE.0000101748.28283.97

Michaud, JP; Grove, JS; Krupitsky, D. (2004). Emergency department visits and "vog"-related air quality in Hilo, Hawai'i. Environ Res 95: 11-19. http://dx.doi.org/10.1016/S0013-9351(03)00122-1

Michikawa, T; Morokuma, S; Fukushima, K; Ueda, K; Takeuchi, A; Kato, K; Nitta, H. (2015). A register-based study of the association between air pollutants and hypertensive disorders in pregnancy among the Japanese population. Environ Res 142: 644-650. http://dx.doi.org/10.1016/j.envres.2015.08.024

Michikawa, T; Morokuma, S; Yamazaki, S; Fukushima, K; Kato, K; Nitta, H. (2016). Exposure to air pollutants during the early weeks of pregnancy, and placenta praevia and placenta accreta in the western part of Japan. Environ Int 92-93: 464-470. http://dx.doi.org/10.1016/j.envint.2016.04.037

Miller, KA; Siscovick, DS; Sheppard, L; Shepherd, K; Sullivan, JH; Anderson, GL; Kaufman, JD. (2007). Long-term exposure to air pollution and incidence of cardiovascular events in women. N Engl J Med 356: 447-458. http://dx.doi.org/10.1056/NEJMoa054409

Milojevic, A; Wilkinson, P; Armstrong, B; Bhaskaran, K; Smeeth, L; Hajat, S. (2014). Short-term effects of air pollution on a range of cardiovascular events in England and Wales: Case-crossover analysis of the MINAP database, hospital admissions and mortality. Heart 100: 1093-1098. http://dx.doi.org/10.1136/heartjnl-2013-304963

Min, JY; Min, KB; Cho, SI; Paek, D. (2008a). Combined effects of cigarette smoking and sulfur dioxide on lung function in Koreans. J Toxicol Environ Health A 71: 301-303. http://dx.doi.org/10.1080/15287390701738475

Min, JY; Min, KB; Cho, SI; Paek, D. (2009). Combined effect of cigarette smoking and sulfur dioxide on heart rate variability [Letter]. Int J Cardiol 133: 119-121. http://dx.doi.org/10.1016/j.ijcard.2007.08.139

Min, KB; Min, JY; Cho, SI; Paek, D. (2008b). The relationship between air pollutants and heart-rate variability among community residents in Korea. Inhal Toxicol 20: 435-444. http://dx.doi.org/10.1080/08958370801903834

Mochizuki, H; Shigeta, M; Kato, M; Maeda, S; Shimizu, T; Mirokawa, A. (1995). Age-related changes in bronchial hyperreactivity to methacholine in asthmatic children. Am J Respir Crit Care Med 152: 906-910. http://dx.doi.org/10.1164/ajrccm.152.3.7663803

Moolgavkar, SH. (2000). Air pollution and hospital admissions for diseases of the circulatory system in three U.S. metropolitan areas. J Air Waste Manag Assoc 50: 1199-1206. http://dx.doi.org/10.1080/10473289.2000.10464162

Moolgavkar, SH. (2003). Air pollution and daily deaths and hospital admissions in Los Angeles and Cook counties. In Revised Analyses of the National Morbidity, Mortality, and Air Pollution Study, Part II (pp. 183-198). Boston, MA: Health Effects Institute.

Moolgavkar, SH; McClellan, RO; Dewanji, A; Turim, J; Luebeck, EG; Edwards, M. (2013). Time-series analyses of air pollution and mortality in the United States: A subsampling approach. Environ Health Perspect 121: 73-78. http://dx.doi.org/10.1289/ehp.1104507

Moon, JS; Kim, YS; Kim, JH; Son, BS; Kim, DS; Yang, W. (2009). Respiratory health effects among schoolchildren and their relationship to air pollutants in Korea. Int J Environ Health Res 19: 31-48. http://dx.doi.org/10.1080/09603120802272201

Morello-Frosch, R; Jesdale, BM; Sadd, JL; Pastor, M. (2010). Ambient air pollution exposure and full-term birth weight in California. Environ Health 9: 44. http://dx.doi.org/10.1186/1476-069X-9-44

Moridi, M; Ziaei, S; Kazemnejad, A. (2014). Exposure to ambient air pollutants and spontaneous abortion. J Obstet Gynaecol Res 40: 743-748. http://dx.doi.org/10.1111/jog.12231

Morikawa, A; Mochizuki, H; Shigeta, M; Tokuyama, K; Kuroume, T. (1994). Age-related changes in bronchial hyperreactivity during the adolescent period. J Asthma 31: 445-451. http://dx.doi.org/10.3109/02770909409089486

Morris, RD; Naumova, EN; Munasinghe, RL. (1995). Ambient air pollution and hospitalization for congestive heart failure among elderly people in seven large US cities. Am J Public Health 85: 1361-1365. http://dx.doi.org/10.2105/ajph.85.10.1361

Mortimer, KM; Neas, LM; Dockery, DW; Redline, S; Tager, IB. (2002). The effect of air pollution on inner-city children with asthma. Eur Respir J 19: 699-705. http://dx.doi.org/10.1183/09031936.02.00247102

Mueller, SF; Mao, Q; Mallard, JW. (2011). Modeling natural emissions in the Community Multiscale Air Quality (CMAQ) model Part 2: Modifications for simulating natural emissions. Atmos Chem Phys 11: 293-320. http://dx.doi.org/10.5194/acp-11-293-2011

Muhajarine, N; Mustard, C; Roos, LL; Young, TK; Gelskey, DE. (1997). Comparison of survey and physician claims data for detecting hypertension. J Clin Epidemiol 50: 711-718. http://dx.doi.org/10.1016/S0895-4356(97)00019-X

Murgia, N; Brisman, J; Claesson, A; Muzi, G; Olin, AC; Torén, K. (2014). Validity of a questionnaire-based diagnosis of chronic obstructive pulmonary disease in a general population-based study. BMC Pulm Med 14: 49. http://dx.doi.org/10.1186/1471-2466-14-49

Myers, DJ; Bigby, BG; Boushey, HA. (1986a). The inhibition of sulfur dioxide-induced bronchoconstriction in asthmatic subjects by cromolyn is dose dependent. Am Rev Respir Dis 133: 1150-1153.

Myers, DJ; Bigby, BG; Calvayrac, P; Sheppard, D; Boushey, HA. (1986b). Interaction of cromolyn and a muscarinic antagonist in inhibiting bronchial reactivity to sulfur dioxide and to eucapnic hyperpnea alone. Am Rev Respir Dis 133: 1154-1158.

Nadel, JA; Salem, H; Tamplin, B; Tokiwa, Y. (1965a). Mechanism of bronchoconstriction during inhalation of sulfur dioxide. J Appl Physiol 20: 164-167.

Nadel, JA; Salem, H; Tamplin, B; Tokiwa, Y. (1965b). Mechanism of bronchoconstriction: During inhalation of sulfur dioxide; reflex involving vagus nerves. Arch Environ Health 10: 175-178. http://dx.doi.org/10.1080/00039896.1965.10663979

Nadziejko, C; Fang, K; Narciso, S; Zhong, M; Su, WC; Gordon, T; Nadás, A; Chen, LC. (2004). Effect of particulate and gaseous pollutants on spontaneous arrhythmias in aged rats. Inhal Toxicol 16: 373-380. http://dx.doi.org/10.1080/08958370490439533

NAEPP (National Asthma Education and Prevention Program). (2007). Expert panel report 3 (EPR-3): Guidelines for the diagnosis and management of asthmasummary report 2007. J Allergy Clin Immunol 120: S94-S138. http://dx.doi.org/10.1016/j.jaci.2007.09.029

Nafstad, P; Haheim, LL; Wisloff, T; Gram, F; Oftedal, B; Holme, I; Hjermann, I; Leren, P. (2004). Urban air pollution and mortality in a cohort of Norwegian men. Environ Health Perspect 112: 610-615.

Nahidi, F; Gholami, R; Rashidi, Y; Majd, HA. (2014). Relationship between air pollution and pre-eclampsia in pregnant women: a case-control study. East Mediterr Health J 19: S60-S66.

NASA (National Aeronautics and Space Administration). (2008a). Okmok Volcano in Alaskas Aleutian Islands. Available online at http://earthobservatory.nasa.gov/IOTD/view.php?id=8939

NASA (National Aeronautics and Space Administration). (2008b). Sulfur dioxide plume from Kilauea. Available online at http://earthobservatory.nasa.gov/IOTD/view.php?id=8614&eocn=image&eoci=related_image

Neas, LM; Dockery, DW; Koutrakis, P; Tollerud, DJ; Speizer, FE. (1995). The association of ambient air pollution with twice daily peak expiratory flow rate measurements in children. Am J Epidemiol 141: 111-122.

Neophytou, AM; White, MJ; Oh, SS; Thakur, N; Galanter, JM; Nishimura, KK; Pino-Yanes, M; Torgerson, DG; Gignoux, CR; Eng, C; Nguyen, EA; Hu, D; Mak, AC; Kumar, R; Seibold, MA; Davis, A; Farber, HJ; Meade, K; Avila, PC; Serebrisky, D; Lenoir, MA; Brigino-Buenaventura, E; Rodriguez-Cintron, W; Bibbins-Domingo, K; Thyne, SM; Williams, LK; Sen, S; Gilliland, FD; Gauderman, WJ; Rodriguez-Santana, JR; Lurmann, F; Balmes, JR; Eisen, EA; Burchard, EG. (2016). Air pollution and lung function in minority youth with asthma in the GALA II (Genesenvironments and admixture in Latino Americans) and SAGE II (Study of African Americans, asthma, genes, and environments) studies. Am J Respir Crit Care Med 193: 1271-1280. http://dx.doi.org/10.1164/rccm.201508-1706OC

Neukirch, F; Segala, C; Le Moullec, Y; Korobaeff, M; Aubier, M. (1998). Short-term effects of low-level winter pollution on respiratory health of asthmatic adults. Arch Environ Occup Health 53: 320-328. http://dx.doi.org/10.1080/00039899809605716

Neupane, B; Jerrett, M; Burnett, RT; Marrie, T; Arain, A; Loeb, M. (2010). Long-term exposure to ambient air pollution and risk of hospitalization with community-acquired pneumonia in older adults. Am J Respir Crit Care Med 181: 47-53. http://dx.doi.org/10.1164/rccm.200901-0160OC

NHLBI NAEPP (National Heart, Lung, and Blood Institute, National Asthma Education and Prevention Program). (2007). Expert panel report 3: Guidelines for the diagnosis and management of asthma. (Report No: 07-4051). Bethesda, MD: U.S. Department of Health and Human Services, National Institutes of Health. http://www.nhlbi.nih.gov/files/docs/guidelines/asthgdln.pdf

Niinimaa, V; Cole, P; Mintz, S; Shephard, RJ. (1981). Oronasal distribution of respiratory airflow. Respir Physiol 43: 69-75. http://dx.doi.org/10.1016/0034-5687(81)90089-X

Nishimura, KK; Galanter, JM; Roth, LA; Oh, SS; Thakur, N; Nguyen, EA; Thyne, S; Farber, HJ; Serebrisky, D; Kumar, R; Brigino-Buenaventura, E; Davis, A; LeNoir, MA; Meade, K; Rodriguez-Cintron, W; Avila, PC; Borrell, LN; Bibbins-Domingo, K; Rodriguez-Santana, JR; Sen, S; Lurmann, F; Balmes, JR; Burchard, EG. (2013). Early-life air pollution and asthma risk in minority children: The GALA II and SAGE II studies. Am J Respir Crit Care Med 188: 309-318. http://dx.doi.org/10.1164/rccm.201302-0264OC

NOAA (National Oceanic and Atmospheric Administration). (2014). HYSPLIT - hybrid single particle lagrangian integrated trajectory model. Available online at http://ready.arl.noaa.gov/HYSPLIT.php

Nordling, E; Berglind, N; Melén, E; Emenius, G; Hallberg, J; Nyberg, F; Pershagen, G; Svartengren, M; Wickman, M; Bellander, T. (2008). Traffic-related air pollution and childhood respiratory symptoms, function and allergies. Epidemiology 19: 401-408. http://dx.doi.org/10.1097/EDE.0b013e31816a1ce3

Nowak, D; Jorres, R; Berger, J; Claussen, M; Magnussen, H. (1997). Airway responsiveness to sulfur dioxide in an adult population sample. Am J Respir Crit Care Med 156: 1151-1156. http://dx.doi.org/10.1164/ajrccm.156.4.9607025

Nowlan, CR; Liu, X; Chance, K; Cai, Z; Kurosu, TP; Lee, C; Martin, RV. (2011). Retrievals of sulfur dioxide from the Global Ozone Monitoring Experiment 2 (GOME-2) using an optimal estimation approach: Algorithm and initial validation. J Geophys Res 116: D18301. http://dx.doi.org/10.1029/2011JD015808

NRC (National Research Council). (2012). Exposure science in the 21st century: a vision and a strategy. Washington, DC: The National Academies Press. http://www.nap.edu/catalog/13507/exposure-science-in-the-21st-century-a-vision-and-a

O'Byrne, PM; Gauvreau, GM; Brannan, JD. (2009). Provoked models of asthma: What have we learnt? [Review]. Clin Exp Allergy 39: 181-192. http://dx.doi.org/10.1111/j.1365-2222.2008.03172.x

O'Connor, GT; Neas, L; Vaughn, B; Kattan, M; Mitchell, H; Crain, EF; Evans, R, III; Gruchalla, R; Morgan, W; Stout, J; Adams, GK; Lippmann, M. (2008). Acute respiratory health effects of air pollution on children with asthma in US inner cities. J Allergy Clin Immunol 121: 1133-1139.e1131. http://dx.doi.org/10.1016/j.jaci.2008.02.020

Office of Transportation and Air Quality. (2010). Designation of North American emission control area to reduce emissions from ships [Fact Sheet]. (EPA-420-F-10-015). Washington, D.C.: U.S. Environmental Protection Agency. https://nepis.epa.gov/Exe/ZyPDF.cgi/P100AU0I.PDF?Dockey=P100AU0I.PDF

Ogawa & Co (Ogawa & Company). (2007). Ambient air passive sampler for NO-NO2, NOx, SO2, O3, NH3. Available online at http://ogawausa.com/passive-sampler/

Ohyama, K; Ito, T; Kanisawa, M. (1999). The roles of diesel exhaust particle extracts and the promotive effects of NO2 and/or SO2 exposure on rat lung tumorigenesis. Cancer Lett 139: 189-197. http://dx.doi.org/10.1016/S0304-3835(99)00040-3

Oiamo, TH; Luginaah, IN. (2013). Extricating sex and gender in air pollution research: a community-based study on cardinal symptoms of exposure. Int J Environ Res Public Health 10: 3801-3817. http://dx.doi.org/10.3390/ijerph10093801

Oiamo, TH; Luginaah, IN; Atari, DO; Gorey, KM. (2011). Air pollution and general practitioner access and utilization: a population based study in Sarnia, 'Chemical Valley,' Ontario. Environ Health 10: 71. http://dx.doi.org/10.1186/1476-069X-10-71

Olesen, HR; Lofstrom, P; Berkowicz, R; Jensen, AB. (1992). An improved dispersion model for regulatory use - The OML model. In H van Dop; G Kallos (Eds.), Air pollution modelling and its application IX (pp. 29-38). New York, New York: Plenum Press. http://dx.doi.org/10.1007/978-1-4615-3052-7_3

Ong, CB; Kumagai, K; Brooks, PT; Brandenberger, C; Lewandowski, RP; Jackson-Humbles, DN; Nault, R; Zacharewski, TR; Wagner, JG; Harkema, JR. (2016). Ozone-induced type 2 immunity in nasal airways. Development and lymphoid cell dependence in mice. Am J Respir Cell Mol Biol 54: 331-340. http://dx.doi.org/10.1165/rcmb.2015-0165OC

Orazzo, F; Nespoli, L; Ito, K; Tassinari, D; Giardina, D; Funis, M; Cecchi, A; Trapani, C; Forgeschi, G; Vignini, M; Nosetti, L; Pigna, S; Zanobetti, A. (2009). Air pollution, aeroallergens, and emergency room visits for acute respiratory diseases and gastroenteric disorders among young children in six Italian cities. Environ Health Perspect 117: 1780-1785. http://dx.doi.org/10.1289/ehp.0900599

Paaso, EM; Jaakkola, MS; Rantala, AK; Hugg, TT; Jaakkola, JJ. (2014). Allergic diseases and asthma in the family predict the persistence and onset-age of asthma: A prospective cohort study. Respir Res 15: 152. http://dx.doi.org/10.1186/s12931-014-0152-8

Paciorek, CJ. (2010). The importance of scale for spatial-confounding bias and precision of spatial regression estimators. Stat Sci 25: 107-125. http://dx.doi.org/10.1214/10-STS326

Paine, R; Samani, O; Kaplan, M; Knipping, E; Kumar, N. (2015). Evaluation of low wind modeling approaches for two tall-stack databases. J Air Waste Manag Assoc 65: 1341-1353. http://dx.doi.org/10.1080/10962247.2015.1085924

Pan, G; Zhang, S; Feng, Y; Takahashi, K; Kagawa, J; Yu, L; Wang, P; Liu, M; Liu, Q; Hou, S; Pan, B; Li, J. (2010). Air pollution and children's respiratory symptoms in six cities of Northern China. Respir Med 104: 1903-1911. http://dx.doi.org/10.1016/j.rmed.2010.07.018

Panasevich, S; Leander, K; Ljungman, P; Bellander, T; de Faire, U; Pershagen, G; Nyberg, F. (2013). Interaction between air pollution exposure and genes in relation to levels of inflammatory markers and risk of myocardial infarction. BMJ Open 3: e003058. http://dx.doi.org/10.1136/bmjopen-2013-003058

Panasevich, S; Leander, K; Rosenlund, M; Ljungman, P; Bellander, T; de Faire, U; Pershagen, G; Nyberg, F. (2009). Associations of long- and short-term air pollution exposure with markers of inflammation and coagulation in a population sample. Occup Environ Med 66: 747-753. http://dx.doi.org/10.1136/oem.2008.043471

Pandis, SN; Seinfeld, JH. (1989). Mathematical modeling of acid deposition due to radiation fog. J Geophys Res 94: 1291112923. http://dx.doi.org/10.1029/JD094iD10p12911

Park, JK; Kim, YK; Lee, SR; Cho, SH; Min, KU; Kim, YY. (2001). Repeated exposure to low levels of sulfur dioxide (SO2) enhances the development of ovalbumin-induced asthmatic reactions in guinea pigs. Ann Allergy Asthma Immunol 86: 62-67. http://dx.doi.org/10.1016/S1081-1206(10)62358-7

Park, JW; Lim, YH; Kyung, SY; An, CH; Lee, SP; Jeong, SH; Ju, YS. (2005). Effects of ambient particulate matter on peak expiratory flow rates and respiratory symptoms of asthmatics during Asian dust periods in Korea. Respirology 10: 470-476. http://dx.doi.org/10.1111/j.1440-1843.2005.00728.x

Parker, JD; Akinbami, LJ; Woodruff, TJ. (2009). Air pollution and childhood respiratory allergies in the United States. Environ Health Perspect 117: 140-147. http://dx.doi.org/10.1289/ehp.11497

Pascal, L; Pascal, M; Stempfelet, M; Goria, S; Declercq, C. (2013). Ecological study on hospitalizations for cancer, cardiovascular, and respiratory diseases in the industrial area of Etang-de-Berre in the South of France. J Environ Public Health 2013: 328737. http://dx.doi.org/10.1155/2013/328737

Patterson, E; Eatough, DJ. (2000). Indoor/outdoor relationships for ambient PM2.5 and associated pollutants: epidemiological implications in Lindon, Utah. J Air Waste Manag Assoc 50: 103-110. http://dx.doi.org/10.1080/10473289.2000.10463986

Pauluhn, J; Thyssen, J; Althoff, J; Kimmerle, G; Mohr, U. (1985). Long-term inhalation study with benzo(a)pyrene and SO2 in Syrian golden hamsters [Abstract]. Exp Pathol 28: 31. http://dx.doi.org/10.1016/S0232-1513(85)80029-3

Peacock, JL; Anderson, HR; Bremner, SA; Marston, L; Seemungal, TA; Strachan, DP; Wedzicha, JA. (2011). Outdoor air pollution and respiratory health in patients with COPD. Thorax 66: 591-596. http://dx.doi.org/10.1136/thx.2010.155358

Peacock, PR; Spence, JB. (1967). Incidence of lung tumours in LX mice exposed to (1) free radicals; (2) SO2. Br J Cancer 21: 606-618. http://dx.doi.org/10.1038/bjc.1967.71

Pearce, JL; Waller, LA; Mulholland, JA; Sarnat, SE; Strickland, MJ; Chang, HH; Tolbert, PE. (2015). Exploring associations between multipollutant day types and asthma morbidity: Epidemiologic applications of self-organizing map ambient air quality classifications. Environ Health 14: 55. http://dx.doi.org/10.1186/s12940-015-0041-8

Peel, JL; Klein, M; Flanders, WD; Mulholland, JA; Freed, G; Tolbert, PE. (2011). Ambient air pollution and apnea and bradycardia in high-risk infants on home monitors. Environ Health Perspect 119: 1321-1327. http://dx.doi.org/10.1289/ehp.1002739

Peel, JL; Metzger, KB; Klein, M; Flanders, WD; Mulholland, JA; Tolbert, PE. (2007). Ambient air pollution and cardiovascular emergency department visits in potentially sensitive groups. Am J Epidemiol 165: 625-633. http://dx.doi.org/10.1093/aje/kwk051

Peel, JL; Tolbert, PE; Klein, M; Metzger, KB; Flanders, WD; Todd, K; Mulholland, JA; Ryan, PB; Frumkin, H. (2005). Ambient air pollution and respiratory emergency department visits. Epidemiology 16: 164-174. http://dx.doi.org/10.1097/01.ede.0000152905.42113.db

Penard-Morand, C; Raherison, C; Charpin, D; Kopferschmitt, C; Lavaud, F; Caillaud, D; Annesi-Maesano, I. (2010). Long-term exposure to proximity air pollution and asthma and allergies in urban children. Eur Respir J 36: 33-40. http://dx.doi.org/10.1183/09031936.00116109

Pereira, LAA; Loomis, D; Conceicao, GMS; Braga, ALF; Arcas, RM; Kishi, HS; Singer, JM; Bohm, GM; Saldiva, PHN. (1998). Association between air pollution and intrauterine mortality in Sao Paulo, Brazil. Environ Health Perspect 106: 325-329. http://dx.doi.org/10.2307/3434038

Perry, SG; Cimorelli, AJ; Paine, RJ; Brode, RW; Weil, JC; Venkatram, A; Wilson, RB; Lee, RF; Peters, WD. (2005). AERMOD: A dispersion model for industrial source applications. Part II: Model performance against 17 field study databases. J Appl Meteorol 44: 694-708. http://dx.doi.org/10.1175/JAM2228.1

Peters, A; Goldstein, IF; Beyer, U; Franke, K; Heinrich, J; Dockery, DW; Spengler, JD; Wichmann, HE. (1996a). Acute health effects of exposure to high levels of air pollution in eastern Europe. Am J Epidemiol 144: 570-581. http://dx.doi.org/10.1093/oxfordjournals.aje.a008967

Peters, J; Hedley, AJ; Wong, CM; Lam, TH; Ong, SG; Liu, J; Spiegelhalter, DJ. (1996b). Effects of an ambient air pollution intervention and environmental tobacco smoke on children's respiratory health in Hong Kong. Int J Epidemiol 25: 821-828. http://dx.doi.org/10.1093/ije/25.4.821

Petroeschevsky, A; Simpson, RW; Thalib, L; Rutherford, S. (2001). Associations between outdoor air pollution and hospital admissions in Brisbane, Australia. Arch Environ Occup Health 56: 37-52. http://dx.doi.org/10.1080/00039890109604053

Phalen, RF; Oldham, MJ; Beaucage, CB; Crocker, TT; Mortensen, JD. (1985). Postnatal enlargement of human tracheobronchial airways and implications for particle deposition. Anat Rec 212: 368-380. http://dx.doi.org/10.1002/ar.1092120408

Pham, M; Muller, JF; Brasseur, GP; Granier, C; Megie, G. (1996). A 3D model study of the global sulphur cycle: Contributions of anthropogenic and biogenic sources. Atmos Environ 30: 1815-1822. http://dx.doi.org/10.1016/1352-2310(95)00390-8

Poloniecki, JD; Atkinson, RW; Ponce de Leon, A; Anderson, HR. (1997). Daily time series for cardiovascular hospital admissions and previous day's air pollution in London, UK. Occup Environ Med 54: 535-540. http://dx.doi.org/10.1136/oem.54.8.535

Pool, BL; Brendler, S; Klein, RG; Monarca, S; Pasquini, R; Schmezer, P; Zeller, WJ. (1988a). Effects of SO2 or NOx on toxic and genotoxic properties of chemical carcinogens. II. Short term in vivo studies. Carcinogenesis 9: 1247-1252. http://dx.doi.org/10.1093/carcin/9.7.1247

Pool, BL; Janowsky, I; Klein, P; Klein, RG; Schmezer, P; Vogt-Leucht, G; Zeller, WJ. (1988b). Effects of SO2 or NOx on toxic and genotoxic properties of chemical carcinogens. I. In vitro studies. Carcinogenesis 9: 1237-1245. http://dx.doi.org/10.1093/carcin/9.7.1237

Pope, CA, III; Burnett, RT; Thun, MJ; Calle, EE; Krewski, D; Ito, K; Thurston, GD. (2002). Lung cancer, cardiopulmonary mortality, and long-term exposure to fine particulate air pollution. JAMA 287: 1132-1141. http://dx.doi.org/10.1001/jama.287.9.1132

Pope, CA, III; Thun, MJ; Namboodiri, MM; Dockery, DW; Evans, JS; Speizer, FE; Heath, CW, Jr. (1995). Particulate air pollution as a predictor of mortality in a prospective study of U.S. adults. Am J Respir Crit Care Med 151: 669-674. http://dx.doi.org/10.1164/ajrccm/151.3_Pt_1.669

Portnov, BA; Reiser, B; Karkabi, K; Cohen-Kastel, O; Dubnov, J. (2012). High prevalence of childhood asthma in Northern Israel is linked to air pollution by particulate matter: evidence from GIS analysis and Bayesian Model Averaging. Int J Environ Health Res 22: 249-269. http://dx.doi.org/10.1080/09603123.2011.634387

Pouliot, G; van Der Gon, HAC, D; Kuenen, J; Zhang, J; Moran, MD; Makar, PA. (2015). Analysis of the emission inventories and model-ready emission datasets of Europe and North America for phase 2 of the AQMEII project. Atmos Environ 115: 345-360. http://dx.doi.org/10.1016/j.atmosenv.2014.10.061

Poursafa, P; Baradaran-Mahdavi, S; Moradi, B; Haghjooy Javanmard, S; Tajadini, M; Mehrabian, F; Kelishadi, R. (2016). The relationship of exposure to air pollutants in pregnancy with surrogate markers of endothelial dysfunction in umbilical cord. Environ Res 146: 154-160. http://dx.doi.org/10.1016/j.envres.2015.12.018

Power, J. (2013). Alaska volcanoes. Available online at http://woodshole.er.usgs.gov/operations/obs/rmobs_pub/html/alaska.html

Prata, AJ; Gangale, G; Clarisse, L; Karagulian, F. (2010). Ash and sulfur dioxide in the 2008 eruptions of Okmok and Kasatochi: Insights from high spectral resolution satellite measurements. J Geophys Res Atmos 115: D00L18. http://dx.doi.org/10.1029/2009JD013556

Qian, Z; Liang, S; Yang, S; Trevathan, E; Huang, Z; Yang, R; Wang, J; Hu, K; Zhang, Y; Vaughn, M; Shen, L; Liu, W; Li, P; Ward, P; Yang, L; Zhang, W; Chen, W; Dong, G; Zheng, T; Xu, S; Zhang, B. (2015). Ambient air pollution and preterm birth: A prospective birth cohort study in Wuhan, China. Int J Hyg Environ Health 219: 195-203. http://dx.doi.org/10.1016/j.ijheh.2015.11.003

Qian, Z; Lin, HM; Chinchilli, VM; Lehman, EB; Duan, Y; Craig, TJ; Wilson, WE; Liao, D; Lazarus, SC; Bascom, R. (2009a). Interaction of ambient air pollution with asthma medication on exhaled nitric oxide among asthmatics. Arch Environ Occup Health 64: 168-176. http://dx.doi.org/10.1080/19338240903240616

Qian, Z; Lin, HM; Chinchilli, VM; Lehman, EB; Stewart, WF; Shah, N; Duan, Y; Craig, TJ; Wilson, WE; Liao, D; Lazarus, SC; Bascom, R. (2009b). Associations between air pollution and peak expiratory flow among patients with persistent asthma. J Toxicol Environ Health A 72: 39-46. http://dx.doi.org/10.1080/15287390802445517

Qin, G; Meng, Z. (2006). The expressions of protooncogenes and CYP1A in lungs of rats exposed to sulfur dioxide and benzo(a)pyrene. Regul Toxicol Pharmacol 45: 36-43. http://dx.doi.org/10.1016/j.yrtph.2006.02.006

Qin, G; Wang, J; Huo, Y; Yan, H; Jiang, C; Zhou, J; Wang, X; Sang, N. (2012). Sulfur dioxide inhalation stimulated mitochondrial biogenesis in rat brains. Toxicology 300: 67-74. http://dx.doi.org/10.1016/j.tox.2012.05.026

Qin, G; Wu, M; Wang, J; Xu, Z; Xia, J; Sang, N. (2016). Sulfur dioxide contributes to the cardiac and mitochondrial dysfunction in rats. Toxicol Sci 151: 334-346.

Qin, XD; Qian, Z; Vaughn, MG; Trevathan, E; Emo, B; Paul, G; Ren, WH; Hao, YT; Dong, GH. (2015). Gender-specific differences of interaction between obesity and air pollution on stroke and cardiovascular diseases in Chinese adults from a high pollution range area: A large population based cross sectional study. Sci Total Environ 529: 243-248. http://dx.doi.org/10.1016/j.scitotenv.2015.05.041

Qiu, H; Yu, IT; Wang, X; Tian, L; Tse, LA; Wong, TW. (2013a). Cool and dry weather enhances the effects of air pollution on emergency IHD hospital admissions. Int J Cardiol 168: 500-505. http://dx.doi.org/10.1016/j.ijcard.2012.09.199

Qiu, H; Yu, ITS; Wang, X; Tian, L; Tse, LA; Wong, TW. (2013b). Season and humidity dependence of the effects of air pollution on COPD hospitalizations in Hong Kong. Atmos Environ 76: 74-80. http://dx.doi.org/10.1016/j.atmosenv.2012.07.026

Radwan, M; Jurewicz, J; Polańska, K; Sobala, W; Radwan, P; Bochenek, M; Hanke, W. (2015). Exposure to ambient air pollution-does it affect semen quality and the level of reproductive hormones? Ann Hum Biol 43: 50-56. http://dx.doi.org/10.3109/03014460.2015.1013986

Rage, E; Siroux, V; Künzli, N; Pin, I; Kauffmann, F. (2009). Air pollution and asthma severity in adults. Occup Environ Med 66: 182-188. http://dx.doi.org/10.1136/oem.2007.038349

Ranguelova, K; Chatterjee, S; Ehrenshaft, M; Ramirez, DC; Summers, FA; Kadiiska, MB; Mason, RP. (2010). Protein radical formation resulting from eosinophil peroxidase-catalyzed oxidation of sulfite. J Biol Chem 285: 24195-24205. http://dx.doi.org/10.1074/jbc.M109.069054

Ranguelova, K; Rice, AB; Khajo, A; Triquigneaux, M; Garantziotis, S; Magliozzo, RS; Mason, RP. (2012). Formation of reactive sulfite-derived free radicals by the activation of human neutrophils: an ESR study. Free Radic Biol Med 52: 1264-1271. http://dx.doi.org/10.1016/j.freeradbiomed.2012.01.016

Ranguelova, K; Rice, AB; Lardinois, OM; Triquigneaux, M; Steinckwich, N; Deterding, LJ; Garantziotis, S; Mason, RP. (2013). Sulfite-mediated oxidation of myeloperoxidase to a free radical: immuno-spin trapping detection in human neutrophils. Free Radic Biol Med 60: 98-106. http://dx.doi.org/10.1016/j.freeradbiomed.2013.01.022

Rankin, J; Chadwick, T; Natarajan, M; Howel, D; Pearce, MS; Pless-Mulloli, T. (2009). Maternal exposure to ambient air pollutants and risk of congenital anomalies. Environ Res 109: 181-187. http://dx.doi.org/10.1016/j.envres.2008.11.007

Rao, KS. (2005). Uncertainty analysis in atmospheric dispersion modeling. Pure Appl Geophys 162: 1893-1917. http://dx.doi.org/10.1007/s00024-005-2697-4

Rao, ST; Galmarini, S; Puckett, K. (2011). Air Quality Model Evaluation International Initiative (AQMEII): Advancing the state of the science in regional photochemical modeling and its applications. Bull Am Meteorol Soc 92: 23-30. http://dx.doi.org/10.1175/2010BAMS3069.1

Raulf-Heimsoth, M; Hoffmeyer, F; van Thriel, C; Blaszkewicz, M; Bünger, J; Brüning, T. (2010). Assessment of low dose effects of acute sulphur dioxide exposure on the airways using non-invasive methods. Arch Toxicol 84: 121-127. http://dx.doi.org/10.1007/s00204-009-0480-5

Reddel, HK. (2009). Characterizing asthma phenotypes: Predictors and outcomes at the extremes of asthma severity [Editorial]. Respirology 14: 778-780. http://dx.doi.org/10.1111/j.1440-1843.2009.01593.x

Reddy, P; Naidoo, RN; Robins, TG; Mentz, G; Li, H; London, SJ; Batterman, S. (2012). GSTM1 and GSTP1 gene variants and the effect of air pollutants on lung function measures in South African children. Am J Ind Med 55: 1078-1086. http://dx.doi.org/10.1002/ajim.22012

Reeves, GK; Cox, DR; Darby, SC; Whitley, E. (1998). Some aspects of measurement error in explanatory variables for continuous and binary regression models. Stat Med 17: 2157-2177. http://dx.doi.org/10.1002/(SICI)1097-0258(19981015)17:19<2157::AID-SIM916>3.0.CO;2-F

Rehbein, PJG; Kennedy, MG; Cotsman, DJ; Campeau, MA; Greenfield, MM; Annett, MA; Lepage, MF. (2014). Combined analysis of modeled and monitored SO2 concentrations at a complex smelting facility. J Air Waste Manag Assoc 64: 272-279. http://dx.doi.org/10.1080/10962247.2013.856817

Reiss, J; Bonin, M; Schwegler, H; Sass, JO; Garattini, E; Wagner, S; Lee, HJ; Engel, W; Riess, O; Schwarz, G. (2005). The pathogenesis of molybdenum cofactor deficiency, its delay by maternal clearance, and its expression pattern in microarray analysis. Mol Genet Metab 85: 12-20. http://dx.doi.org/10.1016/j.ymgme.2005.01.008

Rich, DQ; Demissie, K; Lu, SE; Kamat, L; Wartenberg, D; Rhoads, GG. (2009). Ambient air pollutant concentrations during pregnancy and the risk of fetal growth restriction. J Epidemiol Community Health 63: 488-496. http://dx.doi.org/10.1136/jech.2008.082792

Rich, DQ; Kipen, HM; Huang, W; Wang, G; Wang, Y; Zhu, P; Ohman-Strickland, P; Hu, M; Philipp, C; Diehl, SR; Lu, SE; Tong, J; Gong, J; Thomas, D; Zhu, T; Zhang, JJ. (2012). Association between changes in air pollution levels during the Beijing Olympics and biomarkers of inflammation and thrombosis in healthy young adults. JAMA 307: 2068-2078. http://dx.doi.org/10.1001/jama.2012.3488

Rich, DQ; Kipen, HM; Zhang, J; Kamat, L; Wilson, AC; Kostis, JB. (2010). Triggering of transmural infarctions, but not nontransmural infarctions, by ambient fine particles. Environ Health Perspect 118: 1229-1234. http://dx.doi.org/10.1289/ehp.0901624

Rich, DQ; Liu, K; Zhang, J; Thurston, SW; Stevens, TP; Pan, Y; Kane, C; Weinberger, B; Ohman-Strickland, P; Woodruff, TJ; Duan, X; Assibey-Mensah, V; Zhang, J. (2015). Differences in birth weight associated with the 2008 Beijing olympic air pollution reduction: results from a natural experiment. Environ Health Perspect 123: 880-887. http://dx.doi.org/10.1289/ehp.1408795

Riedel, F; Kramer, M; Scheibenbogen, C; Rieger, CHL. (1988). Effects of SO2 exposure on allergic sensitization in the guinea pig. J Allergy Clin Immunol 82: 527-534. http://dx.doi.org/10.1016/0091-6749(88)90961-X

Ritz, B; Wilhelm, M. (2008). Ambient air pollution and adverse birth outcomes: Methodologic issues in an emerging field [Review]. Basic Clin Pharmacol Toxicol 102: 182-190. http://dx.doi.org/10.1111/j.1742-7843.2007.00161.x

Rivera-González, LO; Zhang, Z; Sánchez, BN; Zhang, K; Brown, DG; Rojas-Bracho, L; Osornio-Vargas, A; Vadillo-Ortega, F; O'Neill, MS. (2015). An assessment of air pollutant exposure methods in Mexico City, Mexico. J Air Waste Manag Assoc 65: 581-591. http://dx.doi.org/10.1080/10962247.2015.1020974

Robledo, CA; Mendola, P; Yeung, E; Männistö, T; Sundaram, R; Liu, D; Ying, Q; Sherman, S; Grantz, KL. (2015). Preconception and early pregnancy air pollution exposures and risk of gestational diabetes mellitus. Environ Res 137: 316-322. http://dx.doi.org/10.1016/j.envres.2014.12.020

Roger, LJ; Kehrl, HR; Hazucha, M; Horstman, DH. (1985). Bronchoconstriction in asthmatics exposed to sulfur dioxide during repeated exercise. J Appl Physiol 59: 784-791.

Rood, AS. (2014). Performance evaluation of AERMOD, CALPUFF, and legacy air dispersion models using the Winter Validation Tracer Study dataset. Atmos Environ 89: 707-720. http://dx.doi.org/10.1016/j.atmosenv.2014.02.054

Rooney, AA; Boyles, AL; Wolfe, MS; Bucher, JR; Thayer, KA. (2014). Systematic review and evidence integration for literature-based environmental health science assessments. Environ Health Perspect 122: 711-718. http://dx.doi.org/10.1289/ehp.1307972

Rosenlund, M; Berglind, N; Pershagen, G; Hallqvist, J; Jonson, T; Bellander, T. (2006). Long-term exposure to urban air pollution and myocardial infarction. Epidemiology 17: 383-390. http://dx.doi.org/10.1097/01.ede.0000219722.25569.0f

Rosenthal, FS; Kuisma, M; Lanki, T; Hussein, T; Boyd, J; Halonen, JI; Pekkanen, J. (2013). Association of ozone and particulate air pollution with out-of-hospital cardiac arrest in Helsinki, Finland: evidence for two different etiologies. J Expo Sci Environ Epidemiol 23: 281-288. http://dx.doi.org/10.1038/jes.2012.121

Rosenthal, RA; Kavic, SM. (2004). Assessment and management of the geriatric patient [Review]. Crit Care Med 32: S92-105. http://dx.doi.org/10.1097/01.CCM.0000122069.56161.97

Rothman, KJ; Greenland, S. (1998). Modern epidemiology. In Modern Epidemiology (2 ed.). Philadelphia, PA: Lippincott-Raven.

Routledge, HC; Manney, S; Harrison, RM; Ayres, JG; Townend, JN. (2006). Effect of inhaled sulphur dioxide and carbon particles on heart rate variability and markers of inflammation and coagulation in human subjects. Heart 92: 220-227. http://dx.doi.org/10.1136/hrt.2004.051672

Roy, A; Gong, J; Thomas, DC; Zhang, J; Kipen, HM; Rich, DQ; Zhu, T; Huang, W; Hu, M; Wang, G; Wang, Y; Zhu, P; Lu, SE; Ohman-Strickland, P; Diehl, SR; Eckel, SP. (2014). The cardiopulmonary effects of ambient air pollution and mechanistic pathways: a comparative hierarchical pathway analysis. PLoS ONE 9: e114913. http://dx.doi.org/10.1371/journal.pone.0114913

Ruan, A; Min, H; Meng, Z; Lu, Z. (2003). Protective effects of seabuckthorn seed oil on mouse injury induced by sulfur dioxide inhalation. Inhal Toxicol 15: 1053-1058. http://dx.doi.org/10.1080/08958370390226558

Rubinstein, I; Bigby, BG; Reiss, TF; Boushey, HA, Jr. (1990). Short-term exposure to 0.3 ppm nitrogen dioxide does not potentiate airway responsiveness to sulfur dioxide in asthmatic subjects. Am Rev Respir Dis 141: 381-385. http://dx.doi.org/10.1164/ajrccm/141.2.381

Rusznak, C; Devalia, JL; Davies, RJ. (1996). Airway response of asthmatic subjects to inhaled allergen after exposure to pollutants. Thorax 51: 1105-1108. http://dx.doi.org/10.1136/thx.51.11.1105

Sacks, J. (2015). Email exchange between Matthew Strickland, Emory University and Jason Sacks, U.S. EPA. RE: Response to Question about 2010 Am J Respir Crit Care Med Paper. Available online at http://www.regulations.gov/#!documentDetail;D=EPA-HQ-ORD-2013-0357-0003

Sacks, JD; Ito, K; Wilson, WE; Neas, LM. (2012). Impact of covariate models on the assessment of the air pollution-mortality association in a single- and multipollutant context. Am J Epidemiol 176: 622-634. http://dx.doi.org/10.1093/aje/kws135

Sagiv, SK; Mendola, P; Loomis, D; Herring, AH; Neas, LM; Savitz, DA; Poole, C. (2005). A time-series analysis of air pollution and preterm birth in Pennsylvania, 1997-2001. Environ Health Perspect 113: 602-606. http://dx.doi.org/10.1289/ehp.7646

Sahsuvaroglu, T; Jerrett, M; Sears, MR; McConnell, R; Finkelstein, N; Arain, A; Newbold, B; Burnett, R. (2009). Spatial analysis of air pollution and childhood asthma in Hamilton, Canada: comparing exposure methods in sensitive subgroups. Environ Health 8: Z. http://dx.doi.org/10.1186/1476-069X-8-14

Saigal, S; Doyle, LW. (2008). An overview of mortality and sequelae of preterm birth from infancy to adulthood. Lancet 371: 261-269. http://dx.doi.org/10.1016/S0140-6736(08)60136-1

Samoli, E; Nastos, PT; Paliatsos, AG; Katsouyanni, K; Priftis, KN. (2011). Acute effects of air pollution on pediatric asthma exacerbation: Evidence of association and effect modification. Environ Res 111: 418-424. http://dx.doi.org/10.1016/j.envres.2011.01.014

San Tam, W; Wong, T; Wong, AHS. (2015). Association between air pollution and daily mortality and hospital admission due to ischaemic heart diseases in Hong Kong. Atmos Environ 120: 360-368. http://dx.doi.org/10.1016/j.atmosenv.2015.08.068

Sander, SP; Abbatt, JPD; Barker, JR; Burkholder, JB; Friedl, RR; Golden, DM; Huie, RE; Kolb, CE; Kurylo, MJ; Moortgat, GK; Orkin, VL; Wine, PH. (2011). Chemical kinetics and photochemical data for use in atmospheric studies: Evaluation number 17. (JPL Publication 10-6). Pasadena, CA: Jet Propulsion Laboratory. http://jpldataeval.jpl.nasa.gov/pdf/JPL%2010-6%20Final%2015June2011.pdf

Sang, N; Yun, Y; Li, H; Hou, L; Han, M; Li, G. (2010). SO2 inhalation contributes to the development and progression of ischemic stroke in the brain. Toxicol Sci 114: 226-236.

Sarnat, JA; Brown, KW; Schwartz, J; Coull, BA; Koutrakis, P. (2005). Ambient gas concentrations and personal particulate matter exposures: Implications for studying the health effects of particles. Epidemiology 16: 385-395. http://dx.doi.org/10.1097/01.ede.0000155505.04775.33

Sarnat, JA; Koutrakis, P; Suh, HH. (2000). Assessing the relationship between personal particulate and gaseous exposures of senior citizens living in Baltimore, MD. J Air Waste Manag Assoc 50: 1184-1198. http://dx.doi.org/10.1080/10473289.2000.10464165

Sarnat, JA; Schwartz, J; Catalano, PJ; Suh, HH. (2001). Gaseous pollutants in particulate matter epidemiology: Confounders or surrogates? Environ Health Perspect 109: 1053-1061.

Sarnat, SE. (2016). Response to data question regarding: Ambient air pollution and emergency department visits for asthma: A multi-city assessment of effect modification by age. Sarnat, SE.

Sarnat, SE; Coull, BA; Schwartz, J; Gold, DR; Suh, HH. (2006). Factors affecting the association between ambient concentrations and personal exposures to particles and gases. Environ Health Perspect 114: 649-654. http://dx.doi.org/10.1289/ehp.8422

Sarnat, SE; Klein, M; Sarnat, JA; Flanders, WD; Waller, LA; Mulholland, JA; Russell, AG; Tolbert, PE. (2010). An examination of exposure measurement error from air pollutant spatial variability in time-series studies. J Expo Sci Environ Epidemiol 20: 135-146. http://dx.doi.org/10.1038/jes.2009.10

Schachter, EN; Witek, TJ, Jr; Beck, GJ; Hosein, HR; Colice, G; Leaderer, BP; Cain, W. (1984). Airway effects of low concentrations of sulfur dioxide: dose-response characteristics. Arch Environ Occup Health 39: 34-42.

Schauberger, G; Piringer, M; Schmitzer, R; Kamp, M; Sowa, A; Koch, R; Eckhof, W; Grimm, E; Kypke, J; Hartung, E. (2012). Concept to assess the human perception of odour by estimating short-time peak concentrations from one-hour mean values. Reply to a comment by Janicke et al. Atmos Environ 54: 624-628. http://dx.doi.org/10.1016/j.atmosenv.2012.02.017

Schildcrout, JS; Sheppard, L; Lumley, T; Slaughter, JC; Koenig, JQ; Shapiro, GG. (2006). Ambient air pollution and asthma exacerbations in children: An eight-city analysis. Am J Epidemiol 164: 505-517. http://dx.doi.org/10.1093/aje/kwj225

Schiller, JS; Lucas, JW; Ward, BW; Peregoy, JA. (2012). Summary health statistics for U.S. adults: National Health Interview Survey, 2010. (DHHS Publication No. 20121580). Hyattsville, MD: National Center for Health Statistics. http://www.cdc.gov/nchs/data/series/sr_10/sr10_252.pdf

Schlesinger, WH. (1997). Biogeochemistry: an analysis of global change. San Diego: Academic Press.

Schwab, RJ; Kim, C; Bagchi, S; Keenan, BT; Comyn, FL; Wang, S; Tapia, IE; Huang, S; Traylor, J; Torigian, DA; Bradford, RM; Marcus, CL. (2015). Understanding the anatomic basis for obstructive sleep apnea syndrome in adolescents. Am J Respir Crit Care Med 191: 1295-1309. http://dx.doi.org/10.1164/rccm.201501-0169OC

Schwartz, J. (1989). Lung function and chronic exposure to air pollution: a cross-sectional analysis of NHANES II. Environ Res 50: 309-321.

Schwartz, J. (1995). Short term fluctuations in air pollution and hospital admissions of the elderly for respiratory disease. Thorax 50: 531-538. http://dx.doi.org/10.1136/thx.50.5.531

Schwartz, J. (1997). Air pollution and hospital admissions for cardiovascular disease in Tucson. Epidemiology 8: 371-377. http://dx.doi.org/10.1097/00001648-199707000-00004

Schwartz, J; Morris, R. (1995). Air pollution and hospital admissions for cardiovascular disease in Detroit, Michigan. Am J Epidemiol 142: 23-35.

Schwartz, J; Spix, C; Touloumi, G; Bacharova, L; Barumamdzadeh, T; le Tertre, A; Piekarksi, T; Ponce de Leon, A; Ponka, A; Rossi, G; Saez, M; Schouten, JP. (1996). Methodological issues in studies of air pollution and daily counts of deaths or hospital admissions. J Epidemiol Community Health 1: S3-S11.

Segala, C; Fauroux, B; Just, J; Pascual, L; Grimfeld, A; Neukirch, F. (1998). Short-term effect of winter air pollution on respiratory health of asthmatic children in Paris. Eur Respir J 11: 677-685.

Ségala, C; Poizeau, D; Mesbah, M; Willems, S; Maidenberg, M. (2008). Winter air pollution and infant bronchiolitis in Paris. Environ Res 106: 96-100. http://dx.doi.org/10.1016/j.envres.2007.05.003

Seinfeld, JH; Pandis, S. (2006). Atmospheric Chemistry and Physics. Hoboken, NJ: John Wiley.

Shadwick, DS; Sickles, IJE. (2004). Sample size for seasonal mean concentration, deposition velocity and deposition: A resampling study. Atmos Environ 38: 477-489.

Shah, AS; Lee, KK; Mcallister, DA; Hunter, A; Nair, H; Whiteley, W; Langrish, JP; Newby, DE; Mills, NL. (2015). Short term exposure to air pollution and stroke: systematic review and meta-analysis [Review]. B M J (Online) 350: h1295. http://dx.doi.org/10.1136/bmj.h1295

Shallcross, DE; Taatjes, CA; Percival, CJ. (2014). Criegee intermediates in the indoor environment: new insights. Indoor Air 24: 495-502. http://dx.doi.org/10.1111/ina.12102

Shen, X; Wu, H; Zhao, Y, ue; Huang, D, ao; Huang, L; Chen, Z. (2016). Heterogeneous reactions of glyoxal on mineral particles: A new avenue for oligomers and organosulfate formation. Atmos Environ 131: 133-140. http://dx.doi.org/10.1016/j.atmosenv.2016.01.048

Sheppard, D; Epstein, J; Bethel, RA; Nadel, JA; Boushey, HA. (1983). Tolerance to sulfur dioxide-induced bronchoconstriction in subjects with asthma. Environ Res 30: 412-419. http://dx.doi.org/10.1016/0013-9351(83)90227-X

Sheppard, D; Eschenbacher, WL; Boushey, HA; Bethel, RA. (1984). Magnitude of the interaction between the bronchomotor effects of sulfur dioxide and those of dry (cold) air. Am Rev Respir Dis 130: 52-55.

Sheppard, L. (2003). Ambient air pollution and nonelderly asthma hospital admissions in Seattle, Washington, 1987-1994. In Revised analyses of time-series studies of air pollution and health (pp. 227-230). Boston, MA: Health Effects Institute. http://pubs.healtheffects.org/view.php?id=4

Sheppard, L. (2005). Acute air pollution effects: Consequences of exposure distribution and measurements. J Toxicol Environ Health A 68: 1127-1135. http://dx.doi.org/10.1080/15287390590935987

Sheppard, L; Levy, D; Norris, G; Larson, TV; Koenig, JQ. (1999). Effects of ambient air pollution on nonelderly asthma hospital admissions in Seattle, Washington, 1987-1994. Epidemiology 10: 23-30. http://dx.doi.org/10.1097/00001648-199901000-00006

Sheppard, L; Slaughter, JC; Schildcrout, J; Liu, J, -S; Lumley, T. (2005). Exposure and measurement contributions to estimates of acute air pollution effects. J Expo Anal Environ Epidemiol 15: 366-376. http://dx.doi.org/10.1038/sj.jea.7500413

Shim, SR; Kim, JH; Song, YS; Lee, WJ. (2015). Association between air pollution and benign prostatic hyperplasia: an ecological study. Arch Environ Occup Health 71: 0. http://dx.doi.org/10.1080/19338244.2015.1093458

Sickles, JE; Shadwick, DS. (2007). Seasonal and regional air quality and atmospheric deposition in the eastern United States. J Geophys Res 112: D17302. http://dx.doi.org/10.1029/2006JD008356

Silverman, RA; Ito, K; Freese, J; Kaufman, BJ; De Claro, D; Braun, J; Prezant, DJ. (2010). Association of ambient fine particles with out-of-hospital cardiac arrests in New York City. Am J Epidemiol 172: 917-923. http://dx.doi.org/10.1093/aje/kwq217

Sim, VM; Pattle, RE. (1957). Effect of possible smog irritants on human subjects. JAMA 165: 1908-1913.

Simeonsson, JB; Matta, A; Boddeti, R. (2012). Direct measurement of SO2 in air by laser induced fluorescence spectrometry using a nontunable laser source. Anal Lett 45: 894-906. http://dx.doi.org/10.1080/00032719.2012.655681

Simpson, D; Winiwarter, W; Borjesson, G; Cinderby, S; Ferreiro, A; Guenther, A; Hewitt, CN; Janson, R; Khalil, MAK; Owen, S; Pierce, TE; Puxbaum, H; Shearer, M; Skiba, U; Steinbrecher, R; Tarrason, L; Oquist, MG. (1999). Inventorying emissions from nature in Europe. J Geophys Res Atmos 104: 8113-8152. http://dx.doi.org/10.1029/98JD02747

Sinclair, AH; Edgerton, ES; Wyzga, R; Tolsma, D. (2010). A two-time-period comparison of the effects of ambient air pollution on outpatient visits for acute respiratory illnesses. J Air Waste Manag Assoc 60: 163-175. http://dx.doi.org/10.3155/1047-3289.60.2.163

Sinclair, AH; Tolsma, D. (2004). Associations and lags between air pollution and acute respiratory visits in an ambulatory care setting: 25-month results from the Aerosol Research and Inhalation Epidemiological Study. J Air Waste Manag Assoc 54: 1212-1218. http://dx.doi.org/10.1080/10473289.2004.10470979

Singer, BC; Hodgson, AT; Hotchi, T; Kim, JJ. (2004). Passive measurement of nitrogen oxides to assess traffic-related pollutant exposure for the East Bay Children's Respiratory Health Study. Atmos Environ 38: 393-403. http://dx.doi.org/10.1016/j.atmosenv.2003.10.005

Slade, D. (1968a). Meteorological instruments for use in the atomic energy industry. In DH Slade (Ed.), Meteorology and atomic energy (pp. 257-300). Washington, DC: U.S. Atomic Energy Commission.

Slade, DH. (1968b). Meteorology and atomic energy 1968. In DH Slade (Ed.). Washington, DC: U.S. Atomic Energy Commission. https://ntrl.ntis.gov/NTRL/dashboard/searchResults.xhtml?searchQuery=TID24190

Slama, R; Bottagisi, S; Solansky, I; Lepeule, J; Giorgis-Allemand, L; Sram, R. (2013). Short-term impact of atmospheric pollution on fecundability. Epidemiology 24: 871-879. http://dx.doi.org/10.1097/EDE.0b013e3182a702c5

Slama, R; Darrow, L; Parker, J; Woodruff, TJ; Strickland, M; Nieuwenhuijsen, M; Glinianaia, S; Hoggatt, KJ; Kannan, S; Hurley, F; Kalinka, J; Sram, R; Brauer, M; Wilhelm, M; Heinrich, J; Ritz, B. (2008). Meeting report: Atmospheric pollution and human reproduction. Environ Health Perspect 116: 791-798. http://dx.doi.org/10.1289/ehp.11074

Smargiassi, A; Kosatsky, T; Hicks, J; Plante, C; Armstrong, B, en; Villeneuve, PJ; Goudreau, S. (2009). Risk of asthmatic episodes in children exposed to sulfur dioxide stack emissions from a refinery point source in Montreal, Canada. Environ Health Perspect 117: 653-659. http://dx.doi.org/10.1289/ehp.0800010

Smith, E. (1993). [Subject data supplied by the researchers for the recent controlled human studies analyzed in the staff paper supplement and accompanying memorandum. Memorandum to docket no. A-84-25, item IV-B-5]. Research Triangle Park, NC: U.S. Environmental Protection Agency. http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OAR-2007-0352-1368

Smith, GS; Van Den Eeden, SK; Garcia, C; Shan, J; Baxter, R; Herring, AH; Richardson, DB; Van Rie, A; Emch, M; Gammon, MD. (2016). Air pollution and pulmonary tuberculosis: A nested case-control study among members of a northern california health plan. Environ Health Perspect 124: 761-768. http://dx.doi.org/10.1289/ehp.1408166

Smith, LG; Busch, RH; Buschbom, RL; Cannon, WC; Loscutoff, SM; Morris, JE. (1989). Effects of sulfur dioxide or ammonium sulfate exposure, alone or combined, for 4 or 8 months on normal and elastase-impaired rats. Environ Res 49: 60-78. http://dx.doi.org/10.1016/S0013-9351(89)80022-2

Snashall, PD; Baldwin, C. (1982). Mechanisms of sulphur dioxide induced bronchoconstriction in normal and asthmatic man. Thorax 37: 118-123. http://dx.doi.org/10.1136/thx.37.2.118

Snell, RE; Luchsinger, PC. (1969). Effects of sulfur dioxide on expiratory flow rates and total respiratory resistance in normal human subjects. Arch Environ Occup Health 18: 693-698. http://dx.doi.org/10.1080/00039896.1969.10665472

Son, JY; Bell, ML; Lee, JT. (2010). Individual exposure to air pollution and lung function in Korea: Spatial analysis using multiple exposure approaches. Environ Res 110: 739-749. http://dx.doi.org/10.1016/j.envres.2010.08.003

Son, JY; Cho, YS; Lee, JT. (2008). Effects of air pollution on postneonatal infant mortality among firstborn infants in Seoul, Korea: Case-crossover and time-series analyses. Arch Environ Occup Health 63: 108-113. http://dx.doi.org/10.3200/AEOH.63.3.108-113

Son, JY; Lee, JT; Park, YH; Bell, ML. (2013). Short-term effects of air pollution on hospital admissions in Korea. Epidemiology 24: 545-554. http://dx.doi.org/10.1097/EDE.0b013e3182953244

Song, A; Liao, Q; Li, J; Lin, F; Liu, E; Jiang, X; Deng, L. (2012). Chronic exposure to sulfur dioxide enhances airway hyperresponsiveness only in ovalbumin-sensitized rats. Toxicol Lett 214: 320-327. http://dx.doi.org/10.1016/j.toxlet.2012.09.010

Soto-Ramos, M; Castro-Rodríguez, JA; Hinojos-Gallardo, LC; Hernández-Saldaña, R; Cisneros-Castolo, M; Carrillo-Rodríguez, V. (2013). Fractional exhaled nitric oxide has a good correlation with asthma control and lung function in Latino children with asthma. J Asthma 50: 590-594. http://dx.doi.org/10.3109/02770903.2013.792349

Souto, JA; Moral, C; Rodriguez, A; Saavedra, S; Casares, JJ. (2014). Simulation of plume dispersion using different stack configurations and meteorological inputs. Int J Environ Pollut 55: 139-147. http://dx.doi.org/10.1504/IJEP.2014.065917

Soyseth, V; Kongerud, J; Broen, P; Lilleng, P; Boe, J. (1995). Bronchial responsiveness, eosinophilia, and short term exposure to air pollution. Arch Dis Child 73: 418-422. http://dx.doi.org/10.1136/adc.73.5.418

Spalt, EW; Curl, CL; Allen, RW; Cohen, M; Williams, K; Hirsch, JA; Adar, SD; Kaufman, JD. (2015). Factors influencing time-location patterns and their impact on estimates of exposure: the Multi-Ethnic Study of Atherosclerosis and Air Pollution (MESA Air). J Expo Sci Environ Epidemiol 26: 341-348. http://dx.doi.org/10.1038/jes.2015.26

Speizer, FE; Frank, NR. (1966). The uptake and release of SO2 by the human nose. Arch Environ Occup Health 12: 725-728. http://dx.doi.org/10.1080/00039896.1966.10664471

Spiegelman, D. (2013). Regression calibration in air pollution epidemiology with exposure estimated by spatio-temporal modeling. Environmetrics 24: 521-524. http://dx.doi.org/10.1002/env.2249

Spira-Cohen, A. (2013). Email from Dr. Spira-Cohen to Dr. Patel; Response to data request. Available online at https://www.regulations.gov/document?D=EPA-HQ-ORD-2013-0232-0015

Spira-Cohen, A; Chen, LC; Kendall, M; Lall, R; Thurston, GD. (2011). Personal exposures to traffic-related air pollution and acute respiratory health among Bronx schoolchildren with asthma. Environ Health Perspect 119: 559-565. http://dx.doi.org/10.1289/ehp.1002653

Stanojevic, S; Wade, A; Stocks, J; Hankinson, J; Coates, AL; Pan, H; Rosenthal, M; Corey, M; Lebecque, P; Cole, TJ. (2008). Reference ranges for spirometry across all ages: A new approach. Am J Respir Crit Care Med 177: 253-260. http://dx.doi.org/10.1164/rccm.200708-1248OC

Steinvil, A; Fireman, E; Kordova-Biezuner, L; Cohen, M; Shapira, I; Berliner, S; Rogowski, O. (2009). Environmental air pollution has decremental effects on pulmonary function test parameters up to one week after exposure. Am J Med Sci 338: 273-279. http://dx.doi.org/10.1097/MAJ.0b013e3181adb3ed

Steinvil, A; Kordova-Biezuner, L; Shapira, I; Berliner, S; Rogowski, O. (2008). Short-term exposure to air pollution and inflammation-sensitive biomarkers. Environ Res 106: 51-61. http://dx.doi.org/10.1016/j.envres.2007.08.006

Stieb, DM; Beveridge, RC; Brook, JR; Smith-Doiron, M; Burnett, RT; Dales, RE; Beaulieu, S; Judek, S; Mamedov, A. (2000). Air pollution, aeroallergens and cardiorespiratory emergency department visits in Saint John, Canada. J Expo Anal Environ Epidemiol 10: 461-477. http://dx.doi.org/10.1038/sj.jea.7500112

Stieb, DM; Judek, S; Burnett, RT. (2003). Meta-analysis of time-series studies of air pollution and mortality: Update in relation to the use of generalized additive models. J Air Waste Manag Assoc 53: 258-261. http://dx.doi.org/10.1080/10473289.2003.10466149

Stieb, DM; Szyszkowicz, M; Rowe, BH; Leech, JA. (2009). Air pollution and emergency department visits for cardiac and respiratory conditions: A multi-city time-series analysis. Environ Health 8. http://dx.doi.org/10.1186/1476-069X-8-25

Stingone, JA; Luben, TJ; Daniels, JL; Fuentes, M; Richardson, DB; Aylsworth, AS; Herring, AH; Anderka, M; Botto, L; Correa, A; Gilboa, SM; Langlois, PH; Mosley, B; Shaw, GM; Siffel, C; Olshan, AF. (2014). Maternal exposure to criteria air pollutants and congenital heart defects in offspring: Results from the national birth defects prevention study. Environ Health Perspect 122: 863-872. http://dx.doi.org/10.1289/ehp.1307289

Straney, L; Finn, J; Dennekamp, M; Bremner, A; Tonkin, A; Jacobs, I. (2014). Evaluating the impact of air pollution on the incidence of out-of-hospital cardiac arrest in the Perth Metropolitan Region: 2000-2010. J Epidemiol Community Health 68: 6-12. http://dx.doi.org/10.1136/jech-2013-202955

Streets, DG; de Foy, B; Duncan, BN; Lamsal, LN; Li, C; Lu, Z. (2014). Using satellite observations to measure power plant emissions and their trends [Magazine]. EM: Environmental Manager, February, 16-21.

Strickland, MJ; Darrow, LA; Klein, M; Flanders, WD; Sarnat, JA; Waller, LA; Sarnat, SE; Mulholland, JA; Tolbert, PE. (2010). Short-term associations between ambient air pollutants and pediatric asthma emergency department visits. Am J Respir Crit Care Med 182: 307-316. http://dx.doi.org/10.1164/rccm.200908-1201OC

Strickland, MJ; Darrow, LA; Mulholland, JA; Klein, M; Flanders, WD; Winquist, A; Tolbert, PE. (2011). Implications of different approaches for characterizing ambient air pollutant concentrations within the urban airshed for time-series studies and health benefits analyses. Environ Health 10: 36. http://dx.doi.org/10.1186/1476-069X-10-36

Strickland, MJ; Klein, M; Correa, A; Reller, MD; Mahle, WT; Riehle-Colarusso, TJ; Botto, LD; Flanders, WD; Mulholland, JA; Siffel, C; Marcus, M; Tolbert, PE. (2009). Ambient air pollution and cardiovascular malformations in Atlanta, Georgia, 1986-2003. Am J Epidemiol 169: 1004-1014. http://dx.doi.org/10.1093/aje/kwp011

Sun, Y; Song, X; Han, Y; Ji, Y; Gao, S; Shang, Y; Lu, SE; Zhu, T; Huang, W. (2015). Size-fractioned ultrafine particles and black carbon associated with autonomic dysfunction in subjects with diabetes or impaired glucose tolerance in Shanghai, China. Part Fibre Toxicol 12: 8. http://dx.doi.org/10.1186/s12989-015-0084-6

Sunyer, J; Ballester, F; Le Tertre, A; Atkinson, R; Ayres, JG; Forastiere, F; Forsberg, B; Vonk, JM; Bisanti, L; Tenias, JM; Medina, S; Schwartz, J; Katsouyanni, K. (2003). The association of daily sulfur dioxide air pollution levels with hospital admissions for cardiovascular diseases in Europe (The Aphea-II study). Eur Heart J 24: 752-760. http://dx.doi.org/10.1016/S0195-668X(02)00808-4

Swaans, W; Goelen, E; De Fré, R; Damen, E; Van Avermaet, P; Roekens, E; Keppens, V. (2007). Laboratory and field validation of a combined NO2-SO2 Radiello passive sampler. J Environ Monit 9: 1231-1240. http://dx.doi.org/10.1039/b708925b

Sykes, RI; Parker, S; Henn, D; Chowdhury, B. (2007). SCIPUFF version 2.3 technical documentation. Princeton, New Jersey: L-3 Titan Corp.

Szpiro, AA; Paciorek, CJ. (2013). Measurement error in two-stage analyses, with application to air pollution epidemiology. Environmetrics 24: 501-517. http://dx.doi.org/10.1002/env.2233

Szpiro, AA; Paciorek, CJ; Sheppard, L. (2011). Does more accurate exposure prediction necessarily improve health effect estimates? Epidemiology 22: 680-685. http://dx.doi.org/10.1097/EDE.0b013e3182254cc6

Szyszkowicz, M. (2008). Ambient air pollution and daily emergency department visits for ischemic stroke in Edmonton, Canada. Int J Occup Med Environ Health 21: 295-300. http://dx.doi.org/10.2478/v10001-008-0029-5

Szyszkowicz, M; Porada, E; Tremblay, N; Grafstein, E. (2012a). Sulfur dioxide and emergency department visits for stroke and seizure. Stroke Res Treat 2012: 824724. http://dx.doi.org/10.1155/2012/824724

Szyszkowicz, M; Rowe, BH; Brook, RD. (2012b). Even low levels of ambient air pollutants are associated with increased emergency department visits for hypertension. Can J Cardiol 28: 360-366. http://dx.doi.org/10.1016/j.cjca.2011.06.011

Taggart, SCO; Custovic, A; Francis, HC; Faragher, EB; Yates, CJ; Higgins, BG; Woodcock, A. (1996). Asthmatic bronchial hyperresponsiveness varies with ambient levels of summertime air pollution. Eur Respir J 9: 1146-1154. http://dx.doi.org/10.1183/09031936.96.09061146

Tam, E; Miike, R; Labrenz, S; Sutton, AJ; Elias, T; Davis, J; Chen, YL; Tantisira, K; Dockery, D; Avol, E. (2016). Volcanic air pollution over the Island of Hawai'i: Emissions, dispersal, and composition. Association with respiratory symptoms and lung function in Hawai'i Island school children. Environ Int 92-93: 543-552. http://dx.doi.org/10.1016/j.envint.2016.03.025

Tan, WC; Cripps, E; Douglas, N; Sudlow, MF. (1982). Protective effect of drugs on bronchoconstriction induced by sulphur dioxide. Thorax 37: 671-676. http://dx.doi.org/10.1136/thx.37.9.671

TFESC and NASPE (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology). (1996). Heart rate variability: Standards of measurement, physiological interpretation and clinical use. Circulation 93: 1043-1065. http://dx.doi.org/10.1161/01.CIR.93.5.1043

Thach, TQ; Wong, CM; Chan, KP; Chau, YK; Thomas, GN; Ou, CQ; Yang, L; Peiris, JSM; Lam, TH; Hedley, AJ. (2010). Air pollutants and health outcomes: Assessment of confounding by influenza. Atmos Environ 44: 1437-1442. http://dx.doi.org/10.1016/j.atmosenv.2010.01.036

Thompson, AM; Zanobetti, A; Silverman, F; Schwartz, J; Coull, B; Urch, B; Speck, M; Brook, JR; Manno, M; Gold, DR. (2010). Baseline repeated measures from controlled human exposure studies: Associations between ambient air pollution exposure and the systemic inflammatory biomarkers IL-6 and fibrinogen. Environ Health Perspect 118: 120-124. http://dx.doi.org/10.1289/ehp.0900550

Thurlbeck, WM. (1982). Postnatal human lung growth. Thorax 37: 564-571. http://dx.doi.org/10.1136/thx.37.8.564

Tolbert, PE; Klein, M; Peel, JL; Sarnat, SE; Sarnat, JA. (2007). Multipollutant modeling issues in a study of ambient air quality and emergency department visits in Atlanta. J Expo Sci Environ Epidemiol 17: S29-S35. http://dx.doi.org/10.1038/sj.jes.7500625

Toren, K; Brisman, J; Jarvholm, B. (1993). Asthma and asthma-like symptoms in adults assessed by questionnaires: A literature review [Review]. Chest 104: 600-608. http://dx.doi.org/10.1378/chest.104.2.600

Trasande, L; Wong, K; Roy, A; Savitz, DA; Thurston, G. (2013). Exploring prenatal outdoor air pollution, birth outcomes and neonatal health care utilization in a nationally representative sample. J Expo Sci Environ Epidemiol 23: 315-321. http://dx.doi.org/10.1038/jes.2012.124

Trenga, CA; Koenig, JQ; Williams, PV. (1999). Sulphur dioxide sensitivity and plasma antioxidants in adult subjects with asthma. Occup Environ Med 56: 544-547.

Trenga, CA; Koenig, JQ; Williams, PV. (2001). Dietary antioxidants and ozone-induced bronchial hyperresponsiveness in adults with asthma. Arch Environ Occup Health 56: 242-249. http://dx.doi.org/10.1080/00039890109604448

Triche, EW; Belanger, K; Bracken, MB; Beckett, WS; Holford, TR; Gent, JF; Mcsharry, JE; Leaderer, BP. (2005). Indoor heating sources and respiratory symptoms in nonsmoking women. Epidemiology 16: 377-384. http://dx.doi.org/10.1097/01.ede.0000158225.44414.85

Tsai, SS; Chen, PS; Yang, YH; Liou, SH; Wu, TN; Sung, FC; Yang, CY. (2012). Air pollution and hospital admissions for myocardial infarction: Are there potentially sensitive groups? J Toxicol Environ Health A 75: 242-251. http://dx.doi.org/10.1080/15287394.2012.641202

Tsai, SS; Chiu, HF; Wu, TN; Yang, CY. (2009). Air pollution and emergency room visits for cardiac arrhythmia in a subtropical city: Taipei, Taiwan. Inhal Toxicol 21: 1113-1118. http://dx.doi.org/10.3109/08958370902758939

Tseng, CY; Huang, YC; Su, SY; Huang, JY; Lai, CH; Lung, CC; Ho, CC; Liaw, YP. (2012). Cell type specificity of female lung cancer associated with sulfur dioxide from air pollutants in Taiwan: An ecological study. BMC Public Health 12: 4. http://dx.doi.org/10.1186/1471-2458-12-4

Tsuji, H; Larson, MG; Venditti, FJ, Jr; Manders, ES; Evans, JC; Feldman, CL; Levy, D. (1996). Impact of reduced heart rate variability on risk for cardiac events. The Framingham Heart Study. Circulation 94: 2850-2855. http://dx.doi.org/10.1161/01.CIR.94.11.2850

Tsuji, H; Venditti, FJ; Manders, ES; Evans, JC; Larson, MG; Feldman, CL; Levy, D. (1994). Reduced heart rate variability and mortality risk in an elderly cohort: The Framingham Heart Study. Circulation 90: 878-883. http://dx.doi.org/10.1161/01.CIR.90.2.878

Tsujino, I; Kawakami, Y; Kaneko, A. (2005). Comparative simulation of gas transport in airway models of rat, dog, and human. Inhal Toxicol 17: 475-485. http://dx.doi.org/10.1080/08958370590964476

Tunnicliffe, WS; Harrison, RM; Kelly, FJ; Dunster, C; Ayres, JG. (2003). The effect of sulphurous air pollutant exposures on symptoms, lung function, exhaled nitric oxide, and nasal epithelial lining fluid antioxidant concentrations in normal and asthmatic adults. Occup Environ Med 60: 1-7. http://dx.doi.org/10.1136/oem.60.11.e15

Tunnicliffe, WS; Hilton, MF; Harrison, RM; Ayres, JG. (2001). The effect of sulphur dioxide exposure on indices of heart rate variability in normal and asthmatic adults. Eur Respir J 17: 604-608.

Turin, TC; Kita, Y; Rumana, N; Nakamura, Y; Ueda, K; Takashima, N; Sugihara, H; Morita, Y; Ichikawa, M; Hirose, K; Nitta, H; Okayama, A; Miura, K; Ueshima, H. (2012). Short-term exposure to air pollution and incidence of stroke and acute myocardial infarction in a Japanese population. Neuroepidemiology 38: 84-92. http://dx.doi.org/10.1159/000335654

Turner, B. (1964). A diffusion model for an urban area. J Appl Meteorol 3: 83-91. http://dx.doi.org/10.1175/1520-0450(1964)003<0083:ADMFAU>2.0.CO;2

Turner, DB. (1970). Workbook of atmospheric dispersion estimates. (999-AP-26). Cincinnati, OH: U.S. Department of Health, Education, and Welfare, Public Health Service.

U.S. Census Bureau. (2011). 2011 American community survey [Database]. Washington, DC: U.S. Department of Commerce, U.S. Census Bureau. Retrieved from http://www.census.gov/programs-surveys/acs/news/data-releases.2011.html

U.S. EPA (U.S. Environmental Protection Agency). (1971). National primary and secondary ambient air quality standards. Fed Reg 36: 8186-8201.

U.S. EPA (U.S. Environmental Protection Agency). (1982a). Air quality criteria for particulate matter and sulfur oxides (final, 1982) [EPA Report]. (EPA 600/8-82/029a). Washington, DC: Environmental Criteria and Assessment Office. http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=46205

U.S. EPA (U.S. Environmental Protection Agency). (1982b). Air quality criteria for particulate matter and sulfur oxides, volume I addendum [EPA Report]. (EPA-600/8-82-029a). Research Triangle Park. NC: Environmental Criteria and Assessment Office.

U.S. EPA (U.S. Environmental Protection Agency). (1986a). Air quality criteria for particulate matter and sulfur oxides (1982): assessment of newly available health effects information, 2nd addendum. (EPA/600/8-86/020F). Washington, DC: Office of Health and Environmental Assessment. http://nepis.epa.gov/exe/ZyPURL.cgi?Dockey=30001FM5.txt

U.S. EPA (U.S. Environmental Protection Agency). (1986b). Second addendum to air quality criteria for particulate matter and sulfur oxides (1982): Assessment of newly available health effects information [EPA Report]. (EPA/600/8-86/020F). Research Triangle Park, NC: Environmental Criteria and Assessment Office.

U.S. EPA (U.S. Environmental Protection Agency). (1991). Guidelines for developmental toxicity risk assessment (pp. 1-71). (EPA/600/FR-91/001). Washington, DC: U.S. Environmental Protection Agency, Risk Assessment Forum. http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=23162

U.S. EPA (U.S. Environmental Protection Agency). (1992). Protocol For Determining The Best Performing Model. (454R92025). http://nepis.epa.gov/exe/ZyPURL.cgi?Dockey=2000DE5J.txt

U.S. EPA (U.S. Environmental Protection Agency). (1994). Supplement to the second addendum (1986) to air quality criteria for particulate matter and sulfur oxides (1982): Assessment of new findings on sulfur dioxide acute exposure health effects in asthmatic individuals [EPA Report]. (EPA/600/FP-93/002). Research Triangle Park, NC: Environmental Criteria and Assessment Office. http://nepis.epa.gov/Exe/ZyPURL.cgi?Dockey=30002382.txt

U.S. EPA (U.S. Environmental Protection Agency). (1996a). Guidelines for reproductive toxicity risk assessment (pp. 1-143). (EPA/630/R-96/009). Washington, DC: U.S. Environmental Protection Agency, Risk Assessment Forum.

U.S. EPA (U.S. Environmental Protection Agency). (1996b). National ambient air quality standards for sulfur oxides (sulfur dioxide)--final decision. Fed Reg 61: 25566-25580.

U.S. EPA (U.S. Environmental Protection Agency). (1998). Guidelines for neurotoxicity risk assessment [EPA Report] (pp. 1-89). (EPA/630/R-95/001F). Washington, DC: U.S. Environmental Protection Agency, Risk Assessment Forum. http://www.epa.gov/risk/guidelines-neurotoxicity-risk-assessment

U.S. EPA (U.S. Environmental Protection Agency). (2005a). Guidelines for carcinogen risk assessment [EPA Report] (pp. 1-166). (EPA/630/P-03/001F). Washington, DC: U.S. Environmental Protection Agency, Risk Assessment Forum. http://www2.epa.gov/osa/guidelines-carcinogen-risk-assessment

U.S. EPA (U.S. Environmental Protection Agency). (2005b). Revision to the guildline on air quality models: adoption of a preferred general purpose (flat and complext terrain) dispersion model and other revisions; Final rule (pp. 216). (40 CFR Part 51). http://www.epa.gov/ttn/scram/guidance/guide/appw_05.pdf

U.S. EPA (U.S. Environmental Protection Agency). (2006). Estimating contributions of outdoor fine particles to indoor concentrations and personal exposures: Effects of household characteristics and personal activities [EPA Report]. (EPA/600/R-06/023). Research Triangle Park, NC: National Exposures Research Laboratory. https://nepis.epa.gov/Exe/ZyNET.exe/9100CCPM.TXT?ZyActionD=ZyDocument&Client=EPA&Index=2006+Thru+2010&Docs=&Query=&Time=&EndTime=&SearchMethod=1&TocRestrict=n&Toc=&TocEntry=&QField=&QFieldYear=&QFieldMonth=&QFieldDay=&IntQFieldOp=0&ExtQFieldOp=0&XmlQuery=&File=D%3A%5Czyfiles%5CIndex%20Data%5C06thru10%5CTxt%5C00000017%5C9100CCPM.txt&User=ANONYMOUS&Password=anonymous&SortMethod=h%7C-&MaximumDocuments=1&FuzzyDegree=0&ImageQuality=r75g8/r75g8/x150y150g16/i425&Display=hpfr&DefSeekPage=x&SearchBack=ZyActionL&Back=ZyActionS&BackDesc=Results%20page&MaximumPages=1&ZyEntry=1&SeekPage=x&ZyPURL

U.S. EPA (U.S. Environmental Protection Agency). (2007a). Integrated plan for review of the primary national ambient air quality standards for sulfur oxides [EPA Report]. Washington, DC. http://www.epa.gov/ttn/naaqs/standards/so2/data/so2_review_plan_final_10-09-07.pdf

U.S. EPA (U.S. Environmental Protection Agency). (2007b). Sulfur dioxide health assessment plan: Scope and methods for exposure and risk assessment draft [EPA Report]. Washington, DC: Office of Air Quality Planning and Standards. http://www.epa.gov/ttn/naaqs/standards/so2/data/20071113_healthassessmentplan.pdf

U.S. EPA (U.S. Environmental Protection Agency). (2008a). Integrated science assessment for oxides of nitrogen - Health criteria: Annexes [EPA Report]. (EPA/600/R-08/072). Research Triangle Park, NC: U.S. Environmental Protection Agency, National Center for Environmental Assessment. http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=194645

U.S. EPA (U.S. Environmental Protection Agency). (2008b). Integrated science assessment for oxides of nitrogen and sulfur: Ecological criteria [EPA Report]. (EPA/600/R-08/082F). Research Triangle Park, NC: U.S. Environmental Protection Agency, Office of Research and Development, National Center for Environmental Assessment- RTP Division. http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=201485

U.S. EPA (U.S. Environmental Protection Agency). (2008c). Integrated science assessment for oxides of nitrogen Health criteria (Final report, 2008) [EPA Report]. (EPA/600/R-08/071). Research Triangle Park, NC: U.S. Environmental Protection Agency, Office of Research and Development, National Center for Environmental Assessment- RTP Division. http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=194645

U.S. EPA (U.S. Environmental Protection Agency). (2008d). Integrated science assessment for sulfur oxides: Health criteria [EPA Report]. (EPA/600/R-08/047F). Research Triangle Park, NC: U.S. Environmental Protection Agency, Office of Research and Development, National Center for Environmental Assessment- RTP. http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=198843

U.S. EPA (U.S. Environmental Protection Agency). (2009a). Integrated science assessment for particulate matter [EPA Report]. (EPA/600/R-08/139F). Research Triangle Park, NC: U.S. Environmental Protection Agency, Office of Research and Development, National Center for Environmental Assessment- RTP Division. http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=216546

U.S. EPA (U.S. Environmental Protection Agency). (2009b). Risk and exposure assessment to support the review of the SO2 primary national ambient air quality standards: Final report [EPA Report]. (EPA-452/R-09-007). Washington, DC: Office of Air Quality Planning and Standards. http://www.epa.gov/ttn/naaqs/standards/so2/data/200908SO2REAFinalReport.pdf

U.S. EPA (U.S. Environmental Protection Agency). (2009c). Risk assessment guidance for superfund volume I: Human health evaluation manual (Part F, supplemental guidance for inhalation risk assessment): Final [EPA Report]. (EPA/540/-R-070/002). Washington, DC. https://www.epa.gov/risk/risk-assessment-guidance-superfund-rags-part-f

U.S. EPA (U.S. Environmental Protection Agency). (2009d). SO2 network review and background. http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OAR-2007-0352-0037

U.S. EPA (U.S. Environmental Protection Agency). (2010a). Dispersion modeling. Available online at http://www.epa.gov/ttn/scram/dispersionindex.htm

U.S. EPA (U.S. Environmental Protection Agency). (2010b). Primary national ambient air quality standards for nitrogen dioxide; final rule. Fed Reg 75: 6474.

U.S. EPA (U.S. Environmental Protection Agency). (2011). Exposure factors handbook: 2011 edition (final) [EPA Report]. (EPA/600/R-090/052F). Washington, DC: U.S. Environmental Protection Agency, Office of Research and Development, National Center for Environmental Assessment. http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=236252

U.S. EPA (U.S. Environmental Protection Agency). (2012a). 10th modeling conference. The 10th Conference on Air Quality Modeling, March 13-15, 2012, Research Triangle Park, NC.

U.S. EPA (U.S. Environmental Protection Agency). (2012b). Air trends: Sulfur dioxide. Available online at https://www.epa.gov/air-trends/sulfur-dioxide-trends

U.S. EPA (U.S. Environmental Protection Agency). (2012c). Total risk integrated methodology (TRIM) air pollutants exposure model documentation (TRIM.Expo / APEX, Version 4) Volume 1: User's Guide. (EPA-452/B-12-001a). Research Triangle Park, North Carolina: Office of Air Quality Planning and Standards, Health and Environmental Impacts Division. http://www2.epa.gov/sites/production/files/2013-08/documents/apex45_usersguide_vol1_aug2012_0.pdf

U.S. EPA (U.S. Environmental Protection Agency). (2013a). 2011 National Emissions Inventory data and documentation. Available online at https://www.epa.gov/air-emissions-inventories (accessed December 1, 2014).

U.S. EPA (U.S. Environmental Protection Agency). (2013b). Integrated science assessment for lead [EPA Report]. (EPA/600/R-10/075F). Research Triangle Park, NC: U.S. Environmental Protection Agency, National Center for Environmental Assessment. http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=255721

U.S. EPA (U.S. Environmental Protection Agency). (2013c). Integrated science assessment for ozone and related photochemical oxidants (final report) [EPA Report]. (EPA/600/R-10/076F). Washington, DC: U.S. Environmental Protection Agency, National Center for Environmental Assessment. http://cfpub.epa.gov/ncea/isa/recordisplay.cfm?deid=247492

U.S. EPA (U.S. Environmental Protection Agency). (2013d). Notice of workshop and call for information on integrated science assessment for oxides of nitrogen and oxides of sulfur. Fed Reg 78: 53452-53454.

U.S. EPA (U.S. Environmental Protection Agency). (2013e). Toxicological review of trimethylbenzenes (CASRN 25551-13-7, 95-63-6, 526-73-8, and 108-67-8) in support of summary information on the Integrated Risk Information System (IRIS): revised external review draft [EPA Report]. (EPA/635/R13/171a). Washington, D.C.: U.S. Environmental Protection Agency, National Center for Environmental Assessment. http://yosemite.epa.gov/sab/SABPRODUCT.NSF/b5d8a1ce9b07293485257375007012b7/ee1e280e77586de985257b65005d37e7!OpenDocument

U.S. EPA (U.S. Environmental Protection Agency). (2014a). Integrated review plan for the primary national ambient air quality standard for sulfur dioxide [EPA Report]. (EPA-452/R-14-007). Research Triangle Park, NC: U.S. Environmental Protection Agency, National Center for Environmental Assessment. http://www.epa.gov/ttn/naaqs/standards/so2/data/20141028so2reviewplan.pdf

U.S. EPA (U.S. Environmental Protection Agency). (2014b). Integrated review plan for the primary national ambient air quality standards for nitrogen dioxide [EPA Report]. (EPA-452/R-14/003). Research Triangle Park, NC: U.S. Environmental Protection Agency, National Center for Environmental Assessment. http://www.epa.gov/ttn/naaqs/standards/nox/data/201406finalirpprimaryno2.pdf

U.S. EPA (U.S. Environmental Protection Agency). (2015a). Evaluation of Prognostic Meteorological Data in AERMOD Applications. (454R15004). http://nepis.epa.gov/exe/ZyPURL.cgi?Dockey=P100OIH4.txt

U.S. EPA (U.S. Environmental Protection Agency). (2015b). Preamble to the Integrated Science Assessments [EPA Report]. (EPA/600/R-15/067). Research Triangle Park, NC: National Center for Environmental Assessment, Office of Research and Development. https://cfpub.epa.gov/ncea/isa/recordisplay.cfm?deid=310244

U.S. EPA (U.S. Environmental Protection Agency). (2015c). Table 5S-1. Summary of epidemiologic studies of SO2 exposure and other morbidity effects (i.e., eye irritation, effects on the nervous and gastrointestinal systems).

U.S. EPA (U.S. Environmental Protection Agency). (2015d). Table 5S-2. Study-specific details of experimental studies of SO2 exposure and other morbidity effects (i.e., hematological and nervous system effects).

U.S. EPA (U.S. Environmental Protection Agency). (2015e). Table 5S-2. Study specific details of experimental studies of SO2 exposure and other morbidity effects (i.e., hematological and nervous system effects).

U.S. EPA (U.S. Environmental Protection Agency). (2015f). Table 5S-9. Summary of epidemiologic studies of long-term exposure to SO2 and respiratory morbidity.

U.S. EPA (U.S. Environmental Protection Agency). (2015g). Table 5S-18 Corresponding risk estimates of ambient sulfur dioxide for hospital admissions for cardiovascular disease in studies conducting copollutants models with NO2 presented in Figure 5S-4.

U.S. EPA (U.S. Environmental Protection Agency). (2015h). Table 5S-19. Corresponding risk estimates of ambient sulfur dioxide for hospital admissions for cardiovascular disease in studies conducting copollutants models with PM presented in Figure 5S-5.

U.S. EPA (U.S. Environmental Protection Agency). (2015i). Table 5S-20. Summary of epidemiologic studies of exposure to sulfur dioxide and fertility/pregnancy effects.

U.S. EPA (U.S. Environmental Protection Agency). (2015j). Table 5S-21. Summary of epidemiologic studies of exposure to sulfur dioxide and fetal growth.

U.S. EPA (U.S. Environmental Protection Agency). (2015k). Table 5S-22. Summary of epidemiologic studies of exposure to sulfur dioxide and preterm birth.

U.S. EPA (U.S. Environmental Protection Agency). (2015l). Table 5S-23. Summary of epidemiologic studies of exposure to sulfur dioxide and birth weight.

U.S. EPA (U.S. Environmental Protection Agency). (2015m). Table 5S-24. Summary of epidemiologic studies of exposure to sulfur dioxide and birth defects.

U.S. EPA (U.S. Environmental Protection Agency). (2015n). Table 5S-25. Summary of epidemiologic studies of exposure to sulfur dioxide and fetal and infant mortality.

U.S. EPA (U.S. Environmental Protection Agency). (2015o). Table 5S-26. Summary of additional epidemiologic studies of short-term sulfur dioxide exposure and mortality.

U.S. EPA (U.S. Environmental Protection Agency). (2016a). 11th modeling conference presentations. Available online at https://www3.epa.gov/ttn/scram/11thmodconfpres.htm

U.S. EPA (U.S. Environmental Protection Agency). (2016b). Figure 5S-3. Results of single-pollutant and copollutant models of short term exposure to sulfur dioxide with and without CO or O3 and hospital admissions for cardiovascular disease.

U.S. EPA (U.S. Environmental Protection Agency). (2016c). Figure 5S-4. Results of single pollutant and copollutant models of short-term exposure to sulfur dioxide with and without NO2 and hospital admissions for cardiovascular disease.

U.S. EPA (U.S. Environmental Protection Agency). (2016d). Figure 5S-5. Results of single-pollutant and copollutant models of short term exposure to sulfur dioxide with and without PM and hospital admissions for cardiovascular disease.

U.S. EPA (U.S. Environmental Protection Agency). (2016e). Integrated science assessment for oxides of nitrogen (final report) [EPA Report]. (EPA/600/R-15/068). Research Triangle Park, NC: U.S. Environmental Protection Agency, National Center for Environmental Assessment. http://ofmpub.epa.gov/eims/eimscomm.getfile?p_download_id=526855

U.S. EPA (U.S. Environmental Protection Agency). (2016f). Memo: List of designated reference and equivalence methods. Available online at https://www3.epa.gov/ttnamti1/files/ambient/criteria/reference-equivalent-methods-list.pdf

U.S. EPA (U.S. Environmental Protection Agency). (2016g). Supplemental figure 5S-1. Associations between short-term increases in ambient sulfur dioxide concentration and respiratory symptoms in adults with asthma.

U.S. EPA (U.S. Environmental Protection Agency). (2016h). Supplemental Figure 5S-2. Epidemiologic studies of respiratory infection as self-reported by children and adults.

U.S. EPA (U.S. Environmental Protection Agency). (2016i). Supplemental Table 5S-3; Details and quantitative results from studies presented in Figure 5-2 [EPA Report].

U.S. EPA (U.S. Environmental Protection Agency). (2016j). Supplemental table 5S-4. Corresponding risk estimates for studies presented in Figure 5-3.

U.S. EPA (U.S. Environmental Protection Agency). (2016k). Supplemental Table 5S-7. Corresponding risk estimates for studies presented in Figure 5-8.

U.S. EPA (U.S. Environmental Protection Agency). (2016l). Table 5S-1. Summary of epidemiologic studies of SO2 exposure and other morbidity effects (i.e., sensory, nervous and gastrointestinal and other effects).

U.S. EPA (U.S. Environmental Protection Agency). (2016m). Table 5S-5. Summary of additional respiratory hospital admission and emergency department visit studies.

U.S. EPA (U.S. Environmental Protection Agency). (2016n). Table 5S-6. Corresponding risk estimates for studies presented in Figure 5-7.

U.S. EPA (U.S. Environmental Protection Agency). (2016o). Table 5S-8. Corresponding risk estimates for studies presented in Figure 5-9.

U.S. EPA (U.S. Environmental Protection Agency). (2016p). Table 5S-10. Cross-sectional asthma prevalence and asthma severity studies.

U.S. EPA (U.S. Environmental Protection Agency). (2016q). Table 5S-11. Summary of cross-sectional epidemiologic studies examining associations between SO2 and respiratory symptoms, allergic responses, bronchitis, COPD, ARD, and infections.

U.S. EPA (U.S. Environmental Protection Agency). (2016r). Table 5S-12. Summary of recent epidemiologic studies examining associations between SO2 concentrations and lung function.

U.S. EPA (U.S. Environmental Protection Agency). (2016s). Table 5S-13. Study-specific details of experimental studies of SO2 and cardiovascular effects.

U.S. EPA (U.S. Environmental Protection Agency). (2016t). Table 5S-14. Corresponding risk estimates for hospital admissions for ischemic heart disease for studies presented in Figure 5-12.

U.S. EPA (U.S. Environmental Protection Agency). (2016u). Table 5S-15. Corresponding risk estimates for hospital admissions or emergency department visits for cerebrovascular disease and stroke for studies presented in Figure 5-13.

U.S. EPA (U.S. Environmental Protection Agency). (2016v). Table 5S-17 Corresponding risk estimates of ambient sulfur dioxide for hospital admissions for cardiovascular disease in studies conducting copollutants models with CO or O3 presented in Figure 5S-3.

U.S. EPA (U.S. Environmental Protection Agency). (2016w). Table 5S-28. Corresponding excess risk estimates for Figure 5-18.

U.S. EPA (U.S. Environmental Protection Agency). (2016x). Table 5S-29. Corresponding risk estimates for Figure 5 26.

U.S. EPA (U.S. Environmental Protection Agency). (2016y). Table 5S-30. Corresponding risk estimates for Figure 5-27.

U.S. EPA (U.S. Environmental Protection Agency). (2016z). Table 5S-31. Summary of epidemiologic studies of SO2 concentration and cancer incidence and mortality.

U.S. EPA (U.S. Environmental Protection Agency). (2016aa). Table 5S-32. Study specific details of experimental studies of SO2 exposure and genotoxicity.

U.S. EPA (U.S. Environmental Protection Agency). (2016bb). Table 5S- 27. Corresponding excess risk estimates for Figure 5-17.

U.S. EPA (U.S. Environmental Protection Agency). (2016cc). Table 5S-16. Corresponding relative risk (95% CI) for hospital admissions and emergency department visits for all CVD for studies presented in Figure 5-14.

Ulirsch, GV; Ball, LM; Kaye, W; Shy, CM; Lee, CV; Crawford-Brown, D; Symons, M; Holloway, T. (2007). Effect of particulate matter air pollution on hospital admissions and medical visits for lung and heart disease in two southeast Idaho cities. J Expo Sci Environ Epidemiol 17: 478-487. http://dx.doi.org/10.1038/sj.jes.7500542

University of Michigan. (2016). The panel study of income dynamics. Available online at http://psidonline.isr.umich.edu/Studies.aspx

USGS (U.S. Geological Survey). (1999). Potentially active volcanoes of Western United States. Available online at http://www.washingtonstatesearch.com/Washington_maps/Potentially_Active_Volcanoes_Western_United_States_map.html

van Aalst, R; Edwards, L; Pulles, T; De Saeger, E; Tombrou, M; Tonnesen, D. (1998). Guidance report on preliminary assessment under EC air quality directives: 5. Modelling (pp. 34-45). (Technical report no. 11). Copenhagen, Denmark: European Environment Agency. http://www.eea.europa.eu/publications/TEC11a/page011.html

van Thriel, C; Schäper, M; Kleinbeck, S; Kiesswetter, E; Blaszkewicz, M; Golka, K; Nies, E; Raulf-Heimsoth, M; Brüning, T. (2010). Sensory and pulmonary effects of acute exposure to sulfur dioxide (SO2). Toxicol Lett 196: 42-50. http://dx.doi.org/10.1016/j.toxlet.2010.03.013

Vandevijvere, S; Temme, E; Andjelkovic, M; De Wil, M; Vinkx, C; Goeyens, L; Van Loco, J. (2010). Estimate of intake of sulfites in the Belgian adult population. Food Addit Contam Part A Chem Anal Control Expo Risk Assess 27: 1072-1083. http://dx.doi.org/10.1080/19440041003754506

Vanos, JK; Cakmak, S; Bristow, C; Brion, V; Tremblay, N; Martin, SL; Sheridan, SS. (2013). Synoptic weather typing applied to air pollution mortality among the elderly in 10 Canadian cities. Environ Res 126: 66-75. http://dx.doi.org/10.1016/j.envres.2013.08.003

Velická, H; Puklová, V; Keder, J; Brabec, M; Malý, M; Bobák, M; Kotlík, B; Jiřík, V; Janout, V; Kazmarová, H. (2015). Asthma exacerbations and symptom variability in children due to short-term ambient air pollution changes in Ostrava, Czech Republic. Cent Eur J Public Health 23: 292-298. http://dx.doi.org/10.21101/cejph.a4548

Venkatram, A. (2002). Accounting for averaging time in air pollution modeling. Atmos Environ 36: 2165-2170.

Venkatram, A; Brode, R; Cimorelli, A; Lee, R; Paine, R; Perry, S; Peters, W; Weil, J; Wilson, R. (2001). A complex terrain dispersion model for regulatory applications. Atmos Environ 35: 4211-4221. http://dx.doi.org/10.1016/S1352-2310(01)00186-8

Vig, PS; Zajac, DJ. (1993). Age and gender effects on nasal respiratory function in normal subjects. Cleft Palate Craniofac J 30: 279-284. http://dx.doi.org/10.1597/1545-1569(1993)030<0279:AAGEON>2.3.CO;2

Villeneuve, PJ; Chen, L; Rowe, BH; Coates, F. (2007). Outdoor air pollution and emergency department visits for asthma among children and adults: A case-crossover study in northern Alberta, Canada. Environ Health 6: 40. http://dx.doi.org/10.1186/1476-069X-6-40

Villeneuve, PJ; Chen, L; Stieb, D; Rowe, BH. (2006a). Associations between outdoor air pollution and emergency department visits for stroke in Edmonton, Canada. Eur J Epidemiol 21: 689-700. http://dx.doi.org/10.1007/s10654-006-9050-9

Villeneuve, PJ; Doiron, MS; Stieb, D; Dales, R; Burnett, RT; Dugandzic, R. (2006b). Is outdoor air pollution associated with physician visits for allergic rhinitis among the elderly in Toronto, Canada? Allergy 61: 750-758. http://dx.doi.org/10.1111/j.1398-9995.2006.01070.x

Villeneuve, PJ; Johnson, JY; Pasichnyk, D; Lowes, J; Kirkland, S; Rowe, BH. (2012). Short-term effects of ambient air pollution on stroke: Who is most vulnerable? Sci Total Environ 430: 193-201. http://dx.doi.org/10.1016/j.scitotenv.2012.05.002

Vincent, GK; Velkoff, VA. (2010). The next four decades: The older population in the United States: 2010 to 2050. (P25-1138). Washington, DC: U.S. Department of Commerce, Economics and Statistics Administration, U.S. Census Bureau. http://www.census.gov/prod/2010pubs/p25-1138.pdf

Vinikoor-Imler, LC; Owens, EO; Nichols, JL; Ross, M; Brown, JS; Sacks, JD. (2014). Evaluating potential response-modifying factors for associations between ozone and health outcomes: A weight-of-evidence approach [Review]. Environ Health Perspect 122: 1166-1176. http://dx.doi.org/10.1289/ehp.1307541

von Elm, E; Altman, DG; Egger, M; Pocock, SJ; Gøtzsche, PC; Vandenbroucke, JP. (2007). The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: Guidelines for reporting observational studies [Review]. PLoS Med 4: e296. http://dx.doi.org/10.1371/journal.pmed.0040296

Wagner, U; Staats, P; Fehmann, HC; Fischer, A; Welte, T; Groneberg, DA. (2006). Analysis of airway secretions in a model of sulfur dioxide induced chronic obstructive pulmonary disease (COPD). J Occup Med Toxicol 1: 12. http://dx.doi.org/10.1186/1745-6673-1-12

Wallace, ME; Grantz, KL; Liu, D; Zhu, Y; Kim, SS; Mendola, P. (2016). Exposure to ambient air pollution and premature rupture of membranes. Am J Epidemiol 183: 1114-1121. http://dx.doi.org/10.1093/aje/kwv284

Wang, AL; Blackford, TL; Lee, LY. (1996). Vagal bronchopulmonary C-fibers and acute ventilatory response to inhaled irritants. Respir Physiol Neurobiol 104: 231-239. http://dx.doi.org/10.1016/0034-5687(96)00014-X

Wang, C; Corbett, JJ; Firestone, J. (2007). Modeling energy use and emissions from North American shipping: application of the ship traffic, energy, and environment model. Environ Sci Technol 41: 3226-3232. http://dx.doi.org/10.1021/es060752e

Wang, L; Wei, B; Li, Y; Li, H; Zhang, F; Rosenberg, M; Yang, L; Huang, J; Krafft, T; Wang, W. (2014a). A study of air pollutants influencing life expectancy and longevity from spatial perspective in China. Sci Total Environ 487: 57-64. http://dx.doi.org/10.1016/j.scitotenv.2014.03.142

Wang, T; Hendrick, F; Wang, P; Tang, G; Clémer, K; Yu, H; Fayt, C; Hermans, C; Gielen, C; Pinardi, G; Theys, N; Brenot, H; Van Roozendael, M. (2014b). Evaluation of tropospheric SO2 retrieved from MAX-DOAS measurements in Xianghe, China. Atmos Chem Phys Discuss 14: 6501-6536. http://dx.doi.org/10.5194/acpd-14-6501-2014

Wang, XY; Hu, W; Tong, S. (2009). Long-term exposure to gaseous air pollutants and cardio-respiratory mortality in Brisbane, Australia. Geospat Health 3: 257-263.

Wannberg, VE; Williams, G; Sawyer, P; Venedam, R. (2010). An experimental field dataset with buoyant, neutral, and dense gas atmospheric releases and model comparisons in lowwind speed (Diffusion) conditions. J Appl Meteor Climatol 49: 1805-1817. http://dx.doi.org/10.1175/2010JAMC2383.1

Ware, JH; Ferris, BG, Jr; Dockery, DW; Spengler, JD; Stram, DO; Speizer, FE. (1986). Effects of ambient sulfur oxides and suspended particles on respiratory health of preadolescent children. Am Rev Respir Dis 133: 834-842.

Ware, LB; Zhao, Z; Koyama, T; May, AK; Matthay, MA; Lurmann, FW; Balmes, JR; Calfee, CS. (2015). Long-term ozone exposure increases the risk of developing the acute respiratory distress syndrome. Am J Respir Crit Care Med 193: 1143-1150. http://dx.doi.org/10.1164/rccm.201507-1418OC

Weakley, J; Webber, MP; Ye, F; Zeig-Owens, R; Cohen, HW; Hall, CB; Kelly, K; Prezant, DJ. (2013). Agreement between obstructive airways disease diagnoses from self-report questionnaires and medical records. Prev Med 57: 38-42. http://dx.doi.org/10.1016/j.ypmed.2013.04.001

Wei, Y; Davis, J; Bina, WF. (2012). Ambient air pollution is associated with the increased incidence of breast cancer in US. Int J Environ Health Res 22: 12-21. http://dx.doi.org/10.1080/09603123.2011.588321

Weil, JC. (1992). Updating the ISC model through AERMIC. 85th Annual Meeting of Air and Waste Management Association, Kansas City, MO.

Weil, JC; Corio, LA; Brower, RP. (1997). A PDF dispersion model for buoyant plumes in the convective boundary layer. J Appl Meteorol 36: 982-1003. http://dx.doi.org/10.1175/1520-0450(1997)036<0982:APDMFB>2.0.CO;2

Wellenius, GA; Bateson, TF; Mittleman, MA; Schwartz, J. (2005a). Particulate air pollution and the rate of hospitalization for congestive heart failure among medicare beneficiaries in Pittsburgh, Pennsylvania. Am J Epidemiol 161: 1030-1036. http://dx.doi.org/10.1093/aje/kwi135

Wellenius, GA; Schwartz, J; Mittleman, MA. (2005b). Air pollution and hospital admissions for ischemic and hemorrhagic stroke among medicare beneficiaries. Stroke 36: 2549-2553. http://dx.doi.org/10.1161/01.STR.0000189687.78760.47

Wellenius, GA; Yeh, GY; Coull, BA; Suh, HH; Phillips, RS; Mittleman, MA. (2007). Effects of ambient air pollution on functional status in patients with chronic congestive heart failure: A repeated-measures study. Environ Health 6. http://dx.doi.org/10.1186/1476-069X-6-26

Welz, O; Savee, JD; Osborn, DL; Vasu, SS; Percival, CJ; Shallcross, DE; Taatjes, CA. (2012). Direct kinetic measurements of Criegee intermediate (CHOO) formed by reaction of CHI with O. Science 335: 204-207. http://dx.doi.org/10.1126/science.1213229

Weng, CH; Hu, CC; Yen, TH; Huang, WH. (2015). Association between environmental particulate matter and arterial stiffness in patients undergoing hemodialysis. BMC Cardiovasc Disord 15: 115. http://dx.doi.org/10.1186/s12872-015-0107-0

Wheeler, AJ; Smith-Doiron, M; Xu, X; Gilbert, NL; Brook, JR. (2008). Intra-urban variability of air pollution in Windsor, Ontario - Measurement and modeling for human exposure assessment. Environ Res 106: 7-16. http://dx.doi.org/10.1016/j.envres.2007.09.004

WHO (World Health Organization). (1948). Preamble to the Constitution of the World Health Organization as adopted by the International Health Conference, New York, 19-22 June, 1946. In Constitution of the World Health Organization (pp. 2). Geneva, Switzerland. http://whqlibdoc.who.int/hist/official_records/constitution.pdf

WHO (World Health Organization). (2006). WHO air quality guidelines for particulate matter, ozone, nitrogen dioxide and sulfur dioxide - global update 2005 - summary of risk assessment. Copenhagen, Denmark. http://www.who.int/phe/health_topics/outdoorair/outdoorair_aqg/en/

Widdicombe, J; Lee, LY. (2001). Airway reflexes, autonomic function, and cardiovascular responses [Review]. Environ Health Perspect 4: 579-584. http://dx.doi.org/10.1.1.276.2059

Widdicombe, JG. (2003). Overview of neural pathways in allergy and asthma [Review]. Pulm Pharmacol Ther 16: 23-30. http://dx.doi.org/10.1016/S1094-5539(02)00178-5

Wiedinmyer, C; Quayle, B; Geron, C; Belote, A; Mckenzie, D, on; Zhang, X; O'Neill, S; Wynne, KK. (2006). Estimating emissions from fires in North America for air quality modeling. Atmos Environ 40: 3419-3432. http://dx.doi.org/10.1016/j.atmosenv.2006.02.010

Williams, M; Barrowcliffe, R; Laxen, D; Monks, P. (2011). Review of air quality modelling in Defra. London, England: King's College, School of Biomedical and Health Sciences. http://uk-air.defra.gov.uk/reports/cat20/1106290858_DefraModellingReviewFinalReport.pdf

Williams, R; Rea, A; Vette, A; Croghan, C; Whitaker, D; Stevens, C; Mcdow, S; Fortmann, R; Sheldon, L; Wilson, H; Thornburg, J; Phillips, M; Lawless, P; Rodes, C; Daughtrey, H. (2009). The design and field implementation of the Detroit exposure and aerosol research study. J Expo Sci Environ Epidemiol 19: 643-659. http://dx.doi.org/10.1038/jes.2008.61

Wilson, AM; Wake, CP; Kelly, T; Salloway, JC. (2005). Air pollution, weather, and respiratory emergency room visits in two northern New England cities: an ecological time-series study. Environ Res 97: 312-321. http://dx.doi.org/10.1016/j.envres.2004.07.010

Wilson, WE; Mage, DT; Grant, LD. (2000). Estimating separately personal exposure to ambient and nonambient particulate matter for epidemiology and risk assessment: Why and how. J Air Waste Manag Assoc 50: 1167-1183. http://dx.doi.org/10.1080/10473289.2000.10464164

Wilson, WE; Suh, HH. (1997). Fine particles and coarse particles: Concentration relationships relevant to epidemiologic studies. J Air Waste Manag Assoc 47: 1238-1249. http://dx.doi.org/10.1080/10473289.1997.10464074

Winquist, A; Kirrane, E; Klein, M; Strickland, M; Darrow, LA; Sarnat, SE; Gass, K; Mulholland, J; Russell, A; Tolbert, P. (2014). Joint effects of ambient air pollutants on pediatric asthma emergency department visits in Atlanta, 1998-2004. Epidemiology 25: 666-673. http://dx.doi.org/10.1097/EDE.0000000000000146

Winterton, DL; Kaufman, J; Keener, CV; Quigley, S; Farin, FM; Williams, PV; Koenig, JQ. (2001). Genetic polymorphisms as biomarkers of sensitivity to inhaled sulfur dioxide in subjects with asthma. Ann Allergy Asthma Immunol 86: 232-238. http://dx.doi.org/10.1016/S1081-1206(10)62697-X

Wiwatanadate, P; Liwsrisakun, C. (2011). Acute effects of air pollution on peak expiratory flow rates and symptoms among asthmatic patients in Chiang Mai, Thailand. Int J Hyg Environ Health 214: 251-257. http://dx.doi.org/10.1016/j.ijheh.2011.03.003

Wiwatanadate, P; Trakultivakorn, M. (2010). Air pollution-related peak expiratory flow rates among asthmatic children in Chiang Mai, Thailand. Inhal Toxicol 22: 301-308. http://dx.doi.org/10.3109/08958370903300327

Woerman, AL; Mendelowitz, D. (2013a). Perinatal sulfur dioxide exposure alters brainstem parasympathetic control of heart rate. Cardiovasc Res 99: 16-23. http://dx.doi.org/10.1093/cvr/cvt057

Woerman, AL; Mendelowitz, D. (2013b). Postnatal sulfur dioxide exposure reversibly alters parasympathetic regulation of heart rate. Hypertension 62: 274-280. http://dx.doi.org/10.1161/HYPERTENSIONAHA.113.01552

Wollmann, HA. (1998). Intrauterine growth restriction: Definition and etiology. Horm Res 49: 1-6. http://dx.doi.org/10.1159/000053079

Wong, CM; Lam, TH; Peters, J; Hedley, AJ; Ong, SG; Tam, AYC; Liu, J; Spiegelhalter, DJ. (1998). Comparison between two districts of the effects of an air pollution intervention on bronchial responsiveness in primary school children in Hong Kong. J Epidemiol Community Health 52: 571-578. http://dx.doi.org/10.1136/jech.52.9.571

Wong, CM; Ou, CQ; Chan, KP; Chau, YK; Thach, TQ; Yang, L; Chung, RY; Thomas, GN; Peiris, JS; Wong, TW; Hedley, AJ; Lam, TH. (2008a). The effects of air pollution on mortality in socially deprived urban areas in Hong Kong, China. Environ Health Perspect 116: 1189-1194. http://dx.doi.org/10.1289/ehp.10850

Wong, CM; Vichit-Vadakan, N; Kan, H; Qian, Z. (2008b). Public Health and Air Pollution in Asia (PAPA): A multicity study of short-term effects of air pollution on mortality. Environ Health Perspect 116: 1195-1202. http://dx.doi.org/10.1289/ehp.11257

Wong, CM; Vichit-Vadakan, N; Vajanapoom, N; Ostro, B; Thach, TQ; Chau, PY; Chan, EK; Chung, RY; Ou, CQ; Yang, L; Peiris, JS; Thomas, GN; Lam, TH; Wong, TW; Hedley, AJ; Kan, H; Chen, B; Zhao, N; London, SJ; Song, G; Chen, G; Zhang, Y; Jiang, L; Qian, Z; He, Q; Lin, HM; Kong, L; Zhou, D; Liang, S; Zhu, Z; Liao, D; Liu, W; Bentley, CM; Dan, J; Wang, B; Yang, N; Xu, S; Gong, J; Wei, H; Sun, H; Qin, Z. (2010). Part 5. Public health and air pollution in Asia (PAPA): A combined analysis of four studies of air pollution and mortality. In Public Health and Air Pollution in Asia (PAPA): Coordinated studies of short-term exposure to air pollution and daily mortality in four cities (pp. 377-418). Boston, MA: Health Effects Institute. http://pubs.healtheffects.org/getfile.php?u=595

Wong, CM; Yang, L; Thach, TQ; Chau, PY; Chan, KP; Thomas, GN; Lam, TH; Wong, TW; Hedley, AJ; Peiris, JS. (2009). Modification by influenza on health effects of air pollution in Hong Kong. Environ Health Perspect 117: 248-253. http://dx.doi.org/10.1289/ehp.11605

Wong, DC; Pleim, J; Mathur, R; Binkowski, F; Otte, T; Gilliam, R; Pouliot, G; Xiu, A; Young, JO; Kang, D. (2012). WRF-CMAQ two-way coupled system with aerosol feedback: Software development and preliminary results. Geosci Model Dev 5: 299-312. http://dx.doi.org/10.5194/gmd-5-299-2012

Wong, TW; Lau, TS; Yu, TS; Neller, A; Wong, SL; Tam, W; Pang, SW. (1999). Air pollution and hospital admissions for respiratory and cardiovascular diseases in Hong Kong. Occup Environ Med 56: 679-683. http://dx.doi.org/10.1136/oem.56.10.679

Wood, AM; Harrison, RM; Semple, S; Ayres, JG; Stockley, RA. (2010). Outdoor air pollution is associated with rapid decline of lung function in alpha-1-antitrypsin deficiency. Occup Environ Med 67: 556-561. http://dx.doi.org/10.1136/oem.2009.047589

Woodruff, TJ; Darrow, LA; Parker, JD. (2008). Air pollution and postneonatal infant mortality in the United States, 1999-2002. Environ Health Perspect 116: 110-115. http://dx.doi.org/10.1289/ehp.10370

Woodruff, TJ; Parker, JD; Adams, K; Bell, ML; Gehring, U; Glinianaia, S; Ha, EH; Jalaludin, B; Slama, R. (2010). International collaboration on air pollution and pregnancy outcomes (ICAPPO). Int J Environ Res Public Health 7: 2638-2652. http://dx.doi.org/10.3390/ijerph7062638

Woodruff, TJ; Parker, JD; Darrow, LA; Slama, R; Bell, ML; Choi, H; Glinianaia, S; Hoggatt, KJ; Karr, CJ; Lobdell, DT; Wilhelm, M. (2009). Methodological issues in studies of air pollution and reproductive health. Environ Res 109: 311-320. http://dx.doi.org/10.1016/j.envres.2008.12.012

Wu, J; Jiang, C; Houston, D; Baker, D; Delfino, R. (2011a). Automated time activity classification based on global positioning system (GPS) tracking data. Environ Health 10: 101. http://dx.doi.org/10.1186/1476-069X-10-101

Wu, J; Jiang, C; Liu, Z; Houston, D; Jaimes, G; McConnell, R. (2010). Performances of different global positioning system devices for time-location tracking in air pollution epidemiological studies. Environ Health Insights 4: 93-108. http://dx.doi.org/10.4137/EHI.S6246

Wu, S; Ni, Y; Li, H; Pan, L; Yang, D; Baccarelli, AA; Deng, F; Chen, Y; Shima, M; Guo, X. (2016). Short-term exposure to high ambient air pollution increases airway inflammation and respiratory symptoms in chronic obstructive pulmonary disease patients in Beijing, China. Environ Int 94: 76-82. http://dx.doi.org/10.1016/j.envint.2016.05.004

Wu, X, (; Bennett, DH; Lee, K; Cassady, DL; Ritz, B; Hertz-Picciotto, I. (2012). Feasibility of using web surveys to collect time-activity data. J Expo Sci Environ Epidemiol 22: 116-125. http://dx.doi.org/10.1038/jes.2011.23

Wu, X; Bennett, DH; Lee, K; Cassady, DL; Ritz, B; Hertz-Picciotto, I. (2011b). Longitudinal variability of time-location/activity patterns of population at different ages: A longitudinal study in California. Environ Health 10. http://dx.doi.org/10.1186/1476-069X-10-80

Xie, J; Li, R; Fan, R; Meng, Z. (2009). Effects of sulfur dioxide on expressions of p53, bax and bcl-2 in lungs of asthmatic rats. Inhal Toxicol 21: 952-957. http://dx.doi.org/10.1080/08958370802629602

Xu, X; Ding, H; Wang, X. (1995). Acute effects of total suspended particles and sulfur dioxides on preterm delivery: A community-based cohort study. Arch Environ Occup Health 50: 407-415. http://dx.doi.org/10.1080/00039896.1995.9935976

Xu, X; Dockery, DW; Wang, L. (1991). Effects of air pollution on adult pulmonary function. Arch Environ Occup Health 46: 198-206. http://dx.doi.org/10.1080/00039896.1991.9937448

Xu, X; Hu, H; Ha, S; Roth, J. (2014). Ambient air pollution and hypertensive disorder of pregnancy. J Epidemiol Community Health 68: 13-20. http://dx.doi.org/10.1136/jech-2013-202902

Xue, J; McCurdy, T; Spengler, J; Ozkaynak, H. (2004). Understanding variability in time spent in selected locations for 7-12-year old children. J Expo Anal Environ Epidemiol 14: 222-233. http://dx.doi.org/10.1038/sj.jea.7500319

Yamamoto, N; Shendell, D; Winer, A; Zhang, J. (2010). Residential air exchange rates in three major US metropolitan areas: results from the Relationship Among Indoor, Outdoor, and Personal Air Study 19992001. Indoor Air 20: 85-90. http://dx.doi.org/10.1111/j.1600-0668.2009.00622.x

Yang, C; Chen, A; Chen, R; Qi, Y; Ye, J; Li, S; Li, W; Liang, Z; Liang, Q; Guo, D; Kan, H; Chen, X. (2014a). Acute effect of ambient air pollution on heart failure in Guangzhou, China. Int J Cardiol 177: 436-441. http://dx.doi.org/10.1016/j.ijcard.2014.09.003

Yang, CL; To, T; Foty, RG; Stieb, DM; Dell, SD. (2011). Verifying a questionnaire diagnosis of asthma in children using health claims data. BMC Pulm Med 11. http://dx.doi.org/10.1186/1471-2466-11-52

Yang, CY. (2008). Air pollution and hospital admissions for congestive heart failure in a subtropical city: Taipei, Taiwan. J Toxicol Environ Health A 71: 1085-1090. http://dx.doi.org/10.1080/15287390802114428

Yang, CY; Tseng, YT; Chang, CC. (2003a). Effects of air pollution on birthweight among children born between 1995 and 1997 in Kaohsiung, Taiwan. J Toxicol Environ Health A 66: 807-816. http://dx.doi.org/10.1080/15287390306385

Yang, Q; Chen, Y; Shi, Y; Burnett, RT; McGrail, KM; Krewski, D. (2003b). Association between ozone and respiratory admissions among children and the elderly in Vancouver, Canada. Inhal Toxicol 15: 1297-1308. http://dx.doi.org/10.1080/08958370390241768

Yang, WS; Wang, X; Deng, Q; Fan, WY; Wang, WY. (2014b). An evidence-based appraisal of global association between air pollution and risk of stroke. Int J Cardiol 175: 307-313. http://dx.doi.org/10.1016/j.ijcard.2014.05.044

Yao, G; Yue, H; Yun, Y; Sang, N. (2015). Chronic SO2 inhalation above environmental standard impairs neuronal behavior and represses glutamate receptor gene expression and memory-related kinase activation via neuroinflammation in rats. Environ Res 137: 85-93. http://dx.doi.org/10.1016/j.envres.2014.11.012

Yao, G; Yun, Y; Sang, N. (2014). Differential effects between one week and four weeks exposure to same mass of SO2 on synaptic plasticity in rat hippocampus. Environ Toxicol 31: 820-829. http://dx.doi.org/10.1002/tox.22093

Yildirim, Z; Kilic, T; Koksal, N; Kotuk, M. (2005). Protective effect of ipratropium bromide on bronchoconstriction induced by sulfur dioxide exposure during apricot sufurization processes that causes asthma-like syndrome in agricultural environment. Pharmacol Res 51: 479-482. http://dx.doi.org/10.1016/j.phrs.2004.12.004

Yogev-Baggio, T; Bibi, H; Dubnov, J; Or-Hen, K; Carel, R; Portnov, BA. (2010). Who is affected more by air pollution-sick or healthy? Some evidence from a health survey of schoolchildren living in the vicinity of a coal-fired power plant in Northern Israel. Health Place 16: 399-408. http://dx.doi.org/10.1016/j.healthplace.2009.11.013

Yokoyama, E; Yoder, RE; Frank, NR. (1971). Distribution of 35S in the blood and its excretion in urine of dogs exposed to 35SO2. Arch Environ Health 22: 389-395. http://dx.doi.org/10.1080/00039896.1971.10665861

Yorifuji, T; Kashima, S; Doi, H. (2015a). Outdoor air pollution and term low birth weight in Japan. Environ Int 74: 106-111. http://dx.doi.org/10.1016/j.envint.2014.09.003

Yorifuji, T; Kashima, S; Higa Diez, M; Kado, Y; Sanada, S; Doi, H. (2015b). Prenatal Exposure to Traffic-related Air Pollution and Child Behavioral Development Milestone Delays in Japan. Epidemiology 27: 57-65. http://dx.doi.org/10.1097/EDE.0000000000000361

Yun, Y; Yao, G; Yue, H; Guo, L, in; Qin, G; Li, G; Sang, N, an. (2013). SO2 inhalation causes synaptic injury in rat hippocampus via its derivatives in vivo. Chemosphere 93: 2426-2432. http://dx.doi.org/10.1016/j.chemosphere.2013.08.063

Zartarian, V; Bahadori, T; McKone, T. (2005). Adoption of an official ISEA glossary. J Expo Anal Environ Epidemiol 15: 1-5.

Zeger, SL; Thomas, D; Dominici, F; Samet, JM; Schwartz, J; Dockery, D; Cohen, A. (2000). Exposure measurement error in time-series studies of air pollution: Concepts and consequences. Environ Health Perspect 108: 419-426. http://dx.doi.org/10.1289/ehp.00108419

Zeman, KL; Bennett, WD. (2006). Growth of the small airways and alveoli from childhood to the adult lung measured by aerosol-derived airway morphometry. J Appl Physiol 100: 965-971. http://dx.doi.org/10.1152/japplphysiol.00409.2005

Zemek, R; Szyszkowicz, M; Rowe, BH. (2010). Air pollution and emergency department visits for otitis media: A case-crossover study in Edmonton, Canada. Environ Health Perspect 118: 1631-1636. http://dx.doi.org/10.1289/ehp.0901675

Zhang, J; Zhu, T; Kipen, H; Wang, G; Huang, W; Rich, D; Zhu, P; Wang, Y; Lu, SE; Ohman-Strickland, P; Diehl, S; Hu, M; Tong, J; Gong, J; Thomas, D. (2013). Cardiorespiratory biomarker responses in healthy young adults to drastic air quality changes surrounding the 2008 Beijing Olympics. Res Rep Health Eff Inst 174: 5-174.

Zhang, JZ; Millero, FJ. (1991). The rate of sulfite oxidation in seawater. Geochim Cosmo Act 55: 677-685. http://dx.doi.org/10.1016/0016-7037(91)90333-Z

Zhang, N; Yu, L; Wan, J; Wang, Y. (2015a). Influences of meteorological conditions on air pollution in peninsula-based city. In 4th International conference on energy and environmental protection (ICEEP 2015). Lancaster, PA: DEStech Publication, Inc. http://www.destechpub.com/product/4th-international-conference-energy-environmental-protection-iceep-2015/

Zhang, PF; Dong, GH; Sun, BJ; Zhang, LW; Chen, X; Ma, NN; Yu, F; Guo, HM; Huang, H; Lee, YL; Tang, NJ; Chen, J. (2011). Long-term exposure to ambient air pollution and mortality due to cardiovascular disease and cerebrovascular disease in Shenyang, China. PLoS ONE 6. http://dx.doi.org/10.1371/journal.pone.0020827

Zhang, Y; Wang, SG; Ma, YX; Shang, KZ; Cheng, YF; Li, X; Ning, GC; Zhao, WJ; Li, NR. (2015b). Association between ambient air pollution and hospital emergency admissions for respiratory and cardiovascular diseases in Beijing: A time series study. Biomed Environ Sci 28: 352-363. http://dx.doi.org/10.3967/bes2015.049

Zhao, A, ng; Chen, R; Kuang, X; Kan, H. (2014). Ambient air pollution and daily outpatient visits for cardiac arrhythmia in Shanghai, China. J Epidemiol 24: 321-326. http://dx.doi.org/10.2188/jea.JE20140030

Zhao, QG; Liang, ZJ; Tao, SJ; Zhu, JA; Du, YK. (2011). Effects of air pollution on neonatal prematurity in Guangzhou of China: A time-series study. Environ Health 10. http://dx.doi.org/10.1186/1476-069X-10-2

Zhao, Y; Qian, Z; Wang, J; Vaughn, MG; Liu, Y; Ren, W; Dong, G. (2013). Does obesity amplify the association between ambient air pollution and increased blood pressure and hypertension in adults? Findings from the 33 Communities Chinese Health Study [Letter]. Int J Cardiol 168: E148-E150. http://dx.doi.org/10.1016/j.ijcard.2013.08.071

Zhao, Z; Zhang, Z; Wang, Z; Ferm, M; Liang, Y; Norbäck, D. (2008). Asthmatic symptoms among pupils in relation to winter indoor and outdoor air pollution in schools in Taiyuan, China. Environ Health Perspect 116: 90-97. http://dx.doi.org/10.1289/ehp.10576

Zheng, S; Wang, M; Wang, S; Tao, Y; Shang, K. (2013). Short-term effects of gaseous pollutants and particulate matter on daily hospital admissions for cardio-cerebrovascular disease in Lanzhou: Evidence from a heavily polluted city in China. Int J Environ Res Public Health 10: 462-477. http://dx.doi.org/10.3390/ijerph10020462

Zheng, XY; Ding, H; Jiang, LN; Chen, SW; Zheng, JP; Qiu, M; Zhou, YX; Chen, Q; Guan, WJ. (2015). Association between air pollutants and asthma emergency room visits and hospital admissions in time series studies: A systematic review and meta-analysis. PLoS ONE 10: 1-24. http://dx.doi.org/10.1371/journal.pone.0138146

Zhou, N; Cui, Z; Yang, S; Han, X; Chen, G; Zhou, Z; Zhai, C; Ma, M; Li, L; Cai, M; Li, Y; Ao, L; Shu, W; Liu, J; Cao, J. (2014). Air pollution and decreased semen quality: A comparative study of Chongqing urban and rural areas. Environ Pollut 187: 145-152. http://dx.doi.org/10.1016/j.envpol.2013.12.030

Zhu, Y; Zhang, C; Liu, D; Grantz, KL; Wallace, M; Mendola, P. (2015). Maternal ambient air pollution exposure preconception and during early gestation and offspring congenital orofacial defects. Environ Res 140: 714-720. http://dx.doi.org/10.1016/j.envres.2015.06.002

Ziemann, C; Hansen, T; Pohlmann, G; Farrar, D; Pohlenz-Michel, C; Tillmann, T; Mangelsdorf, I. (2010). Genotoxicity testing of sulfur dioxide (SO2) in a mouse bone marrow micronucleus test complemented with hematological endpoints. Mutat Res Genet Toxicol Environ Mutagen 697: 38-46. http://dx.doi.org/10.1016/j.mrgentox.2010.02.002

Zmirou, D; Schwartz, J; Saez, M; Zanobetti, A; Wojtyniak, B; Touloumi, G; Spix, C; Ponce de Leon, A; Le Moullec, Y; Bacharova, L; Schouten, J; Ponka, A; Katsouyanni, K. (1998). Time-series analysis of air pollution and cause-specific mortality. Epidemiology 9: 495-503.

Zou, B; Wilson, JG; Zhan, FB; Zeng, Y. (2009a). Air pollution exposure assessment methods utilized in epidemiological studies [Review]. J Environ Monit 11: 475-490. http://dx.doi.org/10.1039/b813889c

Zou, B; Wilson, JG; Zhan, FB; Zeng, Y. (2009b). An emission-weighted proximity model for air pollution exposure assessment. Sci Total Environ 407: 4939-4945. http://dx.doi.org/10.1016/j.scitotenv.2009.05.014

Zou, B; Wilson, JG; Zhan, FB; Zeng, YN. (2009c). Spatially differentiated and source-specific population exposure to ambient urban air pollution. Atmos Environ 43: 3981-3988. http://dx.doi.org/10.1016/j.atmosenv.2009.05.022

Zou, B; Zhan, FB; Zeng, Y; Yorke, C, h; Liu, X. (2011). Performance of kriging and EWPM for relative air pollution exposure risk assessment. International Journal of Environmental Research 5: 769-778.