EPA/600/R-15/066
External Review Draft
November 2015
www.epa.gov/isa

Integrated Science Assessment for Sulfur Oxides—Health Criteria

(External Review Draft)

November 2015

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

DISCLAIMER

This document is an external review draft, for review purposes only. This information is distributed solely for predissemination peer review under applicable information quality guidelines. It has not been formally disseminated by EPA. It does not represent and should not be construed to represent any Agency determination or policy. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

CONTENTS

CONTENTS (Continued)

CONTENTS (Continued)

CONTENTS (Continued)

CONTENTS (Continued)

CONTENTS (Continued)

CONTENTS (Continued)

CONTENTS (Continued)

CONTENTS (Continued)

CONTENTS (Continued)

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 (Acting 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 (Co-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. Lisa Vinikoor-Imler (Co-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

Dr. Elizabeth Oesterling Owens—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

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

Mr. Ryan Jones—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 (Co-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. Lisa Vinikoor-Imler (Co-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. 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. Gregory Wellenius—Department of Community Health (Epidemiology Section), Brown University, Providence, RI

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

Ms. Kaylyn Gootman—Curriculum for the Environment and Ecology, University of North Carolina, Chapel Hill, 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

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

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. 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

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. 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. 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

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 EPA Administrator

**Members of the statutory CASAC appointed by the 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
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

Acronym/ Abbreviation	Meaning
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

Acronym/ Abbreviation	Meaning
cGMP	cyclic guanosine monophosphate
CH_3SH	methyl mercaptan
$CH_3{-}S{-}CH_3$	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
DBP	diastolic blood pressure
DC	District of Columbia
DEcCBP	diesel exhaust particle extract-coated carbon black particles
DEP	diesel exhaust particles

Acronym/ Abbreviation	Meaning
df	degrees of freedom
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 new	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 systems
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 new	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	intra-class 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

Acronym/ Abbreviation	Meaning
ISAAC	International Study of Asthma and Allergies in Children
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 & 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

Acronym/ Abbreviation	Meaning
N	population number
N_2	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% cut-point of 10 ± 0.5 μm aerodynamic diameter (the 50% cut point diameter is the diameter at which the sampler collects 50% of the particles and rejects 50% of the particles) and a penetration curve as measured by a reference method based on Appendix J of 40 CFR Part 50 and designated in accordance with 40 CFR Part 53 or by an equivalent method designated in accordance with 40 CFR Part 53.

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% cut-point of 10 μm aerodynamic diameter and a lower 50% cut-point of 2.5 μm aerodynamic diameter (the 50% cut point diameter is the diameter at which the sampler collects 50% of the particles and rejects 50% of the particles) as measured by a reference method based on Appendix O of 40 CFR Part 50 and designated in accordance with 40 CFR Part 53 or by an equivalent method designated in accordance with 40 CFR Part 53.
$PM_{2.5}$	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% cut-point of 2.5 μm aerodynamic diameter (the 50% cut point diameter is the diameter at which the sampler collects 50% of the particles and rejects 50% of the particles) and a penetration curve as measured by a reference method based on Appendix L of 40 CFR Part 50 and designated in accordance with 40 CFR Part 53, by an equivalent method designated in accordance with 40 CFR Part 53, or by an approved regional method designated in accordance with Appendix C of 40 CFR Part 58.
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
s	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	sulfate
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	Teragrams
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
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 (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), EPA's task is to establish standards that are neither more nor less stringent than necessary for these purposes. In so doing, 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 appropriate …." Section 109(d)(2) requires that an independent scientific review committee "shall complete a review of the criteria … and the national primary and

[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.

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.

SO_2 is the indicator for gaseous sulfur oxides. EPA considers the term sulfur oxides to refer to all forms of oxidized sulfur including multiple gaseous species (e.g., SO_2, sulfur trioxide (SO_3)] and particulate species (e.g., sulfates). The review of the primary SO_2 NAAQS focuses on evaluating the health effects associated with exposure to the gaseous sulfur oxides, particularly SO_2 because other gaseous sulfur oxide species are not present in ambient air at concentrations significant for human exposures (see Chapter 2). The atmospheric chemistry, exposure, and health effects associated with sulfur compounds present in particulate matter (PM) were most recently considered in the EPA’s review of the NAAQS for PM. The welfare effects associated with sulfur oxides 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, 2013c).

The 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 EPA promulgated NAAQS for sulfur oxides in 1971, establishing the indicator as SO_2 [36 FR 8186; (U.S. EPA, 1971)]. The 1971 primary standards were set at 365 $\mu g/m^3$ [equal to

[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.

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; h = hour; ppb = parts per billion; SO_2 = suflur dioxide; yr = year.

[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 or 140 ppb. The initial level of the annual SO_2 standard was 80 μg/m^3 which is equal to 0.03 parts per million 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 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 EPA published a proposed decision not to revise the existing standards (53 FR 14926). However, the 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.

As a result of public comments on the 1988 proposal and other post-proposal developments, the EPA published a second proposal on November 15, 1994 (59 FR 58958). The 1994 reproposal was based in part on a supplement to the second addendum of the criteria document, which evaluated new findings on short-term SO_2 exposures in asthmatics (U.S. EPA, 1994). As in the 1988 proposal, the EPA proposed to retain the existing 24-hour and annual standards. The EPA also solicited comment on three

[1] Note that 0.14 ppm is equivalent to 140 parts per billion (ppb) and 0.03 ppm is equivalent to 30 ppb.

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, one expected exceedance; and (3) augmenting implementation of existing standards by focusing on those sources or source types likely to produce high 5-minute peak 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 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 asthmatics. As a result, the Administrator judged that 5-minute peak SO_2 levels 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 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 EPA had failed to adequately explain its determination that no revision to the SO_2 NAAQS was appropriate and remanded the decision back to EPA for further explanation.[1] Specifically, the court found that EPA had failed to provide adequate rationale to support the Agency judgment that exposures to 5-minute peaks 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 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 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.

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

The last review of the air quality criteria for sulfur oxides (health criteria) 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 Integrated Science Assessment for Sulfur Oxides—Health Criteria (U.S. EPA, 2008b), multiple drafts of which received review by CASAC and the public. The EPA also conducted quantitative human risk and exposure assessments, after consulting 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 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 EPA established a new 1-hour SO_2 standard at a level of 75 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 minutes to 24 hours. More specifically, 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 reported in epidemiologic studies of mostly 1 and 24 hours (e.g., respiratory-related emergency department visits and hospitalizations). In the last review, the EPA also revoked the then-existing 24-hour and annual primary standards based largely on the recognition that a 1-hour standard at 75 ppb would have the effect of maintaining 24-hour and annual SO_2 concentrations generally well below the levels of those 24-hour and annual NAAQS. 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

[1] Documents related to reviews completed in 2010 and 1996 are available at: http://www.epa.gov/ttn/naaqs/standards/so2/s_so2_index.html.

[2] The 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).

respiratory effects in exercising asthmatics—also satisfied the remand by the D.C. Circuit in 1998.

As mentioned above, in the last review EPA placed considerable weight on substantially limiting health effects associated with 5-minute peak SO_2 concentrations. Thus, as part of the final rulemaking, the 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. 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 peaks of concern.

After publication of the final rule, a number of industry groups and states filed petitions for review arguing that the 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).

References for Preface

CAA (Clean Air Act). (1990a). Clean Air Act, as amended by Pub. L. No. 101-549, section 108: Air quality criteria and control techniques, 42 USC 7408. 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). (2005). Clean Air Act, section 302: Definitions, 42 USC 7602. http://www.gpo.gov/fdsys/pkg/USCODE-2005-title42/pdf/USCODE-2005-title42-chap85-subchapIII-sec7602.pdf

HEW (U.S. Department of Health, Education and Welfare). (1969). Air quality criteria for sulfur oxides. Washington, DC: National Air Pollution Control Administration.

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). Research Triangle Park: 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). (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). (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). (2008b). Integrated science assessment for sulfur oxides: Health criteria [EPA Report]. (EPA/600/R-08/047F). Research Triangle Park, NC: U.S. Environmental Protection Agency, National Center for Environmental Assessment. http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=198843

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). (2013c). Notice of workshop and call for information on integrated science assessment for oxides of nitrogen and oxides of sulfur. Fed Reg 78: 53452-53454.

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) NAAQS for sulfur dioxide (SO_2).[2] In 2010, the U.S. Environmental Protection Agency (EPA) established a new 1-hour standard at a level of 75 parts per billion (ppb) SO_2 based on the 3-year average of the 99th percentile of each year's 1-hour daily maximum (max) concentrations (75 FR 35520).[3] The 1-hour standard was established to protect against a broad range of respiratory effects associated with short-term exposures (i.e., 5-minute to 24-hour) in potential at-risk populations such as people with asthma. The 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 based largely on the recognition that a 1-hour standard at 75 ppb would effectively maintain 24-hour and annual SO_2 concentrations well below the then-current NAAQS and thus, these standards would provide little additional public health protection. In light of considerable weight being placed on health effects associated with 5-minute peak SO_2 concentrations, the 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.[4]

This ISA updates the 2008 ISA for Sulfur Oxides (U.S. EPA, 2008b) with studies and reports published from January 2008 through April 2015. EPA conducted in-depth searches to identify peer-reviewed literature on relevant topics such as health effects, atmospheric chemistry, ambient concentrations, and exposure. Subject-area experts and the public were also able to recommend studies and reports during a kick-off workshop held at the EPA in June 2013. To fully describe the state of available science, EPA also

[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, 2015e), www.epa.gov/isa/isa.

[2] This ISA evaluates the health effects of gaseous sulfur oxides, of which only SO_2 is present in the atmosphere at relevant concentrations. Particulate sulfur oxides 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)]. The welfare effects of sulfur oxides 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, 2013c).

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

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

brought forward the most relevant studies from previous assessments to include in this ISA.

As in the 2008 ISA, this ISA determines the causality of relationships with health effects only for SO_2 (Chapter 5); other gaseous SO_X species are not included, as SO_2 is the only gaseous sulfur oxide species that is relevant for public health in ambient air and the health literature is focused on SO_2. The ISA aims to characterize the independent health effects of SO_2, not its role as a marker for a broader mixture of pollutants in the ambient air. 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 subsequent biological mechanisms that may be affected (Chapter 4). Further, the ISA aims to characterize the independent effect of SO_2 on health effects (Chapter 5). The ISA also informs policy-relevant issues (Section 1.7), 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 factors that affect exposure to ambient SO_2 and the ability to understand factors that add uncertainty in estimating exposure, such as spatial variability in SO_2 concentrations, joint exposure to other pollutants, and uncharacterized time-activity patterns.

Emissions of SO_2 have declined by approximately 70% for all major sources since 1990, as a consequence of several federal 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 (coal-fired boilers), emitting 4,500,000 tons of SO_2 annually, according to the 2011 National Emissions Inventory (Section 2.2). Beyond the rate at which a source emits the pollutant, important variables that determine the concentration of SO_2 downwind of a source and/or at monitoring locations include the photochemical removal processes occurring in the emissions plume and local meteorology, including wind, atmospheric stability, humidity, and cloud/fog cover.

On a nationwide basis, the average daily 1-hour maximum SO_2 concentration reported during 2010−2012 is 9 ppb (Section 2.5). However, the 99^{th} percentile of daily maximum SO_2 concentrations can approach 75 ppb at some monitors located near large anthropogenic or natural sources, e.g., volcanoes. Similarly, new 5-minute data demonstrate that most hourly 5-minute maximum concentrations are well below the

short-term health benchmark level of 200 ppb (i.e., the lowest level where lung function decrements were reported in controlled human exposure studies of individuals with asthma engaged in exercise) although on some occasions (99th percentile and above) concentrations can be greater than 200 ppb near anthropogenic sources such as EGUs.

Correlations between ambient SO_2 and copollutants tend to vary across location, study, and SO_2 averaging time (Section 2.5.5). Median daily SO_2 correlations with particulate matter, nitrogen dioxide (NO_2), and carbon monoxide (CO) range from 0.2−0.4 for 2010−2012, while the median daily copollutant correlation of SO_2 with ozone (O_3) is 0.1 (Figure 2-35). Daily SO_2 copollutant correlations for all pollutants can be greater than 0.7 on rare occasions.

Dispersion models can be used to estimate SO_2 concentrations in locations where monitoring is not practical or sufficient (Section 2.6.1). 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. The widely-used dispersion model American Meteorological Society/U.S. EPA Regulatory Model (AERMOD) is designed to simulate hourly concentrations which can then be averaged to yield longer-term concentrations. Multiple evaluations of AERMOD's performance against field study databases over averaging times from 1 hour to 1 year have indicated that the model is relatively unbiased in estimating upper-percentile 1-hour concentration values. Uncertainties in model predictions are influenced by uncertainties in model input data, particularly emissions and meteorological conditions (e.g., wind).

Multiple techniques can be used to assign exposure for epidemiologic studies, including evaluation of data from central site monitoring, personal SO_2 monitoring, and various modeling approaches (Section 3.2). 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 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 across an urban area. Exposure error tends to attenuate health effect estimates in time-series epidemiologic studies for SO_2 measured by central site monitors. For long-term studies, bias of the health effect estimate may occur in either direction. In all study types, use of central site monitors is expected to widen confidence intervals of the health effect estimate. Personal SO_2 monitors can

capture the study participant's 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 hour or less. The time and expense involved to deploy personal monitors makes them more suitable for panel epidemiologic studies. Models can be used to estimate exposure for individuals and large populations when personal exposure measurements are unavailable. Modeling approaches include estimation of concentration surfaces, estimation of time-activity patterns, and microenvironment-based models combining 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 the particular application.

Exposure measurement error, which refers to the bias and uncertainty associated with using exposure metrics to represent the actual exposure of an individual or population, can be an important contributor to variability in epidemiologic study results (Section 3.3.3). Several exposure-related factors, including time-activity patterns, spatial and temporal variability of SO_2 concentrations, and proximity of individuals and populations to central-site monitors, contribute to error in estimating exposure to ambient SO_2. Activity patterns vary both among and within individuals, resulting in corresponding variations in exposure across a population and over time. Spatial and temporal variability in SO_2 concentrations can contribute to exposure error in epidemiologic studies, whether they rely on central-site monitor data or concentration modeling for exposure assessment. SO_2 has low to moderate spatial correlations between ambient monitors across urban geographic scales; thus, using central-site monitor data for epidemiologic exposure assessment introduces exposure error into the resulting effect estimate.

Exposure error can bias epidemiologic associations between ambient pollutant concentrations and health outcomes and tends to widen confidence intervals around those estimates (Section 3.3.5). The importance of exposure error varies with study design and is dependent on the spatial and temporal aspects of the design. For time-series studies, more bias (generally toward the null) would be anticipated for the health effect estimate when using a central site monitor to estimate SO_2 exposure, and more variability in the health effect estimate would be expected when using more spatially resolved exposure metrics such as a population-weighted average. For cohort studies of long-term exposure to SO_2, spatial variability in SO_2 concentrations across the study area could lead to positive or negative bias in the health effect estimate when fixed site monitors are used to

estimate exposure and the distribution of the true exposure data differs from the distribution captured by the monitoring network. In all study types, use of central-site monitors is expected to widen confidence intervals.

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 in providing biological plausibility for linking SO_2 exposure with observed health effects.

SO_2 is readily absorbed in the nasal passages of both humans and laboratory animals under resting conditions (Section 4.2). 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. Due to their increased amount of oral breathing, children and individuals with asthma or allergic rhinitis may be expected to have greater SO_2 penetration into the lower respiratory tract than healthy adults. Children may also be expected to 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 may involve several intermediate chemical reactions and transformations, particularly the formation of sulfite and S-sulfonates. Sulfite is metabolized into sulfate, which is rapidly excreted through the urine in proportion 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.

Although inhaled SO_2 produces sulfite that is distributed through the circulation, sulfite levels in the body are predominately influenced by endogenous production and by ingestion of sulfite in food (Section 4.2.6). Endogenous sulfite from the catabolism of ingested sulfur-containing amino acids far exceeds exogenous sulfite from ingestion of food additives for both adults and young children. 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 (i.e., 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.

SO_2 exposure results in increased airway resistance due to bronchoconstriction in healthy adults and in adults with asthma (Section 4.3), as demonstrated in controlled human

exposure studies. In healthy adults, this response occurs primarily as a result of activation of neural reflexes mediated by pathways involving the vagus nerve. However, in adults with asthma, evidence indicates that the response is only partially due to neural reflexes and that inflammatory mediators also play an important role. Enhancement of allergic inflammation has been observed in adults with asthma who were exposed acutely to SO_2. Animal toxicological studies in both naïve and allergic animal models provide further evidence for allergic sensitization and enhanced allergic inflammatory responses, which may enhance airway hyperresponsiveness (AHR) and promote bronchoconstriction in response to a trigger. Thus, allergic inflammation and AHR may also link short-term SO_2 exposure to the epidemiologic outcome of asthma exacerbation.

For long-term SO_2 exposure, the initiating event in the development of respiratory effects is the recurrent or prolonged redox stress due to the formation of reactive products in the epithelial lining fluid. 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, which together are characteristics of asthma. The resulting outcome may be new asthma onset, which presents as an asthma exacerbation that leads to physician-diagnosed 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. Evidence from controlled human exposure studies points to SO_2 exposure-induced activation/sensitization of neural reflexes possibly leading to altered heart rate or heart rate variability. Evidence also points to transport of sulfite into the circulation. Sulfite is highly reactive and may be responsible for redox stress 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.

Health Effects of Sulfur Dioxide Exposure

In this ISA, information on SO_2 exposure and health effects from controlled human exposure, epidemiologic, and toxicological studies is integrated to form conclusions about the causal nature of relationships between SO_2 exposure and health effects. Health effects examined in relation to the full range of SO_2 concentrations relevant to ambient conditions are considered. Based on peak concentrations (Section 2.5) and the ISA definition that ambient-relevant exposures be within one to two orders of magnitude of current conditions (Preamble (U.S. EPA, 2015e), Section 5c), SO_2 concentrations up to

2,000 ppb[1] are defined to be ambient-relevant. A consistent and transparent framework (Preamble (U.S. EPA, 2015e), 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 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

The conclusions presented in Table ES-1 are informed by recent findings and whether these recent findings, integrated with information from the 2008 ISA for Sulfur Oxides (U.S. EPA, 2008b), support a change in conclusion. Important considerations include judgments of error and uncertainty in the collective body of available studies; the coherence of findings integrated across controlled human exposure, epidemiologic, and toxicological studies demonstrating an independent effect of SO_2 exposure and potential underlying biological mechanisms; consistency in epidemiologic evidence across various methods used to estimate SO_2 exposure; and examination in epidemiologic studies of the potential influence of factors that could bias associations observed with SO_2 exposure.

[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.

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[b]	
	2008 ISA	Current Draft ISA
Respiratory effects–Short-term exposure Section 5.2.1, Table 5-27	Causal relationship	Causal relationship
Respiratory effects–Long-term exposure Section 5.2.2, Table 5-31	Inadequate to infer the presence or absence of a causal relationship	Suggestive but not sufficient to infer a causal relationship
Cardiovascular effects–Short-term exposure Section 5.3.1, Table 5-41	Inadequate to infer the presence or absence of a causal relationship	Suggestive but not sufficient to infer a causal relationship
Cardiovascular effects–Long-term exposure Section 5.3.2, Table 5-43	Not included	Inadequate to infer the presence or absence of a causal relationship
Reproductive and developmental effects[c] Section 5.4, Table 5-46	Inadequate to infer the presence or absence of a causal relationship	Suggestive but not sufficient to infer a causal relationship
Total mortality–Short-term exposure Section 5.5.1, Table 5-51	Suggestive but not sufficient to infer a causal relationship	Suggestive but not sufficient to infer a causal relationship
Total mortality–Long-term exposure Section 5.5.2, Table 5-55	Inadequate to infer the presence or absence of a causal relationship	Suggestive but not sufficient to infer a causal relationship
Cancer–Long-term exposure Section 5.6, Table 5-56	Inadequate to infer the presence or absence of a causal relationship	Suggestive but not sufficient to infer a causal relationship

ISA = integrated Science Assessment.

[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]Since the 2008 ISA for Sulfur Oxides, the phrasing of causal determinations has changed slightly, and the weight of evidence that describes each level in the hierarchy of the causal framework has been more explicitly characterized.

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

Sulfur Dioxide Exposure and Respiratory Effects

The strongest evidence indicates that there is a causal relationship between short-term SO_2 exposure and respiratory effects, particularly in individuals with asthma, which is consistent with the conclusions of the 2008 SO_X ISA. This determination is based on the consistency of findings within disciplines, coherence among multiple lines of evidence, and biological plausibility for effects specifically related to asthma exacerbation. The evidence for this conclusion comes primarily from controlled human exposure studies

available at the time of the 2008 SO_X ISA that showed lung function decrements and respiratory symptoms in adults 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). Epidemiologic evidence is also supportive of a causal relationship, including additional studies that add to the evidence provided by the 2008 SO_X ISA. Studies of asthma hospital admissions and emergency department visits report positive associations with short-term SO_2 exposures that are generally unchanged in copollutant models. There is also some supporting evidence for positive associations between short-term SO_2 exposures and respiratory symptoms among children with asthma. 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.

For long-term SO_2 exposure and respiratory effects the evidence is suggestive of, but not sufficient to infer, a causal relationship. The combined evidence from a limited number of recent longitudinal epidemiologic studies and animal toxicological evidence for the development of an asthma-like phenotype support this causal determination, but overall the evidence is limited. 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 catabolism of endogenous sulfur-containing amino acids.

For short-term and long-term SO_2 exposure, evidence is suggestive of but not sufficient to infer a causal relationship with total mortality, reproductive and developmental effects, and cancer (Table ES-1). For cardiovascular effects, the evidence for short-term SO_2 exposure is also suggestive of a causal relationship, but for long-term exposure the evidence is inadequate to infer the presence or absence of a causal relationship.

These conclusions are similar to those made in the 2008 SO_X ISA, although in several cases, the causal determination has changed from inadequate to suggestive due to a

limited body of new evidence that suggests a relationship between SO_2 exposure and effects but does not reduce important uncertainties present during the last review.

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

The primary SO_2 NAAQS are based on 1-hour daily max concentrations (3-year average of each year's 99th percentile) set to protect against respiratory morbidity associated with short-term SO_2 exposures (Section 1.1). Controlled human exposure studies have reported respiratory effects after exposures of 5−10 minutes. Consistent associations between SO_2 concentrations and asthma hospital admissions and emergency department visits that are generally unchanged in copollutant models have been demonstrated in epidemiologic studies using daily exposure metrics (24-hour average and 1-hour 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, which is also observed in the limited number of epidemiologic studies that examined lag structures and reported associations within the first few days of exposure.

Results from controlled human exposure studies of respiratory morbidity indicate wide interindividual variability in response to SO_2 exposures, with peak (5 to 10 minutes) exposures at levels as low as 200−300 ppb eliciting respiratory responses in some individuals with asthma. A clear increase was observed in the magnitude of respiratory effects with increasing exposure concentrations between 200 and 1,000 ppb during 5−10 minutes SO_2 exposures. That is, both the number of affected individuals with asthma and the severity of the response increased as SO_2 concentrations increased. There is limited epidemiologic research on concentration-response functions relating SO_2 concentrations to respiratory health morbidity, but there is no epidemiologic evidence to support a deviation from linearity or the occurrence of a population-level threshold concentration below which health effects are not observed.

SO_2 concentrations are highly spatially heterogeneous, with SO_2 concentrations at some monitors possibly not highly correlated with the community average concentration. 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 they rely on central-site monitor data or concentration modeling for exposure assessment.

Consistent with the findings of the 2008 SO_X ISA, this ISA concludes that there is adequate evidence that people with asthma are at increased risk for SO_2-related health effects compared with those without asthma. 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. There is also evidence suggestive of increased risk of SO_2-related health effects for children and older adults relative to other lifestages.

References for Executive Summary

U.S. EPA (U.S. Environmental Protection Agency). (2008b). Integrated science assessment for sulfur oxides: Health criteria [EPA Report]. (EPA/600/R-08/047F). Research Triangle Park, NC: U.S. Environmental Protection Agency, National Center for Environmental Assessment. 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, National Center for Environmental Assessment. http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=216546

U.S. EPA (U.S. Environmental Protection Agency). (2013c). 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). (2015e). 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.

CHAPTER 1 SUMMARY OF THE INTEGRATED SCIENCE ASSESSMENT

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 criteria for a broad category of gaseous 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 Standards (NAAQS) for sulfur dioxide (SO_2). Gaseous SO_X include SO_2, sulfur trioxide (SO_3), and their various reaction products (Section 2.3). There also are particulate species of SO_X (e.g., sulfate) that are being considered in the current review of the NAAQS for particulate matter (PM) and were evaluated in the 2009 ISA for PM (U.S. EPA, 2009a). The welfare effects of SO_X 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, 2013c).

This ISA evaluates relevant scientific literature published since the 2008 ISA for Sulfur Oxides (U.S. EPA, 2008b), 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, 1986a, 1982b). Thus, this ISA updates the state of the science that was available for the 2008 ISA, which informed decisions on the primary SO_2 NAAQS in the review completed in 2010. In 2010, the U.S. Environmental Protection Agency (EPA) established a new 1-hour (h) standard at a level of 75 parts per billion (ppb) SO_2 based on the 3-year (yr) average (avg) of the 99th percentile of each year's 1-hour daily maximum (max) concentrations.[2] The 1-hour standard was established to protect against a broad range of respiratory effects associated with short-term (i.e., 5-minutes to 24-hours) exposures in potential at-risk populations such as people with asthma. The 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 a 1-hour standard at

[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, 2015e).

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

75 ppb would effectively maintain 24-hour and annual SO_2 concentrations well below the then-current NAAQS. In light of considerable weight being placed on health effects associated with 5-minute peak SO_2 concentrations, the 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, 2010c).

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, 2014b). To address these questions and update the scientific judgments in the 2008 SO_X ISA, 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 prevalent species of gaseous SO_X in the atmosphere, with other species not present at concentrations relevant for human exposures. Most studies on the health effects of gaseous SO_X focus on SO_2; effects of other gaseous species are considered as information is available. In evaluating the health evidence, this ISA considers possible influences of other atmospheric pollutants, including interactions of SO_2 with other 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, not its role as a marker for a broader mixture of pollutants in the ambient air. 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

EPA uses a structured and transparent process for evaluating scientific information and determining the causality of relationships between air pollution exposures and health effects [see Preamble (U.S. EPA, 2015e)]. 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 gaseous SO_X and potential relationships with health effects. Relevant studies include those examining atmospheric chemistry, spatial and temporal trends, and exposure assessment, as well as 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.

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, 2013c). Thereafter, EPA routinely conducted literature searches to identify relevant peer-reviewed studies published since the previous ISA (i.e., from January 2008 through April 2015). Multiple search methods were used [Preamble (U.S. EPA, 2015e), Section 2] including searches in databases such as PubMed and Web of Science. Subject-area experts and the public were also able to recommend studies and reports during a kick-off workshop held at the EPA in June 2013. 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 (http://hero.epa.gov/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.

Health effects were considered for evaluation in this ISA if they were examined in previous EPA assessments for SO_X or multiple recent studies. Literature 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, 2015f). 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, 2015g)]. 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 toxicological studies were conducted in animal models consistent with studies of other health endpoints and generally focused on nonspecific preclinical outcomes (e.g. oxidative stress, protein expression). The epidemiologic studies were conducted in geographic areas and populations for which associations between SO_2 and other health effects have been demonstrated. Thus, the exclusion of these studies does not exclude the assessment of particular geographic locations, potential at-risk lifestages or populations, or range of ambient concentrations of SO_X.

The Preamble to the Integrated Science Assessments (U.S. EPA, 2015e) 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 characterize quantitative relationships between SO_2 and health effects, examine exposure metrics that well represent the variability in concentrations in the study area, consider the potential influence of other air pollutants and factors correlated with SO_2, examine potential at-risk populations and lifestages, or 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 that are defined in this ISA to be relevant to ambient exposures. Based on peak ambient concentrations (Section 2.5) and the ISA definition that ambient-relevant exposures be within one to two orders of magnitude of current levels, 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, land use regression (LUR) models, and personal exposure monitors. 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

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

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 (U.S. EPA, 2015e)] 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 where 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 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.

1.3 Organization of the Integrated Science Assessment

This ISA comprises the Preface (legislative requirements and history of the primary SO_2 NAAQS), Executive Summary, and six chapters. The general process for developing an ISA is described in a companion document, Preamble to the Integrated Science Assessments (U.S. EPA, 2015e). 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.

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 rather than SO_2 only serving as a marker for effects due to a broader mixture of air pollutants. To that end, this chapter draws upon information about the sources, distribution, and exposure to ambient SO_2 (Section 3.3.5) 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 these factors 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

Because of its historically high atmospheric concentrations and the locations of its sources with respect to human populations, SO_2 is the gaseous sulfur oxide chemical species of greatest importance to public health. Emissions of SO_2 have declined by approximately 70% for all major sources since 1990 as a consequence 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 (coal-fired boilers), emitting 4,500,000 tons of SO_2 annually, according to the 2011 National Emissions Inventory (NEI) (Section 2.2).

Beyond the rate at which a source emits the pollutant, the important variables that determine the concentration of SO_2 downwind of the source are the photochemical removal processes occurring in the emissions plume and local meteorology, including wind, atmospheric stability, humidity, and cloud/fog cover. 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 in areas with high concentrations of Criegee precursors, i.e. small 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 EPA monitoring network as a result of the new 1-hour primary NAAQS standard promulgated in 2010. 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 5-minute data in light of health effects evidence on respiratory effects among exercising individuals with asthma following a 5−10 minute exposure to SO_2. Since the release of the 2008 SO_X ISA (U.S. EPA, 2008b), there are more than 400 monitoring sites across the U.S. reporting 5-minute data. Analysis of environmental concentrations of SO_2 data reported in Chapter 2 reflect the monitoring network changes, particularly the analysis of the recent 5-minute data.

On a nationwide basis, the average daily 1-hour maximum SO_2 reported during 2010−2012 is 9 ppb (Section 2.5). However, peak concentrations (99th percentile) of daily maximum SO_2 concentrations can approach 75 ppb at some monitors located near large anthropogenic or natural sources, e.g., volcanoes. Similarly, new 5-minute data demonstrate that most hourly 5-minute maximum concentrations are well below the short-term health benchmark levels of 200 ppb (i.e., the lowest level where lung function decrements were reported in controlled human exposure studies of individuals with asthma engaged in exercise, see Section 5.2.1.2), although on some occasions (99th percentile and above) concentrations can be greater than 200 ppb at some monitors near anthropogenic sources such as EGUs.

SO_2 concentrations are highly variable across urban spatial scales, exhibiting moderate to poor correlations between SO_2 measured at different monitors across a metropolitan area. This high degree of urban spatial variability may not be fully captured by central site

monitoring estimates, and thus has implications for the interpretation of human exposure and health effects data (Sections 2.5.2.2 and 3.3.3.2).

Sulfur dioxide correlations with copollutants tend to vary across location, study and SO_2 averaging time (Section 2.5.5). Median daily SO_2 correlations with PM, nitrogen dioxide (NO_2), and CO range from 0.2−0.4 for 2010−2012, while the median daily copollutant correlation of SO_2 with O_3 is 0.1 (Figure 2-35). Daily SO_2 copollutant correlations for all pollutants can be greater than 0.7 on rare occasions.

Dispersion models can be used to estimate SO_2 concentrations in locations where monitoring is not practical or sufficient (Section 2.6.1). 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 human exposure to SO_2 in epidemiologic studies (Section 3.2.2.1, Chapter 5). The widely-used dispersion model American Meteorological Society/U.S. EPA Regulatory Model (AERMOD) is designed to simulate hourly concentrations which can then be averaged to yield longer-term concentrations. Multiple evaluations of AERMOD's performance against field study databases over averaging times from 1 hour to 1 year have indicated that the model is relatively unbiased in estimating upper-percentile 1-hour concentration values. 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 various modeling approaches (Section 3.2). Each has strengths and limitations, as summarized in Table 3-2. 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 participant's 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 makes them more suitable for panel epidemiologic studies. Models can be used to estimate exposure for individuals and large populations when personal exposure measurements are unavailable. Modeling approaches include estimation of concentration surfaces, estimation of time-activity patterns, and microenvironment-based models combining air quality data with time-activity patterns. Strengths and limitations of these approaches are summarized in Table 3-1. 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 public buildings. 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 (Table 3-4). 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 concentrations were relatively high (>0.75), suggesting that variations in outdoor concentration are driving indoor concentrations. 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 SO_X ISA (U.S. EPA, 2008b), 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. 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.

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 (Section 3.3.3). 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 various 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 introduce error into population-averaged exposure estimates.

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 monitors 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 monitors 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 monitors may influence how well people's exposure is represented by measurements at the monitors, although factors other than distance play an important role as well. While many SO_2 monitors are located near dense population centers, other monitors are located near sources and may not fully represent SO_2 concentrations experienced by populations in epidemiologic studies. Use of these near-source monitors introduces exposure error into health effect estimates, although this error can be mitigated by using average concentrations across multiple monitors 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 to moderate correlations with other daily NAAQS pollutant concentrations at collocated monitors (Figure 2-35). However, a wide range of copollutant correlations is observed at different monitoring sites, from moderately negative to moderately positive. In studies where daily SO_2 correlations with NO_2 and CO were observed to be high, it is possible the data may have been collected before recent rulemaking to reduce sulfur content in diesel fuel (66 FR 5002). 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 contribute to variability in epidemiologic study results by biasing effect estimates toward or away from the null and widening confidence intervals (Section 3.3.5). The magnitude 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. Low spatial correlations between central site monitors also contribute to exposure error in time-series studies, potentially biasing the health effect estimate towards the null and widening the confidence intervals around the health effect estimate. For long-term studies, bias of the health effect estimate may occur in either direction depending on whether the monitor is over- or under-estimating 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. 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, ambient and nonambient concentration differences, 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 concentration or exposure estimates using various approaches offer an alternative 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 inhalation, 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 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 the physiochemical properties 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 SO_X ISA, 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. 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. 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. Due to their increased amount of oral breathing, individuals with asthma or allergic rhinitis and children may be expected to have greater SO_2 penetration into the lower respiratory tract than healthy 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, the majority of SO_2-derived products in the body at any given time following exposure are found in the respiratory tract and may be detected there for up to a week following inhalation. 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. 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. 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. 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 Chapter 4 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 SO_X ISA (U.S. EPA, 2008b) 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 neural reflexes, (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 or sensitization of neural reflexes, release of inflammatory mediators, and modulation of allergic inflammation or sensitization. These key events may collectively lead to several endpoints, including bronchoconstriction and airway hyperresponsiveness (AHR). Bronchoconstriction is characteristic of an asthma attack, and AHR often leads to bronchoconstriction in response to a trigger. These pathways may be linked to the epidemiologic outcome of asthma exacerbation.

SO_2 exposure results in increased airway resistance due to bronchoconstriction in healthy adults and in adults with asthma, as demonstrated in controlled human exposure studies. In healthy adults, this response occurs primarily as a result of activation of neural reflexes mediated by cholinergic parasympathetic pathways involving the vagus nerve. However, in adults with asthma, evidence indicates that the response is only partially due to neural reflexes 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, although noncholinergic mechanisms may also be involved. Enhancement of allergic inflammation (i.e., leukotriene-mediated increases in numbers of sputum eosinophils) has been observed in adults with asthma who were exposed acutely to SO_2. Animal toxicological studies in both naive and allergic animal models provide further evidence for allergic sensitization and enhanced allergic inflammatory responses, which 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.

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. Evidence for this mode of action comes from studies in both naive and allergic experimental animals, which demonstrate enhanced allergic responses and pathologic changes following exposure to SO_2 over several weeks. 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.

Although there is some evidence that SO_2 inhalation results in extrapulmonary effects, there is uncertainty regarding the mode of action underlying these responses. 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 autooxidation 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.

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

Respiratory Effects Associated with Short-term Exposure to Sulfur Dioxide

The strongest 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 SO_X ISA (U.S. EPA, 2008b). 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 5-27).

The evidence for this conclusion comes primarily from controlled human exposure studies included in the 2008 SO_X ISA (U.S. EPA, 2008b) 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; 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 second (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 the asthmatic population (~5−30%) has also been observed 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 mild asthmatics, 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, they are more limited in reserve 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 asthmatics than healthy adults.

These findings are consistent with the current understanding of dosimetry and modes of action (Section 1.5). Due to their increased contribution 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 or sensitization of neural reflexes, 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 SO_X ISA. Studies of asthma hospital admissions and emergency department (ED) visits report positive associations with short-term SO_2 exposures that are generally unchanged in copollutant models involving PM and other criteria pollutants when examining all ages, children (i.e., <18 years of age) and older adults (i.e., 65 years of age and older) (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). Due to their increased contribution of oral breathing, children may be expected to have greater SO_2 penetration into the lower respiratory tract than healthy adults. Children may also be expected to have a greater intake dose of SO_2 per body mass than adults. 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 5.2.1.7).

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 (Sections 5.2.1.3, 5.2.1.4, 5.2.1.5, and 5.2.1.6). The limited and inconsistent evidence for these nonasthma-related respiratory effects does not contribute heavily to the causal determination.

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. There is a very 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 is coherent with limited animal toxicological evidence of allergic sensitization, airway remodeling, and enhanced airway responsiveness, which are key events (or endpoints) in the mode of action for the development of asthma. 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 5-31.

1.6.2 Health Effects beyond the Respiratory System

Cardiovascular Effects Associated with Short-Term Exposure to Sulfur Dioxide

Overall, the available evidence is suggestive of, but not sufficient to infer, a causal relationship between short-term exposure to SO_2 and cardiovascular health effects (Table 5-41). This conclusion represents a change from the 2008 ISA for Sulfur Oxides that concluded "the evidence as a whole is inadequate to infer a causal relationship" (U.S. EPA, 2008b). The revised causal determination is based on new evidence that supports the potential for independent associations of SO_2 with cardiovascular effects after adjusting for some pollutants, recognizing that uncertainties still remain regarding the potential for SO_2 to serve as an indicator for other pollutants and the lack of support for biologically plausible mechanisms for cardiovascular effects from the limited, inconsistent experimental evidence available.

The primary evidence comes from epidemiologic studies of adults that generally demonstrate an association between short-term exposure to SO_2 and a myocardial infarction (MI). This conclusion is supported by epidemiologic studies reporting SO_2-associated hospitalizations and ED visits for MI, ischemic heart disease (IHD), and aggregated cardiovascular disease (CVD), ST-segment alterations, and mortality from

cardiovascular disease. There is a lack of experimental studies investigating related clinical outcomes in order to evaluate the coherence across disciplines. However dosimetric studies (Section 4.2) show that following absorption in the respiratory tract, SO_2-derived products are widely distributed throughout the body and have been observed in the blood and urine within 5 minutes of starting an SO_2 exposure. Some animal toxicological studies have demonstrated oxidative injury to blood or other tissues and/or inflammation and other effects in tissues distal to the absorption site. The current understanding of modes of action (Section 4.3) is that exposure to SO_2 may potentially result in effects outside the respiratory tract via activation of neural reflexes or mediated by circulating sulfite. 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 an MI. Evidence for other cardiovascular and related metabolic effects is inconclusive.

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 5-43). 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 a lack of experimental evidence to provide coherence or biological plausibility for an independent effect of long-term exposure to SO_2 on cardiovascular health.

Reproductive and Developmental Effects

Overall the evidence is suggestive of, but not sufficient to infer, a causal relationship between exposure to SO_2 and reproductive and developmental outcomes (Table 5-46). The 2008 SO_X ISA (U.S. EPA, 2008b) concluded the evidence was inadequate to infer the presence or absence of a causal relationship with reproductive and developmental effects.

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, there are a number of uncertainties 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., preeclampsia, gestational diabetes), and developmental effects, and there is little coherence or consistency among epidemiologic and toxicological studies for these outcomes. Although there are few toxicological studies at relevant dose ranges of SO_2, many studies provide supportive evidence for health outcomes following SO_2 exposure. Many uncertainties remain when evaluating the evidence for these health endpoints, including exposure measurement error and the potential for copollutant confounding; therefore, the evidence is suggestive of, but not sufficient to infer, a causal relationship between exposure to SO_2 and reproductive and developmental outcomes.

Total Mortality Associated with Short-Term Exposure to Sulfur Dioxide

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 but not sufficient to infer a causal relationship (Table 5-51). This conclusion is consistent with that reached in the 2008 SO_X ISA (U.S. EPA, 2008b). 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, no biological mechanism that could lead to mortality as a result of short-term SO_2 exposures has been characterized.

Total Mortality Associated with Long-Term Exposure to Sulfur Dioxide

The overall evidence is suggestive of, but not sufficient to infer, a causal relationship between long-term exposure to SO_2 and total mortality among adults (Table 5-55). The recent evidence is generally consistent with the evidence in the 2008 SO_X ISA (U.S. EPA, 2008b). The most 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 exposure measurement error, copollutant confounding, or the geographic scale of the analysis.

Cancer

The overall evidence for long-term SO_2 exposure and cancer is suggestive but not sufficient to infer a causal relationship (Table 5-56). The 2008 SO_X ISA concluded that the evidence was inadequate to infer a causal relationship (U.S. EPA, 2008b). 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 (SO_2) exposure and health effects evaluated in the current draft Integrated Science Assessment (ISA) for Sulfur Oxides.

Health Effect Category[a] and Causal Determination[b]		SO_2 Concentrations Associated with Effects
Respiratory Effects and Short-term Exposure (Section 5.2.1): Causal relationship *No change in causal determination from 2008 ISA; new evidence consistent with prior determination*		
Key evidence (Table 5-27)	Strongest evidence is for effects on asthma exacerbation. There is consistent evidence from multiple, high-quality controlled human exposure studies showing 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, in studies of all ages, 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 or sensitization of neural reflexes and/or inflammation leading to bronchoconstriction and allergic inflammation leading to increased airway responsiveness, which are key events or endpoints in the proposed mode of action linking short-term SO_2 exposure and asthma exacerbation.	Overall studies' means: Controlled human exposure studies of decreased lung function: 400−600 ppb, with responses observed in some asthmatics at 200 ppb Controlled human exposure studies of increased respiratory symptoms: 600−1,000 ppb Epidemiologic studies: 1-h max: 9.6−10.8 ppb 24-h avg: 1.03−36.9 ppb
Respiratory Effects and Long-term Exposure (Section 5.2.2): Suggestive but not sufficient to infer a causal relationship *Change in causal determination from 2008 ISA (inadequate to infer a causal relationship) due to new, but limited, evidence.*		
Key evidence[c] (Table 5-31)	Evidence from epidemiologic studies is generally supportive but not entirely consistent for increases in asthma incidence and prevalence related to SO_2 exposure. The limited animal toxicological evidence provides coherence and biological plausibility. There is some evidence for a mode of action involving inflammation, allergic sensitization, AHR, and airway remodeling.	Overall epidemiologic studies' mean (SD): 4.0 (3.4) ppb and 1.98 (0.97) ppb Animal toxicological studies: 2,000 ppb

Table 1-1 (Continued): Key evidence contributing to causal determinations for sulfur dioxide (SO_2) exposure and health effects evaluated in the current draft Integrated Science Assessment (ISA) for Sulfur Oxides.

Health Effect Category[a] and Causal Determination[b]		SO_2 Concentrations Associated with Effects
Cardiovascular Effects and Short-term Exposure (Section 5.3.1) Suggestive but not sufficient to infer a causal relationship *Change in causal determination from 2008 ISA (inadequate to infer a causal relationship) due to new, but limited, evidence.*		
Key evidence[c] (Table 5-41)	There is generally supportive but not entirely consistent 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. There is a lack of 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 studies' 24-h avg: 1.2−30.2 ppb
Cardiovascular Effects and Long-term Exposure (Section 5.3.2) Inadequate to infer a causal relationship *Not included in 2008 ISA*		
Key evidence[c] (Table 5-43)	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 studies' means: 1.3−1.72 ppb
Reproductive and Developmental Effects and Exposure (Section 5.4) Suggestive but not sufficient to infer a causal relationship *Change in causal determination from 2008 ISA (inadequate to infer a causal relationship) due to new, but limited, evidence.*		
Key evidence[c] (Table 5-46)	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 a lack of evidence from epidemiologic studies to support an association of SO_2 exposure with detrimental effects on fertility or pregnancy. Limited evidence is available for an understanding of key reproductive and developmental events in mode of action.	Overall epidemiologic studies' means: 1.9−13.2 ppb
Total Mortality and Short-term Exposure (Section 5.5.1) Suggestive but not sufficient to infer a causal relationship *No change in causal determination from 2008 ISA; new evidence consistent with prior determination*		
Key evidence[c] (Table 5-51)	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 respiratory mortality.	Overall epidemiologic studies' mean 24-h avgs: U.S., Canada, South America, Europe: 0.4−28.2[e] ppb Asia: 0.7−>200 ppb

Table 1-1 (Continued): Key evidence contributing to causal determinations for sulfur dioxide (SO_2) exposure and health effects evaluated in the current draft Integrated Science Assessment (ISA) for Sulfur Oxides.

Health Effect Category[a] and Causal Determination[b]		SO_2 Concentrations Associated with Effects
Total Mortality and Long-term Exposure (Section 5.5.2) Suggestive but not sufficient to infer a causal relationship *Change in causal determination from 2008 ISA (inadequate to infer a causal relationship) due to new, but limited, evidence.*		
Key evidence[c] (Table 5-55)	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 long-term respiratory or cardiovascular health effects to support an association with mortality from these causes.	Overall epidemiologic studies' ambient means: 1.6−24.0 ppb
Cancer and Long-term Exposure (Section 5.6) Suggestive but not sufficient to infer a causal relationship *Change in causal determination from 2008 ISA (inadequate to infer a causal relationship) due to new, but limited, evidence.*		
Key evidence[c] (Table 5-56)	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 studies' means: 1.49−27.87 ppb. Toxicological studies: 5,000, 10,700, 21,400, 32,100 ppb

AHR = airway hyperresponsiveness; CO = carbon monoxide; CVD = cardiovascular disease; ED = emergency department; IHD = ischemic heart disease; ISA = Integrated Science Assessment; MI = myocardial infarction; NAAQS = National Ambient Air Quality Standards; $PM_{2.5}$ = particulate matter with an aerodynamic diameter less than or equal to a nominal 2.5 µm; PM_{10} = particulate matter with an aerodynamic diameter less than or equal to a nominal 10 µm; SO_2 = sulfur dioxide.

[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]Since the completion of the 2008 ISA for Sulfur Oxides, the phrasing of causal determinations has changed slightly, and the weight of evidence that describes each level in the hierarchy of the causal framework has been more explicitly characterized.

[c]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 NAAQS pollutants at collocated monitors, copollutant confounding by these and other pollutants cannot be ruled out.

1.7 Policy-Relevant Considerations

As described in the Preamble (U.S. EPA, 2015e) 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

The primary SO_2 NAAQS is based on the 99th percentile of 1-hour daily maximum concentrations averaged over 3 years, set to protect against respiratory morbidity associated with short-term SO_2 exposures (Section 1.1). Controlled human exposure studies have examined effects after 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-hour average and 1-hour daily maximum), 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 the concentration-response relationship aids in quantifying the public health impact of SO_2 exposure. A key issue is whether the relationship is linear across the full range of ambient concentrations or whether there are deviations from linearity at and below the levels of the current 1-hour standard of 75 ppb. Additionally, there is the question of whether a threshold might exist, which would indicate an ambient concentration below which adverse health outcomes are not elicited. Lack of a threshold

implies that exposure to even the lowest measured ambient SO_2 concentrations has the potential to cause harm.

Results from controlled human exposure studies indicate wide interindividual variability in response to SO_2 exposures, with peak (5 to 10 minutes) exposures at levels as low as 200−300 ppb eliciting lung function decrements in some individuals with asthma. A clear increase in the magnitude of respiratory effects was observed with increasing exposure concentrations between 200 and 1,000 ppb during 5−10 minute SO_2 exposures. There is limited epidemiologic research on concentration-response functions relating SO_2 concentrations to respiratory health morbidity, but overall there is no reason to conclude a deviation from linearity or the appearance of a population-level threshold.

1.7.3 Regional Heterogeneity in Effect Estimates

The 2008 SO_X ISA discussed spatial variability in SO_2 concentrations and its impact on effect estimates from epidemiologic studies. Intermonitor correlations ranged from very low to very high values, suggesting that SO_2 concentrations at some monitors 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 monitors 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 they rely on central-site monitor data or concentration modeling for exposure assessment. SO_2 has low to moderate spatial correlations between ambient monitors 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 intra-urban concentration and exposure differences 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 concentrations to evaluate health effects. Low inter-monitor correlations 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.

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 (ATS, 2000).

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 the 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 SO_X ISA (U.S. EPA, 2008b), 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 (U.S. EPA, 2015e)). 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 (Table 6-16), which is consistent with the findings of the 2008 SO_X ISA (U.S. EPA, 2008b). 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 5.2.1.8). 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. 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. Although the 2008 SO_X ISA (U.S. EPA, 2008b) 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, though those over 75 years were more consistently at increased risk. In addition, there was a lack of toxicological evidence regarding the effect of lifestage on respiratory responses to SO_2 to support observations made across epidemiologic studies that evaluated lifestage.

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

The public health significance of SO_2-related health effects is indicated by many lines of evidence. SO_2 exposure is linked to health effects that are clearly adverse such as ED

visits and hospital admissions for asthma and asthma exacerbation. The public health significance of SO_2-related health effects is also indicated by the evidence for increased risk among people with asthma, and the suggestive evidence for increased risk among children and older adults. The roles of co-occurring risk factors or combined higher SO_2 exposure and health risk within a population in influencing 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 can 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 Conclusions

In summary, studies since the 2008 SO_X ISA have supported the conclusion of that ISA (U.S. EPA, 2008b) that there is a causal relationship between short-term SO_2 exposure and respiratory effects. This determination is based on the 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 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. 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. Other health effects, including cardiovascular morbidity, reproductive and developmental effects, mortality, and cancer had causal determinations of either “suggestive but not sufficient to infer a causal relationship” or “inadequate to infer a causal relationship” with short- and/or long-term SO_2 exposure. Additionally, among various populations and lifestages, there is adequate evidence that people with asthma, and suggestive evidence that children and older adults, are at increased risk for SO_2-related health effects. The large proportions of children and older adults in the U.S. population and the high prevalence of asthma in children can translate into a large number of people affected by SO_2 and thus magnify the public health impact of ambient SO_2 exposure.

References for Chapter 1

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

CAA (Clean Air Act). (1990a). Clean Air Act, as amended by Pub. L. No. 101-549, section 108: Air quality criteria and control techniques, 42 USC 7408. http://www.law.cornell.edu/uscode/text/42/7408

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). Research Triangle Park: 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). (2008b). Integrated science assessment for sulfur oxides: Health criteria [EPA Report]. (EPA/600/R-08/047F). Research Triangle Park, NC: U.S. Environmental Protection Agency, National Center for Environmental Assessment. 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, National Center for Environmental Assessment. http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=216546

U.S. EPA (U.S. Environmental Protection Agency). (2010c). Primary national ambient air quality standards for nitrogen dioxide; final rule. Fed Reg 75: 6474.

U.S. EPA (U.S. Environmental Protection Agency). (2013c). 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). (2014b). 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). (2015e). 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.

U.S. EPA (U.S. Environmental Protection Agency). (2015f). 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). (2015g). Table 5S-2. Study-specific details of experimental studies of SO2 exposure and other morbidity effects (i.e., hematological and nervous system effects).

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

CHAPTER 2 ATMOSPHERIC CHEMISTRY AND AMBIENT CONCENTRATIONS OF SULFUR OXIDES

2.1 Introduction

This chapter provides concepts and findings relating to source emissions, atmospheric chemistry and fate, measurement methods, environmental concentrations, atmospheric modeling of gas-phase SO_X. It is intended as a prologue for detailed discussions on 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 Sources of Sulfur Dioxide

Sulfur dioxide is the most important of the gas-phase sulfur oxides for both atmospheric chemistry and health effects. SO_X was initially defined to include disulfur monoxide (S_2O), SO_3, and gas-phase H_2SO_4, but none of these species is present in the atmosphere in concentrations significant for human exposures. Therefore, this section focuses on sources of SO_2. Additional gas-phase sulfur oxides important for atmospheric chemistry and fate are described in detail in Section 2.3.

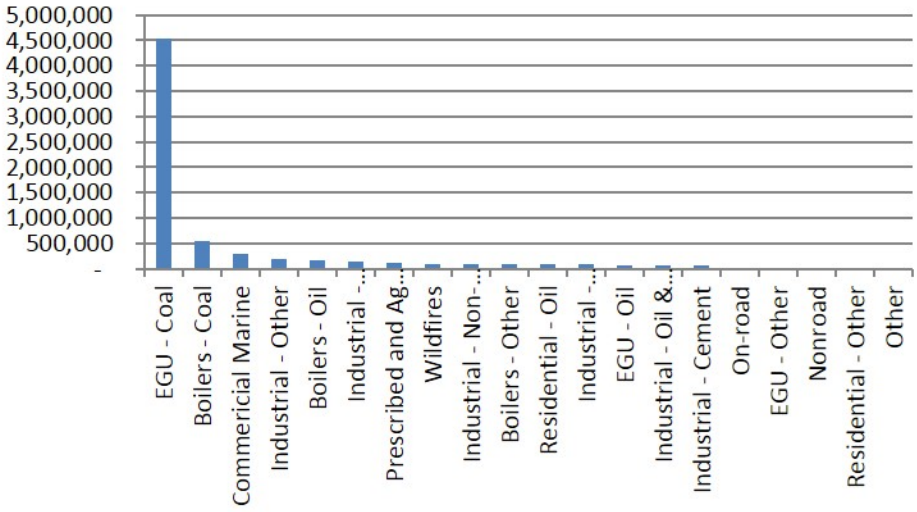
Sulfur dioxide is both a primary gas-phase pollutant (when formed during fuel combustion) and a secondary pollutant [the product of atmospheric gas- or droplet-phase oxidation of reduced sulfur compounds (sulfides)]. Fossil fuel combustion is the main anthropogenic source of primary SO_2, while volcanoes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

This section briefly describes the main U.S. anthropogenic and natural sources of SO_2 emissions. Values 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.

2.2.1 U.S. Anthropogenic Versus Natural Sources

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 metallosulfur minerals) and in its 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). However, with the exception of volcanic and other geologic emissions, naturally occurring SO_2 is largely derived from the oxidation of sulfides emitted by low flux "area" sources, such as the oceans and moist soils. Conversely, anthropogenic emissions of sulfur are primarily in the form of SO_2, emerging from point sources and in quantities that may substantially affect local and regional air quality. The largest SO_2-emitting sector within the U.S. is electricity generation based on coal combustion. The mass of emissions produced by coal-fired electric generating units (EGUs) exceeds those produced by the next largest sector (coal-fired boilers) by nearly a factor of 10. Figure 2-1 provides a sector comparison according to annual emissions rates found in the EPA 2011 National Emissions Inventory.



Note: EGU denotes electric power generating units; Ag denotes agricultural

Source: U.S. EPA National Emissions Inventory, 2011 (www.epa.gov/air-emissions-inventories/2011-national-emissions-inventory-nei-data).

Figure 2-1 Sulfur dioxide emissions by sector in tons, annually (U.S. EPA National Emissions Inventory, 2011).

As shown in Figure 2-1, the NEI also includes estimated SO_2 emissions by fire used in landscape management and agriculture (ag), i.e. "Prescribed and Ag fires," as well as wildfires. Agricultural and prescribed burning emissions are estimated at 26,965 and 85,087 tons, respectively. Wildfires, as a source of SO_X emissions, are discussed in Section 2.2.5.3.

2.2.2 Sources by Category and Geographic Distribution

Most electric power generating unit (EGU) sources are located in the eastern half of the continental U.S., as indicated in Figure 2-2. Figure 2-3, in contrast, shows a sparser geographic distribution for the two highest industrial point source categories, (A) industrial cement and (B) industrial manufacturing. Counties that have not fully achieved the current air quality standard for SO_2, being partially or entirely out of attainment, are outlined in yellow in Figures 2-2, 2-3 and 2-4.

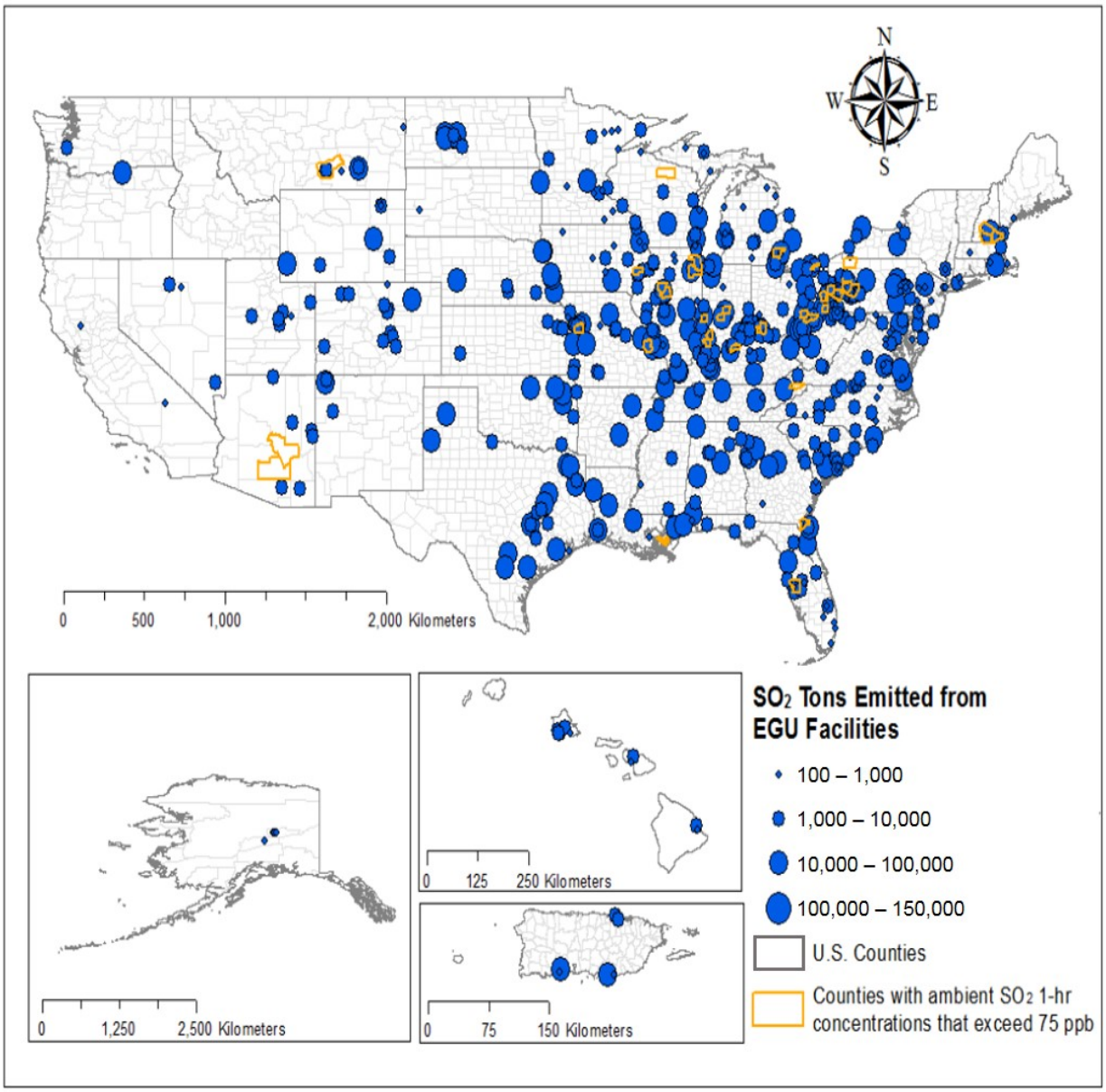


Figure 2-2 **Distribution of electric power generating unit (EGU)-derived sulfur dioxide emissions across the U.S., based on the 2011 National Emissions Inventory.**

(A)

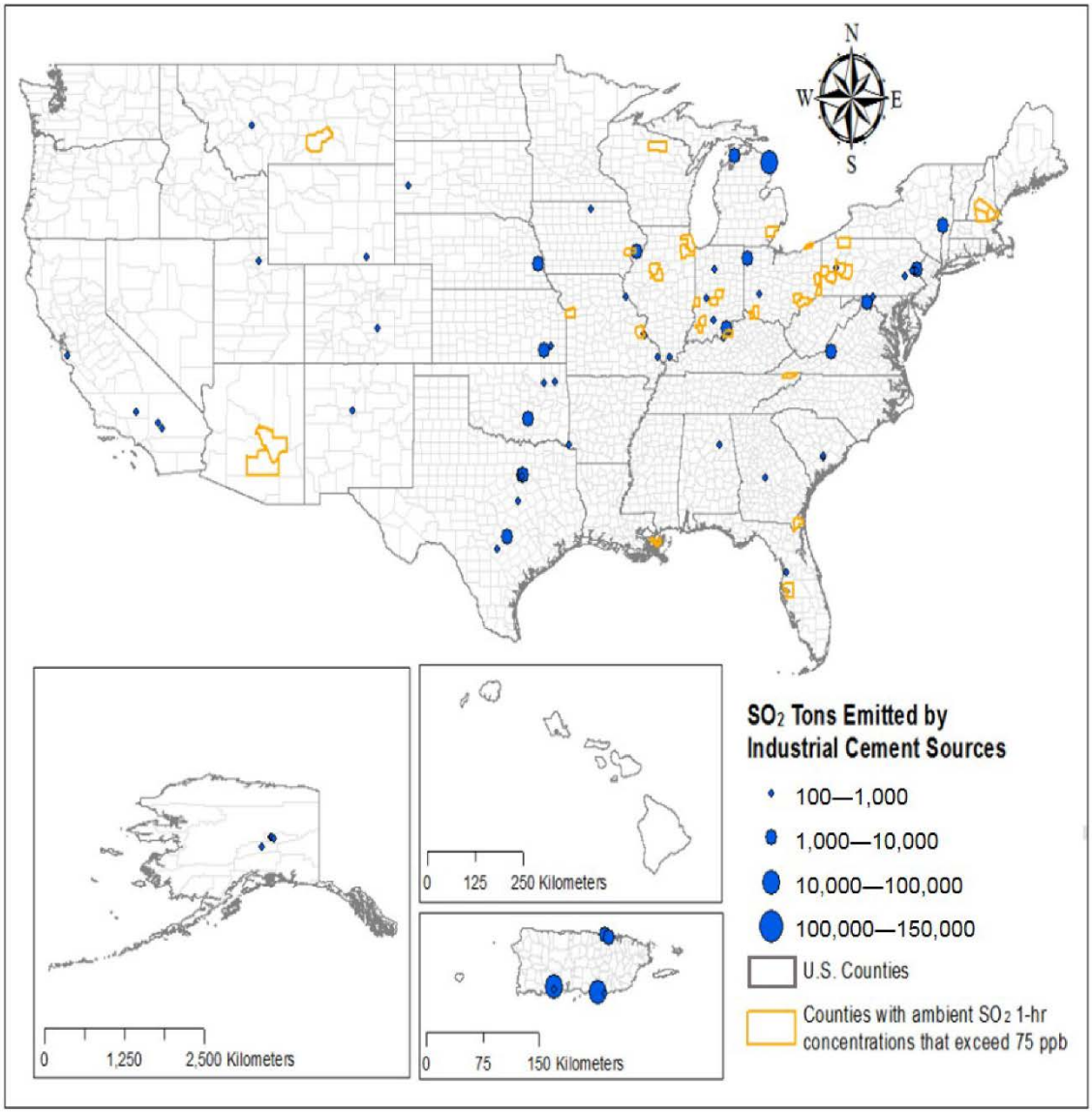


Figure 2-3(A) Distribution of sulfur dioxide (SO_2) emissions produced by (A) industrial cement production, and (B) industrial chemical and allied products manufacturing.

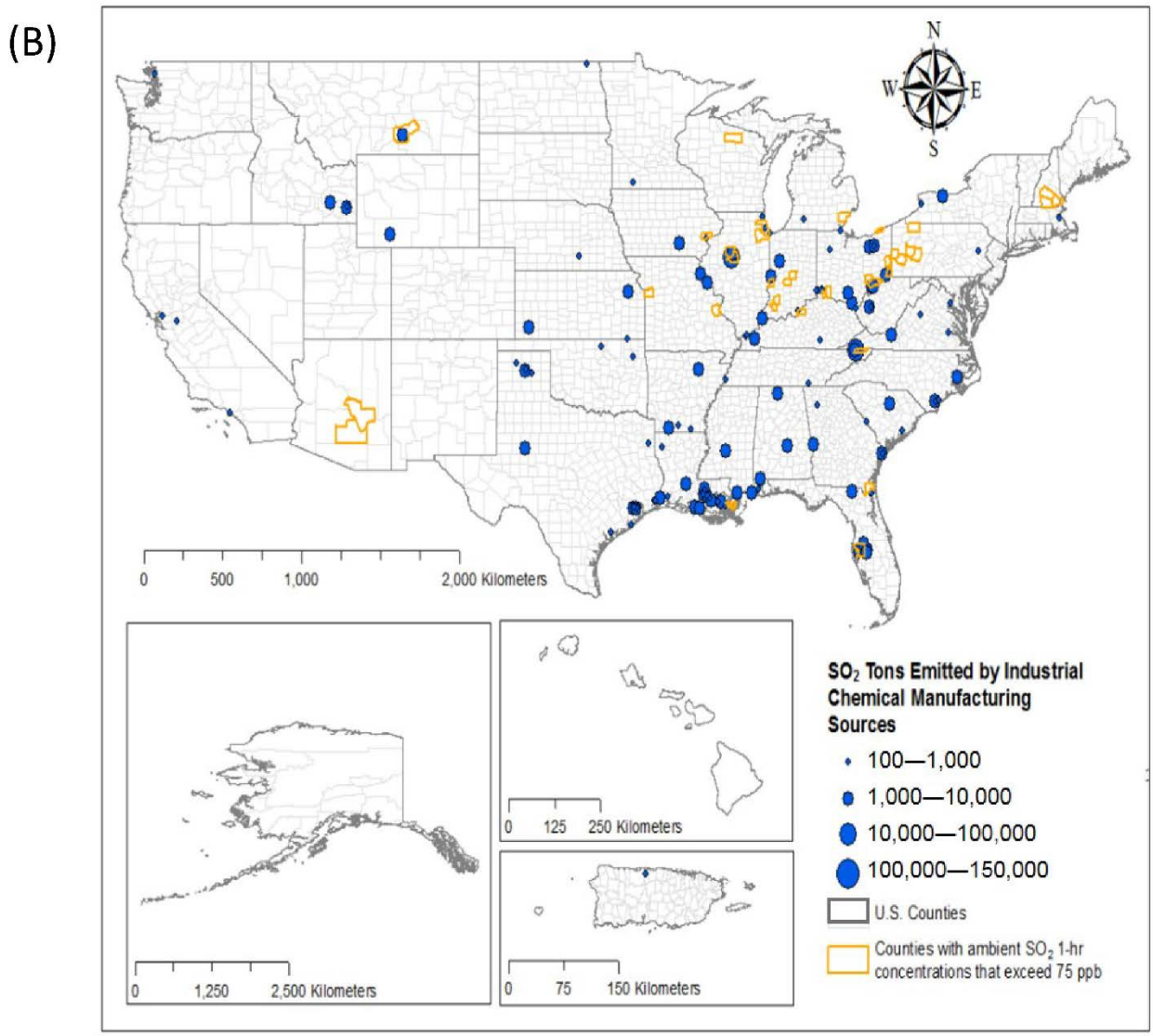
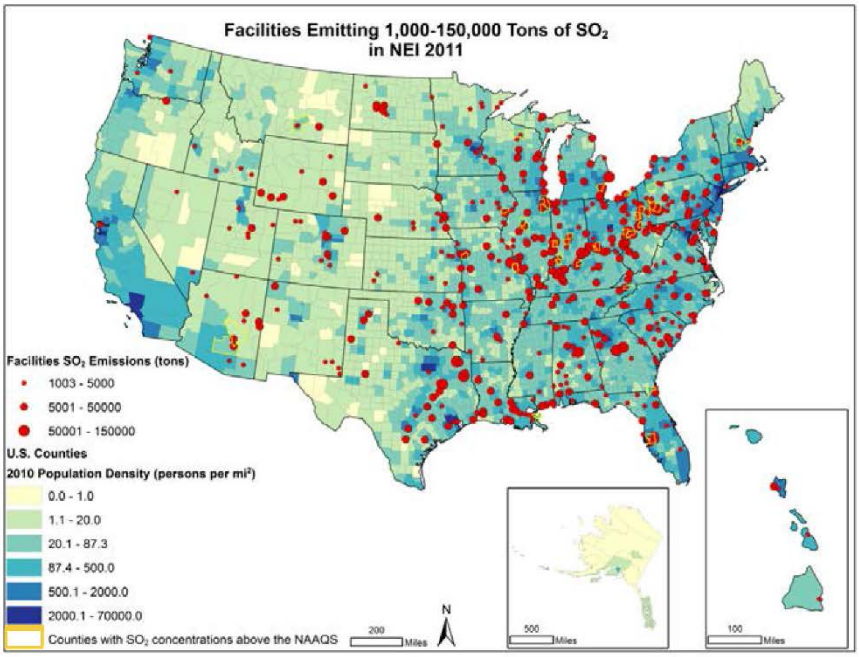


Figure 2-3(B) Distribution of sulfur dioxide (SO_2) emissions produced by (A) industrial cement production, and (B) industrial chemical and allied products manufacturing.

2.2.3 Sources by Facility

The preceding sections have shown SO_2 emissions by sector and source category, but these classifications are not especially helpful for assessing the size of complex point sources that may include more than one SO_2-emitting process. The Clean Air Act coined the term "major emitting facility" for more complex sources, defining these by the total potential emissions of the criteria pollutant (100 tons per year or greater for SO_2). In addition to fossil fuel-fired steam electricity plants, example facilities include coal cleaning plants, kraft pulp mills, Portland Cement plants, iron and steel mill plants, sulfuric acid plants, petroleum refineries, and chemical processing plants. Figure 2-4 shows the geographic distribution of major continental U.S. SO_2 emitting facilities, with an enlargement of the Midwest states including the Ohio River Valley, where a large number of these SO_2-emitting sources are located. All of the counties registering SO_2 concentrations above the current NAAQS level (75 ppb) are shown in association with sources with substantial SO_2 emissions.

(A)



Source: 2011 National Emissions Inventory

(B)

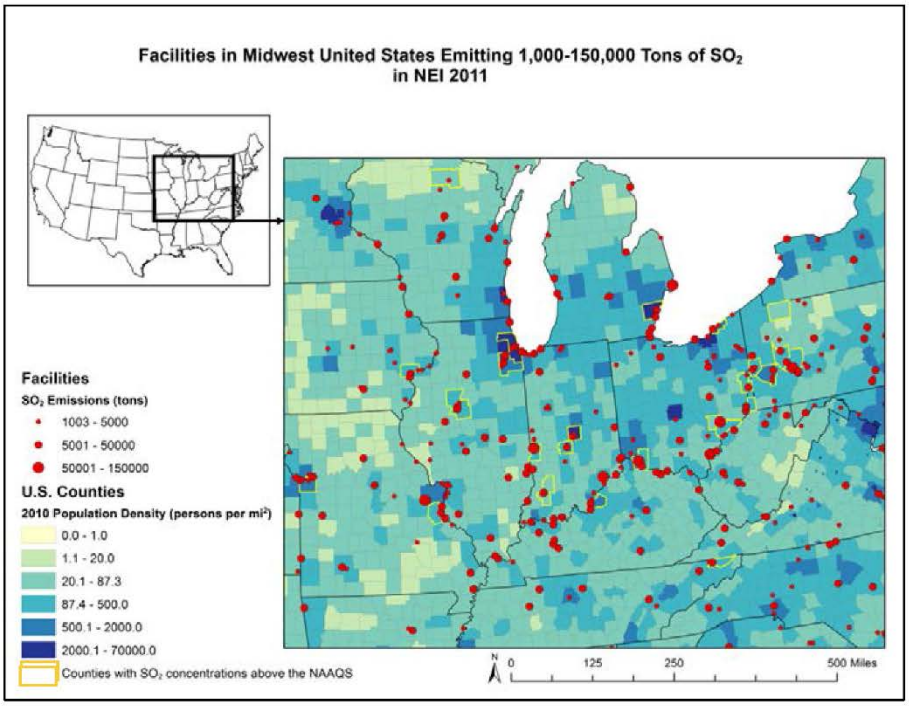
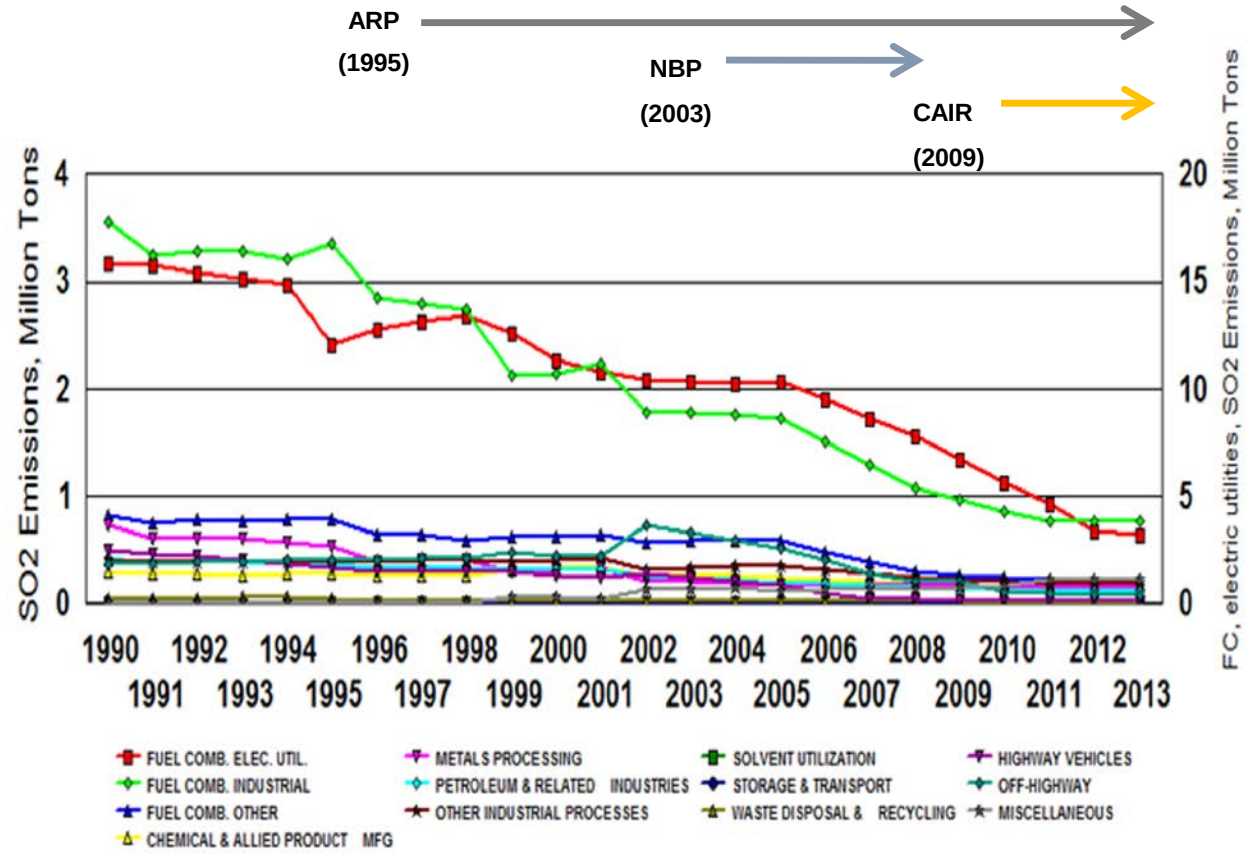


Figure 2-4 **Geographic distribution of (A) major continental U.S. sulfur dioxide (SO_2) emitting facilities, with (B) an enlargement of the Midwest states, including the Ohio River Valley, where a large number of these sources are concentrated (2011 National Emissions Inventory).**

2.2.4 U.S. Emission Trends

Anthropogenic missions of SO_2 in the U.S. have shown dramatic declines since the 1990 amendments to the Clean Air Act were enacted. Figure 2-5 shows the trend in SO_2 emissions since 1990 in relation to the timeline over which the Clean Air Act control programs [Acid Rain Program (ARP), NO_X Budget Program (NBP), and Clean Air Interstate Rule (CAIR)] were implemented. Table 2-1 gives the annual SO_2 emissions, percentage of the U.S. SO_2 emissions budget, and change in emissions rate since 2003 for the important emissions sectors listed in Figure 2-5.



ARP = Clean Air Act 1990 Acid Rain Program; NBP = NO_X Budget Program; CAIR = Clean Air Interstate Rule.
FC = fuel combustion.
The right axis applies to the red (upper) line, only.
Timeline adapted from U.S. EPA (2012b), Figure 1.

Figure 2-5 National sulfur dioxide (SO_2) emissions trends, by major emissions sector.

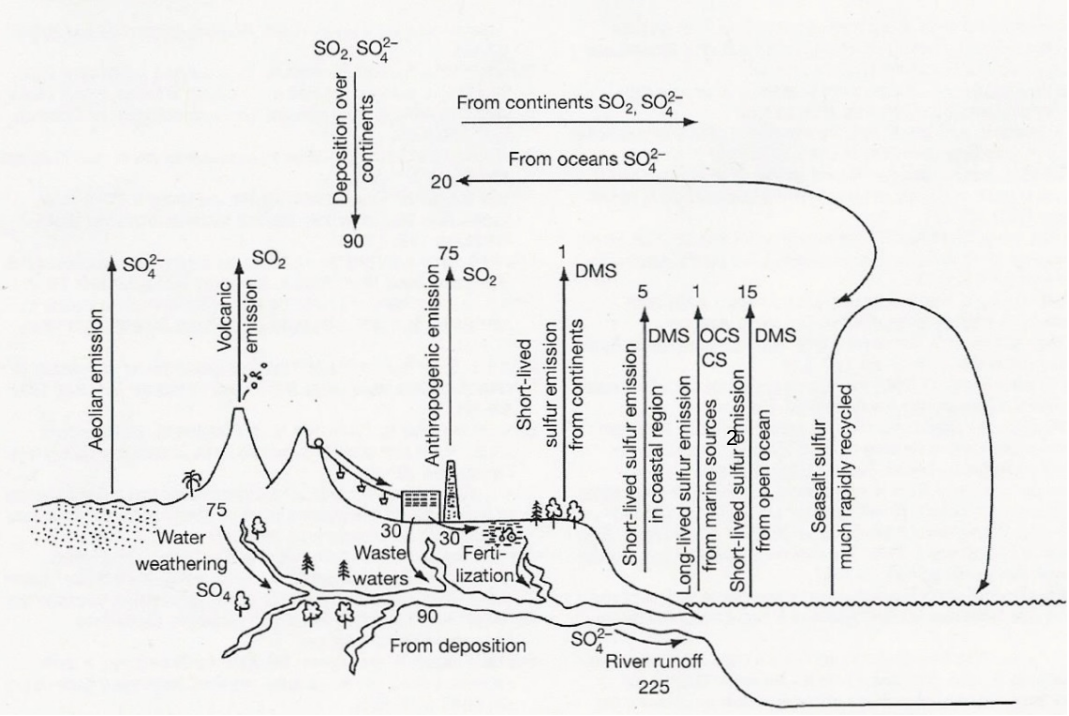
Table 2-1 Summary of 2013 EPA sulfur dioxide trends data for the major emissions sectors shown in Figure 2-5.

Source Type	Kilotons (2013)	Percentage of Total	Percent Change Since 2003
Electric Generating Units (all fuel types)	3,257	63	−68
Industrial (all fuel types)	763	15	−57
Chemical and allied product manufacturing	224	4	−61
Metal processing	126	2	−51
Petroleum and related industries	145	3	−28
Industrial processes	116	2	−51
Solvent utilization	186	4	−45
Highway vehicles	17	0.3	−37
Miscellaneous (fires, dust)	29	0.6	−88

2.2.5 Natural Sources

2.2.5.1 The Global Sulfur Cycle

The total budget for sulfur, in all its forms, at Earth's surface is on the order of 10^{10} Tg (S) (Schlesinger, 1997). The sulfur cycle, summarized in Figure 2-6, comprises the many chemical and biological processes that continuously interconvert the element among 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-}).



Note: Aeolian and volcanic emissions are highly uncertain and, therefore, not included. (1 Tg = 1.1 × 10^6 tons)
Source: Brimblecombe (2003).
CS_2 = carbon disulfide; DMS = dimethyl sulfide; OCS = carbonyl sulfide; SO_2 = sulfur dioxide; SO_4^{2-} = sulfate ion.

Figure 2-6 The global sulfur cycle, showing estimated fluxes (Tg/yr [S]) for the most important sulfur-containing compounds.

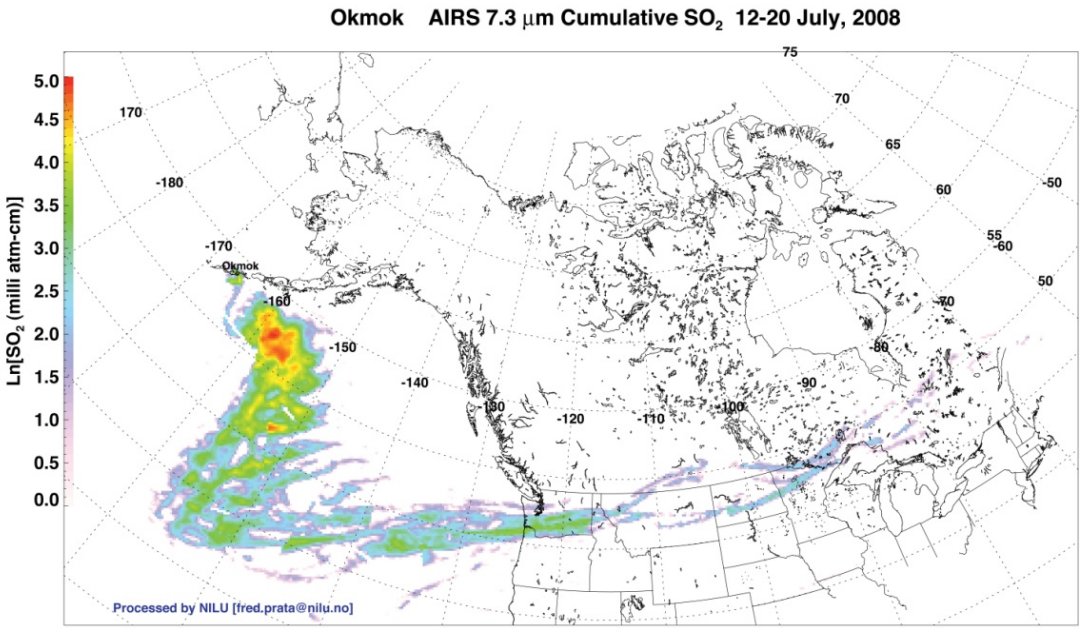
Nonbiological, natural sources of directly emitted atmospheric SO_2 include volcanoes and wildfire. With the exception of volcanoes, natural sources of reduced sulfur that subsequently oxidize in the atmosphere to form SO_2 are largely biological in nature. Under anaerobic conditions, various species of plants, fungi, and prokaryotes convert oxidized sulfur into its reduced forms (Madigan MT, 2006). Photosynthetic green and purple bacteria, and some chemolithotrophs oxidize sulfides to form elemental sulfur. Some species oxidize elemental sulfur to form sulfate and SO_2; others reduce elemental sulfur to sulfides (*dissimilative sulfur reduction*), while others are capable of reducing sulfate all the way down to sulfide (*dissimilative sulfate reduction*).

2.2.5.2 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 are therefore difficult to estimate (Simpson et al., 1999).

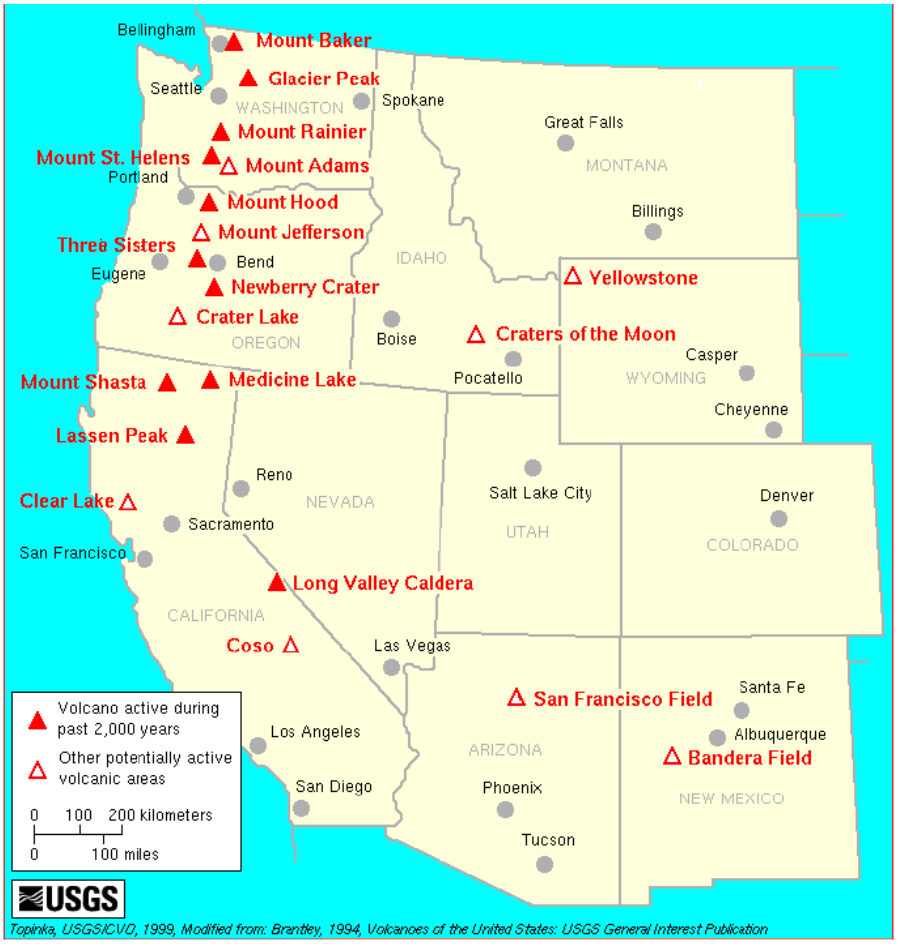
The western United States borders the North American tectonic plate, which is subject to ongoing volcanic activity due to subduction of the Pacific plate. The Aleutian volcanic arc, part of the state of Alaska, comprises 75 volcanic centers. Volcanoes in this chain have erupted once or twice per year, on average over the past 100 years with impacts on local communities (Power, 2013). Figure 2-7 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. 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 0.29 ± 0.01 Tg.



Source: NASA (2008a).

Figure 2-7 Image derived from data collected by the Atmospheric Infrared Sounder (AIRS) instrument aboard the NASA Aqua satellite during the July 12−20, 2008 eruption of the Okmok Volcano.

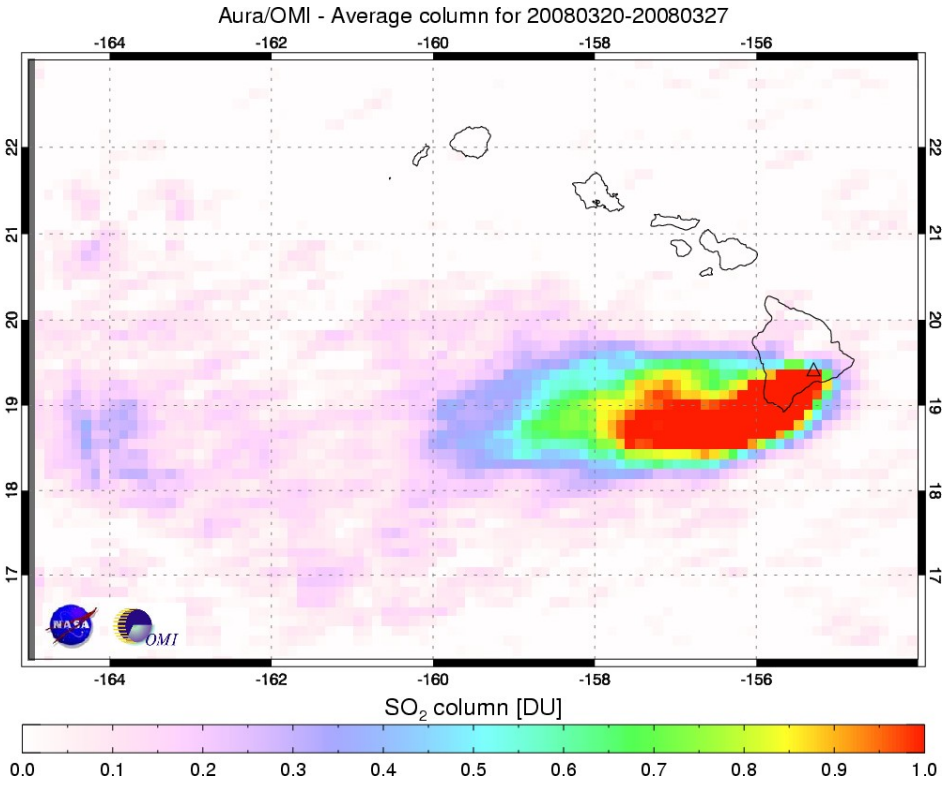
The line of volcanoes that begins with the Aleutian Islands in Alaska, and extends south and east through the states of Washington, Oregon, California, Arizona and New Mexico, with outlying geologically active sites in Idaho (Craters of the Moon) and Wyoming (Yellowstone). Figure 2-8 shows the geographic location and activity potential for these sites within the continental United States.



Source: USGS (1999).

Figure 2-8 Geographic location of volcanoes and other geologically active sites 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 2-9 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 due west, away from major populated areas.



Source: NASA (2008b).

Note: DU = Dobson Units which are 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.

Figure 2-9 NASA/Ozone Monitoring Instrument (OMI) image of the Kīlauea sulfur dioxide (SO_2) 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 the effective SO_2 lifetime as 1−2 days and Kīlauea's SO_2 emission rates as 9−21 kiloton/day.

Several modeling studies have been undertaken to estimate the global emissions of sulfur by volcanoes, arriving at an estimated range for SO_2 emissions of 109−288 Gmols/year (7−18.5 Tg/year) (Chin et al., 2000; Feichter et al., 1996; Pham et al., 1996; Langner and Rodhe, 1991).

2.2.5.3 Wildfires

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 for the U.S. at 0.16 Tg in the year 2000. Canadian fires emitted 0.11 Tg, and Mexican fires emitted 0.05 Tg of SO_2 for the same period. However, wildfire emissions do vary from year to year. The 2011 NEI (Version 1) estimate for wildfire emissions is 105,228 short tons (0.095 Tg). Emissions estimates for SO_2 derived from global modeling studies of wildfire range between 72−91 Gmols/year (4.6−5.8 Tg/year [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, estimates of future wildfire-related SO_2 emissions are highly uncertain, due to deficiencies in the available science 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 estimates for agricultural and prescribed burning emissions at 26,965 and 85,087 short tons (0.025 and 0.077 Tg), respectively.

2.2.6 Indirect Sources

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, i.e. 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 radical and nitrate radical (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 Gg(S)/yr.

Sources	OCS	CS_2	CH_3SH	DMS	DMDS
Seawater and marshes	317	243	4,738	28,187	213
Vegetation and soils		70	1,735	3,470	868
Volcanoes	11	17			
Atmospheric oxidation	463				
Biomass burning (all types)	46	1.84		6	119
Pulp and paper industry	97.2	78.5	1,680	1,462	273
Rayon/cellulosics manufacture		1,060	138	95.4	
Manure			330	660	660
Paddy fields	0.38	26.9	0.76	25	0.57
Pigment industry	74	205			
Food processing and waste	0.63			3.97	28.9
Gas industry	0.7		4.8	0.84	0.1
Wastewater	0.034	1.03	65	5.6	27
Aluminum industry	88	4			
Coal combustion	16.3	0.33			

Table 2-2 (Continued): Global sulfide emissions in Gg(S)/yr.

Sources	OCS	CS_2	CH_3SH	DMS	DMDS
Coke production	9	14			
Biofuel combustion	46.8	1.9			
Vehicles	6	0.3			
Shipping	30	1.5			
Tire wear	1.7	2.3			
Tire combustion	0.003	0.00006			
Landfill	0.079	0.19	0.34	0.26	0.008
Brick making		0.03			
Total global sources	**1,208**	**1,728**	**8,692**	**33,916**	**2,190**

1 Tg = 103 Gg; CH_3SH = methylmercaptan; CS_2 = carbon disulfide; DMDS = dimethyl disulfide; DMS = dimethylsulfide; OCS = carbonyl sulfide.

Adapted from Lee and Brimblecombe (2015).

2.2.6.1 Dimethyl Sulfide

Dimethyl sulfide has significant anthropogenic sources (pulp and paper production, agricultural operations), but these are dwarfed by the quantity emitted by natural biological activity. Dimethyl sulfide originates with the breakdown of dimethyl sulfoniopropionate, a metabolite of methionine, produced by marine organisms living in upwelling or coastal zones and by anaerobic bacteria in marshes and estuaries. Dimethyl sulfide is the main source of cloud condensation nuclei (CCN) in ocean environments, due to its rapid oxidation by OH and NO_3 radicals to form SO_2, followed by SO_4^{2-}, the main component of CCN. Accurate estimates of DMS production at the ocean surface are a critical input into the cloud models needed for calculating the radiative balance of the atmosphere, [e.g., for climate studies, but are difficult to achieve. Lee and Brimblecombe (2015)] provide a literature-derived global estimate of DMS emissions from seawater and marshland of 28 Tg (S)/yr (878 Gmols/year). Older estimates for seawater DMS emissions cover a wide range from 172 to 681 Gmols/year (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

2.3.1 Sulfur Oxide Species

The four known monomeric sulfur oxides are sulfur monoxide (SO), SO_2, SO_3, and S_2O. SO can be formed by photolysis of SO_2 at wavelengths in the ultraviolet range (less than 220 nm), above the stratospheric ozone layer (Pinto et al., 1989). SO_3 can be emitted from power plants and factories, but it reacts within seconds with water (H_2O) in the stacks or immediately after release into the atmosphere to form H_2SO_4. Of the four species, only SO_2 is present at concentrations significant for chemistry in the troposphere, boundary layer, and for human exposures.

Sulfur dioxide is primarily emitted directly from pollutant sources, but is also produced by the photochemical oxidation of reduced sulfur compounds such as dimethyl sulfide (DMS, CH_3-S-CH_3), H_2S, CS_2, OCS, methyl mercaptan (CH_3-SH), and dimethyl disulfide (DMDS, CH_3-S-S-CH_3), which are all mainly biogenic in origin.

Table 2-3 lists the atmospheric lifetimes (τ) of reduced sulfur species with respect to reaction with various oxidants. Except for OCS, a compound that is relatively inert in the troposphere and is mainly removed by photolysis in the stratosphere, all of these species are lost primarily by reaction with OH and NO_3 radicals.

Table 2-3 Atmospheric lifetimes of sulfur dioxide and reduced sulfur species with respect to reaction with hydroxyl (OH), nitrate (NO_3), and chlorine (Cl) radicals.

	OH		NO_3		Cl	
Compound	$k \times 10^{12}$[a]	τ	$k \times 10^{12}$	τ	$k \times 10^{12}$	τ
SO_2	1.6	7.2 days	$<7 \times 10^{-9}$	NR	NA	
CH_3-S-CH_3	6.7	2.3 days	1.1	1.1 h	530	29 days
H_2S	4.7	2.2 days	$<8 \times 10^{-4}$	NR	74	157 days
CS_2	1.2	9.6 days	$<4 \times 10^{-4}$	>116 days	$< 4 \times 10^{-3}$	NR
OCS	1.9×10^{-3}	17 yr	$<1 \times 10^{-4}$	>1.3 yr	$<1 \times 10^{-4}$	NR
CH_3-S-H	33	8.4 h	0.89	1.2 h	200	58 days
CH_3-S-S-CH_3	230	1.2 h	0.53	2.1 h	NA	

CH_3-S-CH_3 = dimethyl sulfide; CH_3-S-H = methyl mercaptan; CH_3-S-S-CH_3 = dimethyl disulfide; Cl = chlorine radical; CS_2 = carbon disulfide; H_2S = hydrogen sulfide; k =reaction rate constant; NA = not available; NO_3 = nitrate radical; NR = not reported; OCS = carbonyl sulfide; OH = hydroxyl radical; SO_2 = sulfur dioxide.

[a]The units of *k* vary depending on the order, i.e., first, second, tertiary, of the reaction.

Reaction with NO_3 radicals at night most likely represents the major loss process for DMS and methyl mercaptan. However, the mechanisms for the oxidation of DMS are not completely understood. Initial attack by NO_3 and OH radicals involves H atom abstraction, with a smaller branch leading to OH addition to the S atom. The smaller OH addition branch increases in importance as temperatures decrease, becoming the major pathway below temperatures of 285 K (12°C) (Ravishankara et al., 1997). The adduct may either decompose to form methane sulfonic acid (MSA) or undergo further reactions in the main pathway to yield dimethyl sulfoxide (Barnes et al., 1994). Following H atom abstraction from DMS, the main reaction products include MSA and SO_2. Oxidation of DMS by bromine oxide (BrO) produces dimethyl sulfoxide [$(CH_3)_2SO$] (Toumi, 1994; Barnes et al., 1991), and oxidation by atomic chlorine leads to formation of SO_2 (Keene et al., 1998). $(CH_3)_2SO$ and SO_2 are precursors for methanesulfonic acid (CH_3SO_3H) and H_2SO_4, respectively. In the marine boundary layer (MBL), virtually all H_2SO_4 and CH_3SO_3H vapor condenses onto existing aerosols or cloud droplets, thereby contributing to aerosol growth and acidification. Based on global-scale, three-dimensional modeling, Long et al. (2013) suggested that reaction of BrO with DMS could add approximately 40% to the DMS loss rate.

The ratio of MSA to SO_2 is strongly temperature dependent, varying from about 0.1 over tropical waters to about 0.4 over Antarctic waters (Seinfeld and Pandis, 1998). Excess sulfate (i.e., over that expected from the sulfate in sea water) in marine aerosol is related mainly to the production of SO_2 from the oxidation of DMS. Sulfur dioxide can be oxidized either in the gas phase or, because it is soluble, in the aqueous phase in cloud drops.

2.3.2 Gas Phase Oxidation of Sulfur Dioxide

Sulfur exists in its S(IV) oxidation state in SO_2. In the atmosphere, SO_2 is oxidized further to form SO_3, taking the sulfur atom from the S(IV) to S(VI) oxidation state. The gas-phase oxidation of SO_2 by OH involves two steps. The first step takes SO_2 to bisulfite ion (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).

As indicated in Table 2-3, the rate coefficient for the reaction between SO_2 and NO_3 is too low to be of importance as an oxidation mechanism. The same is true for the reaction between SO_2 and the hydroperoxyl (HO_2) radical (Sander et al., 2011). Rate coefficients for the reaction of stabilized Criegee intermediates with SO_2 span a wide range from an upper limit of 4×10^{-15} cm^3/second (Johnson et al., 2001) to approximately 3.5×10^{-11} (Liu et al., 2014b) or 3.9×10^{-11} cm^3/second (Welz et al., 2012). Earlier investigations [e.g., (U.S. EPA, 1985; Atkinson and Lloyd, 1984)], which were largely indirect measurements, reported much lower values, 7×10^{-14} and 7×10^{-12} cm^3/second, respectively. Although some of the more recent determinations report rate coefficients

greater than 3×10^{-11} cm^3/second, Berndt et al. (2012) derived a range of (0.9 to 7.7) $\times 10^{-13}$ cm^3/second, well within the range of those given by Atkinson and Lloyd (1984) and U.S. EPA (1985).

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, in particular biogenic alkenes, such as terpenoids emitted by trees.

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.

$$SO_3 + H_2O \rightarrow H_2SO_4$$

Equation 2-4

Because H_2SO_4 is extremely water soluble, it will be removed rapidly by dissolution into the aqueous phase of aerosol particles and cloud droplets.

2.3.3 Aqueous 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 reacts with water. Both exist in the S(IV) oxidation state, which readily oxidizes in the presence of particle 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 copper 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., (Jacobson, 2002; Jacob, 1999; Seinfeld and Pandis, 1998)]. 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 can be summarized as follows (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 sulfate ion (SO_4^{2-}):

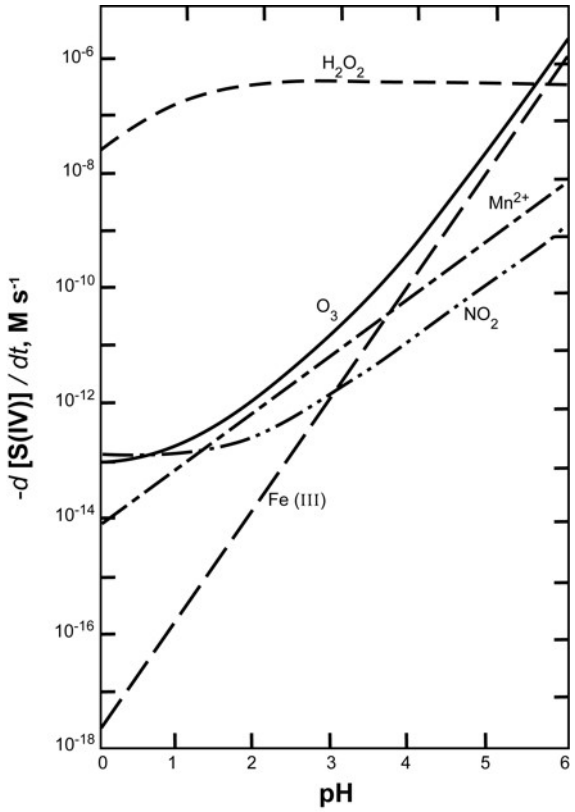
$$HSO_3^- + H_2O_2 + H^+ \Leftrightarrow SO_4^{2-} + H_2O + 2H^+$$

Equation 2-7

The rates of aqueous phase oxidation of S(IV) to S(VI) as a function of pH are shown in Figure 2-10. 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 vapor (NH_3) readily dissolves in acidic cloud drops to form ammonium ion (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.

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).



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 (1998).

Figure 2-10 The effect of pH on the rates of aqueous-phase S(IV) oxidation by various oxidants.

In the same way that SO_2 is removed from the gas-phase by dissolution into cloud droplets, it can be removed by depositing (dry deposition) onto wet surfaces. 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).

2.4 Measurement Methods

This section discusses the federal reference and equivalency methods used for NAAQS compliance as well as the state, local, and tribal monitoring networks across the U.S.

2.4.1 Federal Reference and Equivalency 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, a federal equivalent method (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. The UVF method was added as a FRM as a result of the new 1-hour SO_2 primary NAAQS established in 2010 (75 FR 35520 June 22, 2010). 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 is still sound and 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 some energy, first, by collision with another gas molecule and, then, emits a photon of light at a longer wavelength, to return 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 nanometers [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 photomultiplier tube (PMT) 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 PMT to filter out any stray light from the UV lamp. A lens is located between the filter and the PMT 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.

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 2-4. 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 detectable limit for a routine, automated SO_2 analyzer is required to be 0.002 ppm (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. These new trace-level instruments have detection limits of 0.2 ppb or lower.

Table 2-4 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	± 0.005 ppm (5 ppb)
Total, all interferents	----
Zero drift (12 and 24 h)	±0.004 ppm (4 ppb)
Span drift (24 h)	
20% of upper range limit	----
80% of upper range limit	±3.0%
Lag time	2 min
Rise time	2 min
Fall time	2 min
Precision	
20% of upper range limit	2.0%
80% of upper range limit	2.0%

ppb = parts per billion; ppm = parts per million.

2.4.2 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, etc.), and the 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 cc/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 photomultiplier tube (PMT) is specifically designed to prevent detection of NO fluorescence at the PMT. 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 PMT 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 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.

2.4.3 Other 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 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 seconds. 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 detection limit of 0.5 ppb. Both the tunable and nontunable instruments have low limits of detection ($\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 the

measurement of SO_2. At an absorption wavelength of 308 nm, the CRDS had a detection limit of 3.5 ppb, which was lower 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 UVF methods (a few seconds vs. 80 seconds). 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. 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 do not directly measure pollutant concentration but rather 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) SO_2 absorption occurs at shorter wavelengths that coincide with stronger ozone absorption so that only large SO_2 sources can be observed 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 and smelters), 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; Fioletov et al., 2011; Nowlan et al., 2011; Bobrowski et al., 2010; Li et al., 2010; Khokhar et al., 2008;

Carn et al., 2007). Remote sensing techniques have potential use in targeted applications (e.g., near-source monitoring), and validation of these methods against ground-based and aircraft measurements is ongoing.

2.4.4 Ambient Sampling Network Design

Compliance with NAAQS is primarily carried out through the State and Local Air Monitoring Stations (SLAMS) network, although modeling may also be used to characterize air quality for implementation purposes (75 FR 35520). There are approximately 400 monitors reporting 1-hour SO_2 concentrations to EPA's Air Quality System (AQS). In addition to their use in compliance evaluations, some of these monitors function as central site monitors 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) or all twelve 5-minute average SO_2 concentrations within the hour. The number of monitors reporting 5-minute continuous SO_2 concentrations increased dramatically from 2 to 195 monitors in 2009 and 2012, respectively. The SLAMS network includes the NCore monitoring network, which began January 1, 2011 and consists of about 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 that data with respect to the NAAQS. The Clean Air Status and Trends Network also measures ambient SO_2; however, these data are not used for NAAQS compliance purposes. This network provides weekly averages of total sulfur (dry SO_2, dry sulfate, and wet sulfate) in about 90 sites located in or near rural locations to assess long-term trends in acidic deposition due to emission reduction programs. Figure 2-11 shows the locations of these monitoring networks across the U.S.

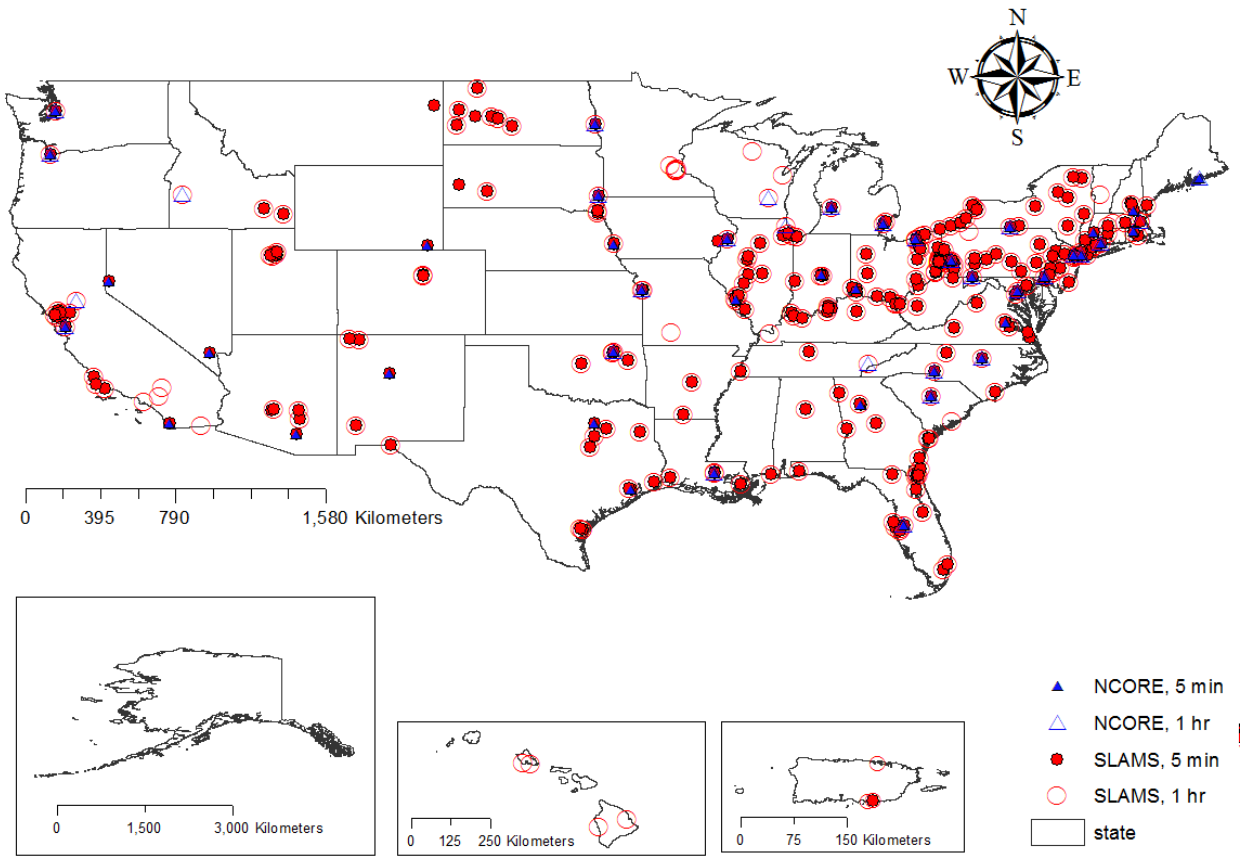


Figure 2-11 Routinely operating sulfur dioxide monitoring networks.

2.4.4.1 Minimum Monitoring Requirements

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

Urban-scale monitors 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 areas of tens to hundreds of kilometers, which are 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, and peak concentrations normally occur near the source of origin. Prior to the revised SO_2 primary NAAQS in 2010, 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, 2009c). To address this deficiency, 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 monitors in a given CBSA. 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 persons-tons per year. A minimum of three SO_2 monitors 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 monitors is required. Lastly, a minimum of one SO_2 monitor 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 monitors in a given state, which is based on the state's contribution to the national SO_2 emissions inventory. This requirement was designed to offer some flexibility in monitor placement, either inside or outside of a CBSA, independent of the PWEI criteria. Additionally, all monitors in the network must be placed at locations where maximum peak hourly SO_2 concentrations are anticipated. Monitors 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 monitor is located in a CBSA that

meets the aforementioned requirements based on the PWEI criteria, that monitor can count towards the minimum monitoring requirements.

2.4.4.2 Siting Criteria for Probe and Monitoring Path

A number of criteria for probe and monitoring path siting are required for SLAMS and NCore sites as specified in 40 CFR Part 58, Subpart G, Appendix E. These criteria are discussed below.

2.4.4.3 Horizontal and Vertical Placement

The probe, or at least 80% of the monitoring path, must be located between 2 and 15 m above ground level (AGL) for all SO_2 monitoring sites. Additionally, the probe, or at least 90% of the monitoring path, must be positioned at least 1 m (vertically or horizontally) from any supporting structure, walls, parapets, penthouses, etc., and away from dusty or dirty areas. If the probe, or a significant portion of the monitoring path, is located near the side of a building, it should be located on the windward side relative to the prevailing wind direction during the season of highest concentration potential for the SO_2 measurement.

2.4.4.4 Spacing from Minor Sources

Local minor sources of a primary pollutant such as SO_2 can heighten concentrations of that particular pollutant at a monitoring site. If the site objective is to investigate local primary pollutant emissions, then the site should be located where the spatial and temporal variability in these emissions can be captured. This type of monitoring site would likely be the microscale type. If a monitoring site is to be used to determine air quality over a much larger area, such as a neighborhood or city, a monitoring agency should avoid placing a monitor probe, path, or inlet near local, minor sources. The plume from the local minor sources should not be allowed to inappropriately influence the air quality data collected. To reduce these potential interferences, the probe, or at least 90% of the monitoring path, must be placed away from furnace flues, incineration flues, or other minor sources of SO_2. The separation distance should take into account the heights of the flues, type of waste or fuel burned, and the sulfur content of the fuel.

2.4.4.5 Spacing from Obstructions

Buildings and other obstacles can scavenge SO_2 and restrict airflow for any pollutant. To avoid this interference, the probe, inlet, or at least 90% of the monitoring path must (1) be located away from obstacles at a distance of at least twice the height of the obstacle and (2) have unrestricted airflow in an arc of at least 180° and the arc must include the predominant wind direction for the season of highest SO_2 concentrations. An exemption can be made for measurements taken in street canyons or at near-source sites where buildings and other structures are unavoidable.

Special consideration must be made for the use of open-path analyzers as they are inherently more sensitive to certain types of interferences or optical obstructions (e.g., trees, brush, buildings, plumes, dust, rain, particles, fog, snow, obstructions that may be moved by wind, human activity, growth of vegetation, etc.). Any temporary obstructions that are of sufficient density to obscure the light beam will affect the ability of the open-path analyzer to measure SO_2 concentrations continuously. Temporary, but significant, obscuration of especially longer measurement paths could occur because certain meteorological conditions (e.g., heavy fog, rain, snow) and/or because aerosol levels are of sufficient density to prevent the analyzer's light transmission. Measures can be implemented to compensate for these obstructions (e.g., shorter path lengths, higher light source intensity) and ensure data recovery during periods when greatest primary pollutant potential could be compromised.

2.4.4.6 Spacing from Trees

Trees can provide surfaces for SO_2 adsorption or reactions and surfaces for particle deposition. Trees can also act as obstructions if they are located between the air pollutant sources or source areas and the monitoring site, and if they have sufficient height and leaf canopy density to interfere with normal airflow around the probe, inlet, or monitoring path. To reduce possible interference, the probe, inlet, or at least 90% of the monitoring path must be at least 10 meters or further from the drip line of trees. For microscale sites, trees or shrubs should not be located between the probe and the source under investigation, such as a roadway or a stationary source.

2.5 Environmental Concentrations

This section provides an overview of SO_2 ambient and background concentrations as well as copollutant correlations with SO_2. SO_2 data discussed in this section were obtained from the AQS, EPA's repository for detailed air pollution data that is subject to quality control and assurance procedures. 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. Background SO_2 concentrations from natural sources are subsequently discussed in Section 2.5.4. Lastly, temporal correlations between SO_2 and other NAAQS copollutants are 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 2.4.4, hourly and 5-minute concentration data are routinely reported to 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 2-5 provides information on how different SO_2 metrics are derived. Two common daily metrics are the daily average SO_2 concentration (i.e., 24-hour average) and the daily 1-hour maximum (1-hour maximum) SO_2 concentration. Hourly metrics include (1) the 5-minute maximum concentration reported during a given hour and (2) the 1-hour average concentration. The averaging time used to construct SO_2 metrics can represent different exposure scenarios or windows. For example, while average daily metrics (24-hour average) represent overall concentration during a given day, metrics derived using maximum concentration statistics (i.e., 1-hour maximum or 5-minute maximum) provide insight to peak ambient concentration levels 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 averaging time when comparing the magnitude and range of ambient concentrations related to different metrics.

Table 2-5 Summary of sulfur dioxide (SO_2) metrics and averaging times.

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

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

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.

2.5.2.1 Nationwide Spatial Variability

In the previous Integrated Science Assessment of Sulfur Oxides (U.S. EPA, 2008b), daily (24-hour average, 1-hour maximum) and hourly (1-hour average) SO_2 concentrations measured at AQS monitoring sites during 2003−2005 were reported. Nationwide statistics of 5-minute maximum SO_2 data were not reported in the previous assessment due to a lack of monitors reporting such data. From 2003−2005, nationwide, central statistics (mean and median) of daily 1-hour maximum and 24-hour average 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 daily 1-hour maximum concentrations (99th percentile: 116 ppb). In addition, concentrations of 1-hour average SO_2 exhibited low mean concentrations (4 ppb), with 99th percentile values near 34 ppb. Relatively high concentrations were typically observed at sites near major stationary anthropogenic sources (e.g., electric generating units).

Similar statistics were computed for more recent AQS SO_2 monitoring data reported during 2010−2012. AQS SO_2 data used to compute national statistics meet the data quality and completeness criteria listed in Table 2-6. Based on these criteria, statistics

were computed for data from a total of 309 monitors across the U.S. for 5-minute maximum SO_2 concentrations and for data from a total of 337 monitors for the remaining daily (1-hour maximum, 24-hour average) and hourly (1-hour average) SO_2 metrics.

Table 2-6 Summary of sulfur dioxide data sets originating from the Air Quality System database.

Years	2010−2012
Months	January−December Except during 2010
Completeness criteria	75% of hours in day
	75% of days in calendar quarter
	All 4 quarters of the yr
Number of monitors meeting completeness criteria	309 monitors reporting 5-min data (2010−2012) 337 monitors reporting 1-h data (2010−2012)

Five-minute data is only available for 3rd and 4th quarter during 2010.

As expressed in Table 2-7, more recent, nationwide concentrations are similar, but slightly lower than concentrations reported in the 2008 SO_X ISA (U.S. EPA, 2008b). For all daily (24-hour average, 1-hour maximum) and hourly (5-minute maximum, 1-hour average) metrics, mean and median statistics are below 15 ppb, while SO_2 concentrations in the upper range of the distribution (99th percentile) cover a wide range of values and can be greater than the primary NAAQS level of 75 ppb. Across all metrics, large differences are observed between mean and 99th percentile concentrations, particularly among SO_2 metrics representing maximum, daily, and hourly concentrations (1-hour maximum, 5-minute maximum). Such large differences between mean and 99th percentile values are consistent with the highly variable nature of SO_2, which is characterized by periodic peak concentrations superimposed on a relatively low background concentration.

Table 2-7 National statistics of sulfur dioxide concentrations (parts per billion) from Air Quality System monitoring sites during 2010−2012.

Year	N of Obs	Mean	5	10	25	50	75	90	95	98	99	AQS Max ID[a]
5-min max												
2010	955,660	3	0	0	0	1	3	7	11	24	41	51390006
2011	2,555,841	3	0	0	0	1	3	6	10	19	32	490110004
2012	2,557,263	2	0	0	0	1	2	5	8	16	27	40071001
2010−2012	6,068,764	3	0	0	0	1	2	5	9	19	31	51390006
1-h avg												
2010	2,844,021	3	0	0	0	1	2	5	8	15	24	150010007
2011	2,845,106	2	0	0	0	1	2	4	7	12	20	150010007
2012	2,840,900	2	0	0	0	1	2	4	6	11	18	150010007
2010−2012	8,530,027	2	0	0	0	1	2	4	7	13	21	150010007
1-h max												
2010	120,845	11	0	0	1	3	7	18	31	67	125	150010007
2011	121,000	8	0	0	1	3	7	15	27	55	88	150010007
2012	120,991	8	0	0	1	2	5	13	25	56	105	150010007
2010−2012	362,836	9	0	0	1	3	6	15	28	59	105	150010007
24-h avg												
2010	120,845	3	0	0	0	1	3	5	8	15	25	150010007
2011	121,000	2	0	0	0	1	2	5	7	12	18	150010007
2012	120,991	2	0	0	0	1	2	4	6	12	22	150010007
2010−2012	36,836	2	0	0	0	1	2	5	7	13	21	150010007

AQS = Air Quality System; avg = average; max = maximum; N = population number; Obs = observations.
[a]AQS site ID number reporting the highest 3-year concentration across the U.S.

Focusing on the distribution of daily 1-hour maximum SO_2 concentrations, the absolute highest value is greater than 7,000 ppb (7,131 ppb). This extremely high value is reported at a site near an active volcano in Hawaii (Table 2-7, Figure 2-12). Other sites reporting relatively high 99th percentile, 1-hour maximum values (greater than 200 ppb) occur at sites near industrial or combustion sources in Tennessee, New Hampshire, Arizona, Indiana, and Louisiana. However, as shown in the nationwide map in Figure 2-12, the majority of monitoring sites across the U.S. report 99th percentile, 1-hour maximum concentrations below the primary NAAQS level of 75 ppb.

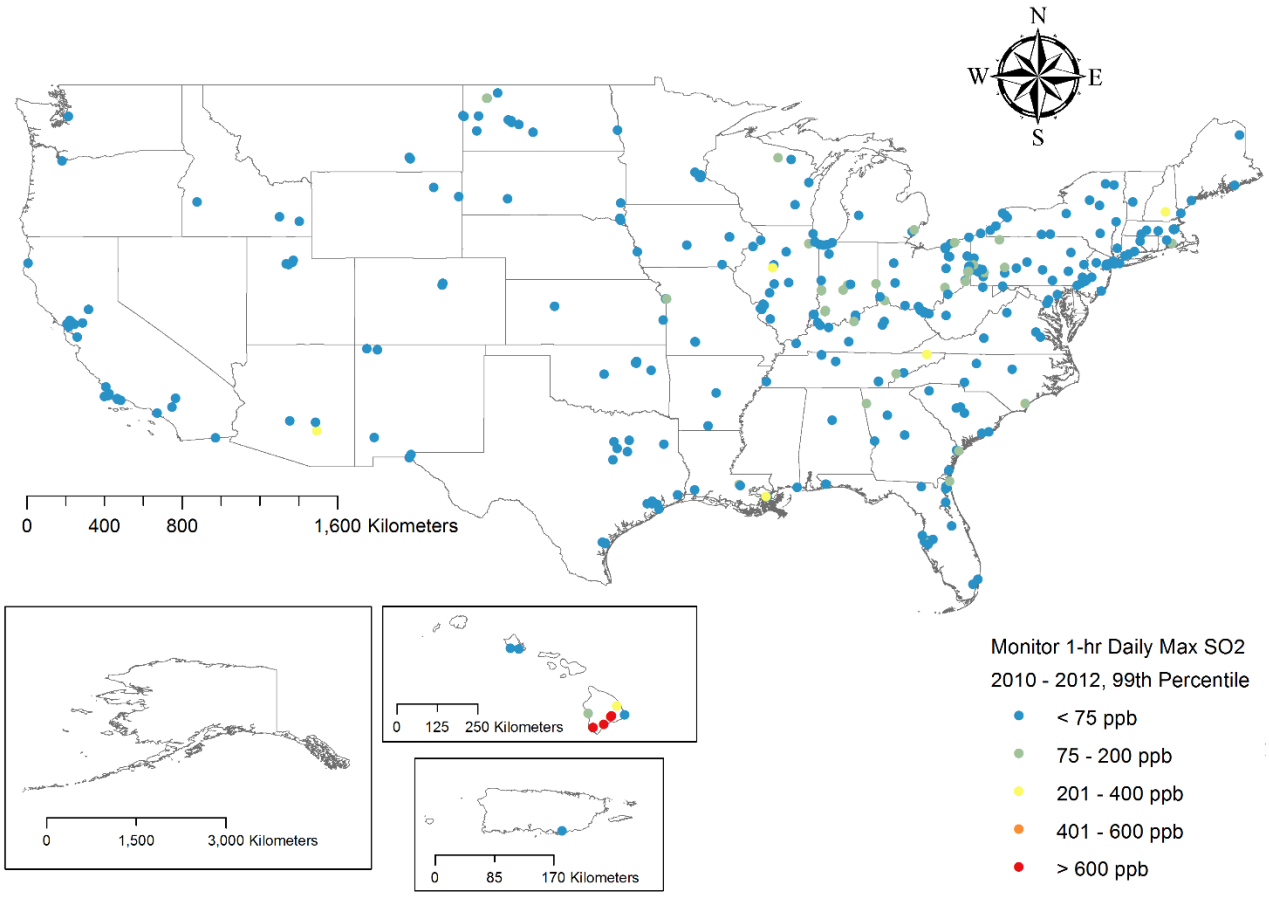


Figure 2-12 Map of 99th percentile of daily 1-h max sulfur dioxide (SO_2) concentration reported at Air Quality System monitoring sites during 2010−2012.

On a national scale, the east-to-west gradient in SO_2 emissions discussed in Section 2.2 corresponds to the higher SO_2 concentrations observed in the eastern portion of the contiguous U.S. (Figures 2-12 and 2-13). The highest SO_2 concentrations are reported in the Ohio River Valley, adjacent to many industrial and power plant facilities. In this area, several monitors in eastern Ohio and western Pennsylvania report 99th percentile, 1-hour maximum concentrations above 75 ppb. Lower SO_2 concentrations are generally reported in the western U.S., where only a small subset of monitors report 1-hour maximum concentrations above 75 ppb. These low concentrations reflect fewer SO_2 sources in the western U.S. in comparison to the eastern U.S., where the vast majority of high-emitting SO_2 sources are located (Figure 2-4).

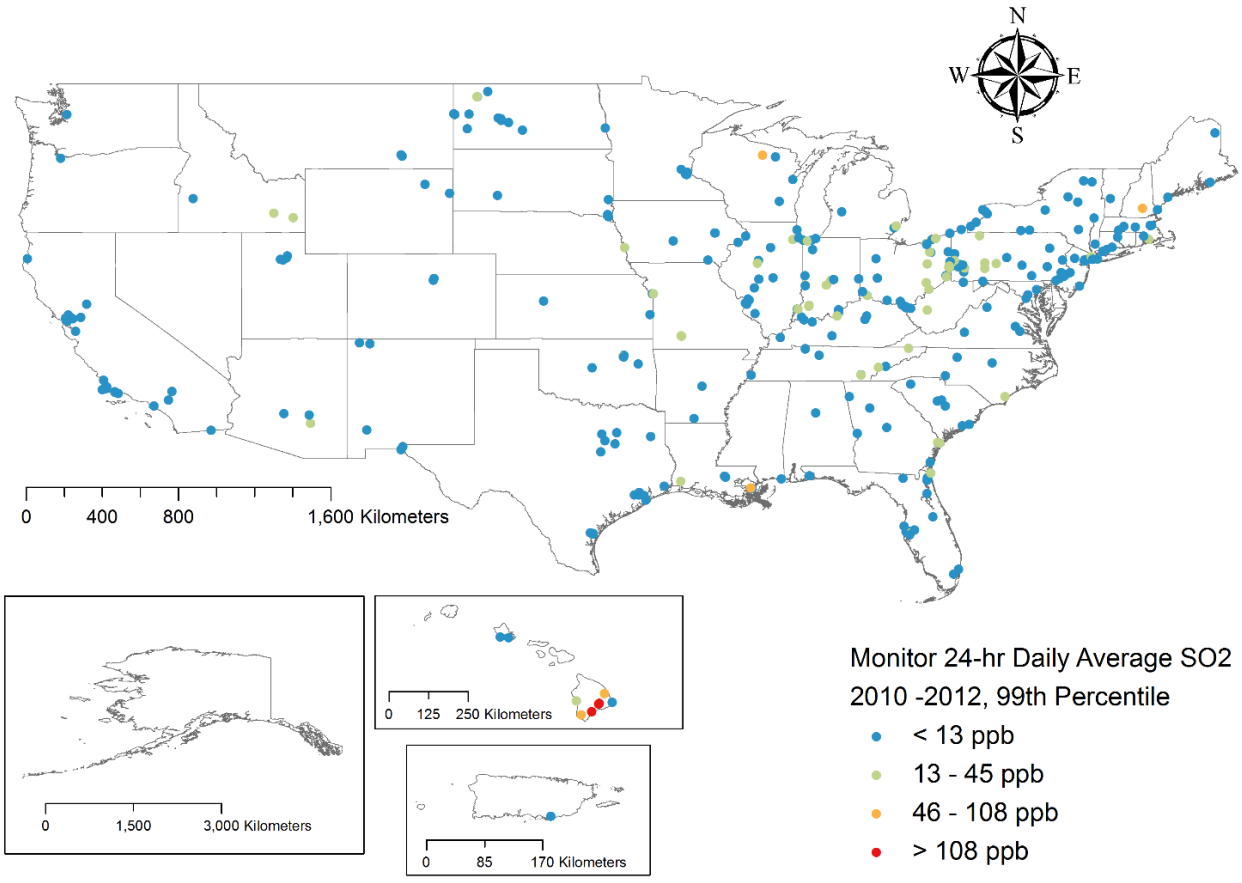


Figure 2-13 Map of 99th percentile of daily 24-h avg sulfur dioxide (SO_2) concentration reported at Air Quality System monitoring sites during 2010−2012.

2.5.2.2 Urban Spatial Variability

Air quality measurements from centrally located, urban monitors 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 large geographical scales. This variation may in turn introduce exposure misclassification and error into a health study (Section 3.3.3.2). The degree of exposure error associated with central site estimates strongly depends on the spatial variability of the pollutant of concern. When utilizing central site estimates for exposure assessment, pollutants with high spatial variability are subject to more exposure error than pollutants that are spatially homogenous across an urban area (Goldman et al., 2010).

To examine the potential for exposure error (due to spatial variability) in health studies, SO_2 spatial variability was characterized in six CBSA/metropolitan focus areas: Cleveland, OH; Pittsburgh, PA; New York City, NY; St. Louis, MO; Houston, TX; and Payson/Phoenix, AZ. These focus areas were selected based on (1) their relevance to current health studies (i.e., areas with peer-reviewed, epidemiologic analysis), (2) high monitor density (four or more monitors located within area boundaries), and (3) the presence of several diverse SO_2 sources within a given CBSA/metropolitan focus area boundary.

Maps of individual CBSA/metropolitan focus areas indicating monitor and point source locations are presented in Figures 2-14−2-19. For each map, CBSA, county, and city limit boundaries are included to provide spatial orientation. As shown by the maps, up to 10 SO_2 monitoring sites are located in individual CBSA/metropolitan focus areas, with most areas having less than six monitors. Monitors in each CBSA/metropolitan focus area are located within various distances of SO_2 sources. Around each monitor, buffer zones up to 15 km are marked to indicate nearby sources. Due to the relatively short atmospheric lifetime of SO_2 (Table 2-3), monitors within 15 km of large point sources (e.g., electric generating units, industrial sources, copper smelting facilities, shipping ports) are expected to experience the greatest impact from source emissions.

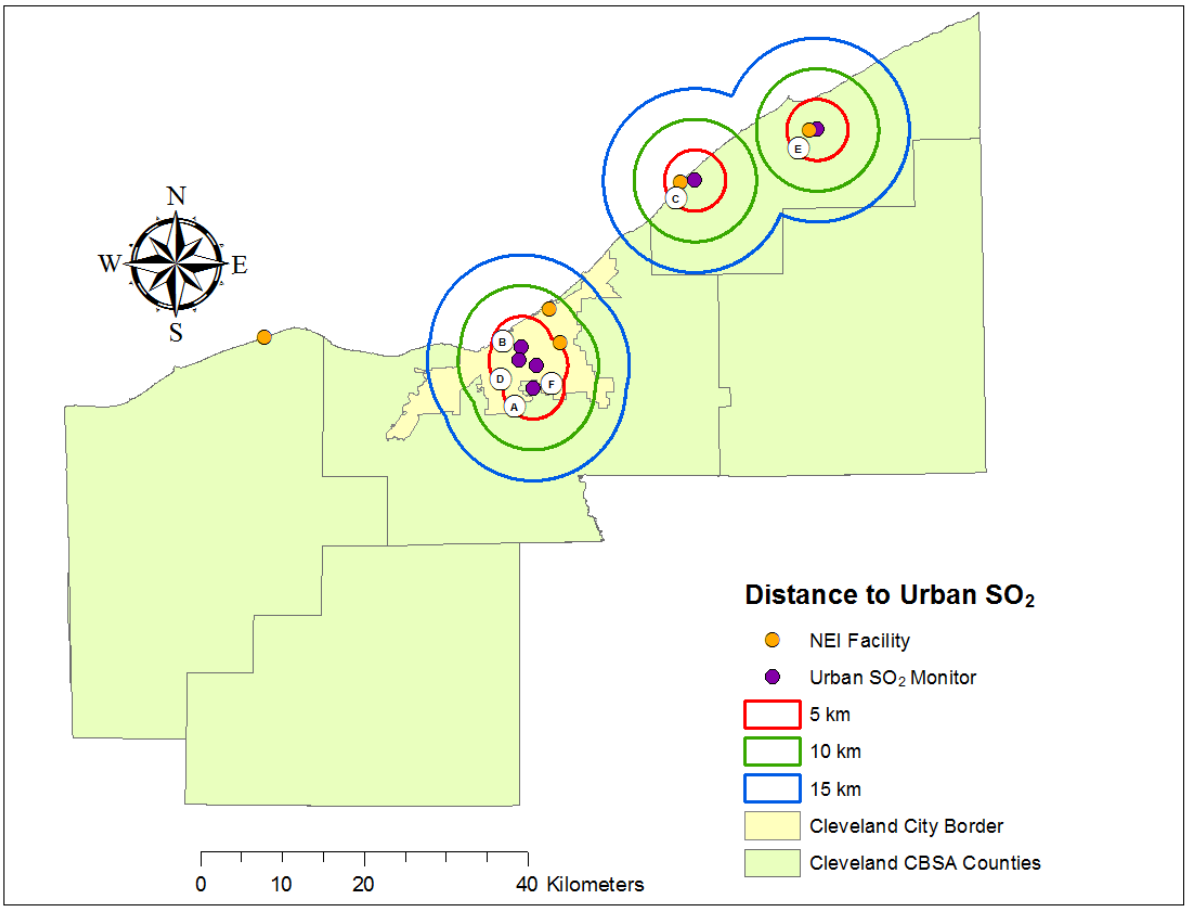


Figure 2-14 Map of Cleveland, OH Core-based Statistical Area (CBSA).

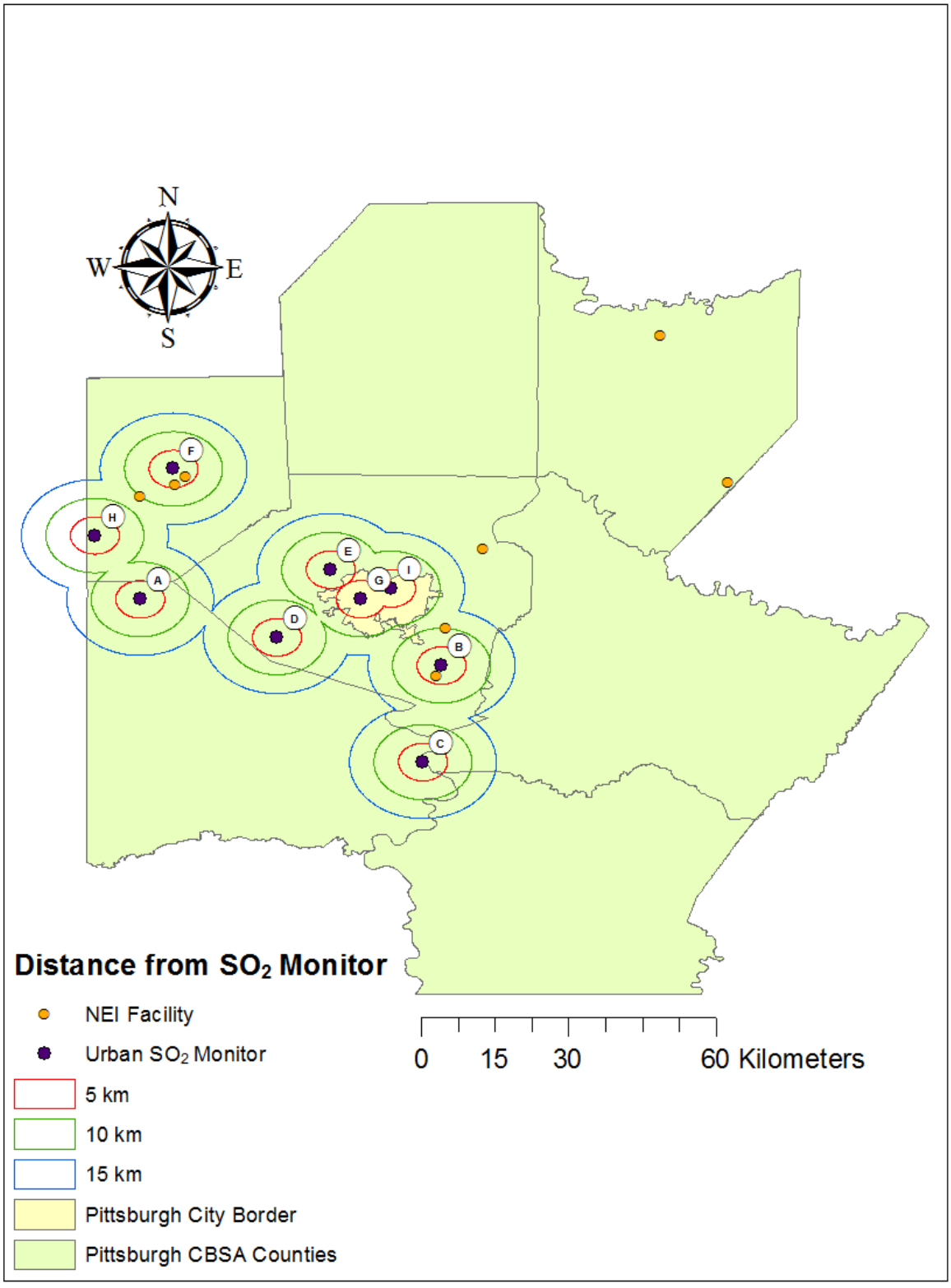


Figure 2-15 Map of Pittsburgh, PA Core-based Statistical Area (CBSA).

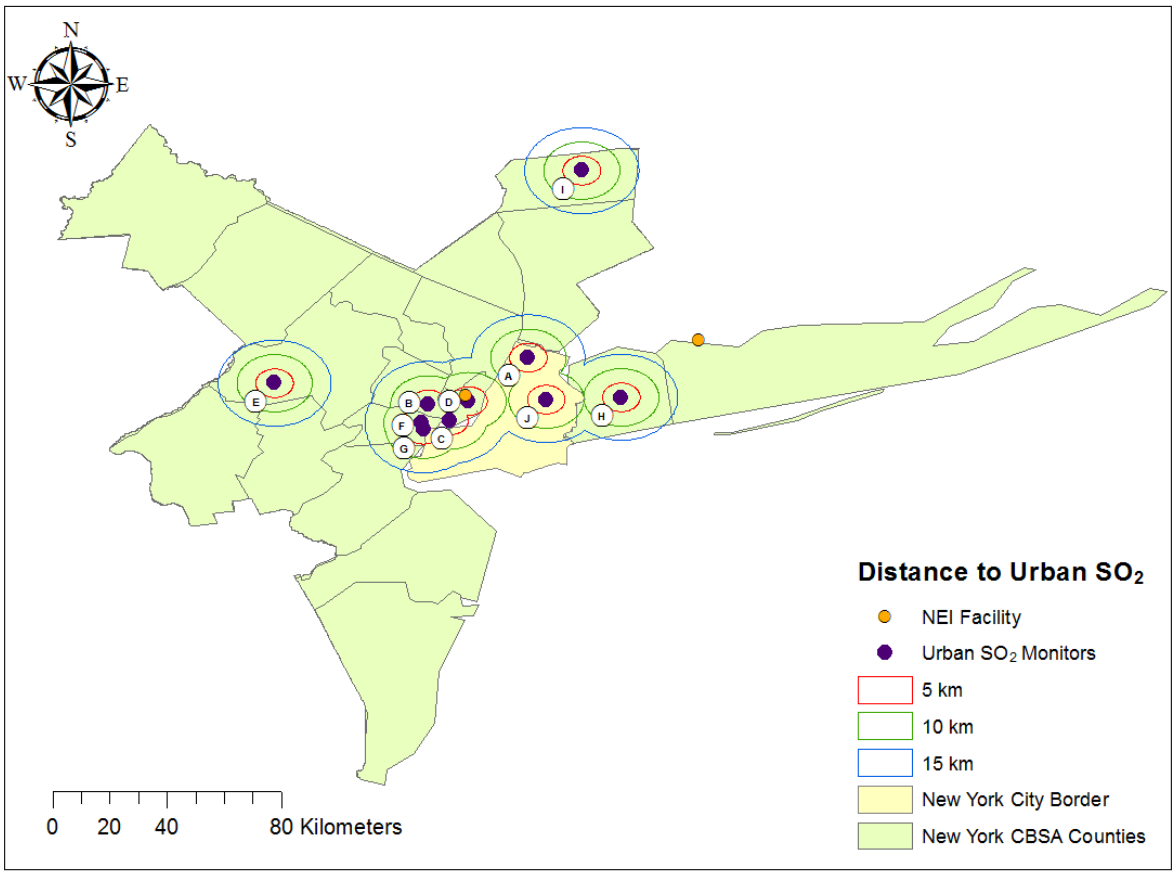


Figure 2-16 Map of New York City, NY Core-based Statistical Area (CBSA).

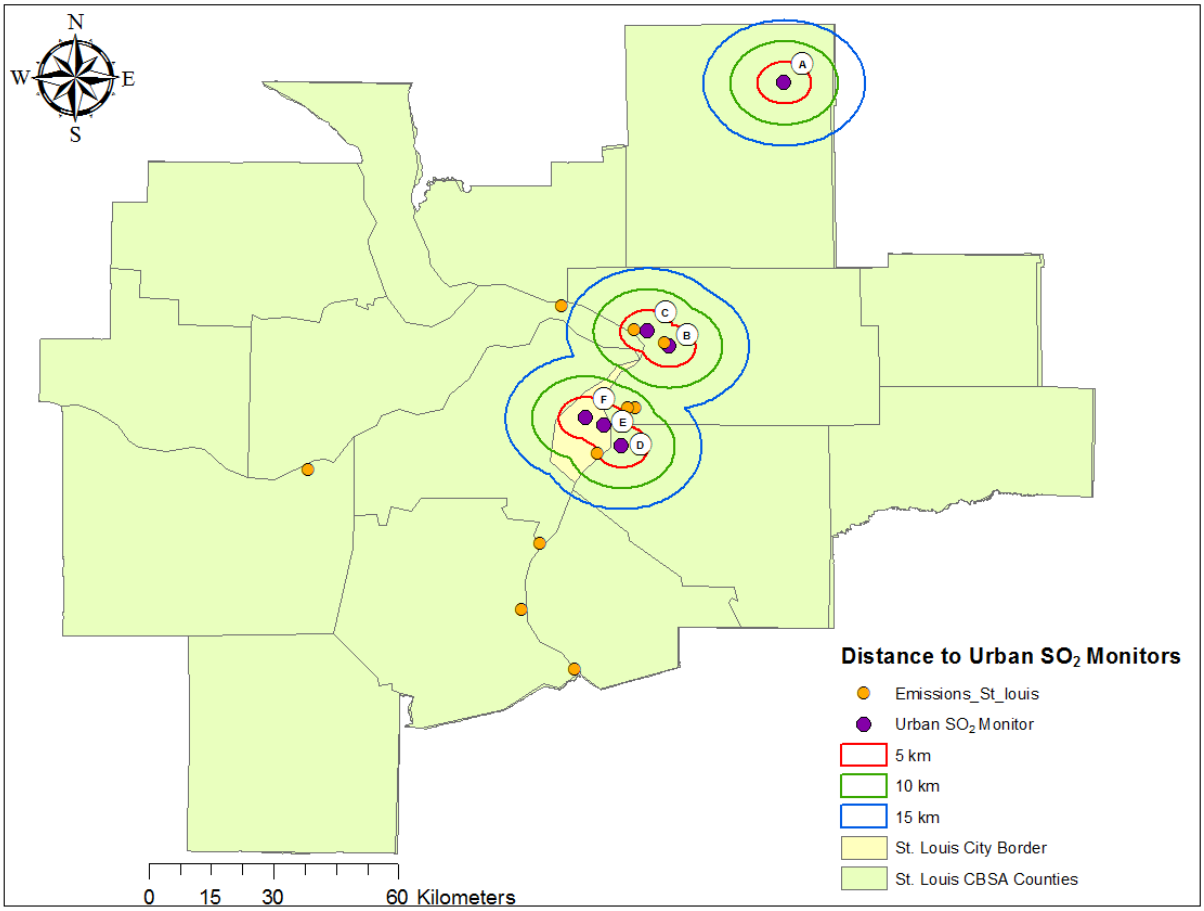


Figure 2-17 Map of St Louis, MO-IL Core-based Statistical Area (CBSA).

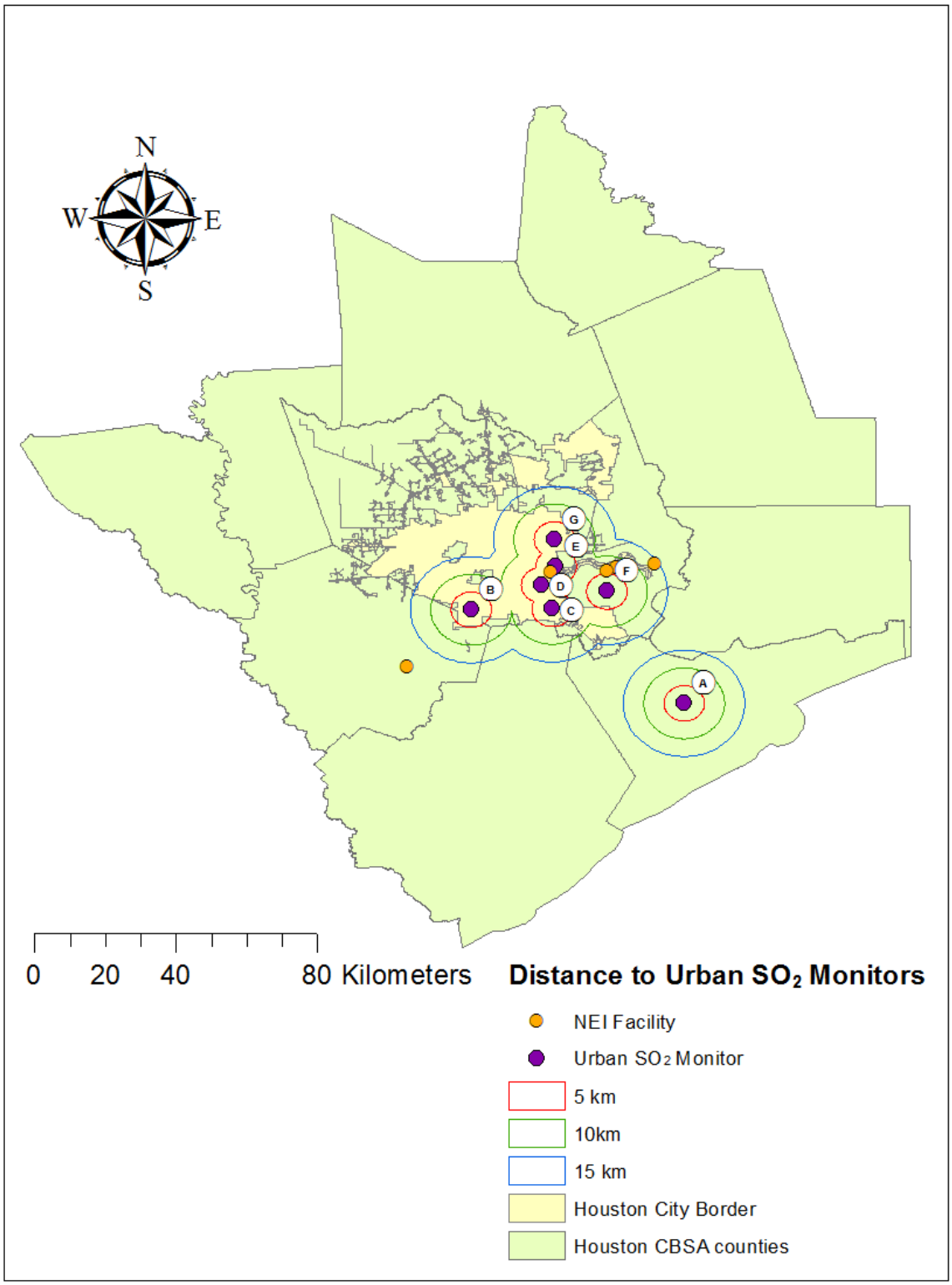


Figure 2-18 Map of Houston, TX Core-based Statistical Area (CBSA).

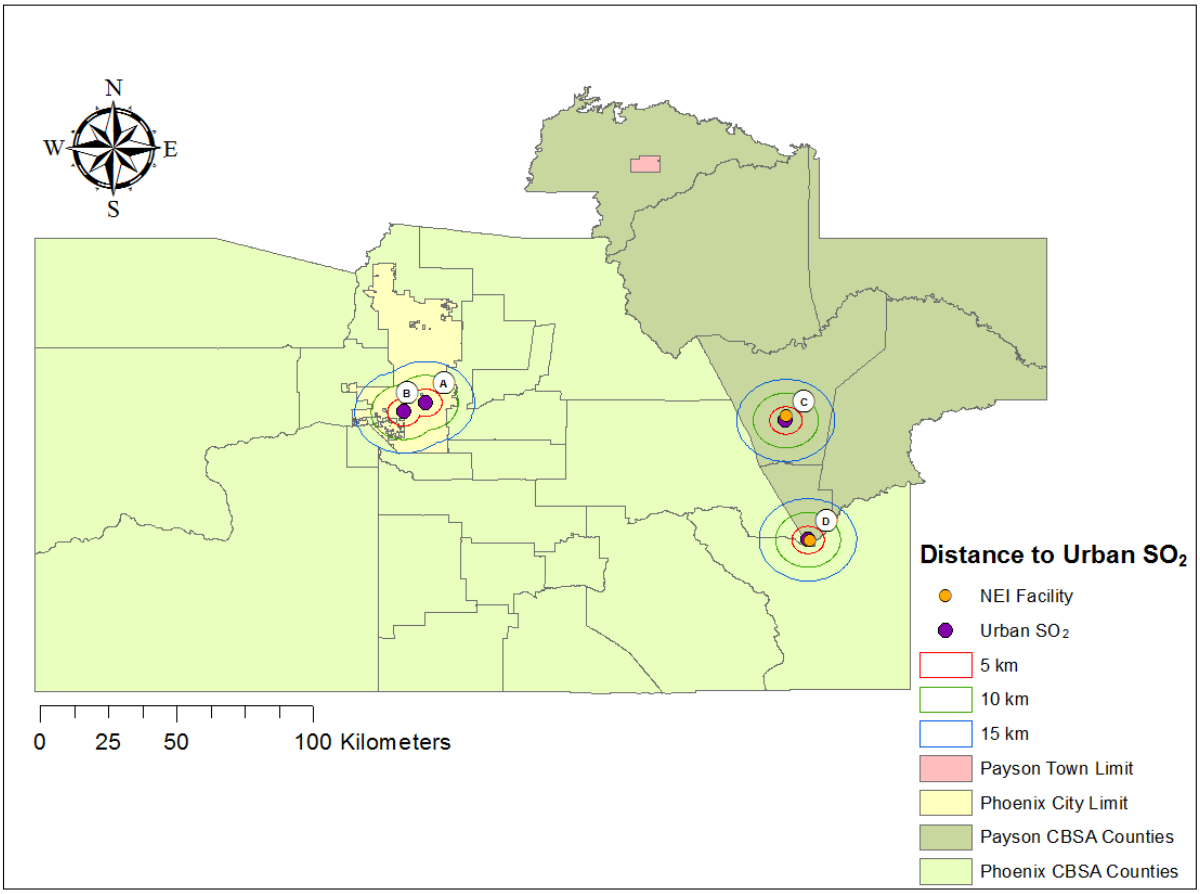


Figure 2-19 Map of Payson/Phoenix, AZ Core-based Statistical Areas (CBSAs) (hereafter referred to as Payson/Phoenix Metropolitan focus area).

Table 2-8 displays the distribution of daily 1-hour maximum SO_2 concentrations and monitor type (standard vs. trace level monitor) reported at individual AQS monitors in the six CBSA/metropolitan focus area. Concentrations reported at these sites are similar to nationwide SO_2 concentrations discussed earlier in this section (Section 5.2.1). For all but one individual monitor, median concentrations are below 15 ppb. The one exception was the monitor in Payson/Phoenix CBSA/metropolitan focus area for which the median concentration was 50 ppb. This particular monitor (Site D in Payson/Phoenix, AZ) is located within 1 km of a copper smelting plant with markedly high annual SO_2 emissions (greater than 21,000 tons of SO_2/year, http://www.epa.gov/ttnchie1/net/2011inventory.html).

Table 2-8 1-Hour max sulfur dioxide concentration distribution by AQS monitor in six core-based statistical area/metropolitan focus areas.

Site Label	AQS Monitor ID	Mean	Min	10	25	50	75	90	99	Max	Monitor Type
Cleveland-Elyria-Mentor, OH											
A	390350065	6	0	0	0	1	6	20	64	138	Standard
B	390350060	17	0	3	6	13	23	40	73	128	Standard
C	390850003	10	0	4	6	8	12	17	34	113	Standard
D	390350038	17	0	2	5	11	24	40	80	117	Standard
E	390850007	28	1	4	5	10	36	86	152	238	Standard
F	390350045	6	0	0	0	3	6	15	59	106	Standard
Pittsburgh, PA											
A	421255001	8	0	4	5	7	9	13	22	46	Standard
B	420030064	24	0	4	7	15	31	55	140	450	Standard
C	421250005	7	0	0	2	5	9	15	39	70	Standard
D	420030067	6	0	1	2	4	8	13	30	108	Standard
E	420030002	7	0	1	2	5	9	15	45	97	Standard
F	420070005	22	0	2	5	12	26	53	145	350	Standard
G	420030010	8	0	2	4	6	9	15	29	57	Standard
H	420070002	11	0	2	4	7	13	21	61	187	Standard
I	420030008	6	0	2	3	5	8	11	27	55	Trace
New York-Northern New Jersey-Long Island, NY-NJ-PA											
A	360050133	9	0	2	4	7	12	20	40	64	Standard
B	340130003	4	0	1	2	3	6	9	17	33	Trace
C	340170006	8	0	2	4	7	11	15	26	45	Standard
D	340171002	4	0	1	2	3	6	9	19	25	Standard
E	340273001	3	0	0	1	1	4	8	23	67	Standard
F	340390003	3	0	0	1	2	3	6	11	22	Standard
G	340390004	6	0	0	2	4	8	13	32	59	Standard

Table 2-8 (Continued): 1-Hour max sulfur dioxide concentration distribution by AQS monitor in six core-based statistical area/metropolitan focus areas

Site Label	AQS Monitor ID	Mean	Min	10	25	50	75	90	99	Max	Monitor Type
H	360590005	4	0	1	1	3	5	9	23	50	Standard
I	360790005	2	0	0	1	1	2	4	10	26	Standard
J	360810124	6	0	1	2	4	7	12	26	64	Trace
St. Louis, MO-IL											
A	171170002	2	0	1	1	2	3	5	12	23	Standard
B	171191010	6	0	1	2	3	7	15	39	69	Standard
C	171193007	8	0	1	2	5	10	17	42	106	Standard
D	171630010	5	0	1	2	4	7	13	24	44	Standard
E	295100085	*	*	*	*	*	*	*	*	*	Trace
F	295100086	9	0	2	3	7	13	20	47	76	Standard
Houston-Sugar Land-Baytown, TX											
A	481670005	5	0	1	2	3	7	12	34	58	Standard
B	482010051	2	0	0	0	1	2	7	19	73	Standard
C	482010062	3	0	0	0	1	4	8	19	56	Standard
D	482010416	5	0	0	1	2	6	13	32	60	Standard
E	482011035	5	0	0	0	2	6	14	38	75	Standard
F	482011039	*	*	*	*	*	*	*	*	*	Trace
G	482011050	3	0	0	1	2	4	7	14	22	Standard
Payson/Phoenix CBSA											
A	40133002	3	0	1	2	3	4	6	9	12	Standard
B	40139812	*	*	*	*	*	*	*	*	*	Standard
C	40070009	1	0	2	2	8	40	84	213	1501	Standard
D	40071001	65	0	8	25	50	86	135	295	1501	Trace

AQS= Air Quality System; CBSA = core-based statistical area; max = maximum; min = minimum.

*1-h max SO_2 concentrations not reported at monitor.

More substantial monitor-to-monitor differences are observed in the 99th percentile of SO_2 concentrations. Across these monitors, 99th percentile concentrations range from 9 to 295 ppb, with the majority of sites exhibiting 99th percentile concentrations below 50 ppb. Relatively high 99th percentile concentrations are generally reported at monitors within 5 km of a major SO_2 point source, particularly in Pittsburgh, PA and Payson-Phoenix, AZ. This trend is 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 electric generation (Clougherty et al., 2013; Wheeler et al., 2008).

To evaluate the extent of SO_2 spatial variability over urban geographical scales, concentrations were correlated between monitor pairs in each of the six CBSA/metropolitan focus areas. Pairwise monitor comparisons were evaluated using Pearson correlations to estimate the degree to which concentrations at two different monitoring locations follow similar temporal trends. Across the six CBSA/metropolitan focus areas, Pearson correlations range from 0 to 0.9. Correlations close to 1 represent strong correspondence between pairwise monitor concentrations, while values close to 0 represent poor correspondence between monitor values.

Figure 2-20 shows scatterplots of pairwise monitor correlations of 24-hour average SO_2 concentrations versus distance between monitor pairs. The distribution of pairwise correlations for each CBSA/metropolitan focus area is presented as histograms in Figures 2-21, 2-22, and 2-23 show similar information on spatial correlations but focus on the comparison among hourly 5-minute maximum concentrations.

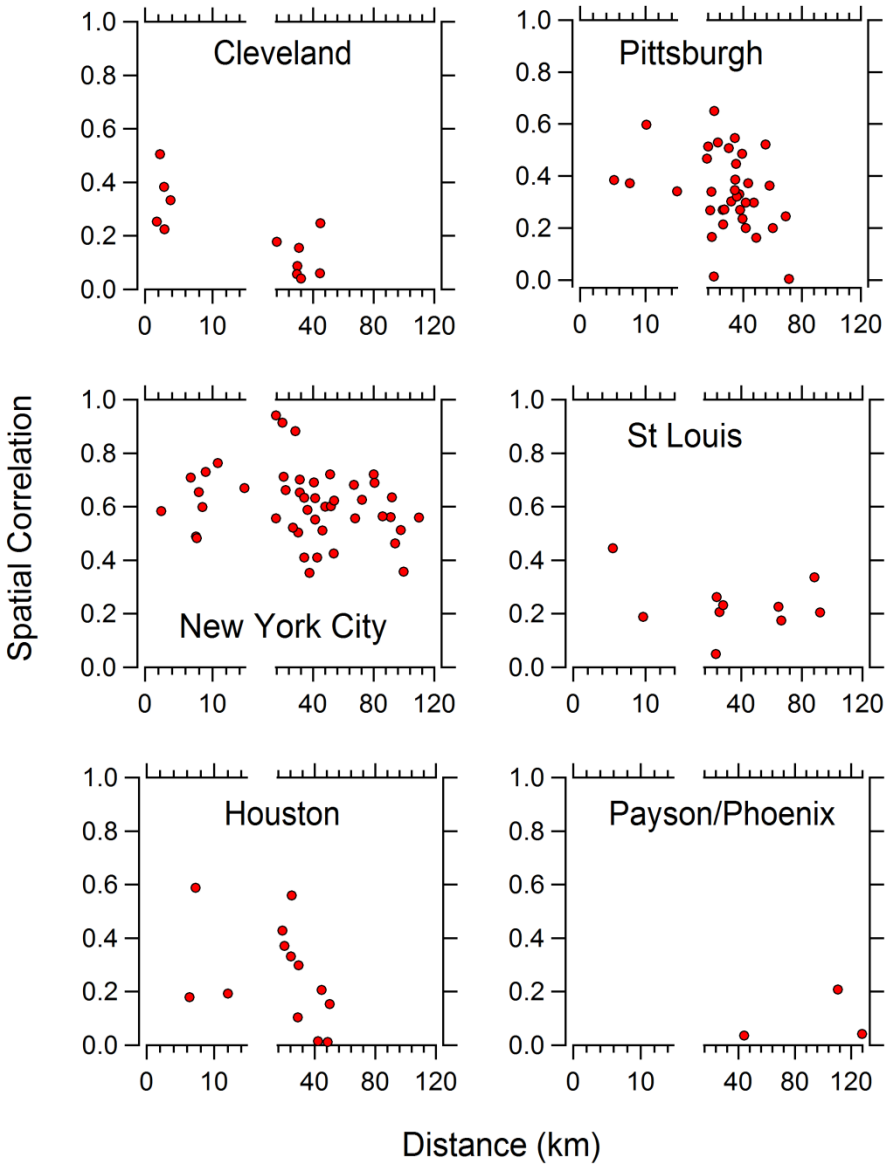


Figure 2-20 **Pairwise monitor correlations of 24-hour average sulfur dioxide versus distance between monitor pairs in six core-based statistical area/metropolitan focus area, 2010−2012.**

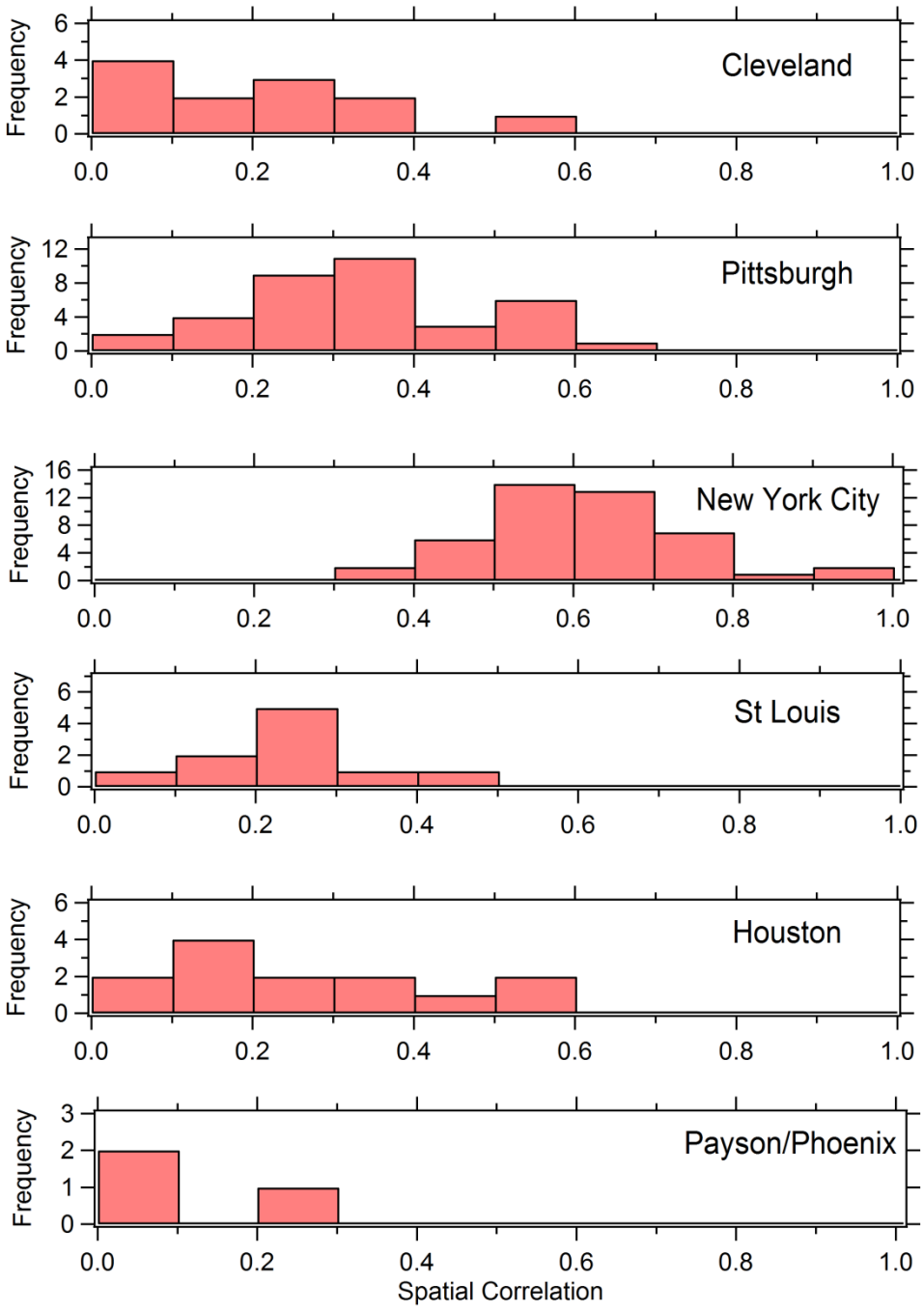


Figure 2-21 Histogram of pairwise correlations of 24-hour average sulfur dioxide data in six core-based statistical area/metropolitan focus areas, 2010−2012 data.

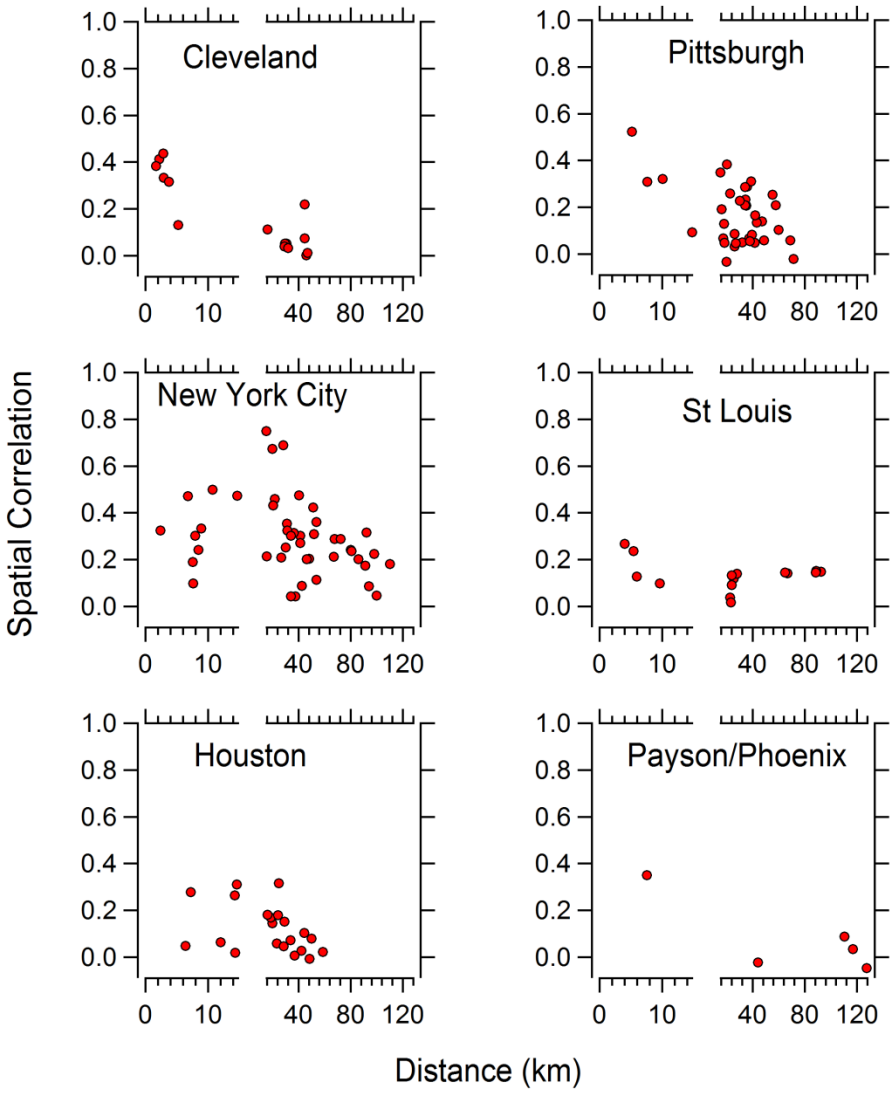


Figure 2-22 **Pairwise monitor correlations of hourly 5-minute maximum data versus distance between monitors in six core-based statistical area/metropolitan focus areas, 2010−2012.**

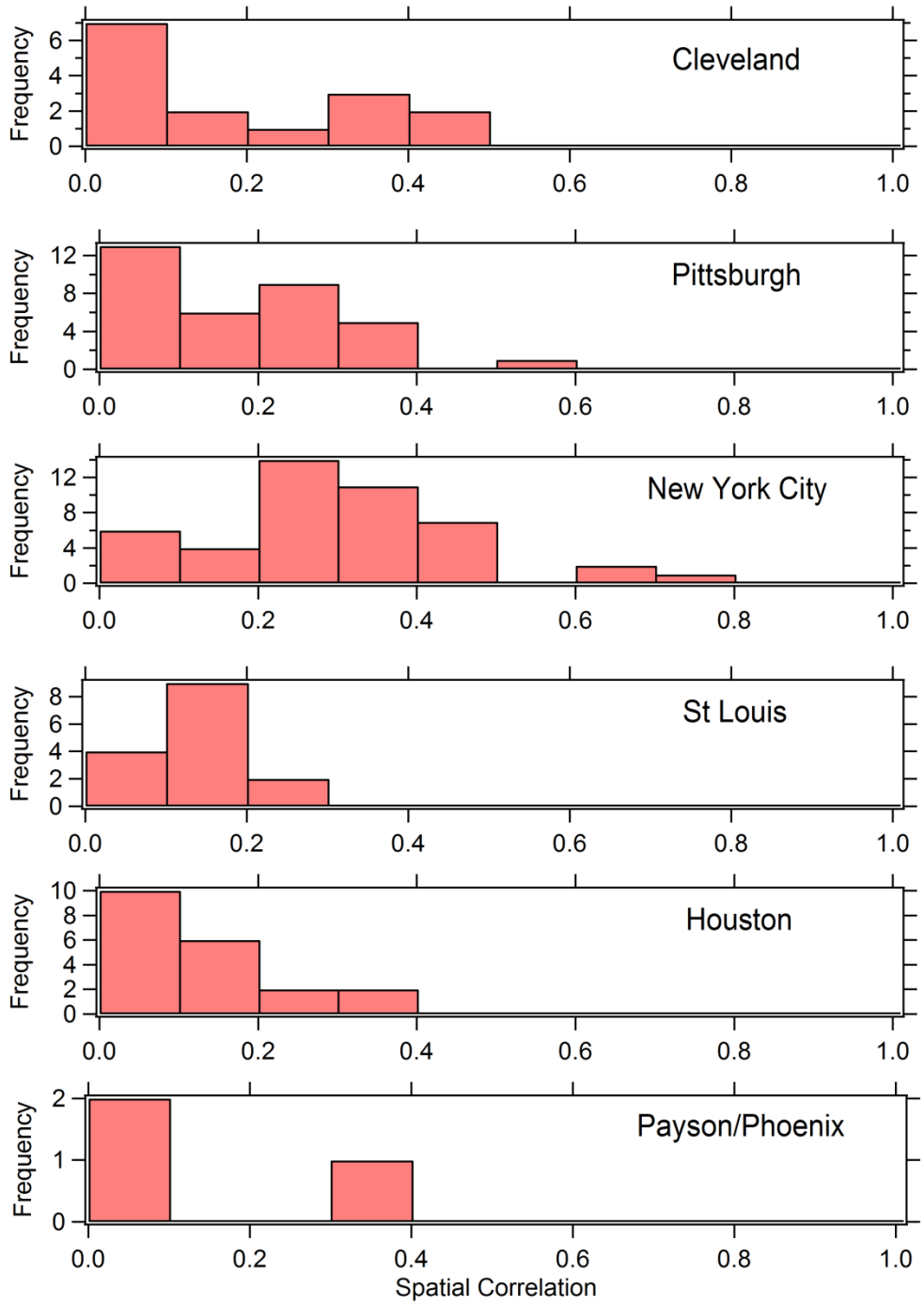


Figure 2-23 Histogram of pairwise correlations of hourly 5-minute maximum sulfur dioxide data in six core-based statistical area/metropolitan focus areas, 2010−2012 data.

Pairwise comparisons in Figure 2-20 demonstrate that daily 24-hour average SO_2 concentrations are highly variable across urban spatial scales. In every CBSA/metropolitan focus area, low to moderate pairwise correlations of daily 24-hour average SO_2 values are observed, with the majority of Pearson correlations below 0.6 (Figure 2-20). In general, correlations tend to decrease with distance. Even within relatively short distances (up to 15 km), most pairwise correlations are low and decay rapidly, reflecting the variable nature of ambient SO_2 across urban spatial scales primarily due to its short atmospheric residence time and the episodic nature of emissions discussed earlier in this chapter (Chapter 2).

In comparison, hourly 5-minute maximum SO_2 values show a similar, but enhanced level of spatial variability across urban spatial scales (Figure 2-22). In most cases, pairwise correlations of hourly 5-minute maximum values are generally lower (less than 0.4) and decline more dramatically with distance than pairwise correlations of daily 24-hour average concentrations. Greater spatial variability in hourly 5-minute maximum values 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-hour average 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. Comparatively, pairwise correlations in New York City, NY are generally high and uniform across tens of kilometers, demonstrating relatively good agreement between pairwise SO_2 concentrations despite dramatic changes in distance between monitors. Stronger pairwise correlations in New York City, NY may be directly related to low background SO_2 concentrations due to fewer large SO_2 sources within the CBSA/metropolitan focus area boundaries. Such low concentrations may be less variable over spatial and temporal scales than higher concentrations. On the other hand, spatial variations in Cleveland, OH and St. Louis, MO may be amplified because emissions from local sources impact various locations within these cities differentially.

In summary, SO_2 concentrations vary substantially across urban spatial scales as evidenced by poor to moderate pairwise monitor correlations observed in SO_2 data in six CBSA/metropolitan focus areas. Greater spatial heterogeneity tends to occur in cities impacted by a wide variety of local SO_2 sources rather than areas with few SO_2 sources, characterized by low concentrations (New York City, NY). Additionally, metrics representing maximum SO_2 concentrations (5-minute maximum, 1-hour maximum) generally exhibit more spatial heterogeneity than daily average metrics (24-hour average). Given the high degree of spatial variability of daily or hourly SO_2 concentrations across metropolitan areas, exposure assessment based on central site

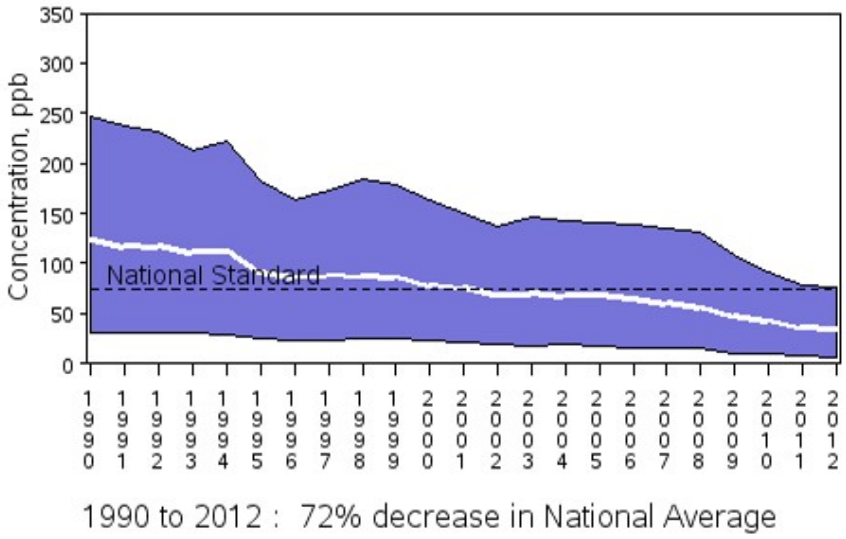
monitors is subject to some degree of uncertainty, which may introduce health effect biases in epidemiologic analyses (Section 3.3.5).

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. The variability in ambient concentrations is discussed in the context of short-term and long-term exposure and health effects analyses.

2.5.3.1 Long-Term Trends

Trends in SO_2 concentrations reported at AQS monitoring sites across the U.S. from 1990 to 2012 are shown in Figure 2-24. The white line shows the mean annual values. The upper and lower borders of the blue (shaded) areas represent the 10th and 90th percentile values, respectively. Information on trends at individual, local air monitoring sites can be found at http://www.epa.gov/air/airtrends/sulfur.html (U.S. EPA, 2012b).



The white line shows the mean values and the upper and lower borders of the blue (shaded) areas represent the 10th and 90th percentile values.

Data reported by the Environmental Protection Agency Air Quality Trends Network.

Figure 2-24 National sulfur dioxide air quality trend (1990−2012), based on 163 sites, showing a 72% decrease in the national average.

The steady decline in SO_2 concentrations over the past 25 years is largely attributed to emissions reductions at electric utilities due to the Acid Rain Program under the Clean Air Act Amendments of 1990 [Section 2.2.4]. The goal of this program was to reduce power plant SO_2 emissions by 10 million tons from 1980 levels. Reductions in SO_2 emissions from the Acid Rain Program commenced in 1996 and continued into the 2000s, resulting in dramatic decreases in total, nationwide SO_2 emissions and concentrations. Additional environmental regulations on sulfur content in diesel fuel for mobile sources resulted in further reductions in ambient SO_2 over the past decade. From 1990−2012, the annual 99th percentile average of daily 1-hour maximum SO_2 concentration has decreased by 72% 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 (AL, FL, GA, MS), 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%/year) reported at monitoring sites across these four states.

2.5.3.2 Seasonal Trends

In the 2008 SO_X ISA (U.S. EPA, 2008b), month-to-month trends for SO_2 were observed across a number of metropolitan areas; however, seasonal profiles varied by location. Some cities, such as Steubenville, PA 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 daily 1-hour maximum concentrations (2010−2012) is shown for the six CBSA/metropolitan focus areas introduced earlier in this chapter (Section 2.5.2.2). Figure 2-25 displays the range of SO_2 concentrations reported at all monitors within each CBSA/metropolitan focus area. For every month, median concentrations are displayed by black lines inside the box, and mean concentrations are displayed by red markers. The interquartile range (IQR) (25th to 75th percentile range) is outlined by the box, and 5th and 95th percentiles are shown by the top and bottom whiskers of the box, respectively.

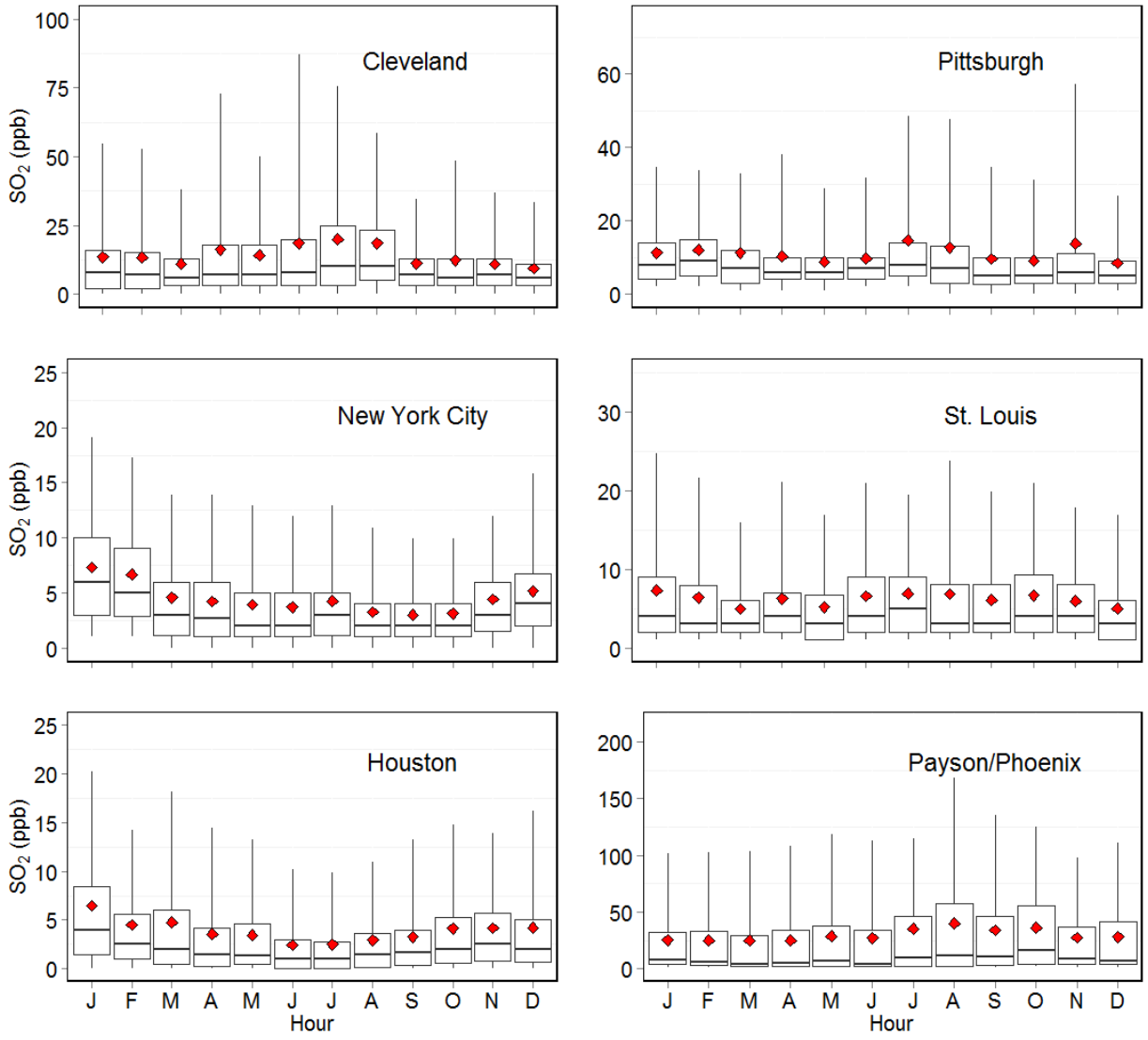


Figure 2-25 Sulfur dioxide month-to-month variability based on 1-hour maximum concentrations at Air Quality System sites in each core-based statistical area.

Recent data indicate that daily 1-hour maximum SO_2 data vary across seasons, especially in the upper end of monthly SO_2 concentrations. Across CBSA/metropolitan focus areas, median concentrations (50th percentile: black line) tend to exhibit little variability throughout the year, while large variations are observed in the upper range (greater than 75th percentile) of SO_2 values. Notably, mean monthly SO_2 concentrations are higher and more variable than median values, indicating that mean concentrations tend to be skewed right by extremely high ambient concentrations that infrequently occur.

Recent data also further demonstrate that seasonal profiles vary by location. While each CBSA/metropolitan focus area exhibits some extent of seasonal variation, no distinct seasonal profile was observed across all areas. For example, summertime maxima in daily 1-hour maximum SO_2 are evident in Cleveland, OH and Gila County, AZ corresponding to CBSA/metropolitan focus areas with the highest SO_2 concentrations. Alternatively, New York City, NY and Houston, TX show clear wintertime maxima. The remaining CBSA/metropolitan focus areas, Pittsburgh, PA and St. Louis, MO exhibit both summer and winter peaks.

Month-to-month variations in SO_2 concentrations appear to be related to different sources within each location and, to some extent, the atmospheric chemistry of SO_2. For all CBSA/metropolitan focus areas, wintertime and summertime SO_2 enhancements likely correspond to higher power plant emissions due to increased demands for heating and cooling of residential/commercial buildings during seasons with extreme temperatures. Summertime minima, observed in some CBSA/metropolitan focus areas (New York City, NY, and Houston, TX), may correspond to more rapid oxidation of SO_2 to SO_4^{2-} by photochemically derived atmospheric oxidants that are more prevalent during the summer. Other seasonal variations are likely due to SO_2 sources specific to a given location. The difference in seasonality among these cities suggest that SO_2 can be substantially variable across local and regional scales.

2.5.3.3 Diel Variability

The 2008 SO_X ISA (U.S. EPA, 2008b) explored nationwide diel patterns in SO_2 concentrations 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 as it expands throughout the day due to convective mixing.

Diel patterns were investigated in the six CBSA/metropolitan focus areas using more recent hourly average (1-hour average) and maximum (5-minute maximum) SO_2 data. Figures 2-26 and 2-27 show variations in 1-hour average and hourly 5-minute maximum SO_2 concentrations in the six focus areas. For every hour, median concentrations are displayed as black lines inside the box, and the mean concentrations are displayed as 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.

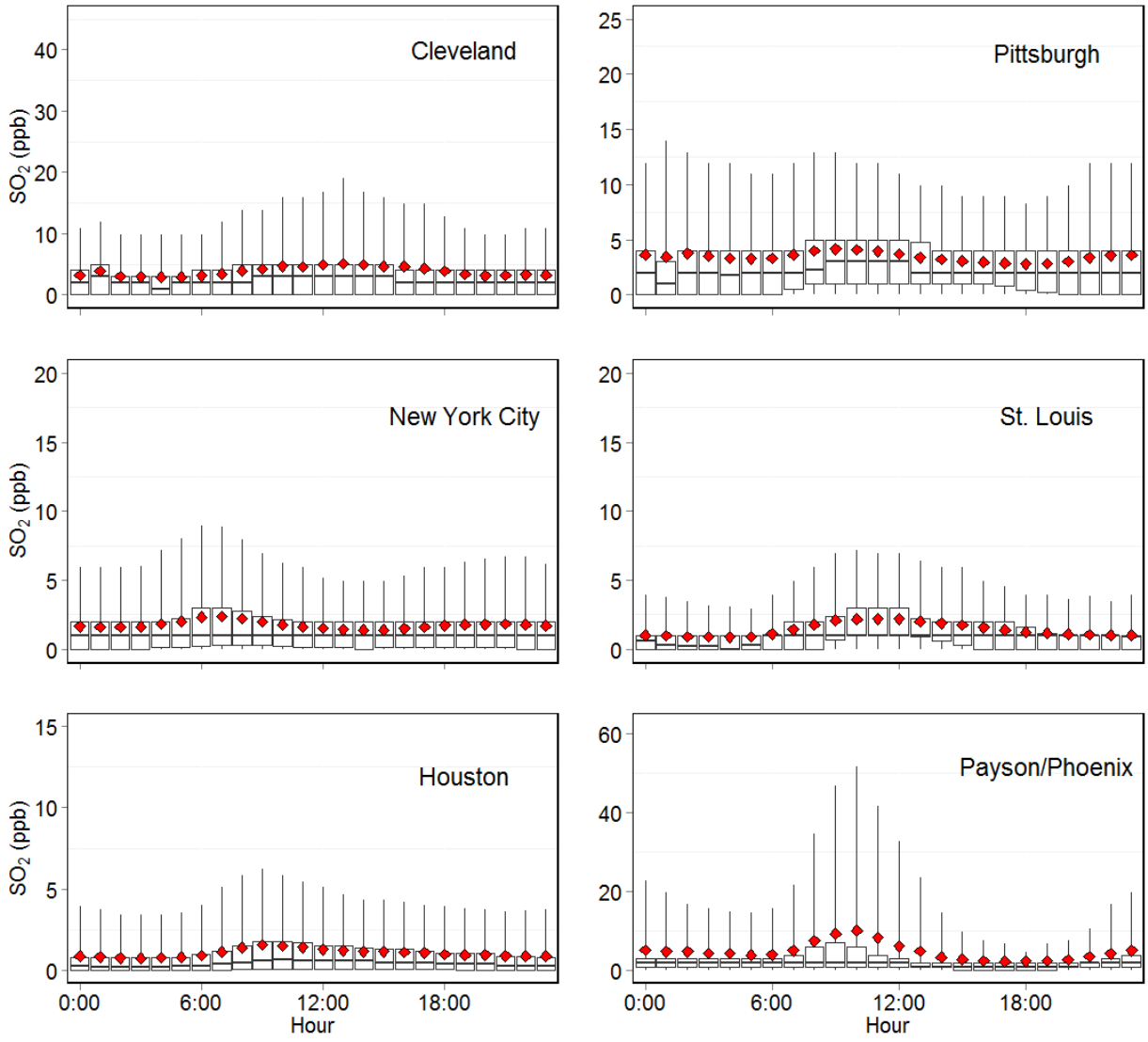


Figure 2-26 Diel variability based on 1-hour average sulfur dioxide concentrations.

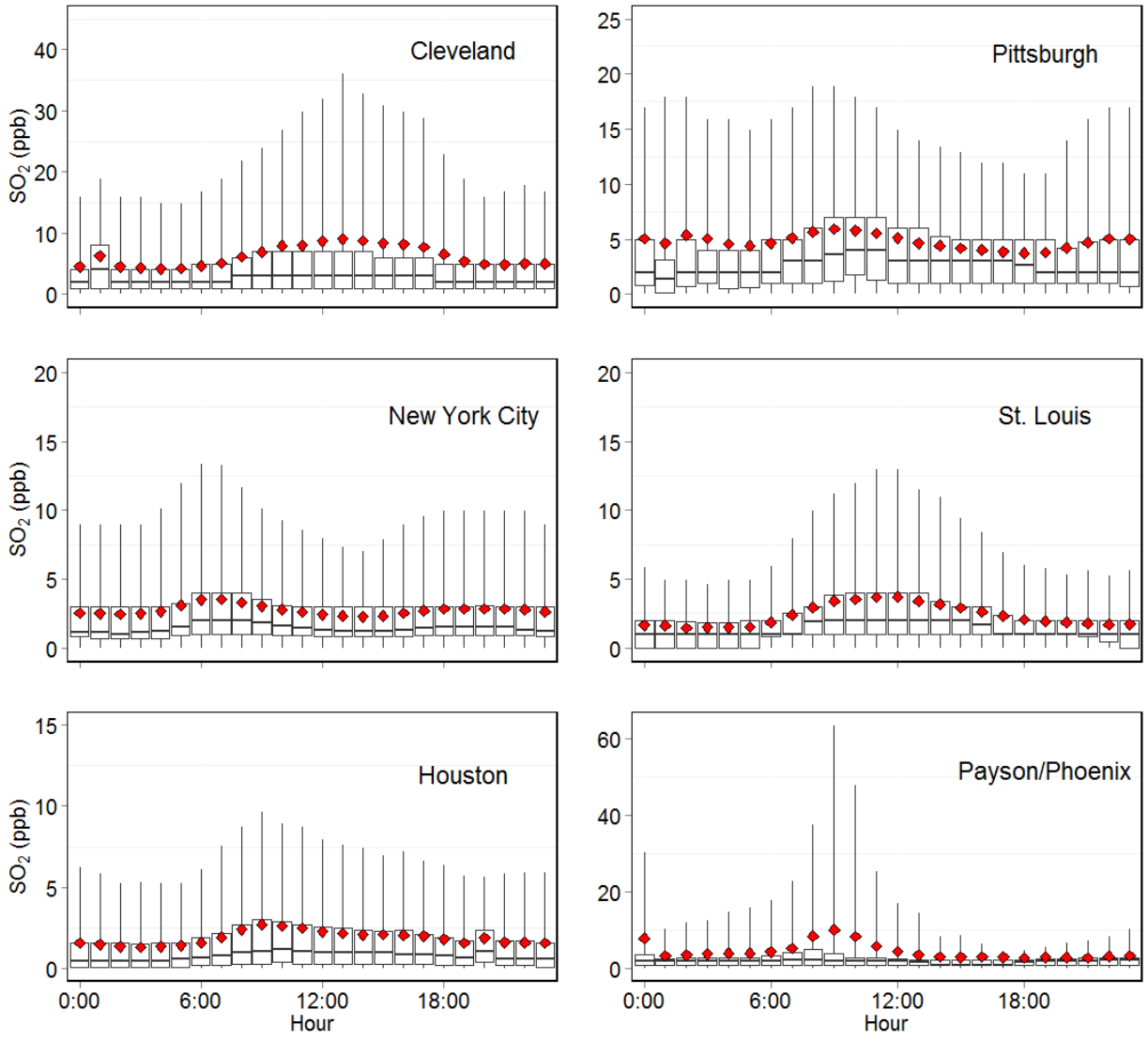


Figure 2-27 Diel trend based on hourly 5-minute maximum data in the six core-based statistical area focus areas.

Consistent with the nationwide diel patterns reported in the 2008 SO_X ISA (U.S. EPA, 2008b), SO_2 concentrations in the six CBSA/metropolitan focus areas are generally low during nighttime and approach maxima values during daytime hours (Figures 2-26 and 2-27). The timing of daytime maxima, however, varies by location. In New York City, NY and Payson/Phoenix, AZ daytime maxima occur during early morning hours (6:00 to 9:00 a.m. LST), whereas SO_2 tends to peak later in the morning or in some cases early/midafternoon in the remaining urban areas (Cleveland, OH; Pittsburgh, PA; St. Louis, MO; Houston, TX).

The timing and duration of daytime SO_2 peaks in the six focus areas are likely a result of a combination of source emissions and meteorological parameters. Similar to conclusions in the 2008 SO_X ISA, higher daytime SO_2 likely reflects 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 in New York City, NY may be related to an increase in mobile source emissions from diesel vehicles during morning rush hour when traffic activity is high and atmospheric conditions are stable. Stable atmospheric conditions tend to trap atmospheric pollution near the ground, resulting in an overall increase in ground-level pollution. This result is consistent with Wheeler et al. (2008) who found that a large portion of SO_2 variability in Ontario, Canada, can be explained by diesel truck traffic.

Notably, SO_2 concentrations are all well below primary NAAQS levels during all hours of the day in every CBSA/metropolitan focus area. In each location, median hourly maxima (5-minute maximum) and average (1-hour average) concentrations are roughly 5 ppb. Even when examining the upper end of the distribution (90th percentile) of hourly 5-minute maximum values, concentrations are for the most part below 15 ppb. However, concentrations (1-hour average) above primary NAAQS levels of 75 ppb are reported at some sites and generally comprise the highest concentrations (99th percentile and above) reported at a given monitoring sites.

2.5.3.4 Sulfur Dioxide 5-Minute Data

The previous EPA NAAQS review concluded that short-term exposure (5−10 minutes) to SO_2 above 200 ppb can cause lung function decrements among exercising asthmatics, with the severity of the effect increasing with concentration (U.S. EPA, 2008b). Based on these findings, state monitoring networks have been expanding over the past 5 years in an effort to characterize hourly 5-minute maximum concentrations and to understand the extent to which these maximum values approach health-relevant levels. Under the recent monitoring guidelines, states currently report subhourly concentrations in the form of either (1) a 5-minute maximum concentration reported every hour or (2) twelve 5-minute average concentrations reported every hour. These 5-minute metrics are used to estimate the range of ambient concentrations and potential community exposures occurring on short time scales. In this section, subhourly concentrations are evaluated to understand the distribution of 5-minute concentrations observed in the six CBSA/metropolitan focus areas introduced in Section 2.5.2.2.

Over the past decade, the number of AQS monitoring sites reporting 5-minute SO_2 concentrations has significantly increased. During 1997−2007, a total of 95 monitoring

sites periodically reported hourly 5-minute maximum concentrations. Of these 95 sites, only 16 sites posted all twelve 5-minute average concentrations per hour, limiting the amount of information reported on 5-minute data in the 2008 SO_X ISA (U.S. EPA, 2008b). To date, approximately 309 sites report 5-minute data, including urban sites within CBSAs, sites near city centers, sites near major SO_2 sources, and sites in rural areas. Figure 2-11 displays a map of the AQS 5-minute SO_2 monitoring network during 2010−2012.

In the 2008 SO_X ISA, analyses were conducted on hourly 5-minute maximum data in 16 metropolitan focus areas to understand SO_2 variability over short time scales (minutes to hours). In these 16 metropolitan areas, concentrations of hourly 5-minute maximum data ranged from 0 ppb to approximately 4,000 ppb, with median concentrations below 10 ppb. The 99th percentile of hourly 5-minute maximum SO_2 reported at all 16 locations was below benchmark levels of 200 ppb; however, maximum concentrations at several monitors often reported values above 200 ppb. While strong agreement between hourly 5-minute maximum and 1-hour average metrics was observed (Pearson $r > 0.87$ in 16 cities), the magnitude of hourly 5-minute maximum concentrations was not often captured by 1-hour average values.

Similar analyses on hourly 5-minute maximum concentrations were performed on more recent data reported at individual monitors in the six CBSA/metropolitan focus areas introduced earlier in this chapter (Cleveland, OH; Pittsburgh, PA; New York City, NY; Houston, TX; St Louis, MO; and Payson/Phoenix, AZ). Table 2-9 shows the range in 5-minute maximum SO_2 concentrations reported at individual monitors within the six CBSA/metropolitan focus areas during 2010−2012. In general, median 5-minute maximum concentrations are below 5 ppb, while maximum concentrations range from 32 to 2,001 ppb.

Table 2-9 Five-minute sulfur dioxide concentrations by AQS monitor in select core-based statistical area/metropolitan focus areas.

Site Label	AQS Monitor ID	N	Mean	Min	25	50	75	90	99	Max	Monitor Type
Cleveland-Elyria-Mentor, OH											
A	390350065	20,424	4	0	0	1	5	10	39	241	Standard
B	390350060	19,694	8	0	2	4	8	18	62	266	Standard
C	390850003	21,025	5	0	2	4	6	9	23	183	Standard
D	390350038	20,496	7	0	1	2	7	19	57	206	Standard
E	390850007	20,740	12	0	1	3	5	18	171	522	Standard
F	390350045	20,422	2	0	0	1	2	4	25	285	Standard
Pittsburgh, PA											
A	421255001	19,776	3	0	0	2	3	6	19	228	Standard
B	420030064	25,826	10	0	2	4	10	23	81	704	Standard
C	421250005	19,825	5	0	3	4	6	8	15	68	Standard
D	420030067	26,112	2	0	0	1	3	6	17	390	Standard
E	420030002	25,416	3	0	0	1	3	8	28	505	Standard
F	420070005	23,278	9	0	1	4	8	19	87	889	Standard
G	420030010	18,883	4	0	2	3	5	8	16	128	Standard
H	420070002	19,880	5	0	2	3	5	9	28	202	Standard
I	420030008	22,938	3	0	1	2	4	6	15	94	Trace

Table 2-9 (Continued): Five-minute sulfur dioxide concentrations by AQS monitor in select core-based statistical area/metropolitan focus areas.

Site Label	AQS Monitor ID	N	Mean	Min	25	50	75	90	99	Max	Monitor Type
New York-Northern New Jersey-Long Island, NY-NJ-PA											
A	360050133	17,300	5	0	2	3	7	12	27	68	Standard
B	340130003	19,684	2	0	1	1	3	5	13	32	Trace
C	340170006	18,332	5	0	1	3	6	12	26	83	Standard
D	340171002	20,073	2	0	1	2	3	5	14	64	Standard
E	340273001	20,024	2	0	1	1	2	3	11	94	Standard
F	340390003	18,088	2	0	1	1	2	4	8	33	Standard
G	340390004	20,183	3	0	1	1	3	7	27	288	Standard
H	360590005	15,833	2	0	1	1	2	4	15	73	Standard
I	360790005	15,811	1	0	1	1	1	2	6	91	Standard
J	360810124	15,893	3	0	1	2	4	8	19	90	Trace
St. Louis, MO-IL											
A	171170002	19,522	1	0	1	1	1	2	5	65	Standard
B	171191010	19,088	2	0	0	1	2	4	19	112	Standard
C	171193007	18,924	3	0	1	1	3	6	27	112	Standard
D	171630010	19,132	2	0	1	1	3	5	17	96	Standard
E	295100085	16,335	4	0	1	2	4	9	34	154	Trace
F	295100086	17,003	3	0	1	2	4	8	24	241	Standard

Table 2-9 (Continued): Five-minute sulfur dioxide concentrations by AQS monitor in select core-based statistical area/metropolitan focus areas.

Site Label	AQS Monitor ID	N	Mean	Min	25	50	75	90	99	Max	Monitor Type
Houston-Sugar Land-Baytown, TX											
A	481670005	20,099	2	0	1	1	3	6	17	80	Standard
B	482010051	19,408	1	0	0	0	0	1	10	92	
C	482010062	20,322	1	0	0	1	1	3	12	81	Standard
D	482010416	20,139	2	0	0	1	2	4	23	103	Standard
E	482011035	20,232	2	0	0	0	1	4	27	206	
F	482011039	16,954	1	0	0	0	1	3	14	99	Trace
G	482011050	19,694	2	0	1	2	3	4	11	41	Standard
Payson/Phoenix CBSA											
A	40133002	21,297	2	0	1	2	2	4	7	29	
B	40139812	17,129	2	0	1	2	3	4	8	91	Standard
C	40070009	20,357	8	0	2	3	5	18	101	422	Standard
D	40071001	21,448	26	0	1	3	18	70	301	2,001	Trace

AQS = Air Quality System; CBSA = core-based statistical area; max = maximum; min = minimum; N = population number.

Table 2-10 shows the range in temporal correlations between collocated, hourly 5-minute maximum and 1-hour average SO_2 measurements reported at these monitors within the six CBSA/metropolitan focus areas. Similar to results in the 2008 SO_X ISA (U.S. EPA, 2008b), 5-minute maximum concentrations tend to correlate well with 1-hour average metrics, suggesting that 1-hour average metrics, in most cases, adequately represent changes in 5-minute maximum data over time. However, 5-minute maximum values tend to be higher than 1-hour average concentrations.

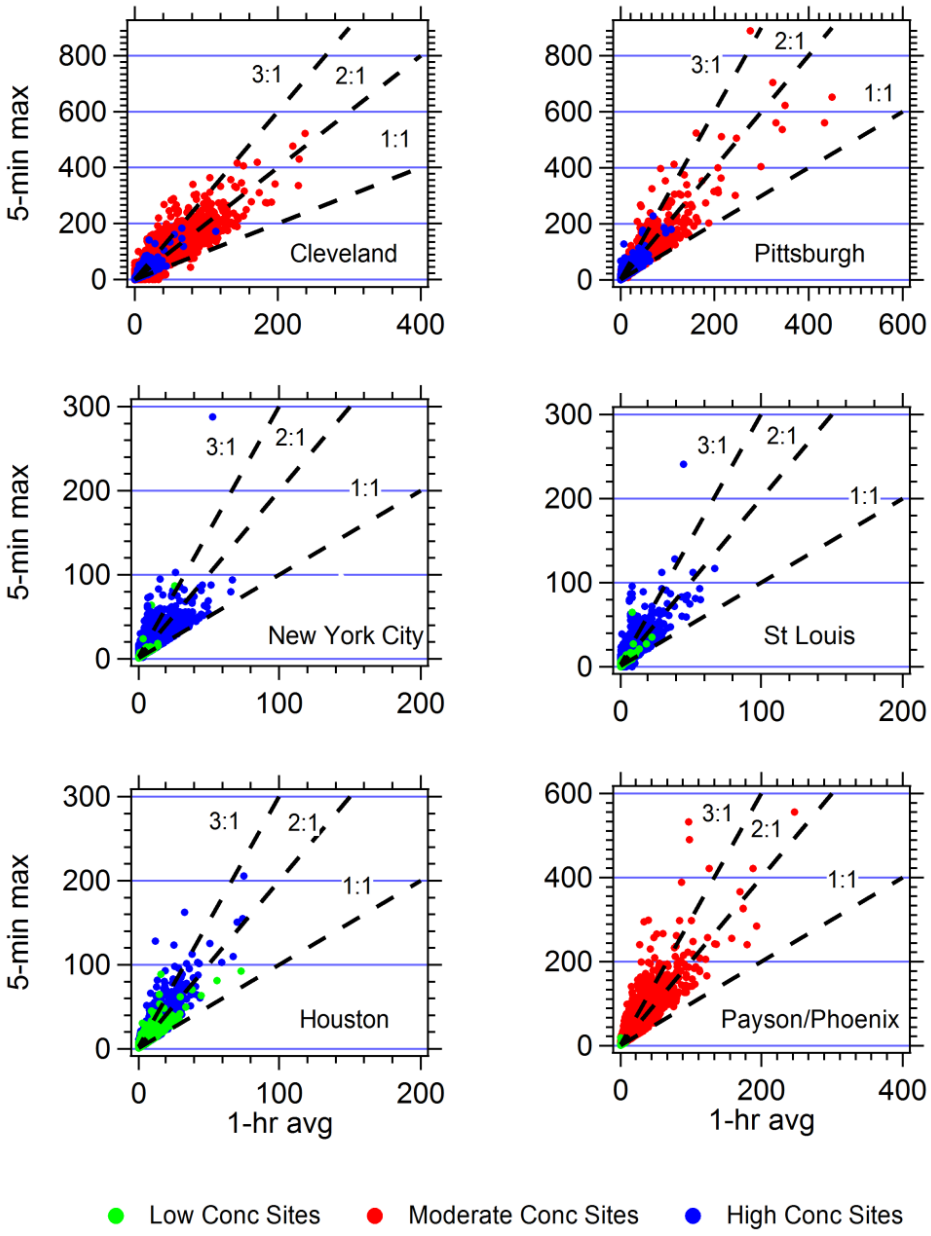
The hourly 5-minute maximum to 1-hour average SO_2 relationship was further evaluated at these same monitors in the six CBSA/metropolitan focus areas to identify the magnitude and location of hourly 5-minute maximum SO_2 values approaching levels relevant to human health impacts (greater than 200 ppb). This relationship also informs the degree to which 5-minute maximum values are higher than 1-hour average concentrations across different types of monitoring sites (i.e., sites near major sources vs. sites far downwind of sources).

To evaluate the 5-minute maximum 1-hour average relationship across different monitor types, individual monitors were classified into three categories based on the highest (99th percentile) daily 1-hour maximum SO_2 concentration. The categories consisted of "low concentration," "moderate concentration," and "high concentration" monitors. This classification approach was employed to systematically distinguish between near-source monitors reporting relatively high SO_2 concentrations versus monitors located far downwind from major sources that typically report low concentrations. As demonstrated in Table 2-8 (Section 2.5.2.2), the distribution of the 99th percentile of 1-hour maximum SO_2 concentrations reported at these monitors [population number (N) = 42 monitors] range from 9 to 295 ppb. Monitors with relatively high 99th percentile concentrations (upper quartile of all monitors) were classified as "high concentration" monitors, while monitors with moderate (IQR of all monitors) or low (lower quartile of all monitors) concentrations were classified as "moderate concentration" and "low concentration" monitors, respectively. Of the 42 monitors examined, the majority (N = 24) were classified as "moderate concentration" and were characteristic of urban, central site monitors. "High concentration" and "low concentration" sites were primarily representative of near-source and background monitors, respectively. However, not all monitors within 15 km of a point source report high SO_2 values. These select monitors near sources were instead classified as "moderate concentration" or "low concentration" sites.

Out of nine monitors classified as "high concentration" sites, the majority (N = 5 monitors) were located in Cleveland, OH, which has a substantial number of power plant and industrial SO_2 sources. The remaining four "high concentration"

monitors were located near large stationary sources in Pittsburgh, PA and Gila County, AZ. Notably, no monitors in St. Louis, MO or Houston, TX were classified as "high concentration" monitors even although both metropolitan areas contain a number of SO_2 sources, including power plants, chemical manufacturing facilities, shipping ports. The lack of "high concentration" monitors in St Louis, MO and Houston, TX indicate relatively lower SO_2 concentrations, which may reflect more widespread implementation of control technologies on point sources or meteorological factors reducing overall ambient SO_2 levels.

Scatterplots of collocated hourly 5-minute maximum and 1-hour average measurements are displayed by CBSA/metropolitan focus area in Figure 2-28. Each scatterplot indicates data reported at "high," "moderate," and "low" concentration monitors. Furthermore, a variety of peak-to-mean ratios (PMRs) are displayed on each plot to further evaluate the difference in magnitude between hourly 5-minute maximum and 1-hour average concentrations.



Within each focus area, individual monitoring sites are displayed by marker color ("Low Conc" = green, "Moderate Conc" = red, "High Conc" = blue). Peak-to-Mean ratios (PMR) are displayed on each scatter plot as 1:1 (hourly 5-max = 1-h avg), 2:1 (hourly 5-minute maximum is 2 times higher than 1-h avg), and 3:1 (hourly 5-minute maximum is 3X times higher than 1-h avg). Conc = concentration.

Figure 2-28 Scatterplot of hourly 5-minute maximum versus 1-hour average sulfur dioxide concentrations by core-based statistical area/metropolitan focus area.

PMRs have been used extensively in the previous SO_2 NAAQS review to evaluate the distribution of hourly 5-minute maximum concentrations corresponding to a given 1-hour SO_2 concentration (U.S. EPA, 2009b). PMRs are determined by dividing the hourly 5-minute maximum concentration over the 1-hour average concentration. Using this approach, a PMR of 1 demonstrates that hourly 5-minute maximum and 1-hour average concentrations are equivalent. Increasing PMR values (up to a maximum value of 12 in this case) indicate that hourly 5-minute maximum values are increasingly higher than 1-hour average concentrations. For example, a PMR of 2 (shown as 2:1 on Figure 2-28) indicates that hourly 5-minute maximum values are 2 times higher than 1-hour average concentrations, while a value of 3 (shown as 3:1 on Figure 2-28) corresponds to hourly 5-minute maximum peaks 3 times higher than 1-hour average concentrations. PMR values 1 (1:1) through 3 (3:1) are displayed in Figure 2-28.

As demonstrated by the scatterplots in Figure 2-28, the majority of hourly 5-minute maximum SO_2 concentrations fall between a PMR value of 1 and 3, indicating that hourly 5-minute maximum SO_2 concentrations are generally between 1 and 3 times higher than 1-hour average concentrations. On occasion, hourly 5-minute maximum concentrations can be more than 3 times higher than 1-hour average concentrations, and in rare cases, can be up to 12 times higher, particularly when SO_2 concentrations are low (less than 25 ppb). However, at such low concentrations, 5-minute maximum SO_2 values very rarely approach health-relevant concentrations of 200 ppb (i.e., the lowest level where lung function decrements were reported in controlled human exposure studies of individuals with asthma engaged in exercise, see Section 5.2.1.2).

Of all data reported at these sites during 2010−2012, only a small portion of hourly 5-minute data is greater than 200 ppb. As shown in Figure 2-28, these high values primarily occur at the nine "high concentration" sites located in Cleveland, OH; Pittsburgh, PA; and Payson/Phoenix, AZ. At these nine "high concentration" sites, most hourly 5-minute maximum values above 200 ppb occur when 1-hour average concentrations are greater than the primary NAAQS level of 75 ppb. On rare occasions, hourly 5-minute maximum concentrations above 200 ppb correspond to 1-hour average concentrations below 75 ppb. For example, in Cleveland, less than 10% of hourly 5-minute maximum data above 200 ppb approximately 10 hours over a 3 year period) correspond to 1-hour average concentrations below primary NAAQS levels. These results emphasize that 1-hour average concentrations at or below 75 ppb, for the most part, represent hourly 5-minute maximum values below 200 ppb.

To understand how often 5-minute maximum values exceed 200 ppb, Figures 2-29−2-31 display time-series and frequency analysis of hourly 5-minute maximum concentrations reported at "high concentration" sites by CBSA/metropolitan focus area during

2010−2012. As demonstrated by these figures, most hourly 5-minute maximum concentrations above 200 ppb fall between 200 ppb and 400 ppb, with far fewer values above 400 ppb. Among these "high concentration" monitors, the absolute highest hourly 5-minute maximum concentration of 889 ppb is reported at a site in Pittsburgh, PA located within 10 km of three large electric-generating and industrial point sources. Other monitors reporting hourly 5-minute maximum concentrations above 400 ppb are located in Cleveland, OH and Payson/Phoenix, AZ and correspond to monitors located near a large power plant (Cleveland, OH) or a copper smelting facility (Gila County, AZ).

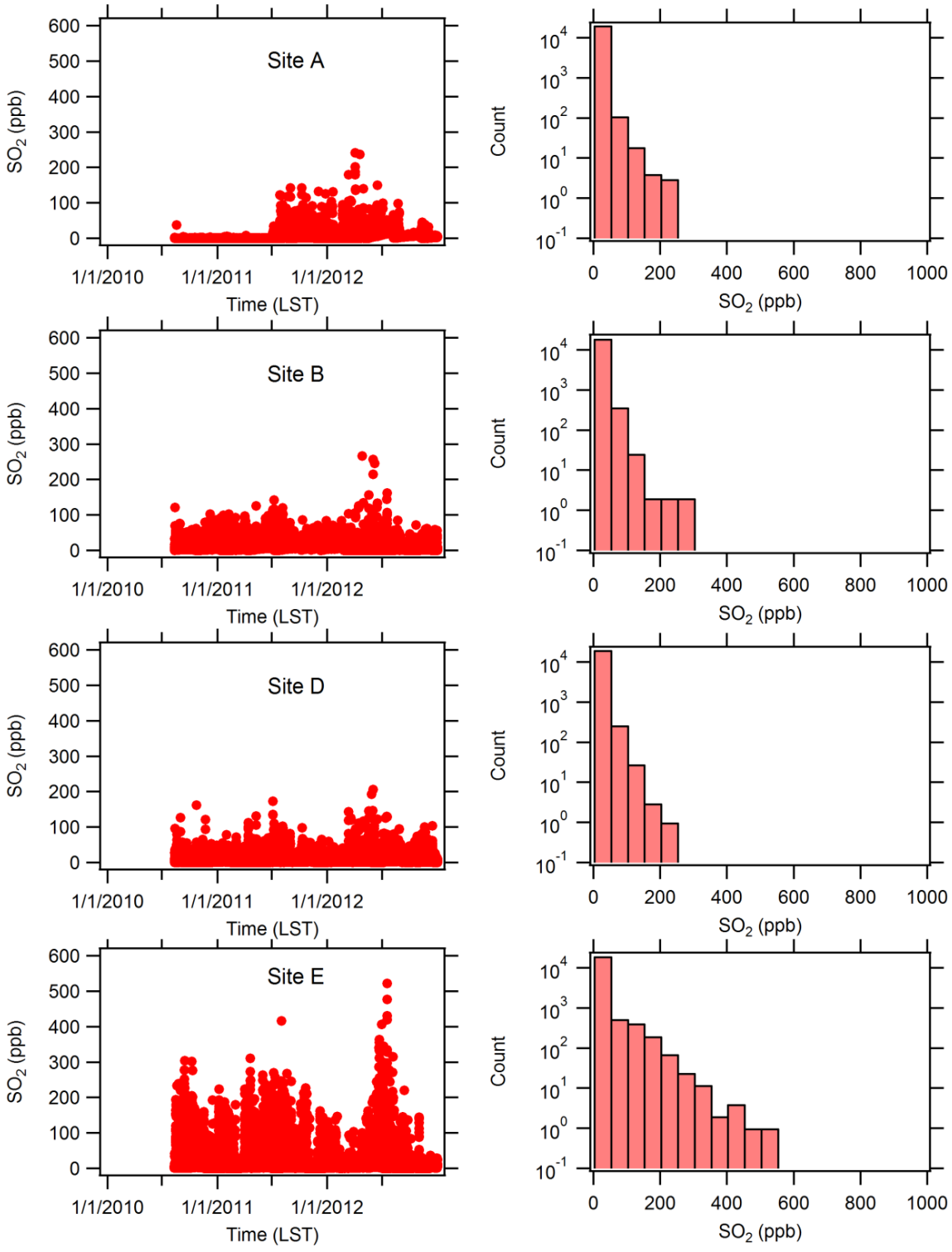


Figure 2-29 Time-series and frequency distribution of hourly 5-minute maximum sulfur dioxide (SO_2) concentrations from four "high concentration" monitors in the Cleveland core-based statistical area.

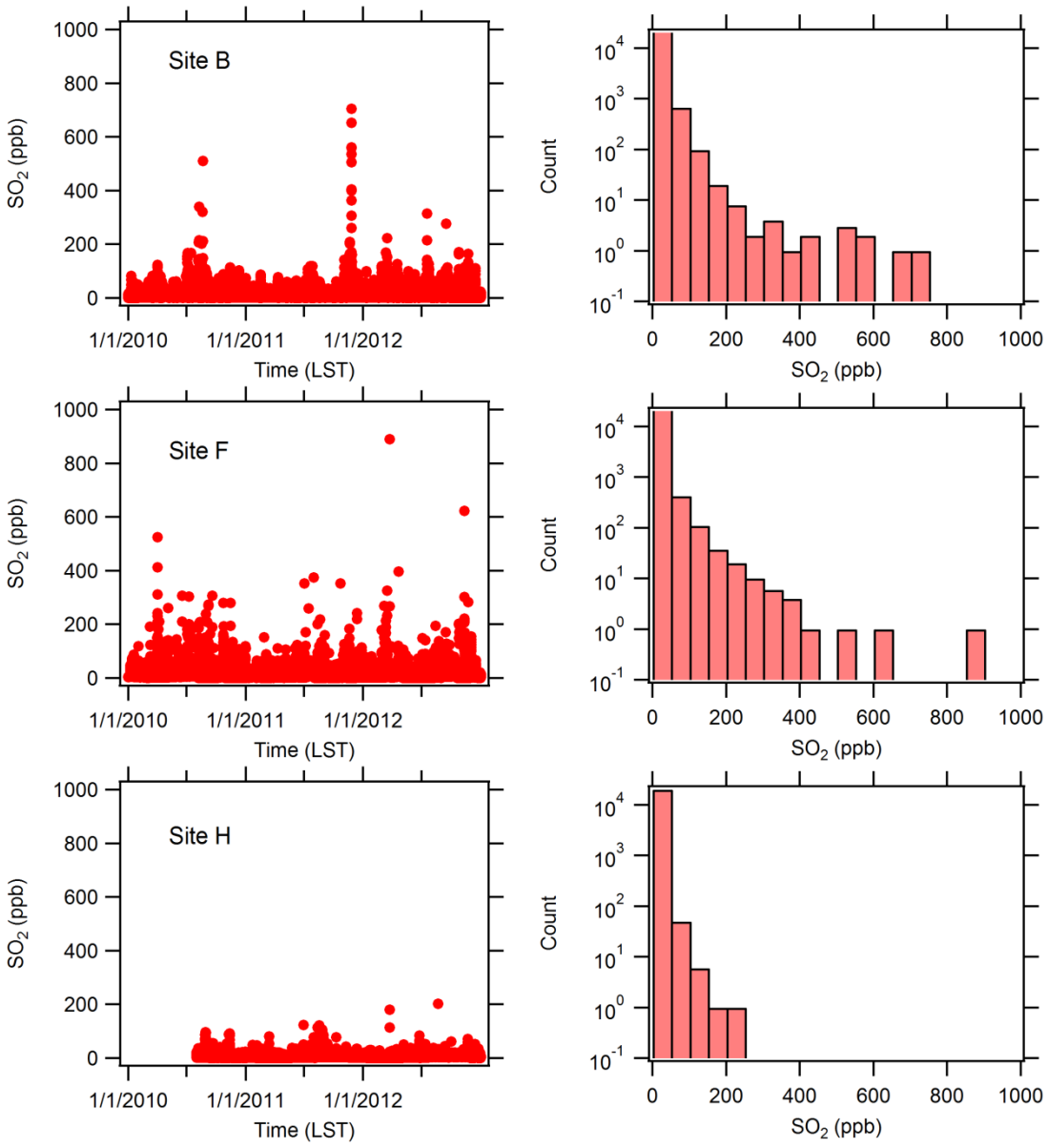


Figure 2-30 Time-series and frequency distribution of hourly 5-minute, maximum sulfur dioxide (SO_2) concentrations from three "high concentration" monitors in the Pittsburgh core-based statistical area.

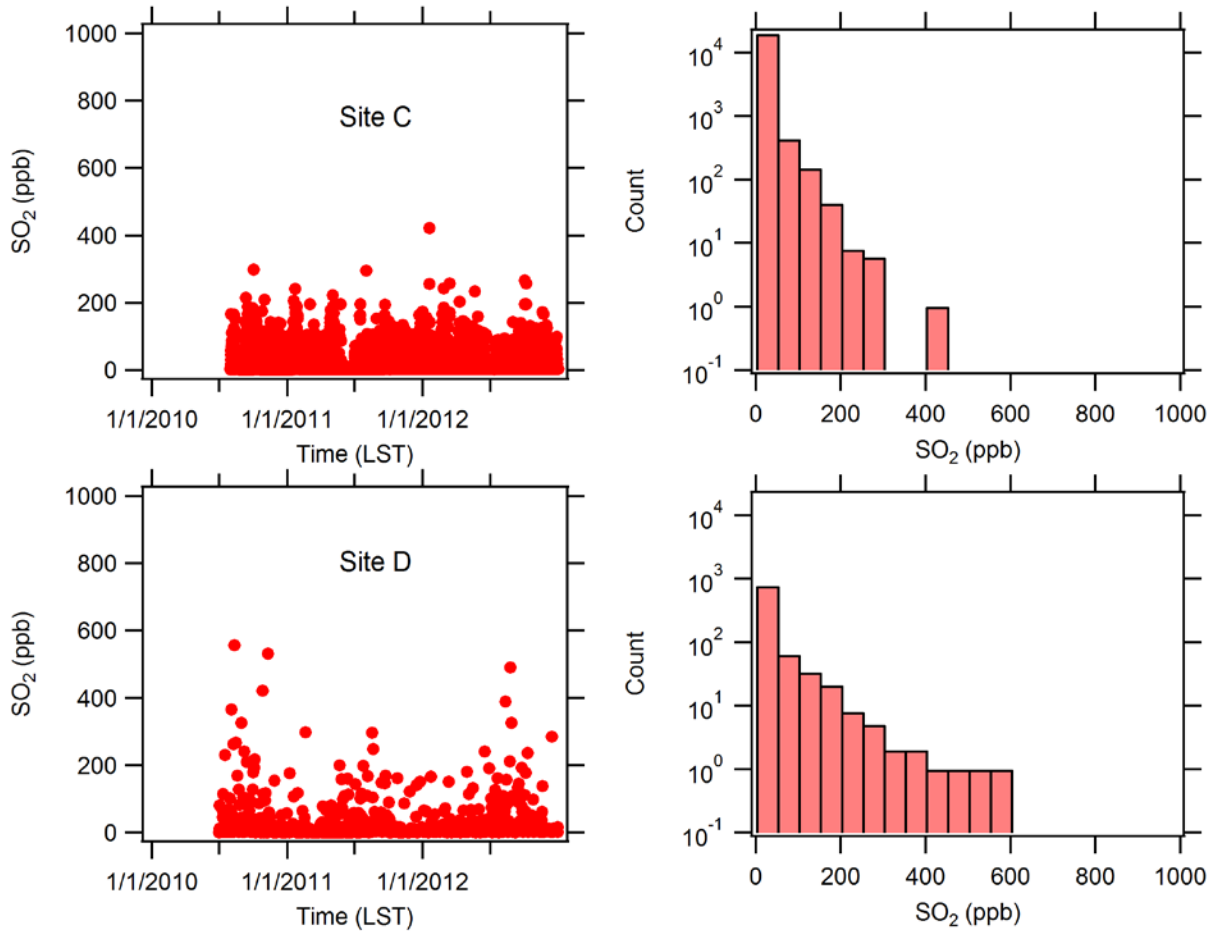


Figure 2-31 Time-series and frequency distribution of hourly 5-minute, maximum sulfur dioxide (SO_2) concentrations from 2 "high concentration" monitors in the Payson/Phoenix, AZ core-based statistical area/metropolitan focus area.

Table 2-11 presents the percent of 5-minute maximum values (during 2010−2012) above 200 ppb at "high concentration" sites in Cleveland, OH; Pittsburgh, PA; and Payson/Phoenix, AZ. The number of hourly 5-minute maximum SO_2 values above 200 ppb varies dramatically by site. For the most part, sites closer to major point sources more frequently report hourly 5-minute peak values above health benchmark levels. This trend is particularly evident in Pittsburgh, PA where up to 44 hourly 5-minute maximum concentrations are above 200 ppb at Site F (located within 10 km of three major point sources). Conversely, only a single 5-minute maximum concentration value was greater than 200 ppb at Site E, located in the urban center. Furthermore, although health-relevant 5-minute peaks (200 ppb, 400 ppb, and 600 ppb) are recorded at every "high

concentration" site, they generally comprise only a small fraction of total data (up to 2%) over the 3-year sampling period (2010−2012).

Table 2-10 Pearson correlation coefficient and peak-to-mean ratio for maximum sulfur dioxide concentrations in core-based statistical areas.

CBSA	N monitors	Correlation Coefficient	Mean PMR[a]	Median PMR[a]
Cleveland, OH	6	0.87−0.94	1.5	1.2
Pittsburgh, PA	9	0.92−0.97	1.4	1.2
New York City, NY	10	0.87−0.98	1.6	1.4
St Louis, MO	6 (only 5 with both measurements)	0.82−0.91	1.8	1.7
Houston, TX	6	0.89−0.95	2.0	1.5
Payson, AZ	4 (only 3 with measurements)	0.84−0.93	1.7	1.4

CBSA = core-based statistical area; N = population number.

[a]Peak-to-mean ratio (PMR) = 5 min max/1-h average.

In summary, hourly 5-minute maximum concentrations above 200 ppb can be expected to occur on rare occasions at some, but not all, monitors located within close proximity to sources. For example, in analyses within six CBSA/metropolitan focus areas, most peak values above 200 ppb are observed at sites classified as "high concentration" monitors, generally corresponding to near-source monitors. However, peak values may not always be detected by near-source monitors, due to meteorological effects or implementation of strategies to reduce local impacts (e.g., effective stack height on power plants).

Table 2-11 Number of hours (percent hours) which hourly 5-minute maximum sulfur dioxide concentrations are above health benchmark levels during 2010−2012.

CBSA	Site ID	Site Label[a]	>200 ppb	>400 ppb	>600 ppb
Cleveland, OH	360350065	A	3 (0.01%)	0 (0%)	0 (0%)
	390350060	B	4 (0.02%)	0 (0%)	0 (0%)
	390350038	D	1 (0.005%)	0 (0%)	0 (0%)
	390850007	E	115 (0.6%)	6 (0.003%)	0 (0%)
	390350045	F	2 (0.009%)	0 (0%)	0 (0%)
Pittsburgh, PA	420030064	B	24 (0.09%)	9 (0.03%)	2 (0.007%)
	420070002	E	1 (0.005%)	0 (0%)	0 (0%)
	420070005	F	44 (0.1%)	5 (0.02%)	2 (0.007%)
Payson, AZ	40070009	C	14 (0.07%)	1 (0.005%)	0 (0%)
	40071001	D	17 (2%)	4 (0.4%)	0 (0%)

CBSA = core-based statistical area; ppb = parts per billion.
[a]Label on CBSA maps [Cleveland (Figure 2-14), Pittsburgh (Figure 2-15), and Payson, AZ (Figure 2-19)]

2.5.4 Background Concentrations

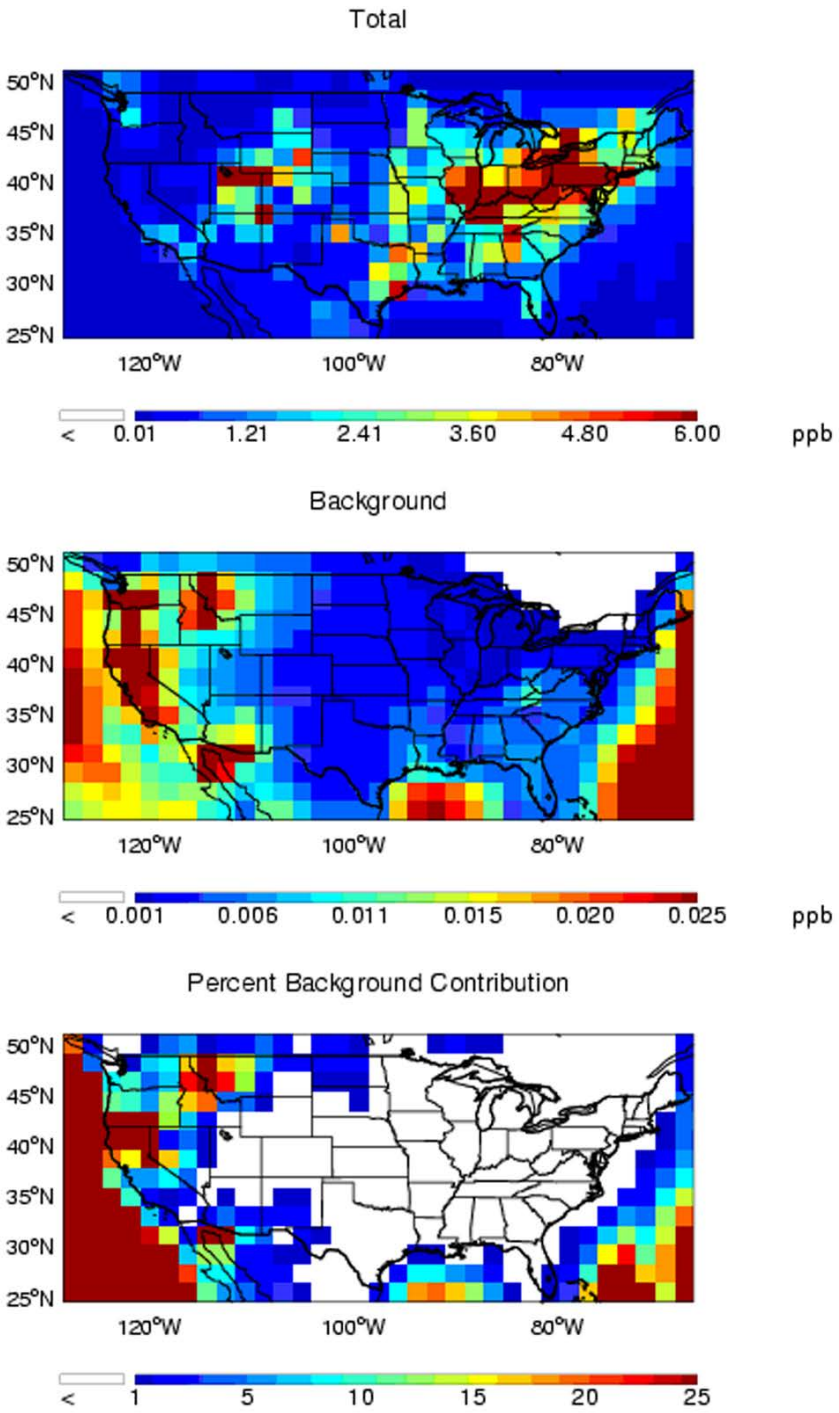
An understanding of the sources and contributions of background SO_2 to SO_2 concentrations in the U.S. is potentially useful in reviewing the SO_2 NAAQS, especially related to days at the upper end of the distribution of SO_2 concentrations. In the context of a review of the NAAQS, it is useful to define background SO_2 concentrations in a way that distinguishes among concentrations that result from precursor emissions that are relatively less controllable from those that are relatively more controllable through U.S. policies.

In previous NAAQS reviews, a specific definition of background concentrations was used and referred to as policy-relevant background (PRB). In those previous reviews, PRB concentrations were defined by EPA as those concentrations that would occur in the U.S. in the absence of anthropogenic emissions in continental North America, defined

here as the U.S., Canada, and Mexico. In the current round of reviews, other definitions are possible depending on the pollutant under consideration.

Contributions to background concentrations include natural emissions of SO_2 and photochemical reactions involving reduced sulfur compounds of natural origin, as well as their long-range transport from outside of North America from any source. As an example, transport of SO_2 from Eurasia across the Pacific Ocean or the Arctic Ocean would carry background SO_2 into the U.S. Section 2.2.5.1 contains a schematic diagram (Figure 2-6) showing the major photochemical processes involved in the sulfur cycle, including natural sources of reduced sulfur species from anaerobic microbial activity in wetlands and volcanic activity. Volcanoes and wildfires are the major natural sources of SO_2. Biogenic emissions from agricultural activities are not considered in the formation of PRB concentrations.

Figure 2-32, which is taken from the 2008 SO_X ISA (U.S. EPA, 2008b), shows global scale three-dimensional model simulations for annual mean SO_2 concentrations in surface air including all sources (both anthropogenic and natural), or the "base case" (top panel); the background simulation (middle panel); and the percentage contribution of the background to the total base case SO_2 (bottom panel). Results shown in Figure 2-32 are for the meteorological year 2001. Maximum concentrations in the base case simulation, greater than 5 ppb, occur along the Ohio River Valley (upper panel). Background SO_2 concentrations are orders of magnitude smaller, below 0.01 per billion (ppb) over much of the U.S. (middle panel). Maximum PRB concentrations of SO_2 are 0.03 ppb. In the U.S. Northwest, there are geothermal sources of SO_2 responsible for 70 to 80% of the background SO_2 concentration; even so, absolute SO_2 concentrations are still of the order of ~2 ppb or less. In these simulations, background contributes less than 1% to present-day SO_2 concentrations in surface air (bottom panel) with the exception of the West Coast where volcanic SO_2 emissions cause high background contributions.



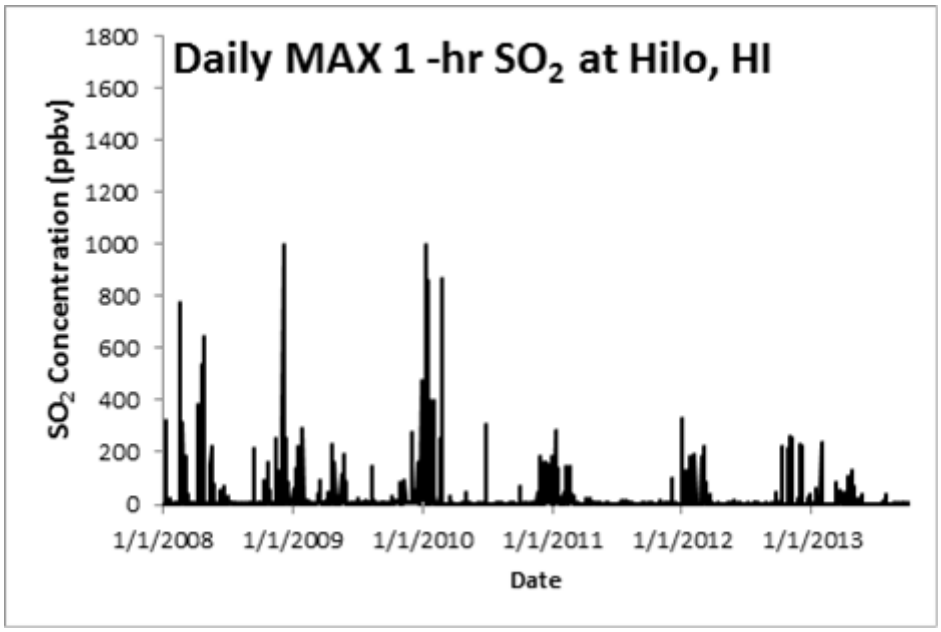
Source: NOAA Geophysical Fluid Dynamics Laboratory.

Figure 2-32 Annual mean model-predicted concentrations of sulfur dioxide (parts per billion) calculated using the MOZART three-dimensional, chemistry-transport model.

Satellite-borne instruments have mapped major SO_2 sources globally and have obtained data showing intercontinental transport. Fioletov et al. (2013) identified a number of "hot-spots" for continuous SO_2 emissions, both anthropogenic and volcanic. Major industrial sources in the Northern Hemisphere are found (e.g., in China, Russia, the United States, the Gulf of Mexico and Saudi Arabia). Major volcanic sources include: Kīlauea, Hawaii 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.

When estimating background concentrations, it is instructive to consider measurements of SO_2 at relatively remote monitoring sites (i.e., sites located in sparsely populated areas not subject to obvious local sources of pollution). Berresheim et al. (1995) used a type of APIMS at Cheeka Peak, WA (48.30EN 124.62EW, 480 m asl) in April 1991 during a field study for DMS oxidation products. SO_2 concentrations ranged between 20 and 40 ppt. Thornton et al. (2002) have also used an APIMS with an isotopically labeled internal standard to determine background SO_2 levels. SO_2 concentrations of 25 to 40 ppt were observed in northwestern Nebraska in October, 1999 at 150 m above ground using the National Center for Atmospheric Research's C-130 research aircraft. These data are comparable to remote central South Pacific convective boundary layer SO_2 data (Thornton et al., 1999).

As noted earlier, volcanic sources of SO_2 in the U.S. are found in the Pacific Northwest, Alaska, and Hawaii. The greatest potential domestic effects from volcanic SO_2 occur on the island of Hawaii. Nearly continuous venting of SO_2 from Mauna Loa and Kīlauea produces SO_2 in high concentrations that can affect populated areas on the island. Figure 2-33a shows the time series for daily 1-hour maximum SO_2 concentrations at Hilo, HI, (population of approximately 40,000) which is located about 50 km northeast of Kīlauea. Figure 2-33b shows the same time series at Pahala (population ~1,300) which is located about 30 km southeast of Kīlauea. As demonstrated by these figures, daily 1-hour maximum levels can reach levels greater than 1,000 ppb. In addition to these two sites, other communities scattered throughout the southern half of the island are exposed to such high SO_2 levels as indicated in Figure 2-34 (Longo et al., 2010).



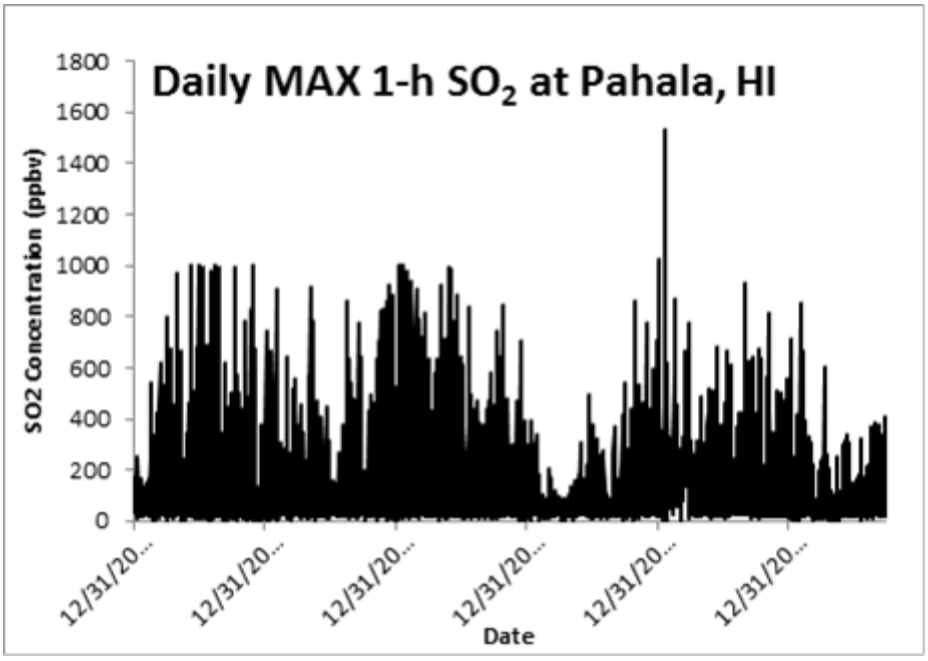
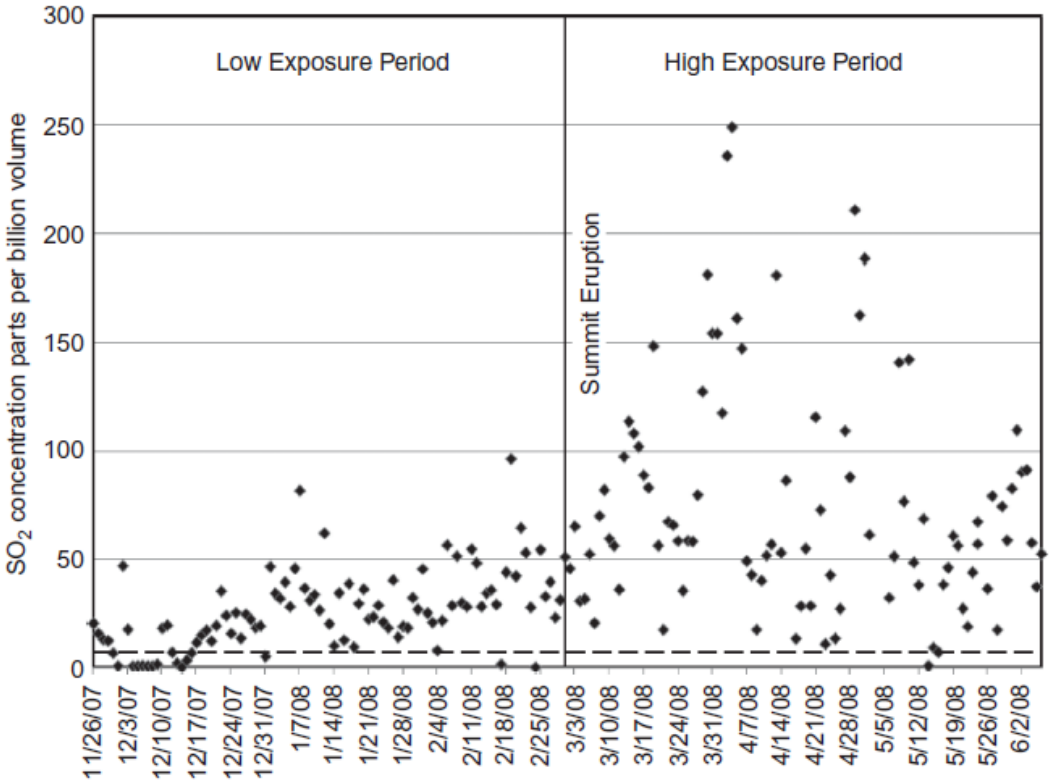


Figure 2-33 Daily maximum 1-hour sulfur dioxide (SO_2) concentrations measured at (a) Hilo, HI and (b) Pahala, HI.



Note. The dashed line represents the World Health Organization 24-hour average 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).

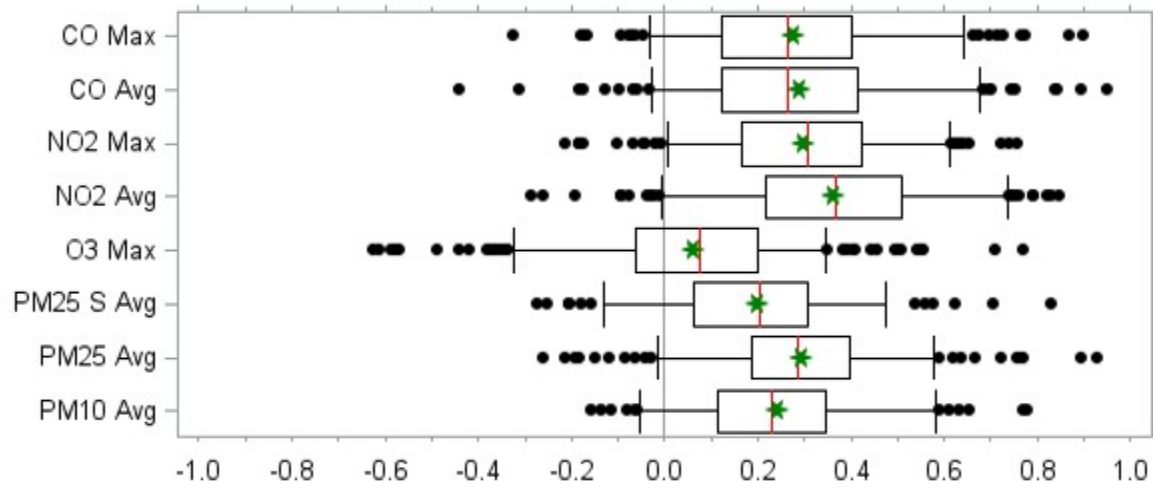
Figure 2-34 Average 24-hour ambient sulfur dioxide concentrations during low and high (volcanic gas) vog-exposure study periods (November 26, 2007 to June 6, 2008) for Ka'u District, located downwind of Kīlauea Volcano.

2.5.5 Copollutant Correlations

Determining independent health effects of a given air pollutant is an important, yet complex, component of air pollution health studies. In an epidemiologic study, health effects of an individual pollutant can be subject to biases (positive or negative) if other copollutants within the analyses are strongly correlated with the pollutant of concern. In this section, correlations between SO_2 and other NAAQS pollutants are discussed to evaluate the potential for copollutant confounding of SO_2 health effects in epidemiologic analyses.

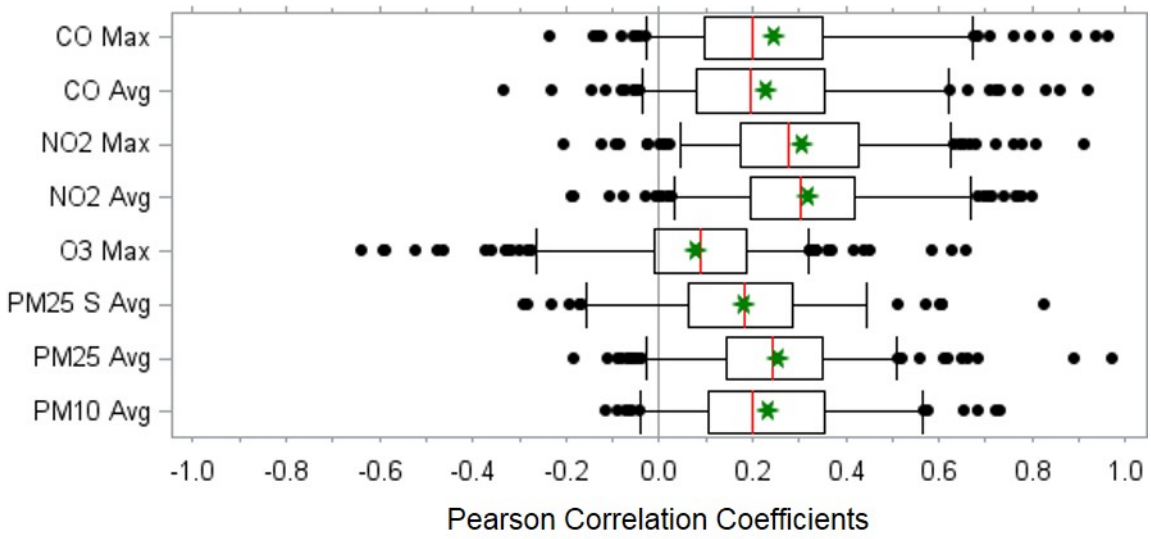
For copollutant correlation analysis, colocated air quality data reported within the EPA AQS repository system during 2010−2012 were used. Air quality data met the 75% data completeness criteria presented earlier in this chapter in Table 2-6. Daily air quality metrics representing either maximum or average concentration values were used. Pearson correlations were utilized to evaluate temporal correlations among SO_2 and NAAQS copollutants. In addition, correlations between SO_2 and $PM_{2.5}$ sulfur were examined because $PM_{2.5}$ sulfur serves as a proxy for SO_2 oxidation products (i.e., sulfate) and may have confounding effects on SO_2 health outcomes. Correlations were also stratified by season to determine whether copollutant confounding varied by time of year.

Figures 2-35 and 2-36 display the distribution of correlations between NAAQS copollutants and SO_2 daily metrics (24-hour average, 1-hour maximum). In these boxplots, the interquartile range of collocated copollutant correlations are expressed in the box median values are reported by the red line within the box; and mean values are presented as a green star. The 10th and 90th percentile of correlations are shown by the bottom and top whiskers, respectively. Outlier copollutant correlations are presented by black markers.



Note: Shown are the median (red line), mean (green star), and inner-quartile range (box), 5th and 96th percentile (whiskers) and extremes (black circles)

Figure 2-35 Distribution of Pearson correlation coefficients for comparison of daily 24-hour average sulfur dioxide from the year-round data set with colocated National Ambient Air Quality Standards pollutants (and $PM_{2.5}$ S) from Air Quality System during 2010−2012.



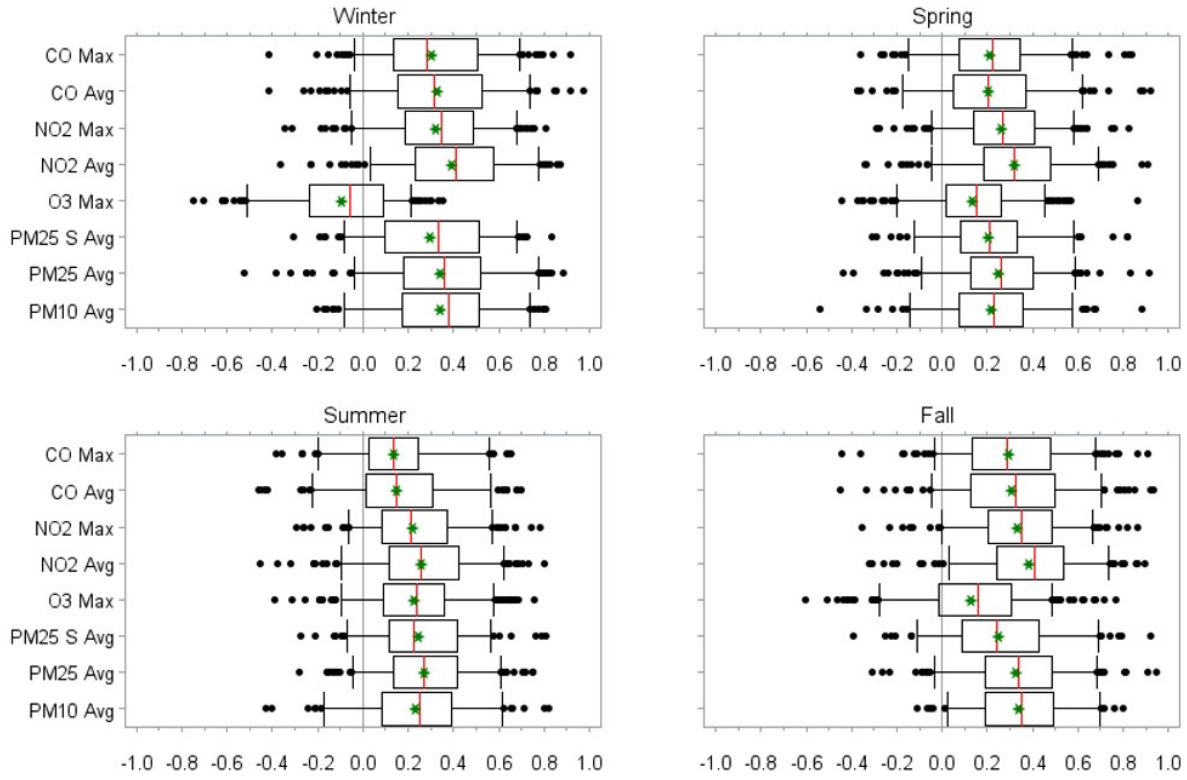
Note: Shown are the median (red line), mean (green star), and inner-quartile range (box), 5th and 96th percentile (whiskers) and extremes (black circles)

Figure 2-36 Distribution of Pearson correlation coefficients for comparison of daily 1-hour maximum sulfur dioxide from the year-round data set with colocated National Ambient Air Quality Standards pollutants (and $PM_{2.5}$ S) from Air Quality System during 2010−2012.

While 24-hour average SO_2 exhibits a wide range of correlations with NAAQS copollutants, correlations are generally low to moderate, with all median Pearson correlations below 0.4 (Figure 2-35). The lowest correlations are observed between SO_2 and O_3, with median Pearson correlations below 0.1. Slightly higher correlations are observed between SO_2 and other primary NAAQS pollutants (NO_2 and CO), with median correlations between 0.3 and 0.4. On occasion, correlations close to 1 or below 0 are observed, but only occur at a few outlier monitoring sites. Comparatively, copollutant correlations of daily 1-hour maximum SO_2 in Figure 2-36 are similar, but slightly lower than copollutant correlations based on SO_2 24-hour average values in Figure 2-35. The range of Pearson correlations between daily 1-hour maximum SO_2 and NAAQS pollutants is below 0.3, with the exception of NO_2, which exhibits median correlations slightly above 0.3.

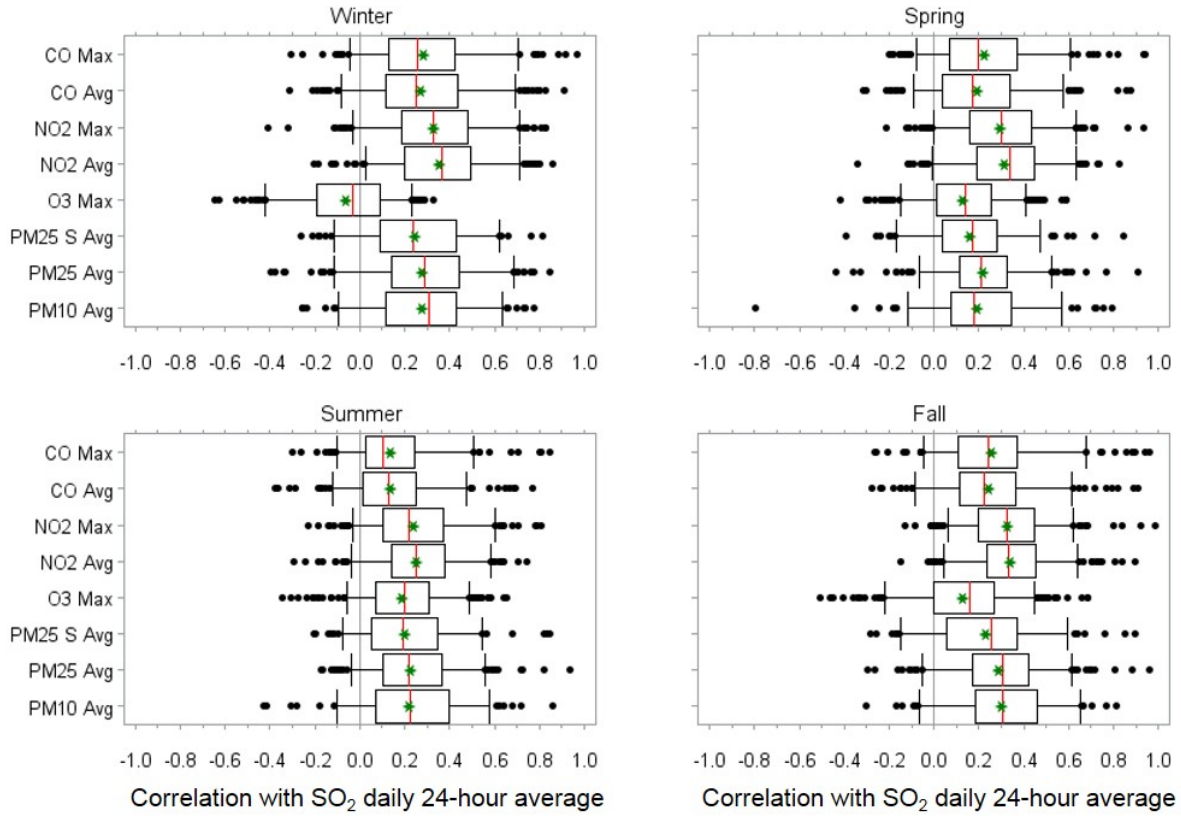
Correlations between SO_2 and NAAQS copollutants demonstrate very little variability across seasons (Figures 2-37 and 2-38). All median and average copollutant correlations are below 0.4 across every season. The only substantial seasonal difference in SO_2 correlations occurs during the winter, when SO_2 exhibits lower negative correlations with O_3 (median winter correlations = −0.1). The lower wintertime SO_2-O_3 correlation could

be directly linked to relatively low O_3 concentrations during this time of year due to less photochemical O_3 production. At such low ambient levels that are presumably near the instrument detection limit, O_3 measurements may be subject to substantial measurement error, which may lead to poor correlations between O_3 and other pollutants, including SO_2.



Note: Shown are the median (red line), mean (green star), and inner-quartile range (box), 5th and 96th percentile (whiskers) and extremes (black circles).

Figure 2-37 Distribution of Pearson correlation coefficients for comparison of daily 24-hour average sulfur dioxide stratified by season with colocated National Ambient Air Quality Standards pollutants (and $PM_{2.5}$ S) from Air Quality System during 2010−2012.



Note: Shown are the median (red line), mean (green star), and inner-quartile range (box), 5th and 96th percentile (whiskers) and extremes (black circles).

Figure 2-38 Distribution of Pearson correlation coefficients for comparison of daily 1-hour maximum sulfur dioxide stratified by season with colocated National Ambient Air Quality Standards pollutants (and $PM_{2.5}$ S) from Air Quality System during 2010−2012.

Overall, daily and hourly SO_2 metrics generally exhibit low to moderate correlations with other collocated NAAQS copollutants at AQS monitors, exhibiting median Pearson correlations around 0.2−0.4. However, given that a small subset of monitors report relatively strong copollutant correlations, confounding may need to be considered on a study-by-study basis.

2.6 Atmospheric Modeling

This section discusses various modelling techniques to estimate ambient concentrations of SO_2. Different types of models are discussed in terms of their capabilities, strengths and limitations.

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. Using equations that represent the physical and chemical atmospheric processes that govern dispersal and fate, they 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 with 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-hour average concentrations associated with major sources often contain extreme gradients, 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 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 is 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 the following: 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)], that are 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)], where chemical processes are explicitly handled and 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 were available.

It is not uncommon for the terms "dispersion model" and "Gaussian model" to be associated with each other to the exclusion of other types of ATD models. For primary pollutants such as SO_2, dispersion models used within the United States for applications such as determination of compliance with standards and determination of primary pollutant impacts from new or proposed sources are most commonly of a steady-state Gaussian form (U.S. EPA, 2010a). 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 where 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 meters of the source. Near field or near-to-the-source dispersion is the real strength of steady state modeling.

In addition to compliance and new source analyses, dispersion models and particularly Gaussian models have been used in support of environmental health studies where the temporal and spatial distribution of concentrations are needed at a resolution beyond that of typical grid models such as CMAQ or that of available monitoring networks (Özkaynak et al., 2013; Vette et al., 2013). In these studies, models are applied in combination with monitoring data either separately where the monitoring establishes background or by statistically blending the modeling and monitoring together.

While there are several dispersion models recommended by the EPA (U.S. EPA, 2013d) for specialized applications involving SO_2 (e.g., BLP for aluminum reduction plants;

CALPUFF for Class I applications in complex flow), AERMOD is the workhorse. 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 consideration for the source characteristics of point, area, and volume source types. In convective conditions, where dispersion provides for 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). In light wind conditions, the model simulates a meandering plume and has turbulence-based lower limits on the transport wind speed.

AERMOD and models like it are designed to simulate concentrations on an hourly increment. Longer term concentrations are obtained by averaging the 1-hour values. While the model may be appropriate in some cases for averages less than 1 hour (should the input data be available), model evaluations have focused on averaging periods of 1 hour and greater [e.g., Perry et al. (2005)]. 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). This, however, can be challenging especially for light winds and long transport distances. AERMOD is also somewhat 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). In urban areas, AERMOD uses a simple 4-hour half-life assumption for reducing SO_2 in the plume with travel time. 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 relatively close to the source, chemistry is not expected to play a significant role in determining compliance with primary standards.

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 concentrations and measured concentrations. Monitored data (within sampling error) represents actual realizations of events while modeling estimates represent ensemble mean values (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%. He points out that these levels of model to monitor differences 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 value will likely differ, sometimes significantly, because of 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). Therefore, for evaluations of a model's ability to simulate high concentrations within the modeling domain, it is important to include an analysis of modeled and monitored concentration distributions.

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 square 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) that also provided for the estimation of confidence limits on the values computed. Chang and Hanna (2004) also discussed exploratory analysis methods of plotting and analyzing the modeled and measured values. They also pointed out that the most useful model evaluation studies are those that examine a number of models with a number of field studies.

The intended use of a model and the objective of a model evaluation guide the selection of evaluation criteria. For models intended for application to compliance assessments

(e.g., related to the 1-hour 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 26 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.

At the time of its inclusion into the EPA Guideline on Air Quality Models (U.S. EPA, 2005b), AERMOD's performance was evaluated against seventeen field-study databases (Perry et al., 2005) over averaging times from 1 hour to 1 year. 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-hour average RHC to monitored RHC to range 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-hour average ratios ranged from 1.0 to 1.35 (i.e., a slight tendency to over-predict the high concentrations). Examination of quantile-quantile plots supported the findings that the model was capturing the upper end of the 1 and 3-hour average 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 for AERMOD was 0.77 and for ADMS was 0.80, each a small under-prediction. 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 over-predict (with ADMS less biased). Unlike the ratio of maximum values, MG is a measure of performance over the entire distribution of concentrations.

In a recent evaluation involving a study of tracer emissions and measurements along a four-lane freeway in California (Heist et al., 2013), AERMOD and ADMS displayed a slight average under-prediction (FB, of 0.13 and 0.09, respectively with FB = 0 representing an unbiased model). While there is expected scatter in these time and space pairings of model to observations, over 75% of the estimates for both models were within a factor of two. Finally, Hurley (2006) evaluated AERMOD and two Australian models

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

With the adoption of the new 1-hour SO_2 and NO_2 standards, 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 Modeling Conference on Air Quality in 2012 (U.S. EPA, 2012a). Among them were concerns about simulations in stable conditions with light and meandering winds, modeling of emissions from haul roads, plume chemistry and building downwash. Research in many of these areas is underway. 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 reducing model uncertainty and expanding the applicability. Model evaluations over a wide range of conditions have demonstrated the skill that dispersion models possess and the value they provide in estimating hourly averaged concentrations.

2.7 Summary

Of the several reactive sulfur oxide chemical species, only SO_2 is of importance to U.S. air quality, due to its historically high atmospheric concentrations and the locations of its sources with respect to human populations. As a consequence of several U.S. air quality regulatory programs, emissions of SO_2 have declined by approximately 70% for all major sources since 1990. Coal-fired electric generating units (EGUs) remain the dominant source by nearly an order of magnitude above the next highest source (coal-fired boilers), emitting 4,500,000 tons of SO_2 annually, according to the 2011 NEI.

Beyond the strength 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 and local meteorology. The primary gas phase photochemical SO_2 oxidation mechanism requires the hydroxyl radical. Another 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., small 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.

The atmospheric photochemical SO_2 oxidation processes, coupled with variable meteorological conditions, including wind, atmospheric stability, humidity, and cloud/fog cover, influence observed SO_2 concentrations at monitoring locations.

Dispersion models can be used to estimate SO_2 concentrations in locations where monitoring is not practical or sufficient (Section 2.6.1). 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 human exposure to SO_2 in epidemiologic studies (Section 3.2.2.1, Chapter 5). The widely-used dispersion model AERMOD is designed to simulate hourly concentrations which can then be averaged to yield longer-term concentrations. Multiple evaluations of AERMOD's performance against field study databases over averaging times from 1 hour to 1 year have indicated that the model is relatively unbiased in estimating upper-percentile 1-hour concentration values. Uncertainties in model predictions are influenced by uncertainties in model input data, particularly emissions and meteorological conditions (e.g., wind).

Changes were undertaken to the existing EPA monitoring network as a result of the new 1-hour primary NAAQS standard promulgated in 2010. 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 asthmatics following a 5−10 minute exposure of SO_2 above 200 ppb (Section 5.2.1.2). Since the publication of the 2008 SO_X ISA (U.S. EPA, 2008b), there are more than 400 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 daily 1-hour maximum SO_2 concentration reported during 2010−2012 is 9 ppb. However, peak concentrations (99th percentile) of daily maximum SO_2 concentrations can approach 75 ppb at some monitors located near large anthropogenic or natural sources (e.g., volcanoes). Similarly, new 5-minute data demonstrate that most hourly 5-minute maximum concentrations are well below the short-term health benchmark levels of 200 ppb, and under rare occasions (99th percentile and above) can be greater than 200 ppb at some monitors near anthropogenic sources such as EGUs.

Given the relatively short atmospheric lifetime of SO_2, urban spatial variability was emphasized in this chapter. SO_2 is highly variable across urban spatial scales, exhibiting

moderate to poor correlations between SO_2 measured at different monitors across a metropolitan area. This high degree of urban spatial variability may not be fully captured by central site monitoring estimates; thus, it has implications for the interpretation of human exposure and health effects data.

Sulfur dioxide correlations with copollutants tend to vary across location, study and SO_2 averaging time. Daily SO_2 correlations with other NAAQS copollutants are generally moderate to low. Median daily SO_2 correlations with PM, NO_2, and CO range from 0.2−0.4 for 2010−2012, while the median daily copollutant correlation of SO_2 with O_3 is 0.1. Daily SO_2 copollutant correlations for all pollutants can be greater than 0.7 on rare occasions. Given that a small subset of monitors report relatively strong copollutant correlations, the potential for SO_2 copollutant confounding may need to be considered on a study-by-study basis.

References for Chapter 2

Atkinson, R; Lloyd, AC. (1984). Evaluation of kinetic and mechanistic data for modeling of photochemical smog. J Phys Chem Ref Data 13: 315-344.

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

Barnes, I; Becker, KH; Mihalopoulos, N. (1994). An FTIR product study of the photooxidation of dimethyl disulfide. J Atmos Chem 18: 267-289.

Barnes, I; Becker, KH; Starcke, J. (1991). Fourier-transform ir spectroscopic observation of gaseous nitrosyl iodine, nitryl iodine, and iodine nitrate. 95: 9736-9740.

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

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

Berresheim, H; Wine, PH; Davis, DD. (1995). Sulfur in the atmosphere. In HB Singh (Ed.), Composition, chemistry, and climate of the atmosphere (pp. 251-307). New York, NY: Van Nostrand Reinhold.

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

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? (pp. 8-21). (ME522). Wellington, New Zealand: Ministry for the Environment. http://www.mfe.govt.nz/publications/air/atmospheric-dispersion-modelling-jun04/html/page5.html

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

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

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 TKK Holland H.D (Ed.), Treatise on geochemistry, second edition (pp. 559-591). Oxford: Elsevier.

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

Calkins, WH. (1994). The chemical forms of sulfur in coal - a review. Fuel 73: 475-484.

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

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

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.

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

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.

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.

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

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

Cox, WM; Tikvart, JA. (1990). A statistical procedure for determining the best performing air quality simulation model. Atmos Environ 24: 2387-2395. http://dx.doi.org/10.1016/0960-1686(90)90331-G

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

Draxler, RR. (1999). HYSPLIT_4 user's guide. Available online

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.

Fioletov, VE; McLinden, CA; Krotkov, N; Moran, MD; Yang, K. (2011). Estimation of SO2 emissions using OMI retrievals. Geophys Res Lett 38. 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

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

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 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 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

Heist, D; Isakov, V; Perry, S; Snyder, M; Venkatram, A; Hood, C; Stocker, J; Carruthers, D; Arunachalam, S; Owen, RC. (2013). Estimating near-road pollutant dispersion: A model inter-comparison. Transport Res Transport Environ 25: 93-105. http://dx.doi.org/10.1016/j.trd.2013.09.003

Hidy, GM. (1994). Atmospheric sulfur and nitrogen oxides: Eastern North American source-receptor relationships. San Diego: Academic Press.

Honninger, G; von Friedeburg, C; Platt, U. (2004). Multi axis differential optical absorption spectroscopy (MAX-DOAS). Atmos Chem Phys 4: 231-254.

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

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.

Jacob, DJ. (1999). Introduction to atmospheric chemistry. Princeton, NJ: Princeton University Press.

Jacobson, MZ. (2002). Atmospheric pollution: History, science, and regulation. New York: Cambridge University Press.

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

Keene, WC; Sander, R; Pszenny, AAP; Vogt, R; Crutzen, PJ; Galloway, JN. (1998). Aerosol pH in the marine boundary layer: A review and model evaluation [Review]. J Aerosol Sci 29: 339-356.

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

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

Langner, J; Rodhe, H. (1991). A global three-dimensional model of the tropospheric sulfur cycle. J Atmos Chem 13: 225-263.

Lee, C; Brimblecombe, P. (2015). Sources of global carbonylsulfide, carbondisulfide and organosulfides. Earth Sci Rev.

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

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, 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

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; Yang, W, ei; 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

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: 16,255-216,265. http://dx.doi.org/10.1029/96JD03347

Madigan MT, M, artino JM. (2006). Brock biology of microorganisms (11th ed.). New Jersey: Pearson.

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; 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

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: n/a-n/a. http://dx.doi.org/10.1002/2013JD019771

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

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

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

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

Olesen, HR; Lofstrom, P; Berkowicz, R; Jensen, AB. (1992). An improved dispersion model for regulatory use - The OML model. In Air pollution modelling and its application IX. New York, New York: Plenum Press. http://dx.doi.org/10.1007/978-1-4615-3052-7_3

Özkaynak, H; Baxter, LK; Burke, J. (2013). Evaluation and application of alternative air pollution exposure metrics in air pollution epidemiology studies [Editorial]. J Expo Sci Environ Epidemiol 23: 565. http://dx.doi.org/10.1038/jes.2013.50

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

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.

Pinto, JP; Turco, RP; Toon, OB. (1989). Self-limiting physical and chemical effects in volcanic eruption clouds. J Geophys Res 94: 11,165-111,174.

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. http://dx.doi.org/10.1029/2009JD013556

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

Ravishankara, AR; Rudich, Y; Talukdar, R; Barone, SB. (1997). Oxidation of atmospheric reduced sulphur compounds: Perspective from laboratory studies. Philos Trans R Soc Lond B Biol Sci 352: 171-181.

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

Schlesinger, WH. (1997). Biogeochemistry: an analysis of global change. San Diego: Academic Press.

Seinfeld, JH; Pandis, SN. (1998). Atmospheric chemistry and physics: From air pollution to climate change. New York: John Wiley & Sons. http://dx.doi.org/10.1063/1.882420

Seinfeld, JH; Pandis, SN. (2006). Atmospheric chemistry and physics: from air pollution to climate change. Hoboken, New Jersey: John Wiley & Sons.

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.

Streets, DG; Lu, Z; de Foy, B; Duncan, BN; Lamsal, LN; Li, C. (2014). Using satellite observations to measure power plant emissions and their trends [Magazine]. EM: Environmental Manager, February.

Sykes, RI; Parker, S; Henn, D; Chowdhury, B. (2007). SCIPUFF version 2.3 technical documentation. Princeton, New Jersey: L-3 Titan Corp.

Thornton, DC; Bandy, AR; Blomquist, BW; Driedger, AR; Wade, TP. (1999). Sulfur dioxide distribution over the Pacific Ocean 1991-1996. J Geophys Res Atmos 104: 5845-5854. http://dx.doi.org/10.1029/1998JD100048

Thornton, DC; Bandy, AR; Tu, FH; Blomquist, BW; Mitchell, GM; Nadler, W; Lenschow, DH. (2002). Fast airborne sulfur dioxide measurements by atmospheric pressure ionization mass spectrometry (APIMS). J Geophys Res 107: 13-11 - 13-19. http://dx.doi.org/10.1029/2002JD002289

Toumi, R. (1994). BrO as a sink for dimethylsulfide in the marine atmosphere. Geophys Res Lett 21: 117-120. http://dx.doi.org/10.1029/93GL03536

U.S. EPA (U.S. Environmental Protection Agency). (1985). Chemical transformation modules for eulerian acid deposition models. Volume 1 The gas-phase chemistry. Project Summary. (600S385015). Research Triangle Park, NC: National Center for Atmospheric Research. http://nepis.epa.gov/exe/ZyPURL.cgi?Dockey=2000TST9.txt

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). (2008b). Integrated science assessment for sulfur oxides: Health criteria [EPA Report]. (EPA/600/R-08/047F). Research Triangle Park, NC: U.S. Environmental Protection Agency, National Center for Environmental Assessment. http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=198843

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). SO2 network review and background. http://www.regulations.gov

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). (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 http://www.epa.gov/air/airtrends/sulfur.html

U.S. EPA (U.S. Environmental Protection Agency). (2013d). Preferred/recommended models. U.S. Environmental Protection Agency, Technology Transfer Network Support Center for Regulatory Atmospheric Modeling. http://www.epa.gov/ttn/scram/dispersion_prefrec.htm

USGS (U.S. Geological Survey). (1999). Potentially active volcanoes of Western United States. U.S. Department of the Interior, USGS. http://vulcan.wr.usgs.gov/LivingWith/VolcanicPast/Notes/map_potentially_active.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

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

Vette, A; Burke, J; Norris, G; Landis, M; Batterman, S; Breen, M; Isakov, V; Lewis, T; Gilmour, MI; Kamal, A; Hammond, D; Vedantham, R; Bereznicki, S; Tian, N; Croghan, C. (2013). The Near-Road Exposures and Effects of Urban Air Pollutants Study (NEXUS): Study design and methods. Sci Total Environ 448: 38-47. http://dx.doi.org/10.1016/j.scitotenv.2012.10.072

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

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

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

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). (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/

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

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

CHAPTER 3 EXPOSURE TO AMBIENT SULFUR DIOXIDE

3.1 Introduction

The 2008 SO_X ISA (U.S. EPA, 2008b) evaluated 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 exposure and ambient concentrations, and discussed the implications of using ambient SO_2 concentrations to estimate exposure in epidemiologic studies. As discussed previously, this chapter will focus on SO_2 because other gaseous SO_X species are not present in the atmosphere in concentrations significant for human exposures. This chapter summarizes that information and presents new information regarding exposure to ambient SO_2. Specific 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 Methodological Considerations for Use of Exposure Data

This section describes techniques that have been used to measure microenvironmental concentrations of SO_2 for estimating personal SO_2 exposures and the results of the studies using those techniques. Previous studies from the 2008 SO_X ISA (U.S. EPA, 2008b) are described along with newer studies that evaluate indoor−outdoor concentration relationships, associations between personal exposure and ambient monitor concentration, and exposure to multiple copollutants in conjunction with SO_2. Tables are provided to summarize important study results.

3.2.1 Measurements

3.2.1.1 Central Site Monitoring

Central site monitors are primarily used to determine whether attainment goals are met under the Clean Air Act. However, central site monitoring data are also often used in epidemiologic studies to represent exposure to SO_2, as discussed previously in

Section 2.5.2.2 and in this chapter in Section 3.3.5. Methods and uncertainties regarding measurements made by central site monitors are described in Section 2.4. Various uses of these data are possible depending on the design of the epidemiologic study. Short-term (e.g., daily) 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 emissions of SO_2 (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. Section 3.3.3.2 discusses exposure error due to spatial variability in SO_2 concentration and the potential influence of that error on epidemiologic effect estimates. Briefly, SO_2 has moderate to high spatial variability within an urban area, resulting in some level of exposure error for individuals not living near a monitor. This exposure error typically attenuates effect estimates in time-series studies, while bias may occur in either direction for effect estimates in long-term studies. This topic will be discussed further in Section 3.3.5. Widening of confidence intervals due to this exposure error is generally expected for all study types.

Central site monitoring is also subject to instrument biases and uncertainties that introduce error into the measurement, as described in detail in Section 2.4.2 and Section 3.3.3.4. Ultraviolet fluorescence (UVF) detection of SO_2 has a high detection limit relative to ambient levels, potentially introducing uncertainty into exposure estimates. UVF detection is subject to positive biases in concentration measurements due to stray light in the optical measurement chamber and fluorescence at or near the same wavelength as SO_2 by volatile organic compounds (VOCs), PAHs, other aromatic hydrocarbons, and NO. Relative humidity can cause negative biases in concentration measurements and can cause suppression of fluorescence. The effect of positive or negative biases depends on epidemiologic study design, as described further in Section 3.3.5.

3.2.1.2 Personal Monitoring Techniques

As described in the 2008 SO_X ISA (U.S. EPA, 2008b), both active and passive samplers have been used to measure personal exposure to SO_2. The Harvard-EPA annular denuder system is an active sampler initially developed to measure particles and acid gases simultaneously (Brauer et al., 1989; Koutrakis et al., 1988). The system draws air at 10 L/minute past an impactor to remove particles and then through an annular denuder coated with sodium carbonate to trap SO_2 and other acid gases. The denuder is 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 exposure.

An emerging area in environmental monitoring is the development of small, low-cost sensors and sensing platforms suitable for use by the general public. For example, Al-Ali et al. (2010) set up a mobile data acquisition system consisting of a commercial sensor array and global positioning system (GPS) unit interfaced via modem to a stationary server with the capability to improve spatiotemporal resolution. Additionally, several different designs have been proposed in recent years for sensors using nanomaterials or light-based detection. For example, microelectrodes using nanomaterials, such as a film of single-walled carbon nanotubes (Zhang et al., 2013b; Cai et al., 2012; Yao et al., 2011), a CdS semiconductor sensor (Fu, 2013), a zinc phthalocyanine film (Jaisutti and Osotchan, 2012), ZnO nanorod flowers (Peng et al., 2013), graphene (Ren et al., 2012), and a palladium polymer (Meka et al., 2008), reduce noise from ionization of interferents with shorter sensing times and hence improved sensitivity and specificity. New designs, such as that of Zhang et al. (2013b), in which a triple carbon nanotube sensor with two electric fields in opposite direction acts to reduce spurious charge, enhance sensitivity of the detectors. Light absorption techniques have been developed based on the absorption of SO_2 in the ultraviolet spectrum at 286 nm; because the absorption differs from that of NO_2 (at 403 nm in the visible/ultraviolet range), these detectors can attain improved specificity using a light-emitting diode (LED) (Degner et al., 2010; Hawe et al., 2008) or

laser (Simeonsson et al., 2012; Gondal and Dastageer, 2008) light source. Moreover, the LED designs have achieved detection limits of 1 ppm (Degner et al., 2010) and 15 ppm (Hawe et al., 2008), while the laser-based sensors have detection limits of 0.5 ppb (Simeonsson et al., 2012) and 4 ppb (Gondal and Dastageer, 2008). These devices are also limited by their sensitivity to water vapor, both because water vapor can react with SO_2 to form sulfites and sulfates and because it can adsorb to the sensor to change its resistance (Rubasinghege and Grassian, 2013). These devices are generally in early stages of development and not now commercially available. Until sensors achieve both data quality and cost objectives, they will not be suitable for widespread use.

3.2.2 Modeling

Because existing ambient SO_2 monitors may not be sited in locations to capture peak 1-hour concentrations (75 FR 35520), the implementation program for the 2010 primary SO_2 NAAQS allows for air quality modeling to be used to characterize air quality, and for such air quality information to be used in the process for informing final designation decisions. The SO_2 NAAQS is currently the only criteria pollutant standard for which modeling is used to characterize air quality for the purpose of the area designation process. Computational models of various designs can also be used to estimate exposure of individuals and populations when personal exposure measurements are unavailable or for separating personal exposure to ambient SO_2 from total personal exposures. This section describes several modeling approaches used for exposure assessments, including (1) estimating concentration as a surrogate for exposure, (2) estimating time-activity patterns, and (3) modeling of building air exchange rates (AERs) and microenvironmental exposure. The strengths and limitations for several specific exposure modeling methods are summarized in Table 3-1. The remainder of this section describes each modeling approach.

Table 3-1 Characteristics of exposure modeling approaches.

Model Type	Model	Description	Strengths	Limitations
Proximity to sources	SPM	Exposures are estimated from distance of receptor from source	Few input data required	Does not consider emission rate and duration, atmospheric chemistry, and physics
	EWPM	Exposures are estimated from distance of receptor to pollution source, emission rate, and duration	Considers emission rate and duration	Does not consider atmospheric chemistry and physics
	Land use regression (LUR)	Measured concentrations are regressed on local variables (e.g., land use factors), and the resulting model is used to estimate concentrations at specific locations	High spatial resolution	Does not account for atmospheric chemistry and physics, limited generalizability, moderate resources needed
Local outdoor concentration	Spatial interpolation (e.g., nearest monitor, inverse distance weighting, kriging)	Measured concentrations are interpolated to estimate concentration surfaces across regions	High spatial resolution, few input data needed	Does not fully capture spatial variability among monitors
	Chemistry-transport (e.g., CMAQ)	Grid-based concentrations are estimated from emissions, meteorology, and atmospheric chemistry and physics	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 emissions sources
	Gaussian plume dispersion (e.g., AERMOD)	Concentrations at specific locations are estimated from emissions, meteorology, and atmospheric physics	High spatial and temporal resolution, accounts for atmospheric physics from local emission sources	Resource intensive, very limited representation of atmospheric chemistry or background concentrations
Time-location patterns of people	Micro-environment classifier based on personal sensors (e.g., MicroTrac)	Personal sensor data (e.g., GPS, temperature, light) are used to estimate time people spend in various microenvironments (e.g., indoors and outdoors at home)	Accounts for time spent in different microenvironments with different concentrations	Input data from personal sensors (e.g., GPS) is required

Table 3-1 (Continued): Characteristics of exposure modeling approaches.

Model Type	Model	Description	Strengths	Limitations
Micro-environment-based exposure	Population (e.g., APEX, SHEDS)	Estimates distributions of microenvironmental concentrations, exposures, and doses for populations (e.g., census tracts) based on air quality data, demographic variables, and activity patterns	Accounts for variability of exposures across large populations, accounts for different concentrations in different microenvironments, accounts for location-activity information	Input data from outdoor concentrations is required, does not estimate exposures for individuals

AERMOD = American Meteorological Society/U.S. EPA Regulatory Model; APEX = Air Pollution Exposure model; CMAQ = Community Multiscale Air Quality; EWPM = emission-weighted proximity model; GPS = global positioning system; LUR = land use regression; SHEDS = Stochastic Human Exposure and Dose Simulation; SPM = source proximity model.

3.2.2.1 Estimation of Concentration as an Exposure Surrogate

Models can be used to predict the outdoor concentration of SO_2 across geographic regions (e.g., concentration surfaces) 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 actual human exposure to SO_2. This method does not estimate exposures directly because time-activity patterns and indoor concentrations at various microenvironments are not considered. However, local outdoor concentration models can improve exposure assessment by their ability to estimate concentrations at locations among monitors. Approaches described include distance to SO_2 source, dispersion models, chemistry-transport models, and LUR. These models can be applied at urban, regional, or national scales to estimate daily, or longer, average concentrations. Short-term (e.g., daily) estimates are needed for acute exposure assessments, whereas long-term (e.g., annual) estimates can be used for chronic exposure assessments. This discussion will focus on modeled concentrations used for exposure assessment studies.

Source Proximity Models

Source proximity models (SPMs) provide a simple method to estimate human exposure to air pollution. These models calculate the distance from receptors (e.g., homes, schools) to a source of pollution (e.g., industrial facilities, roads). It is assumed that concentration, as a surrogate for exposure, is some function of distance from the source. SO_2 from a point source is thought to disperse as a meandering plume, such that average concentration decreases with distance from the source (Section 2.6.1). Exposure

assessments based on SPMs assume that higher exposures occur at locations closer to emission sources. These models do not necessarily account for the effect of stack height to limit SO_2 concentrations in the immediate vicinity of the point source. For example, Burstyn et al. (2008) modeled SO_2 concentration as a function of distance within 2 km and 50 km buffers of gas plants and oil wells. The study authors used the natural log of the distance to the −2/3 power for each SO_2 point source to reflect the inverse relationship between SO_2 concentration and distance to source. In another epidemiologic model, proximity to source was treated as a Boolean variable as a proxy for high and moderate SO_2 exposure (Cambra et al., 2011). Likewise, Liu et al. (2012b) computed relative risk of respiratory disease using zip code 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 SO_2 concentration and found no statistically significant decrease in SO_2 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 large 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)]. In addition, while SPMs can be used to associate distance to sources with health effects, their ability to determine health risk under various exposure scenarios is limited.

To improve the accuracy of SPMs, an emission-weighted proximity model (EWPM) was developed that considers the emission rate and duration of each pollutant source, in addition to the distance from source. Zou et al. (2009b) evaluated the SPM and EWPM to estimate SO_2 concentrations in Dallas and Ellis counties, Texas. Normalized exposure estimates based on SPM and EWPM were compared to normalized measurements at three monitoring sites. Similarly, Zou (2010) compared SPM and EWPM to a kriged representation of SO_2 concentrations and concentrations estimated by the AERMOD dispersion model. In both studies, the EWPM estimates agreed more closely to the observed concentrations than the SPM estimates. Epidemiologic estimates of risk also were in closer agreement for EWPM and AERMOD compared with SPM (Zou et al., 2011). In addition, surface maps of EWPM and SPM exposure estimates across two counties showed that with SPM, exposure risks are 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 concentrations that individuals were exposed to across these regions.

Land Use Regression Models

LUR fits a multiple linear regression model of concentration based on land use data and then applies that model to locations without monitors as an attempt to increase heterogeneity in the spatial resolution of the concentration field compared with other methods, such as central site monitoring (Marshall et al., 2008). The spatial variability in estimated ambient concentrations captured by the LUR model can be used for large health studies because it provides variability in exposure estimates across the study population. Recently, it has been implemented to examine local-scale concentration estimates for PM, NO_2, and other pollutants across the United States (Novotny et al., 2011; Hart et al., 2009) and Canada (Hystad et al., 2011). Although LUR is more typically employed for NO_2, LUR has also been used to study spatial variability in SO_2 concentration [e.g., Atari et al. (2008)]. Models are typically calibrated using data from passive sampler measurements and several predictor variables, such as land use, road length, population density, and proximity to areas of high concentrations (e.g., point sources). Given that most passive 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. Hence, LUR is commonly used to estimate air pollution exposure in long-term epidemiologic studies. 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 SO_2 concentration in a city is represented by the LUR.

LUR has been applied to estimate exposures to industrial SO_2 sources. Atari et al. (2008) developed an LUR model to predict SO_2 concentrations in Sarnia, Ontario, Canada. 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 SO_2 concentration for model training were collected with passive samplers at 39 locations across the city for 2 weeks in the fall of 2005. The in-sample coefficient of determination (found by comparing the model with the measurements used to train the model) for the LUR model fit to the measurements was $R^2 = 0.66$. An out-of-sample coefficient of determination was calculated to cross-validate the model with measurements that were not used to train the model. The coefficient ranged from $R^2 = 0.62$ to $R^2 = 0.73$, and the root-mean-square error (RMSE) of the out-of-sample predictions were 0.3 to 1 ppb. The SO_2 validation produced a wider range of errors and lower out-of-sample R^2 compared with LUR simulations for NO_2; Atari et al. (2008) attributed this moderate validation to a skewed SO_2 concentration distribution compared

with the concentration distribution of NO_2. These LUR results were then used by Atari et al. (2009) to correlate modeled concentrations with individual and community perceptions of odor, by Oiamo and Luginaah (2013) to study whether males and females are affected differently by SO_2 exposure, and by Oiamo et al. (2011) to investigate the relationship between air pollution exposure and access to a general practitioner. Kanaroglou et al. (2013) used a spatial autocorrelation LUR model to estimate SO_2 concentrations 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 SO_2 concentration ($p < 0.001$, RMSE = 1.24).

LUR has also been applied to predict SO_2 exposures in the vicinity of urban sources. Clougherty et al. (2013) modeled concentrations of SO_2, NO_2, $PM_{2.5}$, and black carbon (BC) across New York City. 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 $R^2 = 0.77$. These findings were thought to reflect the presence of large combustion boilers in Manhattan and western Bronx, where SO_2 concentrations were predicted to be highest because sulfur content in residential heating fuel is high. SO_2 concentration was not influenced by vehicle traffic, unlike the other air pollutants studied. Beelen et al. (2007) modeled SO_2, NO_2, NO, and black smoke (BS) 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 still contained sulfur. 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. The Beelen et al. (2007) study was applied in a longitudinal cohort study of vascular damage among young adults (Section 5.3.2.5) (Lenters et al., 2010). Wheeler et al. (2008) applied LUR for a study of air pollutant 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 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 SO_2 concentration across seasons by comparing the LUR results with measurements for a study of air pollutant exposure in Windsor, Ontario. They found that correlation of summer SO_2 predictions with those from other seasons was lower, suggesting that photochemistry might not be well represented in the LUR model.

Inverse Distance Weighting

Inverse distance weighting (IDW), in which concentration at a receptor point is calculated as the weighted average of concentration measured at monitoring locations, has been used to estimate exposure with 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 SO_2 and other industrial pollutants within 10 km of point sources using an IDW sum of 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 SO_2 concentration surface. The results from IDW were correlated with the other three methods (r = 0.88−0.97), and the mean estimated SO_2 concentration estimated with IDW was within 10% of the mean computed with the other methods. However, Neupane et al. (2010) estimated the SO_2 concentration surface using both bicubic spline functions 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 splines produced a lower mean and larger IQR compared with IDW; 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 concentration data set.

Gaussian Plume Dispersion Models

Gaussian dispersion models can be applied to estimate human exposure to SO_2. A detailed description of Gaussian dispersion modeling, along with strengths and limitations for modeling SO_2 concentrations, can be found in Section 2.6. Zou et al. (2009c) developed a modeling system to spatially estimate source-specific population exposure to ambient SO_2 across Dallas County in Texas. A hybrid dispersion modeling approach was used to predict SO_2 concentrations at a fine spatial resolution by combining modeled air pollution concentrations with population distributions. This hybrid method included air dispersion modeling (AERMOD) and kriging interpolation to produce an ambient SO_2 concentration grid map (100 m × 100 m) that was used to estimate population exposures. The AERMOD simulation included three SO_2 source classifications (industrial, vehicle, and industrial/vehicle). A population density map was generated at the block level based on 2000 census data and converted to a grid map (100 m × 100 m) to match the spatial resolution of the ambient SO_2 concentration grid

map. The population exposure was estimated by multiplying the 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 population exposure estimates were moderately correlated with vehicle sources (r = 0.440) and weakly with industrial sources (r = 0.069); this study used emissions data from the year 2000, prior to the ultra-low sulfur diesel fuel regulations. This population exposure modeling system provides a potential method to develop exposure metrics for health studies, urban planning, and mitigation strategies.

Lagrangian particle modeling has also been employed to model SO_X concentrations from specific sources (Ancona et al., 2015). The Lagrangian particle model represents the pollutant of interest as a group of nonreactive, massless particles and tracks their positions over space based on simulated mean and turbulent wind components (Tinarelli et al., 1994). Note that Ancona et al. (2015) called the pollutant "SO_X" throughout the paper. Given that the simulated particles were nonreactive, "SO_X" in this case can be considered a marker of the emission source representing some combination of directly emitted SO_2 and sulfate formed in the atmosphere (Section 2.3). The wind velocity at every location in the domain is simulated as the sum of (1) a mean three-dimensional wind using a meteorological model and (2) a turbulence component modeled as the product of observed dispersion parameters and a random number generated at each time step (Gariazzo et al., 2004). Then, each pollutant particle's position is updated at each 30-minute time step as the sum of its original position and the product of wind velocity at that position and time step. Gariazzo et al. (2004) compared the SPRAY Lagrangian particle model against SO_2 observations at a measurement station and observed reasonable agreement, although the observations seemed to lag the modeled SO_2 concentration at times.

Chemical Transport Models

Chemical transport models (CTMs), such as the CMAQ model, can be used to estimate SO_2 exposures when measurement data are unavailable or not available for portions of a study area. CTMs, such as CMAQ, are deterministic of chemical transport that account for physical processes including advection, dispersion, diffusion, gas-phase reaction, and mixing while following the constraint of mass conservation (Byun and Schere, 2006). These models provide regional concentration estimates and are typically run with surface grid resolutions of 4, 12, or 36 km. Temporal resolution of CTMs can be as fine as 1 hour, although larger temporal aggregation often occurs for the purpose of maintaining reasonable data file size. Lipfert et al. (2009) estimated SO_2 concentration based on the CMAQ model for use as an exposure surrogate. The SO_2 concentrations were estimated with a 36-km by 36-km grid across the contiguous United States. The modeled SO_2

concentrations were used 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 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 SO_2 but are more commonly used in long-term exposure studies. These models are used to compute interactions among 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 prediction models. Values for meteorological state variables such as winds and temperatures are taken from operational analyses, reanalyses, or weather circulation models. In most cases, these are off-line meteorological analyses, meaning that they are not modified by radiatively active species generated by the air quality model. Work to integrate meteorology and chemistry was done in the mid-1990s by Lu et al. (1997a) and Lu et al. (1997b) and references therein, although limits to computing power prevented their widespread application. More recently, new integrated models of meteorology and chemistry are available; see, for example, Binkowski et al. (2007) and the Weather Research and Forecast model with chemistry (WRF Chem) (http://ruc.noaa.gov/wrf/WG11/). Given observed biases in the CTMs [e.g., U.S. EPA (2008a)], much attention has been given to bias correction of these models for application in exposure assessment. Chen et al. (2014a) evaluated CMAQ results for several pollutants and found that SO_2 was underpredicted by roughly a factor of two, but this problem was largely ameliorated through bias correction techniques.

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. For example, 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 sulfate (Alexander et al., 2009). Therefore, when using CMAQ for estimation of exposure to SO_2, attention must be given to the version of the program so that any inherent biases are understood.

CMAQ has been used to explore vertical emissions of SO_X, NO_X, and PM_{10} from power plants, industrial combustion, and other industrial processes with stack heights that varied by facility. Guevara et al. (2014) modeled the vertical concentration distribution of these

emissions in Spain and found that the distribution varied with source. The lower atmosphere was partitioned into 11 layers spanning 1,250 m AGL. Within the layer closest to the ground (0−39 m AGL) where people are exposed, negligible SO_2 concentrations were modeled for the largest emissions sources (power plants emitted 53% of SO_X and refineries emitted 20% of SO_X in the study area). The highest modeled ground layer SO_2 emissions were for the paper and pulp industries, industrial boilers, and nonferrous metallurgy, which contributed between <1 to 3% of emissions. One major limitation of CTMs for estimating SO_2 concentrations in exposure assessment 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 SO_2 concentrations can be underestimated along the plume path. Baldasano et al. (2014) recognized this limitation and merged HYSPLIT with a CTM simulation of SO_2 and PM_{10} transport in the vicinity of a refinery. HYSPLIT models dispersion of pollutants such as 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. Similarly, Karamchandani et al. (2010) coupled a plume-in-grid model with CTM that treats dispersion as a Gaussian process whose parameters are set using micrometeorological conditions. Inclusion of subgrid-scale modeling enables fine-scale calculation of the SO_2 plume such that maximum concentration, and potentially maximum exposures, can be estimated by the model suite (Baldasano et al., 2014).

3.2.2.2 Time-Activity Models

The time people spend in various microenvironments (ME) is a critical aspect of exposure assessment. Future improvements in SO_2 exposure assessment are anticipated by accounting for time spent in different MEs with different SO_2 concentrations. Exposure models can account for variations in time spent by people in different locations by using time-weighted pollutant concentrations in each ME. For population-level exposure assessments, exposure models rely on databases of time-activity diary data from other studies, such as the Consolidated Human Activity Database (CHAD) (see Section 3.3.3.1) (U.S. EPA, 2014a; McCurdy et al., 2000). For individual exposure assessments, diaries from the study participants can be used. However, diaries have limitations, including burden on participants, inaccuracies due to recall and reporting errors, and missing data.

To address the limitations of diaries, 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 MEs 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 MEs (e.g., wooden structures have no substantial indoor/outdoor differences in satellite signal strength). To address these limitations, automated ME 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 MEs (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 ME 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).With a high percentage of the U.S. population using GPS-enabled smartphones, large sets of GPS data collected with low participant burden could be classified in various MEs by MicroTrac to increase the sample size and update the older diary data in the time-activity databases (e.g., CHAD), which are used for population-level exposure assessments (U.S. EPA, 2014a; McCurdy et al., 2000).

3.2.2.3 Models of Building Air Exchange Rates and Microenvironmental Exposures

Models of Building Air Exchange Rates

The AER, which is the airflow into and out of a building, influences the rate of entry of ambient SO_2 and removal of nonambient SO_2. Because people living in the United States spend an average of 87% of their time within enclosed buildings (Klepeis et al., 2001), the AER is a critical parameter for air pollution exposure models, such as Air Pollutants Exposure Model (APEX) and Stochastic Human Exposure and Dose Simulation (SHEDS), discussed below under Microenvironmental Exposure Models.

AER models can reduce the uncertainty of exposure models by accounting for various factors, 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 exposure may help explain any possible differences in epidemiologic associations between ambient SO_2 concentrations and health effects in different U.S. communities (Breen et al., 2014b).

Microenvironmental Exposure Models

Microenvironmental exposure models can account for the variations in the time people spend in different locations by using time-weighted pollutant concentrations in each microenvironment (e.g., outdoors; indoors at home, school, workplace; in-vehicle). Models such as SHEDS and APEX are not used for exposure assessment in epidemiologic studies, but they are described here because they are 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 state of the science for stochastic population exposure models has not changed substantially since the 2008 ISA for Oxides of Nitrogen, as described in detail in the 2008 NO_X ISA Annex 3.6 (U.S. EPA, 2008a).

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). These models simulate the movement of individuals across time and space and their exposure to air pollutants in various microenvironments. The inputs required for population exposure models include outdoor pollutant data, indoor−outdoor pollutant ratios for mass-balance indoor air quality models to estimate indoor microenvironmental concentrations, population demographic databases (e.g., U.S. census), and human time-activity pattern databases (e.g., CHAD) to determine the time spent and the activity performed in different microenvironments (McCurdy et al., 2000).

3.2.3 Choice of Exposure Metrics in Epidemiologic Studies

Epidemiologic studies use a variety of methods to assign exposure. Study design, data availability, and research objectives are all important factors for epidemiologists when selecting an exposure assessment method. Common methods for assigning exposure from monitoring data include using a single fixed-site monitor to represent population exposure, averaging concentrations from multiple monitors, and selecting the closest monitor. Investigators may also use statistical adjustment methods, such as trimming extreme values, to prepare the concentration data set. Epidemiologic study design influences the relevance and utility of exposure metrics. Table 3-2 summarizes various exposure metrics used in SO_2 epidemiologic studies, appropriate applications for the metrics, and errors and uncertainties that may be associated with the metrics. Table 3-3 lists relevant exposure information for the epidemiologic studies found in Chapter 5 where models were used to estimate exposure.

Table 3-2 Summary of exposure assignment methods, their typical use in sulfur dioxide epidemiologic studies, and related errors and uncertainties.

Exposure Assignment Method	Epidemiologic Application	Errors and Uncertainties
Central site monitors	Short-term community time-series exposure of a population within a city	Correlation between true outdoor concentrations and outdoor measurement typically decreases with increasing distance from the monitor (Section 3.3.5), potentially leading to decreased precision and bias towards the null
	Long-term exposure to compare populations among multiple cities	Potential for exposure bias and reduced precision if the monitor site does not correspond to the location of exposed population (Section 3.3.5)
Passive monitors	Short-term panel (e.g., personal or residential samples) within a city	High detection limit potentially leads to reduced precision (Section 3.2.1.2)
	Long-term exposure within a city or among multiple cities	Potential for exposure bias and reduced precision (Section 3.3.5)
SPM and EWPM	Long-term exposure within a city or among multiple cities or regions	Potential for exposure bias and reduced precision if concentration at a receptor location is higher or lower than the average over the area of the circle formed around the source with radius equal to the distance between the source and receptor (Section 3.2.2.1)

Table 3-2 (Continued): Summary of exposure assignment methods, their typical use in sulfur dioxide epidemiologic studies, and related errors and uncertainties.

Exposure Assignment Method	Epidemiologic Application	Errors and Uncertainties
LUR model	Long-term exposure, usually across a city but sometimes among multiple cities	Potential for exposure bias and reduced precision if grid is not finely resolved (Section 3.2.2.1) Potential for bias and reduced precision if the model is misspecified or applied to a location different from where the model was fit (Section 3.3.5)
IDW and kriging	Long-term exposure within a city	Potential for negative bias and reduced precision if sources are not captured or overly smoothed (Section 3.2.2.1)
Gaussian plume dispersion modeling	Long-term exposure within a city	Potential for exposure 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) (Section 3.2.2.1)
CTM	Long-term exposure, sometimes within a city but more typically across a larger region	Potential for exposure bias and reduced precision when grid cells are too large to capture spatial variability of exposures (Section 3.2.2.1)
Microenvironmental model	Panel studies	Potential for exposure bias and reduced precision when the modeled distributions of ambient concentration, indoor−outdoor pollutant ratios, and time-activity patterns differ from the true distributions (Section 3.2.2.3)

CTM = chemical transport model; EWPM = emission-weighted proximity model; IDW = inverse distance-weighting; LUR = land use regression; SPM = source proximity model.

Table 3-3 Exposure data for epidemiologic studies using modeling for exposure estimation.

Reference	Location	Population	Time Period	Averaging Time	Spatial Scale of Exposure	Exposure Model Type	Model Resolution	Exposure Validation Metric	Concentration Summary Stats units = ppb
Longitudinal cohort									
Darrow et al. (2011) Ivy et al. (2008)	Atlanta, GA	406,627 full-term births	1994–2004	1 h daily max averaged over 28 days during first trimester, gestational day 196 to birth during third trimester	Urban	Population-weighted average	NR	NR	First mo gestation: mean (SD): 11 (3.4), IQR: 4; third trimester: mean (SD): 9.5 (2.0), IQR: 3
Atkinson et al. (2013)	U.K.	836,557 adults ages 40−89 yr	2003–2007	1 yr	National	Dispersion model	1 km × 1 km	R^2 = 0.23−0.45	Mean (SD): 1.5 (0.80), IQR: 0.84
Beelen et al. (2008a) Beelen et al. (2007)	Netherlands	114,378 adults ages 55−69 yr	1986–1997	1 yr	Regional, urban, local	Sum of regional, urban, and local models; regional SO_2 modeled with IDW, urban and local SO_2 modeled with LUR	NR	R = .34, RMSE = 1.23 (NLCS-AIR method)	Mean (SD): 5.2 (2.0)

Table 3-3 (Continued): Exposure data for epidemiologic studies using modeling for exposure estimation.

Reference	Location	Population	Time Period	Averaging Time	Spatial Scale of Exposure	Exposure Model Type	Model Resolution	Exposure Validation Metric	Concentration Summary Stats units = ppb
Brunekreef et al. (2009) Beelen et al. (2007)	Netherlands	120,852 adults ages 55−69 yr	1986–1997	1 yr	Regional, urban, local	Sum of regional, urban, and local models; regional SO_2 modeled with IDW, urban and local SO_2 modeled with LUR	NR	R^2 = 0.35, RMSE = 3.23	Mean (SD): 5.2 (2.0)
Carey et al. (2013)	U.K.	835,607 adults ages 40−89 yr	2003–2007	1 yr	National	Dispersion model	1 km × 1 km	R^2 = 0−0.39	Mean (SD): 1.5 (0.80), IQR: 0.8
Hart et al. (2011) Hart et al. (2009)	U.S.	53,814 men ages 15−84 yr working in the trucking industry	1985–2000	1 yr	National	Generalized additive model using spatial smoothing and GIS-based covariates	NR	Not given for SO_2, but favorable exposure method comparison with IDW for PM_{10} and NO_2	Mean (SD): 4.8 (2.9), IQR: 4
Lipfert et al. (2009)	U.S.	70,000 U.S. male veterans by mortality period	1976–2001	1 yr	National	CMAQ-MADRID-APT chemical transport with reactive plume-in-grid model	36 km × 36 km	Compared model to AIRS data; unweighted r = 0.26−0.29; weighted r = 0.36−0.39	Raw mean (SD): 1.9 (1.8); subject-weighted mean (SD): 4.3 (3.1); high traffic subject mean (SD): 6.4 (3.2)

Table 3-3 (Continued): Exposure data for epidemiologic studies using modeling for exposure estimation.

Reference	Location	Population	Time Period	Averaging Time	Spatial Scale of Exposure	Exposure Model Type	Model Resolution	Exposure Validation Metric	Concentration Summary Stats units = ppb
Nafstad et al. (2004) Gram et al. (2003)	Oslo, Norway	16,209 males ages 40−49 yr	1972–1998	1 yr	Urban	AirQUIS dispersion model ran for 1979 and 1995, then projected for other yr based on changes in point source and traffic emissions	NR	NR	5-yr median average (range): 3.6 (0.076−21)
Wood et al. (2010) Stedman and Kent (2008)	U.K.	399 adults; mean age 51.1 yr	1997–2006	1 yr	Regional	Dispersion model with weighted regression to incorporate sources	1 km × 1 km	Relative error typically within 50% for O_3 (not reported for SO_2), daily mean r = 0.43; daily max r = 0.36	Mean (SD): 1.6 (0.1)
Nishimura et al. (2013)	U.S. (Chicago, Bronx, Houston, San Francisco Bay Area)	3,343 Latino and 977 African-American participants ages 8−21 yr	2006–2011	1 yr	National	IDW	NR	NR	Mean (SD): 4.0 (3.4)
Portnov et al. (2012)	Greater Haifa Area, Israel	3,922 school children mean age 10.2 yr	2006–2008	1 yr	Regional	(1) IDW, (2) kriging	NR	Similar epidemiologic model results with IDW and kriging	Mean (SD): 5.4 (1.3)

Table 3-3 (Continued): Exposure data for epidemiologic studies using modeling for exposure estimation.

Reference	Location	Population	Time Period	Averaging Time	Spatial Scale of Exposure	Exposure Model Type	Model Resolution	Exposure Validation Metric	Concentration Summary Stats units = ppb
Clark et al. (2010) Brauer et al. (2008)	South-western British Columbia, Canada	3,482 children classified as asthma cases, 33,919 classified as nonasthma, and 17,410 random controls, 1999 and 2000 births, mean age at follow up 48 ± 7 mo	1999–2003	Duration of pregnancy plus first yr of life	Regional	IDW	NR	7% difference between mean SO_2 when comparing IDW with nearest monitor	Mean (SD) (in utero): 2.0 (0.95); mean (SD) (first yr): 2.1 (1.0)
Panasevich et al. (2009) Bellander et al. (2001)	Stockholm, Sweden	1,028 men, 508 women ages 45−70 yr	1992–1994	1 yr, 5 yr, and 30 yr	Urban	Dispersion model coupled with street canyon model for central city	Four layers of different resolution applied to countryside area (2 km × 2 km), regional area (500 m × 500 m), urban area (100 m × 100 m), and inner-city area (25 m × 25 m)	Reported modeled concentration within 20% of measure-ments for the same model for NO_2 (not reported for SO_2)	Mean (last 1 yr): 1.1, mean (last 5 yr): 1.8, mean (last 30 yr): 9.9
Case-cohort									
Beelen et al. (2008b) Beelen et al. (2007)	The Netherlands	120,852 adults ages 55−69 yr in 204 municipalities	1987–1006	1 yr	Regional, urban, local	Sum of regional, urban, and local models; regional SO_2 modeled with IDW, urban and local SO_2 modeled with LUR	NR	In-sample R^2 = 0.56	Mean (SD): 5.2 (1.9)

Table 3-3 (Continued): Exposure data for epidemiologic studies using modeling for exposure estimation.

Reference	Location	Population	Time Period	Averaging Time	Spatial Scale of Exposure	Exposure Model Type	Model Resolution	Exposure Validation Metric	Concentration Summary Stats units = ppb
Case-control									
Johnson et al. (2010)	Edmonton, Canada	All patients who presented with stroke to 1 of 11 emergency department sites in and around Edmonton	2003–2007	1 yr, 5 yr, and 30 yr	Urban	IDW	NR	NR	Mean (IQR): 1.3 (0.1)
Rosenlund et al. (2006) Bellander et al. (2001)	Stockholm, Sweden	1,397 first-time MI cases 45 to 70 yr, 1,870 controls	1992–1994	30 yr	Regional	Dispersion model coupled with street canyon model for central city	Three layers of different resolution applied to regional/country-side area (500 m × 500 m), urban area (100 m × 100 m), and inner-city area (25 m × 25 m)	Reported modeled concentration within 20% of measure-ments for the same model for NO_2	Cases median (range): 9.7 (2.6−18); controls median (range): 9.4 (2.7−18)
Prospective cohort									
Lipsett et al. (2011)	California	124,614 female California public school teachers ages 20−80 yr	1996–2004	1 mo	Regional	IDW	250 m × 250 m	NR	Mean (IQR): 1.7 (0.43)
Case-crossover									
Smargiassi et al. (2009)	Montreal, Canada	3,470 children ages 2−4 yr	1996–2004	1 yr	Neighborhood	AERMOD dispersion model	3,469 receptor locations	Relative error <50%, daily mean r = 0.43; daily max r = 0.36	Mean (SD): 4.3 (2.9)

Table 3-3 (Continued): Exposure data for epidemiologic studies using modeling for exposure estimation.

Reference	Location	Population	Time Period	Averaging Time	Spatial Scale of Exposure	Exposure Model Type	Model Resolution	Exposure Validation Metric	Concentration Summary Stats units = ppb
Cross-sectional									
Son et al. (2010)	Ulsan, South Korea	2,102 participants ages 7−97 yr	2003–2007	1 day	Urban	(1) average across monitors, (2) nearest monitor, (3) IDW, (4) kriging	NR	Mean SO_2 calculation within 16% across models	Average across monitors mean (SD): 8.6 (4.1); nearest monitor mean (SD): 7.3 (5.9); IDW mean (SD): 8.4 (5.3); kriging mean (SD): 8.3 (4.4)
Deger et al. (2012) Smargiassi et al. (2009)	Montreal, Canada	842 children ages 6−12 mo	2006	1 yr	Neighborhood	AERMOD dispersion model	3,469 receptor locations	Relative error <50%, daily mean r = 0.43; daily max r = 0.36	Mean (SD): 1.8 (1.2)
Forbes et al. (2009c) Forbes et al. (2009b)	England, U.K.	32,712 adults ages 16 yr and older	1995, 1996, 1997, 2001	1 yr	National	Dispersion model	1 km × 1 km	Compared to national network: R^2 = 0.45, relative error = 20%; compared to verification sites, R^2 = 0.56, relative error = 6.0%	1995 median (IQR): 3.5 (2.9); 1996 median (IQR): 3.5 (2.9); 1997 median (IQR): 3.5 (2.7); 2001 median (IQR): 1.5 (1.0)

Table 3-3 (Continued): Exposure data for epidemiologic studies using modeling for exposure estimation.

Reference	Location	Population	Time Period	Averaging Time	Spatial Scale of Exposure	Exposure Model Type	Model Resolution	Exposure Validation Metric	Concentration Summary Stats units = ppb
Forbes et al. (2009b)	England, U.K.	36,350 residences	1994, 1998, 2003	1 yr	National	Dispersion model	1 km × 1 km	Compared to national network: R^2 = 0.45, relative error = 20%; compared to verification sites, R^2 = 0.56, relative error = 6.0%	1994 median (IQR): 3.6 (3.2); 1998 median (IQR): 2.4 (2.3); 2003 median (IQR): 1.6 (1.1)
Forbes et al. (2009a) Forbes et al. (2009b)	England, U.K.	19,000 adults ages 45 yr and older	1994, 1998, 2003	1 yr	National	Dispersion model	1 km × 1 km	Compared to national network: R^2 = 0.45, relative error = 20%; compared to verification sites, R^2 = 0.56, relative error = 6.0%	1994 median (IQR): 3.6 (3.2); 1998 median (IQR): 2.4 (2.3); 2003 median (IQR): 1.6 (1.1)
Rage et al. (2009)	France (Paris, Lyon, Marseille, Montpellier, Grenoble)	328 adults diagnosed with asthma with episodes of breathlessness/ wheezing and asthma attack within 12 mo	1991–1995	1 yr	Urban	(1) Closest monitor, (2) multi-variate geostatistical models compared with IDW or univariate kriging	4 km × 4 km	r > 0.73 for all comparisons	Mean (SD): 8.1 (3.3)

Table 3-3 (Continued): Exposure data for epidemiologic studies using modeling for exposure estimation.

Reference	Location	Population	Time Period	Averaging Time	Spatial Scale of Exposure	Exposure Model Type	Model Resolution	Exposure Validation Metric	Concentration Summary Stats units = ppb
Wang et al. (2009)	Brisbane, Australia	51,233 deaths	1996–2004	1 yr average of 1 h daily max	Regional	IDW	NR	NR	Mean 1 h daily max: 5.4
Gorai et al. (2014)	New York State	19.3 million residents	2005–2007	1 yr average of 1 h daily max	Regional	Kriging	NR	MSE = −0.01, RMSSE = 0.85	2005 mean (SD): 8.5 (2.9); 2006 mean (SD): 6.9 (2.3); 2007 mean (SD): 7.2 (2.4)
Penard-Morand et al. (2010) Penard-Morand et al. (2006)	France (Bordeaux, Clermont-Ferrand, Creteil, Marseille, Strasbourg, Reims)	9,615 children; mean age 10.4 yr	1999–2000	3 yr	Urban	STREET dispersion model	NR	72% of model estimates within 15% of measure-ments, 100% within 50% of measure-ments.	Mean (minimum to maximum across six French cities): 1.6−5.0
Sahsuvaroglu et al. (2009)	Hamilton, Canada	1,467 children age 6−7 yr and 13−14 yr	1994–1995	3 yr	Urban	IDW, kriging	NR	NR	Mean: 5.8

AERMOD = American Meteorological Society/U.S. EPA Regulatory Model; AIRS = Aerometric Information Retrieval System; CMAQ = Community Multiscale Air Quality; GIS = geographic information systems; IDW = inverse distance weighting; IQR = interquartile range; LUR = land use regression; MSE = mean standardized error; NLCS-AIR = Netherlands Cohort Study on Diet and Cancer—air pollution mortality study; NO_2 = nitrogen dioxide; NR = not reported; O_3 = ozone; RMSE = root-mean-square error; RMSSE = root-mean-square standardized error; SD = standard deviation; SO_2 = sulfur dioxide.

3.3 Exposure Assessment and Epidemiologic Inference

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

3.3.1 Conceptual Model of Total Personal Exposure

A theoretical model of personal exposure is presented to highlight measurable quantities and the uncertainties that exist in this framework. 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:

$$E_{\mathrm{T}} = \int C_j \, dt$$

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:

$$E_{\mathrm{T}} = E_{\mathrm{a}} + E_{\mathrm{na}}$$

Equation 3-2

Although indoor combustion of sulfur-containing fuels, particularly kerosene, is a nonambient source of SO_2 (see Section 3.3.2), these sources are specific to individuals and may not be important sources of population exposure. This assessment 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 microenvironments (U.S. EPA, 2006; Wilson et al., 2000):

$$E_{\mathrm{a}} = \Sigma f_{\mathrm{o}} C_{\mathrm{o}} + \Sigma f_{\mathrm{i}} F_{\mathrm{inf,i}} C_{\mathrm{o,i}}$$

Equation 3-3

where f = fraction of the relevant time period (equivalent to dt in Equation 3-1); subscript o = index of outdoor microenvironments; subscript i = index of indoor

microenvironments; subscript o,i = index of 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:

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

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 $C_o = C_a$ 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:

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

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 3.3.5 with respect to implications for interpreting epidemiologic studies. Epidemiologic studies often 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 Equations 3-5 and 3-6 yields:

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

Equation 3-7

where α varies between 0 and 1. 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 can vary with building and meteorology-related air exchange characteristics. 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, LUR models, receptor models, fine-scale CTMs, or some combination of these techniques. These techniques are described in Section 3.2.2.

3.3.2 Relationships between Personal Exposure and Ambient Concentration

Several factors influence the relationship between personal SO_2 exposure and ambient concentration. Due to the lack of indoor SO_2 sources, and the fact that ambient SO_2 tends to deposit on surfaces after it penetrates into enclosed microenvironments, indoor SO_2 concentrations are highly dependent on air exchange rate and therefore vary widely in different microenvironments. People spending the bulk of their time indoors has a substantial impact on personal exposure. Personal exposures are often much lower than ambient concentrations; for example, Brown et al. (2009) reported the mean winter personal exposure in Boston to be 1.8 ppb, while the ambient concentration was 11.3 ppb. Both personal exposure and ambient concentration was lower in summer, with mean values of −0.2 and 3.6 ppb, respectively. The negative mean value reflects the large fraction of personal exposure samples below the detection limit (99% in summer, 93% in winter).

3.3.2.1 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, 2008b), 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 concentration versus the concentration immediately outside the indoor microenvironment show an extremely wide range, from near zero to near unity (Table 3-4). One of the most detailed older studies 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 (Patterson and Eatough, 2000). Studies conducted since the 2008 SO_X ISA (U.S. EPA, 2008b) have focused on public buildings and show generally similar results to older studies.

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), personal activities affecting air exchange rates, indoor deposition of SO_2, and analytical capabilities. When reported, correlations between indoor and outdoor concentrations were relatively high (>0.75), suggesting that variations in outdoor concentration are driving indoor concentrations (Table 3-4). These high correlations were observed across seasons and geographic locations. This is supported by the relative lack of indoor sources of SO_2. The main indoor source is combustion of sulfur-containing fuels, such as kerosene, which is generally considered an emergency or supplemental source of heat in the United States. Triche et al. (2005) measured SO_2 concentrations in homes where secondary heating sources (fireplaces, kerosene heaters, gas space heaters, and wood stoves) were used and found elevated concentrations only when kerosene heaters were used. Median indoor SO_2 concentrations were 6.4 ppb during kerosene heater use, compared with 0.22 ppb at other times. For other criteria pollutants, nonambient sources can be an important contributor to total personal exposure. Because there are relatively few indoor sources of SO_2, personal SO_2 exposure is expected to be dominated by ambient SO_2 in outdoor microenvironments and in indoor microenvironments with high air exchange rates (e.g., with open windows).

Table 3-4 Relationships between indoor and outdoor sulfur dioxide concentration.

Study	Location	Years/ Season	Population	Study Design	Sample Duration	Ratio[a]	Correlation	Micro-Environment	Comment	Concentration/ Detection limit (ppb)
Brauer et al. (1989)	Boston, MA	Jul−Aug 1988	NR	Pooled	24 h	0.23	NR	Home	Concent-ration and ratio estimated from Figure 2	Mean (LOD) *Indoor* 0.6 (0.25) *Outdoor* 3 (0.77)
Brauer et al. (1991)	Boston, MA	Jul−Aug	NR	Pooled	24 h	GM: 0.39 GSD: 1.57 Slope (SE): 0.55 (0.04)	0.94	Home	Intercept nonsignificant at $p < 0.01$	Mean (SD) *Indoor* 1.47 (1.52) Range: <LOD-8.34 *Outdoor* 3.46 (2.67) Range: 0.62–13.86 LOD: 0.07 Fraction above LOD: 90%
		March (late winter)			In: 24 h Out: 48 h	GM: 0.05 GSD: 1.71 Slope (SE): 0.12 (0.02)	0.85		Intercept nonsignificant at $p < 0.01$	Mean (SD) *Indoor* 0.39 (0.40) Range: <LOD-1.57 *Outdoor* 4.74 (2.49) Range: 2.05−10.46 LOD: 0.07 Fraction above LOD: 70%

Table 3-4 (Continued): Relationships between indoor and outdoor sulfur dioxide concentration.

Study	Location	Years/ Season	Population	Study Design	Sample Duration	Ratio[a]	Correlation	Micro-Environment	Comment	Concentration/ Detection limit (ppb)
Chan et al. (1994)	Taipei, Taiwan	May 1992	Non-asthmatics	Pooled	12 h	GM: 0.24 GSD: 2.46	NR	Home	I-O regression slope nonsignificant at $p < 0.05$	Mean (SD) *Indoor* 2.5 (1.9) *Outdoor* 7.6 (4.6) LOD: NR
		Jan−Apr 1993	Children with asthma		24 h	GM: 0.23 GSD: 2.30 Slope (SE): 0.77 (0.13) Intercept (SE): −1.02 (0.28)	0.55			Mean (SD) *Indoor* 2.4 (2.9) *Outdoor* 8.2 (4.6) LOD: NR
Chao (2001)	Hong Kong, China	May−Jun 1997	NR	Pooled	48 h	1.01 SD: 0.78 Range 0.25−3.0	NR	Apartment	Units had high AER (mean 5.4 h^{-1}, median 2.7 h^{-1}) Two of 10 units had I/O ratio >1 Some units reported incense burning	Mean (SD) *Indoor* 2.4 (0.84) Range: 1.0−4.0 *Outdoor* 3.1 (1.5) Range: 1.0−6.0 LOD: NR

Table 3-4 (Continued): Relationships between indoor and outdoor sulfur dioxide concentration.

Study	Location	Years/ Season	Population	Study Design	Sample Duration	Ratio[a]	Correlation	Micro-Environment	Comment	Concentration/ Detection limit (ppb)
Godoi et al. (2013)	Curitiba, Brazil	Nov/Dec 2009, June 2010, May−Oct 2011	Children	Pooled	2 weeks	0.7	NR	Urban school	Ratio of indoor and outdoor means	Mean *Indoor* 0.70 *Outdoor* 1.0 LOD: NR
						1.0		Suburban school		*Indoor* 0.34 *Outdoor* 0.34
Kindzierski and Sembaluk (2001)	Boyle, Alberta, Canada	Late fall	NR	Pooled	7 days	0.13[b] Range 0.05−0.52	<0.41	Single-family dwellings	Replaced values below LOD with 0.1 ppb	Median (Range) *Indoor* 0.2 (0.1−0.9) *Outdoor* 1.6 (1.4−2.1)
	Sherwood Park, Alberta, Canada					0.13[b] Range 0.08−0.4				*Indoor* 0.5 (0.3−2.0) *Outdoor* 3.8 (3.1−5.0) LOD: 0.13

Table 3-4 (Continued): Relationships between indoor and outdoor sulfur dioxide concentration.

Study	Location	Years/ Season	Population	Study Design	Sample Duration	Ratio[a]	Correlation	Micro-Environment	Comment	Concentration/ Detection limit (ppb)
Lee et al. (1999)	Hong Kong	Oct 1996−Mar 1997	NR	Pooled	20 min	Slope: 0.87 Intercept: 0.0002	0.75	Public spaces	Smoking occurred in some locations	Range: *Indoor* 3−12 *Outdoor* 3−9 LOD: 1
						0.60		Car Park		
						0.93		Library		
						0.95		Restaurant		
						1.10		Recreation Place		
						1.00		Sport Center		
						0.78		Shopping Mall		
Li and Harrison (1990)	Essex, U.K.	Jun−Jul 1989	NR	Pooled	24 h	0.22 Range 0.1−0.4 Slope[c] (SE): 0.14 (0.03) Intercept[c] (SE): 0.72 (0.46)	0.84	University buildings		Mean (SD) *Indoor* 1.1 (NR) *Outdoor* 5.7 (NR) LOD: 0.014 Fraction above LOD: 100%

Table 3-4 (Continued): Relationships between indoor and outdoor sulfur dioxide concentration.

Study	Location	Years/ Season	Population	Study Design	Sample Duration	Ratio[a]	Correlation	Micro-Environment	Comment	Concentration/ Detection limit (ppb)
López-Aparicio et al. (2011)	Prague, Czech Republic	Jul 2009–Mar 2010	All age groups	Longi-tudinal cohort	1 mo	Mean (SD) 0.49 (0.16) Range 0.25−0.74	NR	Historic Library	No heating or air conditioning Ratio: Indoor mean/ outdoor mean	Range* *Indoor* 0.8−2 *Outdoor* 1−7 *Estimated from Figure 2 LOD: 0.04
Patterson and Eatough (2000)	Lindon, UT	Jan−Feb 1997	Children (during school hours)	Longi-tudinal cohort	10 h daytime	Slope (SE): 0.023 (.004) Intercept (SE): 0.018 (.006)	0.79	School		Mean (SD) *Outdoor* 0.93 (0.34)
			Children		14 h nighttime	0.030 (.003) 0.002 (.002)	0.91			*Outdoor* 1.4 (0.17)
			Children		All	0.027 (.002) 0.008 (.003)	0.85			*Outdoor* 0.49 (0.12)

Table 3-4 (Continued): Relationships between indoor and outdoor sulfur dioxide concentration.

Study	Location	Years/ Season	Population	Study Design	Sample Duration	Ratio[a]	Correlation	Micro-Environment	Comment	Concentration/ Detection limit (ppb)
Spengler et al. (1979)	Portage, WI	May 1977–Apr 1978	NR	Pooled	1 yr	0.67	NR	Residences	Ratio of indoor and outdoor annual means of 24-h, 6th-day samples Ratios reported in Kindzierski and Ranganathan (2006)	Range* *Indoor* 0.4−8.4 *Outdoor* 0.8−20 LOD: NR
	Topeka, KS					0.50				
	Kingston, TN					0.08				
	Watertown, MA					0.33				
	St. Louis, MO					0.31				
	Steubenville, OH					0.39				
Stock et al. (1985)	Houston, TX	Aug−Oct 2001	NR	Pooled	1 h	0.55	NR	Residence	Ratio: Indoor mean/ outdoor mean	Mean (SD) *Indoor* 2.8 (5.0) *Outdoor* 5.1 (5.3) LOD: NR

AER = air exchange rate; GM = geometric mean; GSD = geometric standard deviation; LOD = limit of detection; NR = not reported; ppb = parts per billion; SD = standard deviation; SE = standard error

[a]Mean value unless otherwise indicated.

[b]Median.

[c]Calculated from Table 1 of Li and Harrison (1990).

3.3.2.2 Personal-Ambient Relationships

As described in the 2008 SO_X ISA (U.S. EPA, 2008b), three main study designs are used to evaluate personal-ambient relationships: (1) longitudinal cohort, (2) pooled, and (3) community-averaged time-series exposure (typically assessed using daily average measurements). Longitudinal studies include measurements made on multiple days for each subject. Thus, they describe the temporal variation in daily personal exposure and ambient concentration for the same subject, and the correlation can differ among study subjects based on activity pattern and other factors. This provides the distribution of correlations for each subject across a study population. Such a study design may be informative for panel epidemiologic studies because variation in longitudinal correlation represent interpersonal variations in ambient exposure. Studies using this design for the health effects of SO_2 exposure have reported a wide variation in 24-hour correlations among subjects, ranging from −0.75 to 0.70, with a median of 0.00−0.10 (Sarnat et al., 2005; Sarnat et al., 2001; Sarnat et al., 2000). However, >95% of personal samples were below the personal monitor detection limit (2−6 ppb), meaning that the reported correlations include substantial noise in the personal exposure measurement. This tends to obscure the true relationship between personal exposure and ambient SO_2 concentrations.

Pooled studies include one or a few measurements per subject, with different subjects studied on different days, and a regression calculated across all subject-days in the study. Studies using this design for SO_2 found personal-ambient slopes of 0.03−0.13 for 24-hour samples (Sarnat et al., 2006; Brauer et al., 1989). Correlations varied across the studies, again due at least in part to detection limit issues. The Brauer et al. (1989) study reported an R^2 value of 0.43 (r = 0.66) in Boston, with all personal samples above the detection limit of 0.19 ppb. Lower correlations were reported by Sarnat et al. (2006); for Steubenville, OH in the fall, R^2 was 0.15 (r = 0.39) with 31.6% of personal samples below the detection limit of 3.8 ppb; while in summer, R^2 was 0.00, with 53.5% of the personal samples below the detection limit of 5.5 ppb.

For the community time-series study design, exposures and ambient concentrations are averaged across subjects for each day and used to calculate the correlation between the daily average exposure and daily average ambient concentration, which is informative for community time-series epidemiologic study designs that evaluate associations between community average concentration and health outcomes. However, no community time-series SO_2 exposure studies reporting personal-ambient correlations have been identified.

Looking across study designs, when nearly all of the personal samples are below the MDL, negligible correlation can be observed in part due to large uncertainties in the measurements. However, when the bulk of the personal samples are above the MDL, personal exposure is moderately correlated with ambient concentration.

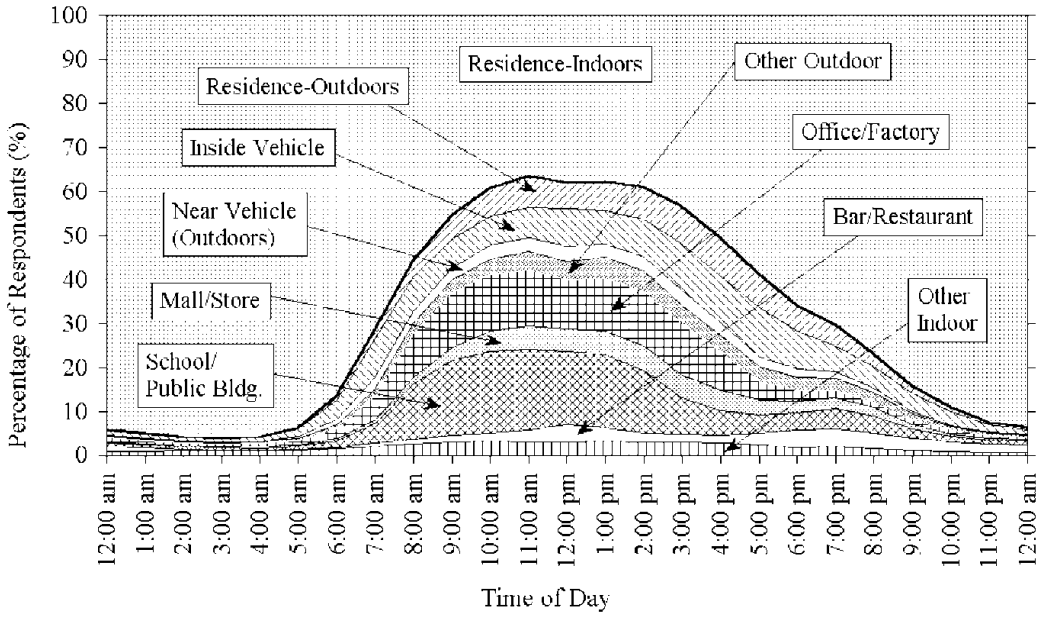
3.3.3 Factors Contributing to Error in Estimating Exposure to Ambient Sulfur Dioxide

In this section, parameters are discussed that are relevant to estimating SO_2 exposure but are not themselves direct measures of exposure. The use of SO_2 measurements from central ambient monitoring sites is the most common method for assigning exposure in epidemiologic studies. However, fixed-site measurements do not account for the effects of spatial variation in SO_2 concentration, ambient and nonambient concentration differences, and varying activity patterns on personal exposures (Brown et al., 2009; Zeger et al., 2000). Inter-individual variability in exposure error across a population will be minimal when (1) SO_2 concentrations are uniform across the region; (2) personal activity patterns are similar across the population; and (3) housing characteristics, such as air exchange rate and indoor reaction rate, are constant over the study area. To the extent that these factors vary by location and population, there will be errors in the magnitude of total exposure based solely on ambient monitoring data. Time-location-activity patterns have a substantial influence on exposure and dose by determining an individual's extent and duration of exposure. Omission of this information can lead to exposure error. Spatial and temporal variability in SO_2 concentrations can contribute to exposure error in epidemiologic studies, whether they rely on central site monitor data or concentration modeling for exposure assessment. Proximity of populations to ambient monitors may also influence how well the populations' exposure is represented by measurements at the monitors.

3.3.3.1 Activity Patterns

The activity pattern of individuals is an important determinant of their exposure. Variation in SO_2 concentrations among various microenvironments means that the amount of time spent in each location, as well as the level of activity, 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.

Activity patterns vary both among and within individuals, resulting in corresponding variations in exposure across a population and over time. Large-scale human activity databases, such as CHAD (McCurdy et al., 2000), which includes the National Human Activity Pattern Survey (NHAPS) (Klepeis et al., 2001) data together with other activity study results, have been designed to characterize exposure patterns among much larger population subsets than can be examined during individual panel studies. The complex human activity patterns across the population (all ages) are illustrated in Figure 3-1 from (Klepeis et al., 2001), which is presented to illustrate the diversity of daily activities among the entire population as well as the proportion of time spent in each microenvironment.



Source: Reprinted with permission of Nature Publishing Group (Klepeis et al., 2001).

Figure 3-1 Distribution of time that National Human Activity Pattern Survey respondents spent in 10 microenvironments based on smoothed 1-minute diary data.

Time spent in different locations has also been found to vary by age. Table 3-5 summarizes 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 comparison of children (mostly less than age 8 years), adults 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). Increased time spent outdoors performing vigorous physical activity is consistent with evidence from the 2008 SO_X ISA (U.S. EPA, 2008b) suggesting that younger age groups are more at risk for SO_2-related health effects.

Table 3-5 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).

Together with location, exertion level is an important determinant of exposure. Table 3-6 summarizes ventilation rates for different age groups at several levels of activity as presented in Table 6-2 of the EPA's *Exposure Factors Handbook* (U.S. EPA, 2011). Most of the age-related variability is seen for moderate and high intensity activities, except for individuals under 1 year. For moderate intensity, ventilation rate increases with age through childhood and adulthood until age 61, after which a moderate decrease is observed. Ventilation rate is most variable for high intensity activities. Children aged 1 to <11 years have ventilation rates of approximately 40 L/minute, while children aged 11+ years and adults have ventilation rates of approximately 50 L/minute. The peak is observed for the 51 to <61 age group, at 53 L/minute, with lower ventilation rates for older adults.

Table 3-6 Mean ventilation rates (L/minute) at different activity levels for different age groups.

Age Group (yr)	Sleep or Nap	Sedentary/ Passive	Light Intensity	Moderate Intensity	High Intensity
Birth to <1	3.0	3.1	7.6	14	26
1 to <2	4.5	4.7	12	21	38
2 to <3	4.6	4.8	12	21	39
3 to <6	4.3	4.5	11	21	37
6 to <11	4.5	4.8	11	22	42
11 to <16	5.0	5.4	13	25	49
16 to <21	4.9	5.3	12	26	49
21 to <31	4.3	4.2	12	26	50
31 to <41	4.6	4.3	12	27	49
41 to <51	5.0	4.8	13	28	52
51 to <61	5.2	5.0	13	29	53
61 to <71	5.2	4.9	12	26	47
71 to <81	5.3	5.0	12	25	47
81+	5.2	4.9	12	25	48

Source: Data from *Exposure Factors Handbook* (U.S. EPA, 2011).

A dramatic increase in ventilation rate occurs as exercise intensity increases. For children and adults <31 years, high intensity activities result in nearly double the ventilation rate for moderate activity, which itself is nearly double the rate for light activity. Children have other important differences in ventilation compared to adults. As discussed in Chapter 4, children tend to have a greater oral breathing contribution than adults, and they breathe at higher minute ventilations relative to their lung volumes. Both of these factors tend to increase dose normalized to lung surface area.

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 age, gender, employment, and lifestyle-dependent factors. These differences may manifest as higher mean 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 intra-class 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.

The EPA's National Exposure Research Laboratory has consolidated many of the most important human activity databases into one comprehensive database called CHAD. The current version of CHAD contains data from nineteen human-activity-pattern studies (including NHAPS), which were conducted between 1982 and 1998 and evaluated to obtain over 33,000 person-days of 24-hour human activities in CHAD (McCurdy et al., 2000). The surveys include probability-based recall studies conducted by EPA and the California Air Resources Board, as well as real-time diary studies conducted in individual U.S. metropolitan areas using both probability-based and volunteer subject panels. All ages of both genders 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.

3.3.3.2 Spatial and Temporal Variability

Spatial and temporal variability in SO_2 concentrations can contribute to exposure error in epidemiologic studies, whether they rely on central site monitor data or concentration modeling for exposure assessment. Spatial variability in the magnitude of concentrations may affect cross-sectional and large-scale cohort studies by undermining the assumption that intra-urban concentration and exposure differences are less important than inter-urban differences. Low inter-monitor correlations contribute to exposure error in time-series studies, including bias toward the null and increased confidence intervals.

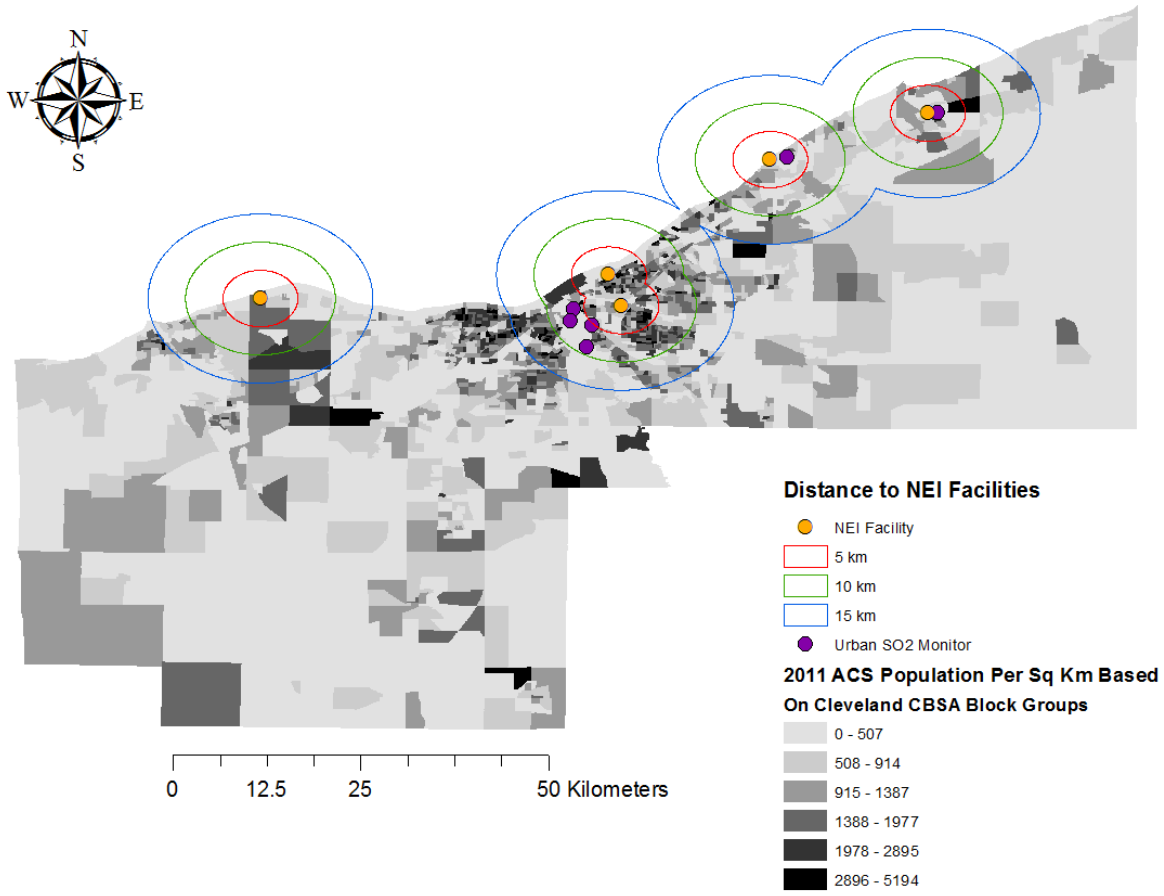
The 2008 SO_X ISA (U.S. EPA, 2008b) discussed spatial variability in SO_2 concentrations and the impact of this variability on effect estimates from epidemiologic studies. Inter-monitor correlations within urban areas ranged from very low to very high values, suggesting that SO_2 concentrations at some monitors 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 monitors include presence of point sources, proximity to point sources, terrain features, and uncertainty regarding the measurement of low SO_2 concentrations. Low correlation between a specific monitor and the community average concentration will tend to bias an effect estimate toward the null.

Several recent studies have evaluated the impact of SO_2 spatial variability on epidemiologic effect estimates. Strickland et al. (2011) reported a relatively low chi-square goodness-of-fit statistic for SO_2 compared with other primary and secondary criteria pollutants in Atlanta, GA. The authors attributed this poor fit to spatial heterogeneity in SO_2 concentrations and the inability of a central site monitor to capture SO_2 plume touch downs in other parts of the city. The chi-squared statistic moderately increased when average 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, especially for effect estimates based on a standardized increment rather than the IQR. This difference is due in part to the spatial heterogeneity of SO_2. The higher concentration reported at the central site monitor is not reflected in the urban averages, resulting in null bias (see Section 5.2.1.2), while spatial variability is partially accounted for in the IQR. The different exposure assignment approaches only altered the magnitude, not direction, of observed associations.

High spatial and temporal variability leading to a null-biased effect estimate was also observed in Atlanta by Goldman et al. (2010). 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 error than primary pollutants such as CO and SO_2, which tend to have higher spatial variability than secondary pollutants. Goldman et al. (2010) simulated error related to assuming the central site monitor represents exposure at a receptor's location. The study authors computed a semivariance term over distance to the central site monitor to estimate error at a distance from the monitor. The observed 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. 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) found that the simulated bias decreased for SO_2 when using unweighted, population-weighted, and area-weighted averages of concentrations from multiple monitors. Similarly, epidemiologic studies in the United States (Kumar, 2012; Morello-Frosch et al., 2010) and Australia Jalaludin et al. (2007), found higher associations between SO_2 and birth outcomes when the analysis was restricted to mothers matched with an SO_2 monitor within 3-5 km of their residence, suggesting bias towards the null remained in the wider spatial averages used in the base case (Section 5.4).

Because SO_2 concentrations can have high spatial variability, exposure estimates may have less error for populations living close to a fixed-site monitor. Figure 3-2 illustrates the location of 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 SO_2 monitors, some of the highest density census block groups are located some distance from central site monitors. This is also illustrated by Table 3-7, which indicates that approximately one-third of the population in various age groups lives more than 15 km from an SO_2 monitor. For the Pittsburgh CBSA (Figure 3-3), 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 an SO_2 monitor (Table 3-8). 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.



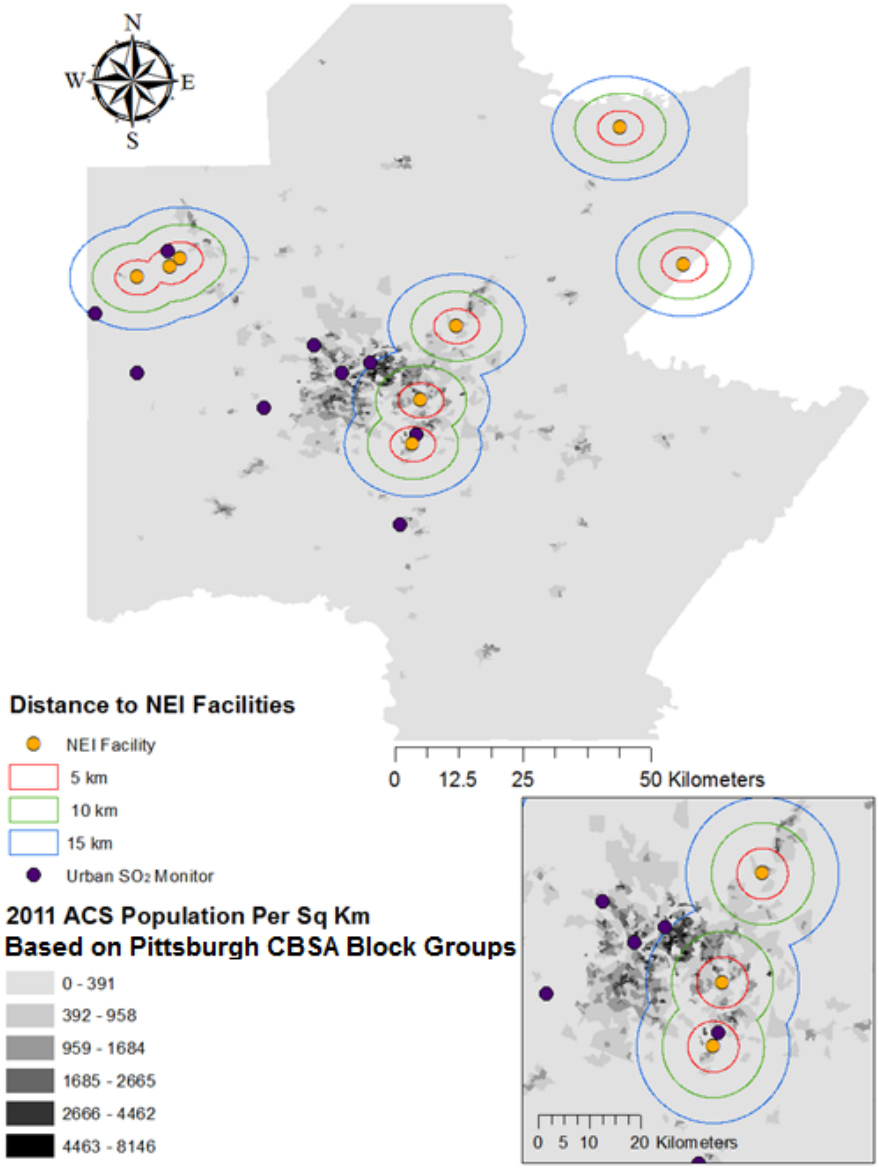
Note that the current map projection (GCS-WGS-1984) creates buffers that take on an elliptical shape instead of a circle. The map projection was chosen to preserve the projection integrity across the data files and reduce error associated with merging data projections.

Figure 3-2 Map of the Cleveland, OH core-based statistical area including National Emissions Inventory facility locations, urban sulfur dioxide monitor locations, and distance from to each facility with respect to core-based statistical area block group population density estimates for 2011. National Emissions Inventory facility emissions ranged from 1,942 tons/year to 48,300 tons/year.

Table 3-7 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.

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



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 3-3 Map of the Pittsburgh, PA core-based statistical area including National Emissions Inventory facility locations, urban sulfur dioxide monitor locations, and distance from 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. The inset map shows National Emissions Inventory facilities located to the southeast of the highly urbanized areas.

Table 3-8 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).

Fewer studies have considered temporal variability. On a seasonal basis, Jalaludin et al. (2007) reported that the association between SO_2 concentration and preterm birth in Sydney, Australia was much higher for conception during autumn (6.489, 95% CI = 4.365−9.648) than in winter (0.826, 95% CI = 0.759−0.898), with winter and spring showing similar effect estimates (1.323, 95% CI = 1.027−1.704; 1.287, 95% CI = 0.955−1.734). However, the study authors noted that other potentially important factors in birth outcomes also vary seasonally, such as outdoor activity, Vitamin D levels, and concentrations of other pollutants. A study in Canada suggests that an exposure metric based on a single year can represent exposure over a multidecade period. The authors compared exposure assessment methods for long-term SO_2 exposure and found that the annual average concentration in the census tract of a subject's residence during 1980 and 1994 was well correlated (Pearson R = 0.83and 0.85 for all subjects, respectively) with a 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 the two methods, to 29% when assigning exposures based on census subdivision, suggesting that improved spatial and temporal resolution in long-term studies may come at the expense of data completeness.

3.3.3.3 Variability in Infiltration and Building Ventilation

Given that people spend the majority of their time indoors, building air exchange rates influence exposure to ambient SO_2, as indicated by Equation 3-4. López-Aparicio et al. (2011) measured 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 $\underline{P}$ = 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 study of SO_2 infiltration. It is difficult to find an analog with other gases that follow similar infiltration patterns to SO_2. While O_3 also has no indoor sources, peak values occur during the summer when photochemical activity is highest. NO_2 has indoor sources from cooking and other combustion. Nonetheless, factors influencing infiltration of other gases may influence SO_2 infiltration as well. In a study of NO_2 infiltration, Meng et al. (2012) found that high air exchange rate (>1.3 air changes per hour), no central air conditioning, use and nonuse of window fans, and presence of old carpeting were determinants of α for NO_2 in summer; none of these factors were determinants of α for NO_2 in winter. In a study of O_3 infiltration and related health effects, Chen et al. (2012a) found that the only influential factor was window opening.

3.3.3.4 Method Detection Limit, Instrument Accuracy, and Instrument Precision

Personal exposure is moderately correlated with ambient SO_2 concentration when personal samples are above the MDL, although the magnitude of personal exposures is often much lower than the magnitude of ambient concentrations (Section 3.3.2). Moderate correlation between personal exposure and ambient concentration indicates that concentration-based exposure metrics are capturing the variability in exposure 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. This results in a high fraction (>90%) of personal samples below the detection limit and are thus unable to provide a signal that could correlate with variations in ambient concentration. Low correlations 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. Data below detection limits are less of an issue for ratios of personal exposure to ambient concentration, for which a low personal sample value likely represents a true low exposure and thus appropriately leads to a low ratio.

Low ratios result from low penetration and high deposition of SO_2 in indoor microenvironments where people spend most of their time.

Instrument error occurs when the SO_2 measurements are subject to interferences that cause biases or noise leading to error in estimating exposure. FRM or FEM SO_2 measurements are subject to positive bias from detection of interfering compounds. See Section 2.4.2 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) investigated instrument precision error at locations where ambient central site monitors were collocated. Instrument precision error increased with increasing concentration for the central site monitors. When instrument error and concentration are correlated, error in the exposure estimates will be larger in locations with more prevalent or stronger sources or at times when SO_2 emissions are higher for a given location. For example, the magnitude of the instrument error would be expected to be largest at times of day when SO_2 emissions are 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) study. 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, instrument error would not be expected to influence the exposure metric on a daily basis. When comparing health effect estimates among cities for a long-term SO_2 exposure epidemiologic study, differences in instrument error among cities could lead to biased exposure estimates, given the reliance on differences in exposure magnitude to study spatial contrasts. Section 3.3.5 describes the influence of instrument error and high MDL on exposure error and health effect estimates for community time-series (Section 3.3.5.1), longitudinal cohort (Section 3.3.5.2), and panel (Section 3.3.5.3) epidemiologic studies.

3.3.4 Confounding

To assess the independent health effects of SO_2 in an epidemiologic study, it is necessary to identify (1) 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 with SO_2 can be tested and, if needed, accounted for in the epidemiologic model; (2) 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 (3) the spatial correlation structure across multiple pollutants, if the epidemiologic study design is for long-term exposure (Bateson et al., 2007). Additionally, confounding can also vary by the health endpoint studied.

For monitors that do show high correlations, copollutant epidemiologic models may be appropriate to adjust the effect estimate for each pollutant for confounding by the other pollutant (Tolbert et al., 2007). As discussed in the 2010 CO ISA (U.S. EPA, 2010b), copollutant 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. However, collinearity potentially affects model performance when highly correlated pollutants are modeled simultaneously, and differences in the spatial distribution of SO_2 and the copollutants may also complicate model interpretation (Gryparis et al., 2007) (Section 5.1.2.1). Because SO_2 exhibits a relatively high degree of exposure error compared with other criteria pollutants, copollutant models in which the SO_2 effect estimate remains robust provide additional evidence for an independent health effect of SO_2.

This section considers temporal copollutant correlations and how relationships among copollutants may change in space. Temporal copollutant correlations are computed from the time series of concentrations for two different collocated pollutants. Temporal correlations are informative for epidemiologic studies of short-term exposure when the sampling interval is a month or less for each of the copollutants. Temporal correlations are informative for epidemiologic studies of long-term exposures when sampling intervals are months to years. 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 SO_2 over different temporal and spatial resolutions.

3.3.4.1 Temporal Relationships among Ambient Sulfur Dioxide and Copollutant Exposures

Short-Term Temporal Correlations

As discussed in Section 2.5.5, daily concentrations of ambient SO_2 generally exhibit low to moderate correlations with other daily NAAQS pollutant concentrations at collocated monitors (Figure 2-35). However, a wide range of copollutant correlations is observed at different monitoring sites, from moderately negative to moderately positive (Table 3-9). This indicates 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 recent rulemaking on use of ultra-low sulfur diesel fuel (66 FR 5002). Some of the studies cited in this ISA may precede 2006 and 2007, when the new sulfur standards took effect for highway vehicles and heavy duty vehicles, respectively. This

change may contribute to wider variation in correlation between SO_2 and copollutants presented in this section. Note that potential for confounding also varies by health endpoint.

Exposure studies have examined correlations between ambient SO_2 and ambient or personal copollutants, generally reporting low or moderate correlations. Spearman correlations between daily ambient concentrations of SO_2 and ambient copollutants reported in Baltimore were generally near zero, although a moderate correlation (0.41) was observed for O_3 (Sarnat et al., 2001). Pearson correlations reported in an exposure study conducted in Steubenville, OH between ambient SO_2 and ambient $PM_{2.5}$, sulfate, and elemental carbon (EC) were higher in the fall (0.47−0.58) than in the spring (0.1−0.22) (Sarnat et al., 2006), although it is difficult to generalize from this single result, particularly because correlations between ambient SO_2 concentration and personal $PM_{2.5}$, sulfate, and elemental carbon were similar in both seasons (r = 0.1−0.3).

Correlations between daily ambient SO_2 concentration and personal exposure to $PM_{2.5}$ were found to vary widely between subjects in both Baltimore and Boston (Sarnat et al., 2005). Both moderately positive (>0.5) and moderately negative (<−0.5) Spearman correlations were reported, with a median correlation near zero. The Sarnat et al. (2001) study in Steubenville, OH reported a Pearson correlation of 0.3 between ambient SO_2 concentration and personal $PM_{2.5}$ exposure. Taken together, this evidence suggests that correlations between copollutant exposure and ambient SO_2 concentration vary among individuals, and thus the potential for copollutant confounding cannot be ruled out.

Long-Term Correlations

Long-term epidemiologic studies that have reported copollutant correlations are also listed in Table 3-9. Similar to daily correlations, no clear pattern is apparent for correlation of ambient SO_2 concentration with any of the other copollutants. A wide range of correlations has been reported among the copollutants, including moderately negative and moderately to strongly positive. Because confounding may occur even when correlations are low, no clear conclusion can be drawn regarding the potential for confounding of long-term SO_2 epidemiologic estimates by copollutants.

Table 3-9 Synthesis of sulfur dioxide ambient-ambient copollutant correlations from short-term and long-term epidemiology studies.

Study	Duration	Location	Correlation Measure	CO	O_3	NO_2	$PM_{2.5}$	PM_{10}	NO_X	TSP
Short Term Studies										
Dales et al. (2006)	1 day	11 Canadian cities	Pearson		−0.41 to 0.13	0.20 to 0.67		−0.09 to 0.61		
Faiz et al. (2013)	1 day	New Jersey	Pearson	0.49		0.51	0.31			
Leem et al. (2006)	1 day	Incheon, South Korea	Pearson	0.31		0.54		0.13		
Liu et al. (2003)	1 day	Vancouver, Canada	Pearson	0.64	−0.35	0.61				
Liu et al. (2007)	1 day	Canada	Pearson	0.21	−0.30	0.34	0.44			
Peel et al. (2011)	1 day	Atlanta, GA	Spearman	0.39	−0.11	0.31	0.20	0.21		
Pereira et al. (1998)	1 day	Sao Paulo, Brazil	Pearson	0.34	0.15	0.41		0.74		
Sagiv et al. (2005)	1 day	Pennsylvania	Pearson				0.46			
Zhao et al. (2011)	1 day	Guangzhou, China	Pearson			0.84		0.75		
Lee et al. (2011a)	7 days	Allegheny County, PA	Pearson	0.30	0.10	0.40	0.20	0.10		
Long term studies										
Clougherty et al. (2013)	2 weeks	5-boroughs of New York City	Pearson			0.51	0.70			
Darrow et al. (2009)	4 weeks	5 counties in Atlanta, GA	Spearman	0.44	−0.32	0.37	0.12	−0.17		
Le et al. (2012)	1 mo	Detroit	NR	0.35		0.27		0.11		
Darrow et al. (2011)	1st mo	5 counties in Atlanta, GA	Spearman	0.44	−0.27	0.32	−0.07	−0.18		

Table 3-9 (Continued): Synthesis of sulfur dioxide ambient copollutant correlations from short-term and long-term epidemiology studies.

Study	Duration	Location	Correlation Measure	CO	O_3	NO_2	$PM_{2.5}$	PM_{10}	NO_X	TSP
Slama et al. (2013)	M1−M1	Teplice District, Czech Republic	NR		−0.69	0.73	0.79			
	M1−M2				−0.69	0.39	0.41			
	M1−M12				−0.74	0.64	0.70			
	M2−M1				−0.47	0.58	0.54			
	M2−M2				−0.70	0.72	0.80			
	M2−M12				−0.63	0.71	0.75			
	M12−M1				−0.65	0.74	0.74			
	M12−M2				−0.78	0.63	0.68			
	M12−M12				−0.77	0.77	0.82			
Strickland et al. (2009)	5 weeks	Atlanta, GA	Spearman	0.23	0.30	0.39		0.41		
Woodruff et al. (2008)	2 mo	United States	Spearman	0.27	−0.22		0.21	0.00		

Table 3-9 (Continued): Synthesis of sulfur dioxide ambient copollutant correlations from short-term and long-term epidemiology studies.

Study	Duration	Location	Correlation Measure	CO	O_3	NO_2	$PM_{2.5}$	PM_{10}	NO_X	TSP
Bobak (2000)	T1−T1	Czech Republic	NR						0.53	0.71
	T1−T2								0.19	0.17
	T1−T3								−0.05	−0.39
	T2−T1								0.33	0.09
	T2−T2								0.62	0.68
	T2−T3								0.26	0.16
	T3−T1								0.04	−0.22
	T3−T2								0.30	0.13
	T3−T3								0.63	0.73
Darrow et al. (2011)	T3			0.61	−0.50	0.39	−0.18	−0.30		

Table 3-9 (Continued): Synthesis of sulfur dioxide ambient copollutant correlations from short-term and long-term epidemiology studies.

Study	Duration	Location	Correlation Measure	CO	O_3	NO_2	$PM_{2.5}$	PM_{10}	NO_X	TSP
Faiz et al. (2012)	T1−T1	New Jersey	Pearson	0.40		0.30	0.07			
	T1−T2			0.25		0.10	0.15			
	T1−T3			0.21		0.05	0.41			
	T1−P			0.39		0.16	0.33			
	T2−T1			0.37		0.26	−0.07			
	T2−T2			0.43		0.31	0.11			
	T2−T3			0.26		0.10	0.17			
	T2−P			0.47		0.23	0.13			
	T3−T1			0.20		0.08	0.40			
	T3−T2			0.38		0.27	−0.04			
	T3−T3			0.43		0.32	0.14			
	T3−P			0.45		0.23	0.30			
	P−T1			0.35		0.30	0.17			
	P−T2			0.37		0.30	0.10			
	P−T3			0.32		0.21	0.33			
	P			0.47		0.28	0.33			
Geer et al. (2012)	T1−T3	Texas	Pearson	0.61	−0.23	−0.30	0.05	−0.07		
Hwang and Jaakkola (2008)	T1	Taiwan	NR	0.24	0.23			0.50	0.45	

Table 3-9 (Continued): Synthesis of sulfur dioxide ambient copollutant correlations from short-term and long-term epidemiology studies.

Study	Duration	Location	Correlation Measure	CO	O_3	NO_2	$PM_{2.5}$	PM_{10}	NO_X	TSP
Lee et al. (2003)	T1	South Korea	NR	0.79				0.78		
	T2			0.86				0.82		
	T3			0.86				0.85		
Lee et al. (2012)	T1	Allegheny Co, PA	Pearson	0.30	−0.60	0.30	−0.30	−0.30		
Lin et al. (2014)	T1	Taiwan	Pearson	0.31	0.18	0.51		0.54		
Lipfert et al. (2000b)	1 yr	United States	NR	−0.15				0.04		
Rich et al. (2009)	T1−T1	New Jersey	Pearson	0.22		0.16	0.17			
	T1−T2			0.18		−0.05	0.04			
	T1−T3			0.02		−0.08	0.37			
	T2−T1			0.12		0.06	−0.11			
	T2−T2			0.25		0.12	0.17			
	T2−T3			0.21		−0.06	0.04			
	T3−T1			0.21		−0.03	0.33			
	T3−T2			0.24		0.16	−0.02			
	T3−T3			0.38		0.17	0.19			
Xu et al. (2014)	T1	Florida	Pearson	0.29	−0.36	0.15	0.20			
	T2			0.25	−0.39	0.08	0.13			
	P			0.18	−0.28	0.06	0.10			

Table 3-9 (Continued): Synthesis of sulfur dioxide ambient copollutant correlations from short-term and long-term epidemiology studies.

Study	Duration	Location	Correlation Measure	CO	O_3	NO_2	$PM_{2.5}$	PM_{10}	NO_X	TSP
Yang et al. (2003a)	T1−T1	Taiwan	NR					0.46		
	T1−T2							0.11		
	T1−T3							−0.06		
	T2−T1							0.32		
	T2−T2							0.45		
	T2−T3							0.08		
	T3−T1							0.00		
	T3−T2							0.31		
	T3−T3							0.45		
Ebisu and Bell (2012)	P	Northeast and Mid-Atlantic states	Pearson	−0.35 to 0.87	−0.76 to 0.66	−0.16 to 0.89	−0.50 to 0.77	−0.61 to 0.63		
Hwang et al. (2011)	P	Taiwan	NR	0.15	0.13	0.41		0.53		
Ha et al. (2001)	2 yr	Seoul, South Korea	Pearson	0.83		0.70				0.67

CO = carbon monoxide; M1 = 1st mo of unprotected intercourse; M2 = 2nd mo of unprotected intercourse; M12 = average of M1 & M2 (2 mo total); NO_2 = nitrogen dioxide; NO_X = the sum of nitric oxide and NO_2; NR = not reported; O_3 = ozone; P = entire pregnancy; $PM_{2.5}$ = 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;TSP = total suspended particulates; T1 = 1st Trimester; T2 = 2nd trimester; T3 = 3rd trimester; T1−T1 = correlation between 1st trimester SO_2 and copollutants.

3.3.4.2 Spatial Variability 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.

3.3.5 Implications for Epidemiologic Studies of Different Designs

Exposure measurement error, which refers to the bias and uncertainty associated with using concentration metrics to represent the actual exposure of an individual or population, 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 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 to 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.

Estimates of SO_2 exposures are subject to errors that can vary in nature, as described in Section 3.3.3. Classical error is defined as error scattered around the true personal exposure and independent of the measured exposure. 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 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.

Definitions for Berkson-like and classical-like errors were developed for modeled exposures. These errors depend on how exposure metrics are averaged across space. Szpiro et al. (2011) defined Berkson-like and classical-like errors as errors sharing some characteristics with Berkson and classical errors, respectively, but with some differences. Specifically, Berkson-like errors occur when the modeled exposure does not capture all of the variability in the true exposure. Berkson-like errors increase the variability around the health effect estimate in a manner similar to pure Berkson error, but Berkson-like errors are spatially correlated and not independent of predicted exposures, unlike pure Berkson errors. Szpiro and Paciorek (2013) simulated Berkson-like errors' influence on health effect estimates. For the case simulated where spatial variability in the exposure estimates from measurements exceeded the spatial variability in the true exposures (which were modeled to be uniform), the health effect estimates were biased away from the null. For the case simulated where covariates were included in the health model but not 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. Classical-like errors can add variability to predicted exposures and can bias health effect estimates in a manner similar to pure classical errors, but they differ from pure classical errors in that the variability in estimated exposures is also not independent across space. Exposure error can bias epidemiologic associations between ambient pollutant concentrations and health outcomes and tends to widen confidence intervals around those estimates (Sheppard et al., 2005; Zeger et al., 2000). The importance of exposure error varies with study design and is dependent on the spatial and temporal aspects of the design. Other 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.

3.3.5.1 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 3.3.1). 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 exposures. Moreover, for community time-series epidemiology studies of short-term exposure, the temporal variability in 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 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. The relative risk (RR) per ppm was negatively biased in the case of classical error (1-hour daily max SO_2: −1.3%) and negligibly positively biased in the case of Berkson error (1-hour daily max SO_2: 0.0042%). The 95% confidence interval range for RR per ppm was wider for Berkson error (1-hour daily max SO_2: 0.028) compared with classical error (1-hour daily max SO_2: 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 or outdoor 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 with distance from the monitoring site. The average of the calculated random term was added to a central site monitoring time series (considered in this study to be the base case) to estimate population exposure to SO_2 subject to spatial error. For the analysis with temporal autocorrelation considered, RR per ppm for 1-hour 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-hour daily max SO_2. The results of Goldman et al. (2010) suggest that spatial exposure error from use of central site monitoring data results in biasing the health effect estimate towards the null, but the magnitude of the change in effect was small.

In a another study analyzing the influence of spatiotemporal variability among ambient or outdoor 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 "true" ambient concentrations of SO_2 and other air pollutant measures. 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 measurements obtained directly from monitors at those sites. Geostatistical-simulated concentrations were considered to be "true" 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, (3) performing a population-weighted average across all monitoring sites, (4) performing an area-weighted average across all monitoring sites, and (5) population-weighted averaging of the geostatistical simulation (see Table 3-10). Goldman et al. (2012) observed that the exposure error was somewhat correlated with both the measured and true values, reflecting both Berkson and classical error components. For the central site monitor, the exposure errors were somewhat inversely correlated with the true value but had relatively higher positive correlation with the measured value. For the other exposure estimation methods, the exposure errors were inversely correlated with the true value, while having positive but lower magnitude correlation with the measured value. 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 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.

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

Table 3-10 The influence of exposure metrics on error in health effect estimates.

Exposure Estimation Approach	Bias[(*Z*−*Z**)/*Z*][a]	R^2(*Z*, *Z**)[b]	*R*[(*Z*−*Z**), *Z**][c]	*R*[(*Z*−*Z**), *Z*][c]
SO_2				
Central site monitor	0.76	0.13	−0.40	0.74
Unweighted average	0.45	0.16	−0.73	0.35
Population-weighted average	0.36	0.18	−0.79	0.25
Area-weighted average	0.15	0.18	−0.88	0.08
Geostatistical model—population-weighted average	N/A	0.28	−0.86	−0.0003

N/A = not applicable; SO_2 = sulfur dioxide.

Note: Model errors were based on comparisons between measured data and simulated data at several monitoring sites. Errors were estimated for a single central site monitor, various monitor averages, and values computed from a geostatistical model. *Z* denotes the measured concentration, and *Z** denotes the true concentration, considered here to be from the geostatistical model. Bias in the exposure metric is given as the proportion of error between the measurement and true value to the measurement.

[a]Data provided by the authors for Figure 5 of Goldman et al. (2012).

[b]Data provided by the authors of Figure 4 of Goldman et al. (2012).

[c]Pearson correlation.

Source: Goldman et al. (2012).

In addition to the effect of the correlations and ratios themselves, spatial variation in their values 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 metrics compared with the central site monitor and more classical error for the central site monitor estimate compared with the other exposure assessment techniques. Hence, more bias would be anticipated for the health effect estimate calculated from the central site monitor, and more variability would be expected for the health effect estimate calculated with the more spatially resolved methods. Differences in the magnitude of exposure 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 (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 assessment methods but was more pronounced for the central site measurement 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 3.3.3.4 describes the influence of high MDL on the relationship between measured ambient SO_2 concentrations and personal exposure to ambient SO_2. When measurements are above detection limit, 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 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 (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 3.3.3.4 also describes the influence of instrument accuracy and precision on the relationship between ambient SO_2 concentrations and personal exposure to ambient SO_2. Exposure measurement error related to instrument precision has a smaller effect on health effect estimates in time-series studies compared with error related to spatial gradients in the concentration because instrument precision would not be expected to modify the ability of the instruments to respond to changes in 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 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 time series to simulate population estimates for ambient air concentrations subject to instrument precision error in 1,000 Monte Carlo simulations. Very little changes in the risk ratios were observed for 1-hour daily max SO_2. For 1-hour daily max SO_2 concentration, the RR per ppm of SO_2 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 3.3.2 nonambient sources of SO_2 are rare. Even in microenvironments where nonambient exposure is substantial, such as in a room with a kerosene heater, such exposure is unlikely to be temporally correlated with ambient SO_2 exposure (Wilson and Suh, 1997), and therefore would not affect epidemiologic associations between ambient SO_2 and a health effect in a time-series study. In simulations of a nonreactive pollutant, Sheppard et al. (2005) concluded that nonambient exposure does not influence the health outcome effect estimate if ambient and nonambient concentrations are independent. Because personal exposure to ambient SO_2 is some fraction of the ambient concentration, it should be noted that effect estimates calculated based on personal exposure rather than ambient concentration will be

positively biased in proportion to the ratio of ambient concentration to ambient exposure, and daily fluctuations in this ratio can widen the confidence intervals in the ambient concentration effect estimate. Uncorrelated nonambient exposure will not bias the effect estimate but may also widen the confidence intervals (Sheppard et al., 2005; Wilson and Suh, 1997).

3.3.5.2 Long-Term Cohort Studies

For cohort epidemiologic studies of long-term human exposure to SO_2, where the difference in the magnitude of the concentration is of most interest, 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 SO_2 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 are clustered in a location where their SO_2 exposure is higher or lower than the exposure 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 in proximity to the study participants and the SO_2 source (e.g., near the plume touch-down of a power plant) and spatial variability of the 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 or dedicated measurements means that investigators must rely on fixed-site monitoring data or model estimates. These concentrations may be used directly, averaged across counties or other geographic areas, or used to construct geospatial or regression models to assign concentrations to unmonitored locations. The number of long-term studies of SO_2 exposure studies that permit evaluation of the relationship between long-term average SO_2 concentrations and personal or population exposure is limited, and the value of short-term exposure data for evaluating long-term concentration exposure 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 exposures 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, as described in Section 3.3.3.2. However, lower correlation between long-term exposures 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 estimate does not always minimize error in the health effect estimate. Szpiro et al. (2011) evaluated bias and uncertainty of the health effect estimate obtained when using correctly specified and misspecified exposure simulation conditions. For comparison purposes, correct specification was considered to be the use of three spatial prediction variables, and misspecification implied unmeasured error in the model. LUR calculations were used to simulate exposure; the misspecified model omitted a geographic covariate in the LUR. Szpiro et al. (2011) also reduced the amount of variability in the third covariate in simulating the monitoring network data in an additional set of simulations. Prediction accuracy of the exposure estimate was higher for the correctly specified model compared with the misspecified model. However, the health effect estimate was more variable for the correctly specified model compared with the misspecified model when the variability in the exposure covariate in the monitoring data decreased. The results of Szpiro et al. (2011) suggest that use of more accurately defined exposure metrics in a cohort study does not necessarily improve health effect estimates, and the influence of the refined metrics depends on the relative variability of the exposure covariates. The Szpiro et al. (2011) simulations were for a generic air pollutant but are relevant to SO_2.

Error correction is a relatively new approach to estimate the correct standard error and to potentially correct for bias in longitudinal cohort studies. Using this approach, Szpiro and Paciorek (2013) established that two conditions must hold for the health effect estimate to be predicted correctly: the exposure estimates from monitors must come from the same underlying distribution as the true exposures, and the health effect model includes all covariates relevant to the population. Szpiro and Paciorek (2013) performed several simulations to investigate what happens when these conditions are violated. In one set of simulations, the distribution of the exposure was varied. When the assigned exposure 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 improved the model prediction, even when the true model contained several degrees of freedom (df). 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. Sections 2.4.1 and

3.2.1 describe how the presence of copollutants can cause SO_2 concentrations measured using central site monitors to be overestimated and how high relative humidity can cause SO_2 measurements to be underestimated. Relative humidity would not be expected to vary greatly within a city. However, local 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 estimate 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 exposures.

3.3.5.3 Panel Studies

Panel or small-scale cohort studies involving dozens of individuals may use more individualized concentration measurements, such as personal exposures, residential fixed-site indoor or outdoor measurements, or concentration data from local study-specific monitors. Modeled concentrations are not typically used as exposure surrogates in panel epidemiologic studies. Probabilistic, distribution-based approaches are not designed to estimate exposures for specific individuals, such as might be needed for panel epidemiologic studies. Another main disadvantage of the modeling approach is that the results of modeling exposure assessment must be compared to an independent set of measured exposure levels (Klepeis, 1999). In addition, resource-intensive development of validated and representative model inputs is required, such as human activity patterns, distributions of air exchange rate, and deposition rate. Therefore, modeled exposures are used much less frequently in panel epidemiologic studies.

Section 3.3.3.4 describes the influence of high method detection limit on the relationship between measured ambient SO_2 concentrations and personal exposure to 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, as discussed. 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-based effect estimate or response function relative to the ambient concentration-based response function (see

Equation 3-6). However, if the ratio is approximately constant over time, the strength of the statistical association would be similar for concentration- and exposure-based effect estimates (Sheppard, 2005; Sheppard et al., 2005).

3.4 Summary and Conclusions

The 2008 SO_X ISA (U.S. EPA, 2008b) evaluated SO_2 concentrations and exposures in multiple microenvironments, discussed methods for estimating personal and population exposure 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 in epidemiologic studies. Key findings were that indoor concentrations and personal exposures 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 concentrations and indoor or personal exposures. 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 estimates on epidemiologic study results, high spatial variability of SO_2 concentrations across an urban area results in highly variable correlations among urban SO_2 monitors. Low correlations between individual monitor concentrations and the community average 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. 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 estimates in epidemiologic studies. Multiple techniques can be used to assign exposure for epidemiologic studies, including the use of central site monitor concentrations, personal SO_2 monitors, and various types of models. Each has strengths and limitations, as summarized in Table 3-2. Central site monitors 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, 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 under-estimating exposure for the population of interest. In all study types, use of central site monitors is expected to widen confidence intervals. Personal SO_2 monitors are a direct measure of exposure, but low ambient SO_2 concentrations often result in a substantial fraction of the samples below the method detection limit 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 for exposure assessments of 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 SO_2 concentrations measured at several monitors. Other spatial interpolation techniques, such as kriging, also require SO_2 concentrations from several monitors and apply more complex mathematical functions to interpolate among monitors. LUR regresses measured concentrations on local variables and then uses the resulting model to predict concentrations across a study area or at the locations of specific receptors. As such, LUR enables higher spatial resolution of predicted 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 SO_2, and in the case of CTMs, the atmospheric chemistry. The strength of mechanistic models is increased accuracy of the 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 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 (Table 3-4). 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 concentrations were relatively high (>0.75), suggesting that variations in outdoor concentration are driving indoor concentrations. The bulk of the evidence for personal-ambient SO_2 relationships was available at the time of the previous

ISA and showed a wide range of correlations between ambient concentration and personal exposure, in part due to a large fraction of samples below the MDL in several studies. 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.

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. Variation in SO_2 concentrations among various microenvironments means that the amount of time spent in each location, as well as the level of exertion, will 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 exposure estimates.

Spatial and temporal variability in SO_2 concentrations can contribute to exposure error in epidemiologic studies, whether they rely on central site monitor data or concentration modeling for exposure assessment. SO_2 has low to moderate spatial correlations between ambient monitors 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 undermining the assumption that intra-urban concentration and exposure differences 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 concentrations to evaluate health effects.

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

correlations with other daily NAAQS pollutant concentrations at collocated monitors (Figure 2-35). However, a wide range of copollutant correlations is observed at different monitoring sites, from moderately negative to moderately positive. In studies where daily SO_2 correlations with NO_2 and CO were observed to be high, it is possible the data may have been collected before recent rulemaking to reduce sulfur content in diesel fuel (66 FR 5002). 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 contribute to variability in epidemiologic study results by biasing effect estimates toward or away from the null and widening confidence intervals. 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. Low spatial correlations between central site monitors also contribute to exposure error in time-series studies, potentially biasing the health effect estimate towards the null and widening the confidence intervals around the health effect estimate. For long-term studies, bias of the health effect estimate may occur in either direction depending on whether the monitor is over- or under-estimating 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. 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, ambient and non-ambient concentration differences, and varying activity patterns on personal exposure to SO_2. Personal exposure measurements, such as those made in panel epidemiologic studies, provide specific exposure estimates that may more accurately reflect spatial variability, but sample size is often small and only a limited set of health outcomes can be studied. Modeled concentration or exposure estimates using various approaches offer an alternative to measurements, with the advantage of estimating exposures 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 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.

References for Chapter 3

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

Al-Ali, AR; Zualkernan, I; Aloul, F. (2010). A mobile GPRS-sensors array for air pollution monitoring. IEEE Sens J 10: 1666-1671. http://dx.doi.org/10.1109/JSEN.2010.2045890

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

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

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; 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

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

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

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

Bellander, T; Berglind, N; Gustavsson, P; Jonson, T; Nyberg, F; Pershagen, G; Jarup, L. (2001). Using geographic information systems to assess individual historical exposure to air pollution from traffic and house heating in Stockholm. Environ Health Perspect 109: 633-639.

Binkowski, FS; Arunachalam, S; Adelman, Z; Pinto, JP. (2007). Examining photolysis rates with a prototype online photolysis module in CMAQ. J Appl Meteor Climatol 46: 1252-1256. http://dx.doi.org/10.1175/JAM2531.1

Bobak, M. (2000). Outdoor air pollution, low birth weight, and prematurity. Environ Health Perspect 108: 173-176.

Brauer, M; Koutrakis, P; Keeler, GJ; Spengler, JD. (1991). Indoor and outdoor concentrations of inorganic acidic aerosols and gases. J Air Waste Manag Assoc 41: 171-181. http://dx.doi.org/10.1080/10473289.1991.10466834

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

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

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. Res Rep Health Eff Inst5-71; discussion 73-89.

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

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

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

Cai, EP; Casimir, M; Schroer, SA; Luk, CT; Shi, SY, u; Choi, D; Dai, XQ; Hajmrle, C; Spigelman, AF; Zhu, D, an; Gaisano, HY; Macdonald, PE; Woo, M. (2012). In vivo role of focal adhesion kinase in regulating pancreatic beta-cell mass and function through insulin signaling, actin dynamics, and granule trafficking. Diabetes 61: 1708-1718. http://dx.doi.org/10.2337/db11-1344

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

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

Chan, CC; Hung, HF; Fu, LF. (1994). The indoor/outdoor relationship of acid aerosols in Taipei. Sci Total Environ 153: 267-273.

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

Chao, CY. (2001). Comparison between indoor and outdoor air contaminant levels in residential buildings from passive sampler study. Build Environ 36: 999-1007.

Chen, C; Zhao, B, in; Weschler, CJ. (2012a). Assessing the influence of indoor exposure to "outdoor ozone" on the relationship between ozone and short-term mortality in us communities. Environ Health Perspect 120: 235-240. http://dx.doi.org/10.1289/ehp.1103970

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

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

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

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. http://dx.doi.org/10.1289/ehp.9044

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.

Degner, M; Damaschke, N; Ewald, H; Lewis, E. (2010). High resolution LED-spectroscopy for sensor application in harsh environment. IEEE international instrumentation and measurement technology conference I2MTC 2010, proceedings 1091-5281, Austin, TX.

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

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

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

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

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

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

Fu, T. (2013). Sensing behavior of CdS nanoparticles to SO2, H2S and NH3 at room temperature. Materials Research Bulletin 48: 1784-1790. http://dx.doi.org/10.1016/j.materresbull.2013.01.037

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.

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

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.

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

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

Gondal, MA; Dastageer, MA. (2008). High-sensitivity detection of hazardous SO(2) using 266 nm UV laser. J Environ Sci Health A Tox Hazard Subst Environ Eng 43: 1126-1131. http://dx.doi.org/10.1080/10934520802171543

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

Gram, F; Nafstad, P; Haheim, LL. (2003). Estimating residential air pollution exposure among citizens in Oslo 1974-1998 using a geographical information system. J Environ Monit 5: 541-546. http://dx.doi.org/10.1039/b303500j

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

Guevara, M; Soret, A; Arevalo, G; Martinez, F; Baldasano, JM. (2014). Implementation of plume rise and its impacts on emissions and air quality modelling. Atmos Environ 99: 618-629. http://dx.doi.org/10.1016/j.atmosenv.2014.10.029

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.

Hart, J; Yanosky, J; Puett, R; Ryan, L; Dockery, D; Smith, T; Garshick, E; Laden, F. (2009). Spatial modeling of PM10 and NO2 in the continental United States, 1985-2000. Environ Health Perspect 117: 1690-1696. http://dx.doi.org/10.1289/ehp.0900840

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

Hawe, E; Fitzpatrick, C; Chambers, P; Dooly, G; Lewis, E. (2008). Hazardous gas detection using an integrating sphere as a multipass gas absorption cell. Sens Actuators A 141: 414-421. http://dx.doi.org/10.1016/j.sna.2007.10.070

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

Hystad, P; Setton, E; Cervantes, A; Poplawski, K; Deschenes, S; Brauer, M; van Donkelaar, A; Lamsal, L; Martin, R; Jerrett, M; Demers, P. (2011). Creating national air pollution models for population exposure assessment in Canada. Environ Health Perspect 119: 1123-1129. http://dx.doi.org/10.1289/ehp.1002976

Ivy, D; Mulholland, JA; Russell, AG. (2008). Development of ambient air quality population-weighted metrics for use in time-series health studies. J Air Waste Manag Assoc 58: 711-720. http://dx.doi.org/10.3155/1047-3289.58.5.711

Jaisutti, R; Osotchan, T. (2012). An investigation of molecular interactions between zinc phthalocyanine thin film and various oxidizing gases for sensor applications. Adv Mater Res 403-408: 48-51. http://dx.doi.org/10.4028/www.scientific.net/AMR.403-408.48

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

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

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

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

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 1: 260-270. http://dx.doi.org/10.5094/APR.2010.033

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

Kindzierski, WB; Ranganathan, HKS. (2006). Indoor and outdoor SO2 in a community near oil sand extraction and production facilities in northern Alberta. J Environ Eng Sci 5: S121-S129. http://dx.doi.org/10.1139/S06-022

Kindzierski, WB; Sembaluk, S. (2001). Indoor outdoor relationship of SO2 concentrations in a rural and an urban community of Alberta. Can J Civ Eng 28: 163-169.

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

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

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

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

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, 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. (2011a). Particulate air pollution exposure and C-reactive protein during early pregnancy. Epidemiology 22: 524-531. http://dx.doi.org/10.1097/EDE.0b013e31821c6c58

Lee, SC; Chan, LY; Chiu, MY. (1999). Indoor and outdoor air quality investigation at 14 public places in Hong Kong. Environ Int 25: 443-450.

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

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

Li, YQ; Harrison, RM. (1990). Comparison of indoor and outdoor concentrations of acid gases, ammonia and their associated salts. Environ Technol 11: 315-326.

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 132C: 273-280. http://dx.doi.org/10.1016/j.envres.2014.04.028

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. http://dx.doi.org/10.3155/1047-3289.59.4.473

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, 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, 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

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

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

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

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

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

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

Meka, D; Onbattuvelli, V; Atre, SV; Prasad, S. (2008). Palladium/polymer nanocomposite based chemiresistive SO(2) sensor. The nanotechnology conference and trade show, June 1-5, Boston, MA.

Meng, Q; Williams, R; Pinto, JP. (2012). Determinants of the associations between ambient concentrations and personal exposures to ambient PM2.5, NO2, and O3 during DEARS. Atmos Environ 63: 109-116. http://dx.doi.org/10.1016/j.atmosenv.2012.09.019

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

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

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: 610-605.

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

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, J. R.; 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

Novotny, EV; Bechle, MJ; Millet, DB; Marshall, JD. (2011). National satellite-based land-use regression: NO2 in the United States. Environ Sci Technol 45: 4407-4414. http://dx.doi.org/10.1021/es103578x

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

Ogawa & Co (Ogawa & Company). (2007). Ambient air passive sampler for NO-NO2, NOx, SO2, O3, NH3. Pompano Beach, FL: Ogawa & Company USA, Inc. http://www.ogawausa.com/passive.html

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

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

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

Patterson, E; Eatough, DJ. (2000). Indoor/outdoor relationships for ambient PM25 and associated pollutants: epidemiological implications in Lindon, Utah. J Air Waste Manag Assoc 50: 103-110.

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

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

Penard-Morand, C; Schillinger, C; Armengaud, A; Debotte, G; Chretien, E; Pellier, S; Annesi-Maesano, I. (2006). Assessment of schoolchildren's exposure to traffic-related air pollution in the French Six Cities Study using a dispersion model. Atmos Environ 40: 2274-2287. http://dx.doi.org/10.1016/j.atmosenv.2005.11.057

Peng, S; Wu, G; Song, W, ei; Wang, Q. (2013). Application of flower-like ZnO nanorods gas sensor detecting sf6 decomposition products. Journal of Nanomaterials. http://dx.doi.org/10.1155/2013/135147

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

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

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

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

Ren, Y; Zhu, C; Cai, W; Li, H; Ji, H; Kholmanov, I; Wu, Y; Piner, RD; Ruoff, RS. (2012). Detection of sulfur dioxide gas with graphene field effect transistor. Appl Phys Lett 100. http://dx.doi.org/10.1063/1.4704803

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

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

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

Rubasinghege, G; Grassian, VH. (2013). Role(s) of adsorbed water in the surface chemistry of environmental interfaces. Chem Commun (Camb) 49: 3071-3094. http://dx.doi.org/10.1039/c3cc38872g

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

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; 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

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; 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

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

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

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

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

Spengler, JD; Ferris, BG, Jr; Dockery, DW; Speizer, FE. (1979). Sulfur dioxide and nitrogen dioxide levels inside and outside homes and the implications on health effects research. Environ Sci Technol 13: 1276-1280. http://dx.doi.org/10.1021/es60158a013

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

Stedman, JR; Kent, AJ. (2008). An analysis of the spatial patterns of human health related surface ozone metrics across the UK in 1995, 2003 and 2005. Atmos Environ 42: 1702-1716. http://dx.doi.org/10.1016/j.atmosenv.2007.11.033

Stock, TH; Kotchmar, DJ; Contant, CF; Buffler, PA; Holguin, AH; Gehan, BM; Noel, LM. (1985). The estimation of personal exposures to air pollutants for a community-based study of health effects in asthmatics--design and results of air monitoring. J Air Waste Manag Assoc 35: 1266-1273.

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

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

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

Tinarelli, G; Anfossi, D; Brusasca, G; Ferrero, E; Giostra, U; Morselli, MG; Moussafir, J; Tampieri, F; Trombetti, F. (1994). Lagrangian particle simulation of tracer dispersion in the lee of a schematic 2-dimensional hill. J Appl Meteorol 33: 744-756.

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

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

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). (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.

U.S. EPA (U.S. Environmental Protection Agency). (2008a). 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, 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 sulfur oxides: Health criteria [EPA Report]. (EPA/600/R-08/047F). Research Triangle Park, NC: U.S. Environmental Protection Agency, National Center for Environmental Assessment. http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=198843

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). (2010b). Integrated science assessment for carbon monoxide [EPA Report]. (EPA/600/R-09/019F). Research Triangle Park, NC: U.S. Environmental Protection Agency, Office of Research and Development, National Center for Environmental Assessment. http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=218686

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). (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). (2014a). Health Risk and Exposure Assessment for Ozone Final Report. (452/R-14/004A). Research Triangle Park, NC: Office of Air and Radiation. http://nepis.epa.gov/exe/ZyPURL.cgi?Dockey=P100KBUF.txt

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.

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

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.

Wilson, WE; Suh, HH. (1997). Fine particles and coarse particles: Concentration relationships relevant to epidemiologic studies. J Air Waste Manag Assoc 47: 1238-1249.

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

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, 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: 80. http://dx.doi.org/10.1186/1476-069X-10-80

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

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

Yao, F; Duong, DL; Lim, SC; Yang, SB; Hwang, HR; Yu, WJ; Lee, IH; Güneş, F; Lee, YH. (2011). Humidity-assisted selective reactivity between NO2 and SO2 gas on carbon nanotubes. J Mater Chem 21: 4502. http://dx.doi.org/10.1039/c0jm03227a

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.

Zhang, Y; Li, S; Zhang, J; Pan, Z; Min, D; Li, X; Song, X; Liu, J. (2013b). High-performance gas sensors with temperature measurement. 3: 1267. http://dx.doi.org/10.1038/srep01267

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: 2. http://dx.doi.org/10.1186/1476-069X-10-2

Zou, B. (2010). How should environmental exposure risk be assessed? A comparison of four methods for exposure assessment of air pollutions. Environ Monit Assess 166: 159-167. http://dx.doi.org/10.1007/s10661-009-0992-8

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.

CHAPTER 4 DOSIMETRY AND MODE OF ACTION

4.1 Introduction

Chapter 4 begins with a discussion of the dosimetry of inhaled SO_2 (Section 4.2). This includes consideration of the chemical properties of SO_2 and the processes of absorption, distribution, metabolism, and elimination, followed by a brief discussion of the sources and levels of exogenous and endogenous sulfite. The biological pathways that potentially underlie health effects are described in the subsequent section, Modes of Action of Inhaled SO_2 (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.

4.2 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, 2008b). 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 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. Henry's law shows that the amount of SO_2 in the aqueous phase is directly proportional to the partial pressure or concentration of SO_2 in the gas phase. 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 (mole/L) air/(mole/L) water at 37°C and 1 atmosphere (Hales and Sutter, 1973). For comparison, Henry's law constant for O_3 is 6.4 (mole/L) air/(mole/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. 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).

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 (2013b)].

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 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 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. The nasal absorption of SO_2 (1 ppm) was effectively 100% at 3.5 L/minute and 96.8% at 35 L/minute. 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.

The above studies indicate that the nasal passages remove SO_2 more efficiently than the oral pathway. With increasing physical activity, there is an increase in ventilatory rate and a shift from nasal to oronasal breathing (Niinimaa et al., 1981). Children and adults

with asthma might be expected to have greater SO_2 penetration into the lower respiratory tract compared to healthy adults, due to differences in route of breathing. Children tend to have a greater oral breathing contribution than adults at rest and during exercise (Bennett et al., 2008; Becquemin et al., 1999). Chadha et al. (1987) found that most (11 of 12) patients with asthma or allergic rhinitis also breathe oronasally at rest. In conjunction with the shift in route of breathing, the pattern of SO_2 absorption shifts from the upper airways to the tracheobronchial airways.

The dose rate to the lower airways of children compared to adults is increased further because children breathe at higher ventilation rates relative to their body mass than adults. 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 adults (25−45 years of age; 0.266 m^3/kg-day), ventilation rates normalized to body mass are increased 1.5 times in normal-weight children (7−10 years of age; 0.388 m^3/kg-day) and doubled in normal-weight infants (0.22−0.5 years of age; 0.534 m^3/kg-day). These ventilation rates normalized to body mass should not be confused with median daily ventilation rates which are 2.41, 7.34, and 10.8 L/minute in infants (0.22−0.5 years of age), children (7−10 years of age), and adults (25−45 years of age), respectively.

Although daily inhalation rates normalized to body weight (m^3/kg-day) are decreased in overweight individuals compared to those of normal weight, the absolute ventilation rates (m^3/day) are increased (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 $\geq$ 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.

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%. 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 and individuals with asthma may be expected to have greater SO_2 penetration into the lower respiratory tract than healthy adults. Children may also be expected to have a greater intake dose of SO_2 per body mass than adults.

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 $^{35}SO_2$ inhalation exposures. 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^{-1}) 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 significant 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. Recently, a subacute study measured sulfite plus S-sulfonate content of the lung, liver, and brain of mice exposed to 5, 10, and 20 ppm SO_2 for 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).

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. 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 its concentration 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, intracellular 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. 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 significant 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, 2008b) and introduces the recent relevant literature. While this section highlights findings of studies published since the 2008 SO_X ISA (U.S. EPA, 2008b), 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., $\leq$2 ppm, see Section 1.1) 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 the dosimetry section, 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 neural reflexes, (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 Neural Reflexes

SO_2 is classified as a sensory irritant in the mouse, guinea pig, rat, and human (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 this response occurs with repeated exposure. Most sensory irritants, including SO_2, also cause bronchoconstriction, but at concentrations higher than those stimulating nerve endings in the nose. These higher concentrations lead to greater penetration of the gas in the respiratory tract.

SO_2 is also classified as a pulmonary 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, vago-vagal reflexes, 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 humans and cats resulted in a decreased response to SO_2 in the second exposure compared with the first. This desensitization response mirrors that observed for decreased respiratory rate when SO_2 exposure is restricted to the upper respiratory tract.

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 utilizing 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 nonasthmatics, 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 asthmatics, 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 asthmatics. 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 asthmatics 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 asthmatics 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).

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 neural reflexes. 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 asthmatics.

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 have generally been observed following chronic exposure to SO_2 concentrations of 10 ppm and higher (U.S. EPA, 2008b). Inflammatory changes have been noted in some animal models following subacute exposure to 5−100 ppm SO_2 (U.S. EPA, 2008b). 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 hours (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, which is involved in inflammation, and for bax (B-cell lymphoma 2-like protein 4), which is 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, 2008b). 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 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., 1994a). 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 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.

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 (2008b). 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 antiovalbumin 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. 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., 2011). 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 mild allergic asthmatics 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., 1994a). 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 asthmatics. 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 Transduction of Extrapulmonary Effects

As described in the 2008 SO_X ISA (U.S. EPA, 2008b), 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 asthmatics (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, 2013b) (Woerman and Mendelowitz, 2013a). Whether these responses were due to activation of neural reflexes or some other mechanism is not known.

Numerous studies over several decades have reported other extrapulmonary effects of inhaled SO_2 (U.S. EPA, 2008b). Most of these occur at concentrations far higher than those measured in ambient air. Studies 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. 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 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, a recent study reporting mitochondrial biogenesis in the brains of rats exposed to SO_2 for several weeks (Qin et al., 2012) suggests that SO_2 exposure induces an adaptive response to oxidative stress in mitochondria of tissues distal to the absorption site. Other recent studies report altered markers of brain inflammation and synaptic plasticity following several weeks to months of exposure to 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 neural reflexes 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 higher concentrations of SO_2.

4.3.5 Role of Endogenous Sulfur Dioxide/Sulfite

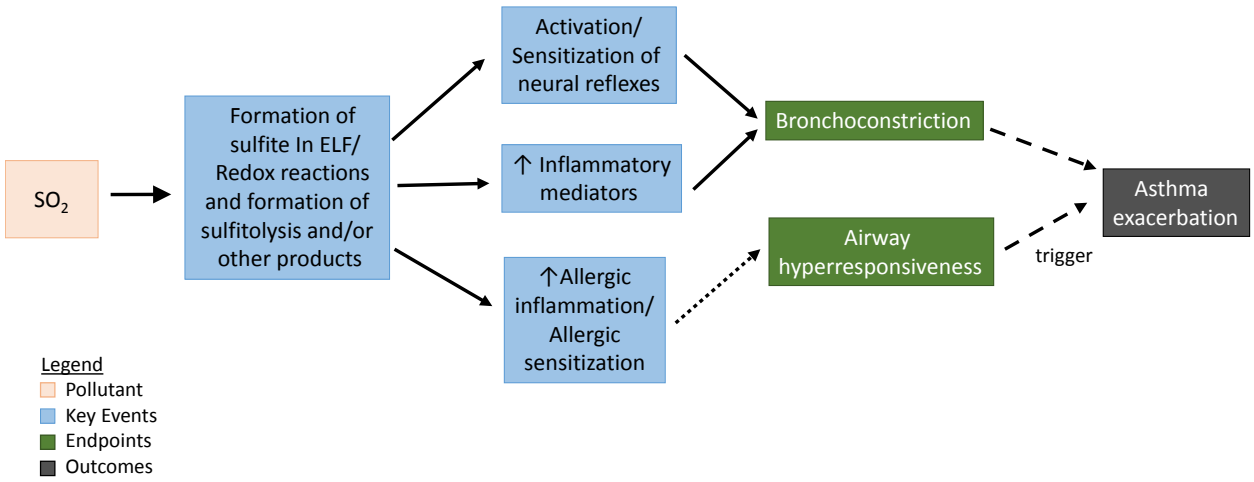
Endogenous SO_2/sulfite is a product of normal metabolism of sulfur-containing amino acids (e.g., cysteine and methionine) (Hwang et al., 2011). While SO_2 gas is measured in the head space gas of preparations of various tissues or bodily fluids (Balazy et al., 2003), sulfite/bisulfite is measured in 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 (Hwang et al., 2011). 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, decreased blood pressure (BP) and vascular remodeling in hypertensive animals, and cytoprotective effects in myocardial ischemia-reperfusion injury (Hwang et al., 2011). 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) (Hwang et al., 2011). 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 4-1 depicts the mode of action for respiratory effects due to short-term exposure to SO_2.



Note: SO_2 = sulfur dioxide. 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 4-1 Summary of evidence for the mode of action linking short-term exposure to sulfur dioxide and respiratory effects.

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 neural reflexes, release of inflammatory mediators, and modulation of allergic inflammation or

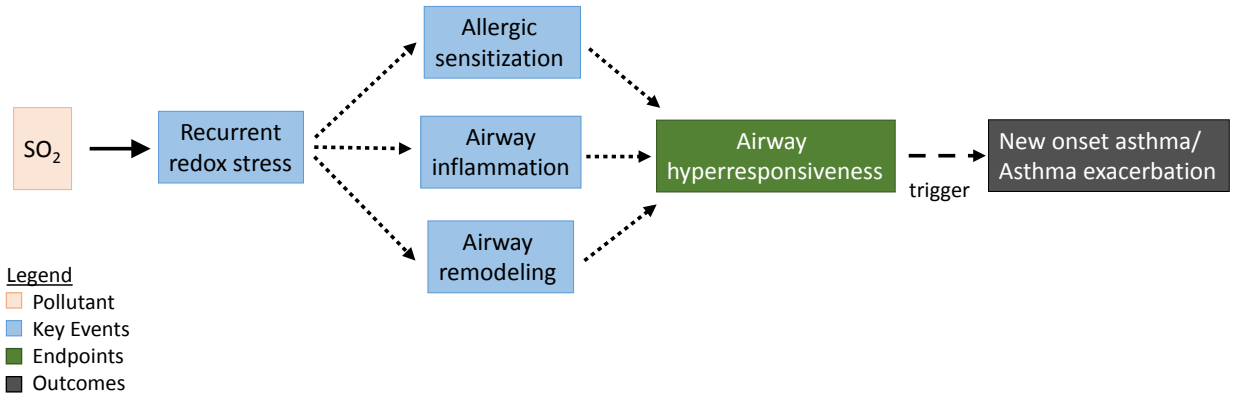
sensitization. These key events may collectively lead to several endpoints, including bronchoconstriction and AHR. Bronchoconstriction is characteristic of an asthma attack, and AHR often leads to bronchoconstriction in response to a trigger. These pathways may be linked to the epidemiologic outcome 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 healthy adults, this response occurred primarily as a result of activation of neural reflexes mediated by cholinergic parasympathetic pathways involving the vagus nerve. However, in adults with asthma, evidence indicates that the response is only partially due to neural reflexes and that inflammatory mediators such as histamine and leukotrienes also play an important role. Activation of neural reflexes results in effects that are frequently measured in studies of human occupational exposure to SO_2. These effects 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 effects are not a part of the mode of action described here. 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 acutely to SO_2 (i.e., leukotriene-mediated increases in numbers of sputum eosinophils). In an animal model of allergic airway disease, repeated exposure to 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, numbers of BALF eosinophils, and serum IgE levels in this same model. In newborn allergic animals exposed repeatedly to SO_2, enhanced allergic inflammation was found, as was evidence of AHR and airway remodeling. Other studies demonstrated that repeated exposure of naive animals to SO_2 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 (Th 2 polarization 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 4-2 depicts the mode of action for respiratory effects due to long-term exposure to SO_2.



Note: SO_2 = sulfur dioxide. 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.

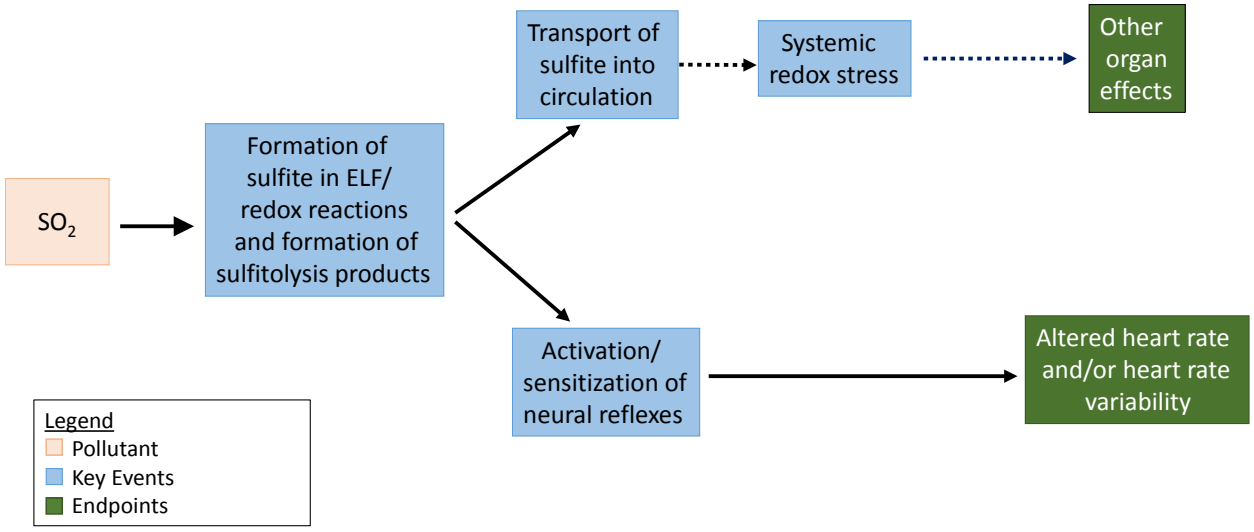
Source: National Center for Environmental Assessment.

Figure 4-2 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 for several weeks resulted in hyperemia in lung parenchyma, inflammation in the airways, and Th2 polarization, 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 over several days led to pathologic changes, including inflammatory cell influx. Th2 polarization and airway inflammation may set the stage for AHR. In addition, short-term SO_2 exposure 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 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 4-3 depicts the mode of action for extrapulmonary effects due to short-term or long-term exposure to SO_2.



Note: SO_2 = sulfur dioxide. 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 4-3 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 points to SO_2 exposure-induced activation/sensitization of neural reflexes 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. Sulfite is highly reactive and may be responsible for redox stress (possibly through autooxidation 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.

References for Chapter 4

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.

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.

Andersen, I; Lundqvist, GR; Jensen, PL; Proctor, DF. (1974). Human response to controlled levels of sulfur dioxide. Arch Environ Occup Health 28: 31-39.

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

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

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

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.

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.

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

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

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.

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

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.

Brain, JD. (1970). The uptake of inhaled gases by the nose. Ann Otol Rhinol Laryngol 79: 529-539.

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

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

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

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. PNAS 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

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.

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

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.

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

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.

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

Gregory, RE; Gunnison, AF. (1984). Identification of plasma-proteins containing sulfite-reactive disulfide bonds. Chem Biol Interact 49: 55-69.

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

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.

Gunnison, AF. (1981). Sulfite toxicity - a critical-review of invitro and invivo data. Food Cosmet Toxicol 19: 667-682.

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.

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

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

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.

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

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

IOM (Institute of Medicine). (2005). Panel on dietary reference intakes for electrolytes and water. Dietary reference intakes for water, potassium, sodium, chloride, and sulfate / panel on dietary reference intakes for electrolytes and water, standing committee on the scientific evaluation of dietary reference intakes, food and nutrition board. Washington, DC: National Academies Press.

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

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

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.

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.

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.

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.

Lee, LY; Widdicombe, JG. (2001). Modulation of airway sensitivity to inhaled irritants: role of inflammatory mediators [Review]. Environ Health Perspect 4: 585-589.

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, X; Bazer, FW; Gao, H; Jobgen, W; Johnson, GA; Li, P; McKnight, J. R.; 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

Lin, HK; Tsai, JJ; Wen, MC; Tsai, MC; Chen, CJ; Fu, LS. (2011). 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

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; 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.

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

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.

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

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.

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

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

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

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

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

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

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

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

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

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

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. http://dx.doi.org/10.1093/toxsci/kfq010

Snashall, PD; Baldwin, C. (1982). Mechanisms of sulphur dioxide induced bronchoconstriction in normal and asthmatic man. Thorax 37: 118-123.

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

Speizer, FE; Frank, NR. (1966). The uptake and release of SO2 by the human nose. Arch Environ Occup Health 12: 725-728.

Tan, WC; Cripps, E; Douglas, N; Sudlow, MF. (1982). Protective effect of drugs on bronchoconstriction induced by sulphur dioxide. Thorax 37: 671-676.

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.

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.

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). Research Triangle Park: Environmental Criteria and Assessment Office. http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=46205

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). (2005a). Guidelines for carcinogen risk assessment. (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). (2008b). Integrated science assessment for sulfur oxides: Health criteria [EPA Report]. (EPA/600/R-08/047F). Research Triangle Park, NC: U.S. Environmental Protection Agency, National Center for Environmental Assessment. http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=198843

U.S. EPA (U.S. Environmental Protection Agency). (2013b). 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

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

Wang, AL; Blackford, TL; Lee, LY. (1996). Vagal bronchopulmonary C-fibers and acute ventilatory response to inhaled irritants. Respir Physiol Neurobiol 104: 231-239.

Widdicombe, J; Lee, LY. (2001). Airway reflexes, autonomic function, and cardiovascular responses [Review]. Environ Health Perspect 4: 579-584.

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

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

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

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. 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

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

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

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 all forms of oxidized sulfur including multiple gaseous (e.g., SO_2, SO_3) and particulate species (e.g., sulfates), this chapter focuses on evaluating the health effects associated with exposure to the gaseous sulfur oxides, particularly SO_2. As discussed in Section 2.1, gaseous sulfur oxide species other than SO_2 are not present in ambient air at concentrations that are significant for human exposures. Additionally, particulate species of sulfur oxides (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).

Sections within this chapter comprise evaluations of 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, 2015f) and 5S-2 (U.S. EPA, 2015g). Exposures including peak (i.e., 5−10 minutes), short-term (i.e., up to 1 month), and long-term (i.e., more than 1 month to years) exposures are evaluated in the chapter. Sections for respiratory, cardiovascular, and mortality effects are divided into subsections describing the evidence for short- (inclusive of peak) and long-term exposures. The evidence for reproductive and developmental and cancer effects is considered within one long-term exposure section, although time-windows of exposure are 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 ISA (U.S. EPA, 2015e)].

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, MI) 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 5.2.1.8). 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 ISA (U.S. EPA, 2015e) (Section 5.a), causal determinations were informed through 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 to Chapter 5 of the ISA and are consistent with current best practices employed in other approaches for reporting or evaluating health science data.[1]

[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).

Additionally, these aspects are compatible with published EPA guidelines related to cancer, neurotoxicity, reproductive toxicity, and developmental toxicity (U.S. EPA, 2005a, 1998, 1996, 1991).

The aspects described in the Annex 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 (U.S. EPA, 2015e), 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 modelled 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 3.3.4). Correlations of short-term SO_2 concentrations with other NAAQS pollutants are generally low to moderate, but may vary by location (Section 3.3.4.1). 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 based on considering the strength of inference from individual studies and on integrating multiple lines of evidence. As detailed in the Preamble (U.S. EPA, 2015e), 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-hour averages, effect estimates were scaled to a 10-ppb increase for SO_2. For 1-hour daily maximum, 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

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

strength of inference from studies comprising the evidence base, and integrate multiple lines of evidence, to characterize relationships between sulfur oxides and various health effects.

5.2 Respiratory Morbidity

5.2.1 Short-Term Exposure

5.2.1.1 Introduction

The 2008 ISA for Sulfur Oxides (U.S. EPA, 2008b) concluded that there is a causal relationship between respiratory morbidity 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 peak exposures of 5−10 minutes in exercising adults with asthma.

The available epidemiologic studies consistently observed a relationship between short-term SO_2 exposure and respiratory effects in locations with ambient concentrations below the previous 24-hour average NAAQS level of 140 ppb. Evidence was strongest for increased respiratory symptoms in children and for respiratory-related hospital admissions and ED visits, especially in children. However, most studies did not adequately assess potential confounding by copollutants.

The current review brings forth additional studies, mostly epidemiologic, that add to the evidence provided by the previous ISA and AQCD (U.S. EPA, 2008b, 1982a). 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.

New studies from all disciplines along with key studies from the previous reviews are integrated in the following sections. These sections are organized by respiratory outcome group (e.g., asthma exacerbation, respiratory infection, etc.) with a separate section for general population studies in order to clearly characterize differences in the weight of evidence and the extent of coherence among disciplines and related outcomes.

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., FEV_1 and sRaw), increased symptoms (wheezing, cough, shortness of breath, etc.), and AHR, as well as some subclinical effects such as inflammation.

As detailed in the previous 2008 ISA for Sulfur Oxides (U.S. EPA, 2008b), controlled human exposure studies reported respiratory effects (i.e., respiratory symptoms and decreased lung function) after short-term peak exposures, defined here as exposures from 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. The majority of the controlled human exposure studies evaluating the respiratory effects of SO_2 in healthy adults demonstrated respiratory effects such as increased airway resistance and decreased FEV_1 following exposures to concentrations >1.0−5.0 ppm. While children may be especially susceptible to the respiratory effects of SO_2 due to dosimetric considerations (Section 4.2.2), there are no available controlled human exposure studies in children under 12.

The evidence from controlled human exposure studies was supported by numerous epidemiologic studies reporting an association between ambient SO_2 exposures and increased respiratory symptoms in children. The 2008 SO_X ISA also noted that few epidemiologic studies were performed that examined the effects of ambient SO_2 exposure on respiratory symptoms in adults; these studies had generally inconsistent findings. Most studies did not adequately assess potential confounding by copollutants. In addition, the 2008 SO_X ISA reported that respiratory morbidity, in the form of respiratory-related hospital admissions and ED visits, including those for asthma, was generally positively associated with short-term SO_2 exposures, with associations often larger in magnitude among children.

The 2008 SO_X ISA (U.S. EPA, 2008b) provided limited evidence for a relationship between SO_2 concentrations and AHR, allergic responses, and inflammation in individuals with asthma, supported by intervention studies and animal models of allergic airway disease. Children and adults with atopy and asthma were found to be at greater risk of effects, such as respiratory symptoms, lung function decrements, and AHR, in association with SO_2 exposure.

Consistent with the body of evidence presented in the 2008 SO_X ISA, recent studies corroborate these respiratory effects related to short-term SO_2 exposure in individuals with asthma. Most of the recent evidence comes from epidemiologic studies that build upon the evidence for ambient SO_2-associated increases in respiratory hospital admissions and ED visits and respiratory symptoms among children. In addition, there are a few new animal toxicological studies. No new controlled human exposure studies in individuals with asthma have been published since the last review: however there are a few new controlled human exposure studies in individuals without asthma (Section 5.2.1.6).

Lung Function Changes in Populations with Asthma

The 2008 SO_X ISA (U.S. EPA, 2008b) 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. Previous controlled human exposure studies also demonstrated a subset of individuals (i.e., responders) within this population that are particularly sensitive to the effects of SO_2. Epidemiologic evidence of lung function decrements in association with SO_2 concentrations consisted of a limited number of short-term studies among adults. These studies found some associations between SO_2 concentration and lung function but were limited by potential copollutants confounding. There was 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. It is observed in free-breathing controlled human exposure studies after approximately 5−10-minute exposures (defined here as peak exposures) and can occur at concentrations as low as 0.2 ppm in exercising individuals, with more consistent decrements seen at 0.4 ppm (U.S. EPA, 2008b). In contrast, healthy adults are relatively insensitive to the respiratory effects of SO_2 below 1 ppm (Section 5.2.1.6). 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 that reaches the airways (Section 4.2.2). Generally speaking, the majority of controlled human exposure studies are conducted in adults, given the ethical considerations for exposing children to air pollutants, and thus provide limited information about children's responses. 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 5.2.1.6.

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

Study	Disease Status[a]; n; Sex; Age (mean ± SD)	Exposure Details (Concentration; Duration)	Outcomes Examined
Balmes et al. (1987)	Asthma; n = 8; 6 M, 3 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 kilopond m/min	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]	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 with exercise (29 L/min) for up to 24 h with or w/o pretreatment with salmeterol (long-acting B2-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/day for 3 days)	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/m^2 x min) (2) 2 ppm SO_2 for 10 min with exercise (treadmill, 21 L/m^2 x min)	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[a]; n; Sex; Age (mean ± SD)	Exposure Details (Concentration; Duration)	Outcomes Examined
Jörres and Magnussen (1990)	Asthma; n = 14; 10 M, 4 F (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 (sixfold 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 sixfold increase in V_E) (2) 0.5 ppm SO_2 + 1mg/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)	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 (0 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 (0, 20, 40, 60 mg cromolyn) 20 min prior	FEV_1 RT
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	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)	FEV_1, RT, FRC, V_{max50} symptoms
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 hyperventilation (20 L/min) for 4 min sequential exposures with pretreatment with zafirlukast (0 or 20 mg) 2 or 10 h earlier	sRaw

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

Study	Disease Status[a]; n; Sex; Age (mean ± SD)	Exposure Details (Concentration; Duration)	Outcomes Examined
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, and FEV_1, symptoms
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)	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, l7, 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; 16 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[a]; n; Sex; Age (mean ± SD)	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 Exposures were repeated so total of eight	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-day after, and 1-week after-symptom score, self-rated activity Immediately after exposure—bronch-ial reactivity percentage change in FEV 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 week 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 (0, 20, or 200 mg)	sRaw

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

Study	Disease Status[a]; n; Sex; Age (mean ± SD)	Exposure Details (Concentration; Duration)	Outcomes Examined
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
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 U	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	Pulmonary function tests (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 Healthy; n = 12	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 second; 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 reistance; 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.

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. Investigators have shown bronchoconstriction to occur in as little as 2 minutes from the start of exposure in exercising adults with asthma (Horstman et al., 1988; Balmes et al., 1987; Sheppard et al., 1983). However, when exposure to SO_2 occurs during 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; 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. It is 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 asthmatic adults in controlled human exposure studies experiencing SO_2-induced decrements in lung function and respiratory symptoms.

SO_2 Conc (ppm)	Exposure Duration (min)	No. Subj	Ventil-ation (L/min)	Cumulative Percentage of Responders (Number of Subjects)[1]				Study	Respiratory Symptoms: Supporting Studies
					sRaw				
					≥100% ↑	≥200% ↑	≥300% ↑		
					FEV_1				
				Lung Func	≥15% ↓	≥20% ↓	≥30% ↓		
0.2	5	23	~48	sRaw	9% (2)[2]	0	0	Linn et al. (1983b)	Limited evidence of SO_2-induced increases in respiratory symptoms in some asthmatics: (Linn et al. (1990); Linn et al. (1988); Linn et al. (1987); Schachter et al. (1984); Linn et al. (1983b))
	10	40	~40	sRaw	5% (2)	0	0	Linn et al. (1987)[3]	
	10	40	~40	FEV_1	13% (5)	5% (2)	3% (1)	Linn et al. (1987)	
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)[4]	
	10	21	~50	sRaw	33% (7)	10% (2)	0	Linn et al. (1990)[4]	
	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)[6], Gong et al. (1995) (Linn et al. (1987); Linn et al. (1983b)) Roger et al. (1985)
	10	40	~40	sRaw	25% (10)	8% (3)	3% (1)	Linn et al. (1987)	
	10	40	~40	FEV_1	30% (12)	25% (10)	13% (5)	Linn et al. (1987)	
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)[6]	

Table 5-2 (Continued): Percentage of asthmatic adults in controlled human exposure studies experiencing SO_2-induced decrements in lung function and respiratory symptoms.

SO_2 Conc (ppm)	Exposure Duration (min)	No. Subj	Ventil-ation (L/min)	Cumulative Percentage of Responders (Number of Subjects)[1]				Study	Respiratory Symptoms: Supporting Studies
				sRaw					
				≥100% ↑	≥200% ↑	≥300% ↑			
				FEV_1					
				Lung Func	≥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	35% (14)	28% (11)	18% (7)	Linn et al. (1987)	
	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	53% (21)	48% (19)	23% (9)	Linn et al. (1987)	
	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)[5]	
	10	10	~40	sRaw	60% (6)	20% (2)	0	Kehrl et al. (1987)	

Conc = concentration; FEV_1 = forced expiratory volume in 1 second; func = function ppm = parts per million; sRaw = specific airway resistance; SO_2 = sulfur dioxide; subj = subject.

[1]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 (sRaw), or a 15, 20, or 30% decrease in FEV_1. Lung function decrements are adjusted for 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).

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

[3]Responses of mild and moderate asthmatics reported in Linn et al. (1987) have been combined. Data reported only for the first 10 min period of exercise in the first round of exposures.

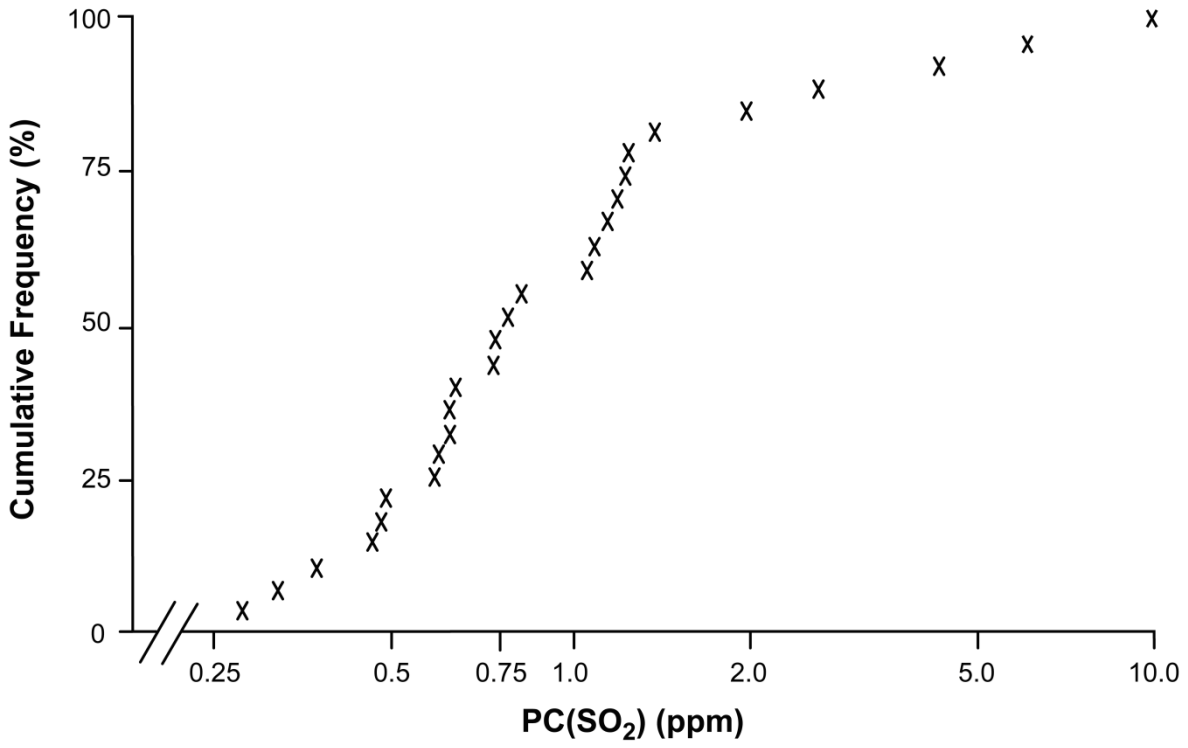
[4]Analysis includes data from only mild Linn et al. (1988) and moderate Linn et al. (1990) asthmatics who were not receiving supplemental medication.

[5]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.

[6]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. 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 pm to elicit a response. These data demonstrate substantial inter-individual variability in sensitivity to the bronchoconstrictive effects of SO_2 in exercising adults with asthma.



Note: Each data point represents the PC(SO_2) for an individual subject. PC(SO_2) = provocative concentration of SO_2.
Source: Horstman et al. (1986).

Figure 5-1 Distribution of individual airway sensitivity to SO_2. The cumulative percentage of subjects is plotted as a function of PC(SO_2), which is the concentration of SO_2 that provoked a 100% increase in specific airway resistance compared to clean air.

Further 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.] 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.

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). Of the 56 individuals included in the Goodman et al. (2015) analysis, eight individuals (14%) were identified as sensitive to the effects of SO_2. 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. Additionally, the statistical assumption of homoscedasticity, as noted in the analysis by Johns et al. (2010), was not met for their linear regression determination of individual subject slopes of response versus concentration in the Goodman et al. (2015) study. For these statistical reasons, no further consideration is given to the Goodman et al. (2015) study.

Table 5-3 Percent change in post- versus pre-exposure measures of FEV_1 relative to clean air control after 5−10-minute exposures to SO_2 during exercise.

	SO_2 Concentration ppm	FEV_1				
		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 second; ppm = parts per million; SO_2 = sulfur dioxide.

A 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 (sRaw) relative to clean air control after 5−10-minute exposures to SO_2 during exercise.

	SO_2 Concentration ppm	sRaw				
		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 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 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, while the moderate/severe group consisted of adults that 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, it is likely that this moderate/severe group would 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, 2008b). 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 do not completely eliminate these effects.

Asthma symptoms are difficult to control in severe asthmatics due to inadequate drug therapy or poor compliance among those who are on regular medication Rabe et al. (2004). Individuals with mild asthma are less likely to use asthma medication than those with a more severe diagnosis (O'Byrne, 2007; Rabe et al., 2004). Therefore, it is reasonable to conclude that individuals with asthma exposed to SO_2 are at high risk of experiencing adverse respiratory effects and proper therapies may not be accessible during exposure.

Adolescents. There is evidence that adolescents (ages 12−18 years) with asthma or atopic symptoms are responsive to coexposures of SO_2 and sodium chloride (NaCl) droplet aerosol (Koenig et al., 1992; Koenig et al., 1990; Koenig et al., 1988; Koenig et al., 1987; Koenig et al., 1983, 1981; Koenig et al., 1980). Exposure concentrations in these controlled human exposure studies ranged from 0.1 to 1.0 ppm SO_2. Koenig et al. (1983) observed that the average lung function changes ranged from 8−47% in exercising adolescents (12 to 16 years old) with asthma after a 10-minute exposure to 0.5 ppm SO_2 + 1 mg/m^3 NaCl droplet aerosol. 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.

Mixtures effects. The health effects of SO_2 can be potentially modified by its 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 minutes exposure to 0.12 ppm O_3 had a significant decrease (8%) in FEV_1 (8%) *($p < 0.05$)*, a significant increase in 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.

Epidemiologic Studies

Adults. The 2008 SO_X ISA (U.S. EPA, 2008b) evaluated a limited number of studies focusing on short-term SO_2 exposures and changes in lung function among adults. These studies found some associations between SO_2 concentration and lung function but were potentially limited by copollutant confounding. One study suggested that elderly adults with both atopy and asthma were at greater risk of changes in lung function in association with short-term SO_2 exposure (Boezen et al., 2005). Recent studies, listed in Table 5-5 and summarized below, were consistent with the 2008 SO_X ISA (U.S. EPA, 2008b), finding some positive associations. However, these were for various lags and treatment groups with no overall consistency among the studies. Copollutant confounding was evaluated in some studies and a few of the observed associations were relatively unchanged with their inclusion.

Table 5-5 Summary of recent panel studies examining associations between SO_2 concentrations and lung function among adults with asthma.

Study Location and Years	Study Population and N	Measure of SO_2	MeanSO_2 and Upper Concentration Level	Adjusted Effect Estimate
Qian et al. (2009b) United States 1997−1999	Patients (12−65 yr) with persistent asthma were recruited from six university-based ambulatory care centers as part of the NHLBI-sponsored Salmeterol Off Corticosteroids Study N = 154	Fixed site monitors; 24-h mean SO_2 concentrations	Mean (SD): 4.8 (3.9) ppb 75th percentile: 6.2 ppb Max: 31.5 ppb	Change (95% CI) in PEF (L/min) per 10-ppb increase in mean SO_2 Lag 0: −0.12 (−2.96, 2.71) Lag 1: −2.15 (−4.97, 0.68) Lag 2: −0.65 (−3.45, 2.14) Lag 0−2: −1.93 (−5.56, 1.70)
Canova et al. (2010) Padua, Italy 2004−2005	Random sample of asthmatic residents (15−44 yr) N = 40	Fixed site monitors; 24-h mean SO_2 concentrations	Mean (SD): 1.36 (1.09) ppb Max: 4.88 ppb	Quantitative effect estimates for SO_2 not reported
Wiwatanadate and Liwsrisakun (2011) Chiang Mai, Thailand 2005−2006	Asthmatics (13−78 yr) who experienced symptoms within the year prior and lived within 10 km of the air monitoring station N = 121	Fixed site monitors; 24-h mean SO_2 concentrations	SO_2 Mean (SD): 1.73 (0.62) ppb 90th percentile: 2.42 ppb Max: 3.89 ppb	Change in evening PEFR (95% CI) per 10-ppb increase in SO_2 Lag 4: 9.1 (3.8, 14.4) Lag 6: 6.4 (1.0, 11.8) Change in average PEFR (95% CI) per 10-ppb increase in SO_2 Lag 4: 5.0 (0.4, 9.6) Lag 6: 5.7 (1.0, 10.3) *Note: quantitative estimates only provided for lags 2, 4, and 6 when results were “statistically significant”

CI = confidence interval; NHLBI = National Heart, Lung, and Blood Institute; PEF = peak expiratory flow; PEFR = peak expiratory flow rates.

A study in the United States assessed airway obstruction effects of ambient air pollutants, considering daily self-measured peak expiratory flow (PEF) from patients with persistent asthma during the 16 weeks of active treatment in the Salmeterol Off Corticosteroids Study trial (Qian et al., 2009b). The three therapies were an inhaled corticosteroid (triamcinolone acetonide), an inhaled long-acting beta-agonist (salmeterol xinafoate), and placebo. The participants were nonsmokers aged 12 through 63 years. Using the U.S. EPA AIRS database, the central site air pollution monitors closest to the ZIP code centroid of the participants’ home addresses were identified. The effect estimates in each

medication group were obtained from the main effect and pollutant*medication group interaction models. Inverse associations were found between PEF and SO_2 concentrations, but only in the triamcinolone group. No association between SO_2 concentration and PEF was observed in the placebo group, and no association was observed in the salmeterol group with the exception of a positive association for the lag averaged over 0−2 days. None of the other pollutants (NO_2, PM_{10}, O_3) demonstrated an association with PEF among those in the triamcinolone group. NO_2 at lag 0 and PM_{10} at lag 2 were associated with PEF in the salmeterol and placebo groups, respectively. In the two-pollutant models, SO_2 associations with PEF in the triamcinolone group were relatively unchanged with inclusion of PM_{10}, O_3, or NO_2 in the models. The only correlation coefficient reported for SO_2 was with NO_2 (correlation coefficient 0.58); correlations with the other copollutants are likely to be low-moderate (Section 3.3.4.1). Although attenuation of the effect estimates is possible due to the use of central site monitors, this is likely to affect results from all treatments to the same extent. Overall, this study indicates that an association appears to be present between SO_2 concentration and PEF in this study, but only among one of the treatment groups.

Studies of SO_2 concentrations and lung function among adults asthmatics have also been conducted in Italy and Thailand, but neither examined associations stratified by therapies as was done by Qian et al. (2009b) (described above). Canova et al. (2010) tested the effects of exposure to air pollutants on lung function in a panel of adult asthmatics that was followed for five 30-day periods during 2 years in Italy. Despite point estimates in the inverse direction, overall null associations were observed for morning and evening PEF and FEV_1. However, in this study population of mainly moderate-to-severe asthmatics (in which two-thirds of the patients used corticosteroid medications), no analysis excluding subjects with steroid use was attempted due to the small sample size (n = 40) although control for corticosteroid use was included in the models. Thus, the small study size, lack of supervised lung function measurements, and inability to stratify by medication use may have diminished the ability to find associations in this study. Null associations were noted for PM_{10} and NO_2; an inverse association was observed between CO and PEF but not FEV_1. Copollutant models were not assessed for SO_2, but SO_2 was correlated with PM_{10} (correlation coefficient 0.509), NO_2 (correlation coefficient 0.535), and CO (correlation coefficient 0.499). Wiwatanadate and Liwsrisakun (2011) assessed the effects of air pollutants on the peak expiratory flow rates (PEFR) among asthmatic patients aged 13−78 years in Thailand. No association was reported between SO_2 and morning PEFR. SO_2 was positively associated with evening PEFR and daily average PEFR using lag Days 4 and 6. In multipollutant models adjusting for $PM_{2.5}$ or PM_{10} and NO_2, as well as O_3 in the models for evening PEFR, the association with lag Day 4 remained. The association with change in PEFR was present only for lag Day 6 and did not persist in the multipollutant model adjusting for PM_{10}, CO, and NO_2. SO_2 was

somewhat correlated with CO (correlation coefficient 0.38), PM_{10} (correlation coefficient 0.23), and NO_2 (correlation coefficient 0.23) but not O_3 (correlation coefficient −0.04) or $PM_{2.5}$ (correlation coefficient −0.07). In summary, some associations were observed between SO_2 concentration and measures of lung function but no consistency was found among the studies.

Children. The 2008 SO_X ISA (U.S. EPA, 2008b) presented multiple studies of SO_2 concentration and lung function among children with asthma, but overall the results were inconsistent. Similarly, recent studies published since the 2008 SO_X ISA, described below and in Table 5-6, have also reported inconsistent findings for the association between SO_2 concentrations and lung function measures among children with asthma. However, some of these studies did report positive associations that were relatively unchanged with the inclusion of other pollutants.

Table 5-6 Summary of recent epidemiologic studies examining associations between SO_2 concentrations and lung function among children with asthma.

Study Location and Years	Study Design	Study Population and N	Measure of SO_2	Mean SO_2 and Upper Concentration Level	Adjusted Effect Estimate
O'Connor et al. (2008)	Panel study	Children (5−12 yr) living in low-income census tracts in big cities across the United States with persistent asthma and atopy, who made up the Inner-City Asthma Study Cohort N = 861	Fixed site monitors; 24-h mean SO_2 concen-trations	Mean and upper level concentration values NR. The authors stated "SO_2 concentrations were well below the 24-h average NAAQS"	Estimated change (95% CI) per 10-ppb increase in 5-day average concentration SO_2 FEV_1, % predicted −1.29 (−2.04, −0.54) PEFR, % predicted −1.73 (−2.49, −0.96)

Table 5-6 (Continued): Summary of recent epidemiologic studies examining associations between SO_2concentrations and lung function among children with asthma.

Study Location and Years	Study Design	Study Population and N	Measure of SO_2	Mean SO_2 and Upper Concentration Level	Adjusted Effect Estimate
Dales et al. (2009) Canada 2005	Longit-udinal repeated measures	School children (9−14 yr) with asthma and living in a home with no cigarette smoke N = 182	Fixed site monitors; 24-h mean SO_2 concen-trations	Mean (SD): 6.0 (4.8) ppb 75th percentile: 8.8 ppb	Percent change (95% CI) in bedtime FEV_1 per 10-ppb increase in SO_2 0−12 h averaging time: −0.17 (−0.98, 0.65) 12−24 h averaging time: 0.00 (−0.92, 0.93) 0−24 h averaging time: −0.14 (−1.03, 0.76) Percent change (95% CI) in morning FEV_1 per 10-ppb increase in $SO_2$0−8 h averaging time: 0.63 (−0.28, 1.55) Diurnal change (95% CI) in FEV_1 per 6.5-ppb increase in SO_2 0−12 h averaging time: −1.41 (−2.73, −0.08)
Liu et al. (2009b) Canada 2005	Longit-udinal repeated measures	School children (9−14 yr) with asthma from a nonsmoking household N = 182	Fixed site monitors; 24-h mean SO_2 concent-rations	Median 1-day average: 4.5 ppb 95th percentile: 15.5 ppb Median 2-day average: 5.0 ppb 95th percentile: 13.0 ppb Median 3-day average: 5.6 ppb 95th percentile: 13.8 ppb	Lag 1 [percent change (95% CI) per 10-ppb increase in SO_2] FEV_1 0.2 (−1.7, 2.0) $FEF_{25-75\%}$ −1.4 (−4.7, 2.1) 2-day average (percent change (95% CI) per 10-ppb increase in SO_2) FEV_1 −0.2 (−2.0, 1.7) −4.2 (−10.0, 1.9)$FEF_{25-75\%}$ −3.2 (−8.2, 2.1) 3-day average (percent change (95% CI) per 10-ppb increase in SO_2) FEV_1 −0.6 (−3.5, 2.5) $FEF_{25-75\%}$

Table 5-6 (Continued): Summary of recent epidemiologic studies examining associations between SO_2 concentrations and lung function among children with asthma.

Study Location and Years	Study Design	Study Population and N	Measure of SO_2	Mean SO_2 and Upper Concentration Level	Adjusted Effect Estimate
Wiwatanadate and Trakultivakorn (2010) Chiang Mai, Thailand 2005−2006	Panel study	Children (4−11 yr) with asthma who experienced symptoms within the previous year and lived within 25 km of the air monitoring station N = 31	Fixed site monitors; 24-h mean SO_2 concentrations	SO_2 mean (SD): 1.73 (0.62) ppb 90th percentile: 2.42 ppb Max: 3.89 ppb	Estimated change in morning PEFR (95% CI) per 10-ppb increase in SO_2 Lag 1: 7.1 (−10.7, 24.8) Lag 2: −8.0 (−26.1, 10.1) Lag 3: −8.9 (−26.7, 8.9) Lag 4: −13.9 (−31.4, 3.6) Lag 5: −0.8 (−18.2, 16.7) Lag 6: −3.0 (−20.5, 14.4) Estimated change in evening PEFR (95% CI) per 10-ppb increase in SO_2 Lag 0: −8.1 (−25.3, 9.2) Lag 1: 3.0 (−14.2, 20.3) Lag 2: −2.5 (−19.7, 14.7)Lag 3: −13.4 (−30.4, 3.6) Lag 4: −21.2 (−38.3, −4.1) Lag 5: 7.5 (−9.8, 24.8) Lag 6: −7.7 (−25.0, 9.6) Estimated change in average PEFR (95% CI) per 10-ppb increase in SO_2 Lag 0: −0.3 (−15.0, −14.5) Lag 1: 7.9 (−7.0, 22.8) Lag 2: −2.3 (−17.7, 13.1) Lag 3: −9.1 (−24.0, 5.7) Lag 4: −17.5 (−32.2, −2.8) Lag 5: 4.9 (−9.9, 19.7) Lag 6: −8.6 (−23.4, 6.2) Estimated change in ΔPEFR (95% CI) per 10-ppb increase in SO_2 Lag 0: 1.4 (−4.7,7.4) Lag 1: −1.7 (−7.9, 4.6) Lag 2: 2.5 (−3.9, 8.8) Lag 3: 5.3 (−0.9, 11.5) Lag 4: −7.3 (−13.3, −1.2) Lag 5: −3.7 (−9.8, 2.5) Lag 6: 1.6 (−4.5, 7.8)

CI = confidence interval; $FEF_{25–75\%}$ = forced expiratory flow at 25−75% of forced vital capacity; FEV_1 = forced expiratory volume in 1 second; N = population number; NAAQS = National Ambient Air Quality Standards; NR = not reported; PEFR = peak expiratory flow rates; ppb = parts per billion; SD = standard deviation; SO_2 = sulfur dioxide.

O'Connor et al. (2008) investigated associations between fluctuations in outdoor air pollution and lung function among inner-city children with asthma. They considered data in seven U.S. urban communities from children with persistent asthma, who performed 2-week periods of twice-daily pulmonary function testing every 6 months for 2 years, and utilized daily air pollution measurements from the EPA AIRS database. In single-pollutant models, higher 5-day average concentrations of SO_2 were associated with lower lung function measured by FEV_1 and PEFR. No association was reported using a 1-day average. Associations were also observed for increased $PM_{2.5}$ and NO_2 concentrations, but not CO or O_3 concentrations. The correlation coefficients between SO_2 and other air pollutants were 0.37 for $PM_{2.5}$, −0.43 for O_3, 0.59 for NO_2, and 0.32 for CO. SO_2 was not included in multipollutant models. In Canada, Dales et al. (2009) investigated the acute effects of air pollution on lung function among children with asthma who lived in cigarette smoke-free homes. They recorded morning and evening FEV_1 for 28 consecutive days. SO_2 concentration was associated with diurnal changes in FEV_1, but SO_2 concentration was not associated with morning or evening FEV_1. Diurnal changes were also observed for NO_2 and $PM_{2.5}$ but not for maximum O_3 concentrations (correlation coefficients for these pollutants and SO_2 were 0.31, 0.43, and −0.02, respectively). In copollutant models, the association between SO_2 and diurnal changes in $FEV_1$was relatively unchanged with adjustment of O_3, NO_2, and $PM_{2.5}$. Using the same study population, Liu et al. (2009b) reported that no association was observed between SO_2 concentration and FEV_1 or $FEF_{25–75\%}$ = forced expiratory flow at 25−75% of forced vital capacity ($FEF_{25–75\%}$). Low to moderate correlations were observed between SO_2 and NO_2 (correlation coefficient 0.18) and $PM_{2.5}$ (correlation coefficient 0.56), but not O_3 (correlation coefficient −0.02). In copollutant models, results were similar to those of single pollutant models when adjusted by NO_2 or O_3, but slight increases in the point estimate were observed when adjusted for $PM_{2.5}$. Associations did not vary by corticosteroid use. Other pollutants (NO_2, O_3, $PM_{2.5}$) were associated with lung function outcomes. Wiwatanadate and Trakultivakorn (2010) examined the association between daily air pollution concentrations and PEFRs among children with asthma in Thailand. SO_2 concentrations (lag Day 4) were inversely associated with evening PEFR, change in PEFR, and daily average PEFR. No association was present between SO_2 concentrations and morning PEFR. No associations were present between $PM_{2.5}$, PM_{10}, CO, or NO_2 and PEFR values, but an inverse association was observed with O_3 concentration and average daily PEFR. In a two-pollutant model for daily average PEFR, the association with SO_2 was relatively unchanged with the inclusion of O_3. No other copollutant models were described. SO_2 was somewhat correlated with PM_{10} (correlation coefficient 0.23), CO (correlation coefficient 0.38), and NO_2 (correlation coefficient 0.23). No correlation was observed between SO_2 and $PM_{2.5}$ (correlation coefficient −0.07) or O_3 (correlation coefficient −0.04). In summary, studies performed among children with asthma have

reported some associations between SO_2 concentration and lung function but overall results are inconsistent.

Summary of Lung Function Changes

Controlled human exposure studies provide strong evidence for SO_2-induced lung function decrements in adults with asthma under increased ventilation conditions. Short-term peak exposures of 5−10 minutes to 0.2−0.3 ppm SO_2 resulted in approximately 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). Exposure of exercising individuals with asthma to 5−10-minute peak exposures of SO_2 at concentrations ≥0.4 ppm results in moderate or greater decrements in lung function, in terms of FEV_1 and sRaw, in approximately 20−60% of tested individuals in these studies.

Both older and more recent epidemiologic studies among adults and children with asthma demonstrate some positive associations between SO_2 concentrations and lung function, but there is no overall consistency among the studies. These studies all utilized 24-hour averages derived from fixed site monitors. SO_2 concentration is highly variable in space, which could lead to reduced correlation of the SO_2 measured at central site monitors with the true SO_2 exposure. For time-series epidemiologic studies, this typically leads to attenuation and uncertainty of the health effect estimate (Section 3.3.5.1). Studies are limited by potential exposure measurement error and potential copollutant confounding. However, some of the studies in adults and children reported positive associations that were relatively unchanged with the inclusion of other pollutants.

Respiratory Symptoms in Populations with Asthma

The 2008 SO_X ISA (U.S. EPA, 2008b) 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. A limited number of epidemiologic studies evaluated the relationship between SO_2 concentrations and respiratory symptoms among adults with asthma or other chronic respiratory symptoms (U.S. EPA, 2008b). While some of these studies reported positive associations, most did not examine copollutant confounding. Evidence for a relationship between SO_2 concentrations and respiratory symptoms was stronger in children with asthma or other chronic respiratory symptoms. Some studies found that atopic adults and children were also at greater risk of respiratory symptoms in association with SO_2 exposure. Recent epidemiologic studies report inconsistent findings.

Controlled Human Exposure Studies

The 2008 SO_X ISA and the Supplement to the Second Addendum (1986) described several studies that evaluated respiratory symptoms in individuals with asthma following controlled human exposures to SO_2 (U.S. EPA, 2008b, 1994) (Tables 5-2 and 5-7). Incidence or severity of respiratory symptoms (i.e., cough, chest tightness, throat irritation) were shown to increase with increasing concentrations of SO_2 between 0.2 and 0.6 ppm in individuals with asthma when exercising, with symptom category scores reaching statistical significance at concentrations ≥0.4 ppm SO_2. These studies are briefly described below.

Table 5-7 Study-specific details from controlled human exposure studies of respiratory symptoms.

Study	Disease Status[a]; n; Sex; Age (mean ± SD)	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 B2-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/day for 3 days)	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

Table 5-7 (Continued): Study-specific details from controlled human exposure studies of respiratory symptoms.

Study	Disease Status[a]; n; Sex; Age (mean ± SD)	Exposure Details (Concentration; Duration)	Time of Symptom Assessment
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 + 1mg/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

Koenig et al. (1987)	Asthma 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. (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
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)	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, l7, 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

Table 5-7 (Continued): Study-specific details from controlled human exposure studies of respiratory symptoms.

Study	Disease Status[a]; n; Sex; Age (mean ± SD)	Exposure Details (Concentration; Duration)	Time of Symptom Assessment

Linn et al. (1984b)	Asthma;
	Phase 1 (Pilot)
	n = 8; 4 M, 4 F;
	(24.5 ± 3.9 yr)
	Phase 2
	n = 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 day after, and 1 week 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 days after exposure

Linn et al. (1987)	Healthy;
	n = 24; 15 M, 9 F;
	(18−37 yr)
	Atopic (sensitive to common airborne allergens but not asthmatic);
	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 week 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

Table 5-7 (Continued): Study-specific details from controlled human exposure studies of respiratory symptoms.

Study	Disease Status[a]; n; Sex; Age (mean ± SD)	Exposure Details (Concentration; Duration)	Time of Symptom Assessment
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 ppm 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.

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 little as 3 minutes to 0.5 ppm SO_2 via mouthpiece during

eucapnic hyperpnea (V_E = 0 L/minute), where 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.

Collectively, these studies report SO_2-induced respiratory symptoms in exercising adults with asthma exposed to 0.2−0.6 ppm SO_2, with the most consistent evidence from exposures ranging from 0.4−0.6 ppm SO_2 (Table 5-2).

Epidemiologic Studies

Adults. The 2008 SO_X ISA (U.S. EPA, 2008b) included studies of respiratory symptoms among adults with asthma and other chronic respiratory symptoms. While some studies observed positive associations in this population, overall the results were inconsistent. One study suggested that elderly adults with both atopy and asthma were at greater risk of respiratory symptoms in association with short-term SO_2 exposure (Boezen et al., 2005).

Since the previous review, a study has reported mixed findings related to the timing of symptoms in association with SO_2 concentrations among adults with asthma. Wiwatanadate and Liwsrisakun (2011) assessed the effects of air pollutants on respiratory symptoms among asthmatic patients aged 13−78 years in Thailand. Daily air pollutant concentrations were measured by a monitor from the Ministry of National Resources and Environment in the city's center. Although study participants were required to live within 10 km of this air monitor, the correlation between SO_2 at the central site monitor and a receptor located several km away may be low (Section 3.3.5.1), possibly biasing the effect estimate downwards and underestimating the magnitude of the effect. The mean SO_2 concentration during the study period was 1.73 ppb (SD 0.62 ppb) with a 90th percentile of 2.42 ppb and a maximum of 3.89 ppb. SO_2 concentrations were inversely associated with daytime asthma symptoms [OR 0.341 (95% CI 0.123, 0.945) per 10 ppb] but positively associated with nighttime asthma symptoms [OR 4.374 (95% CI 1.495, 12.799) per 10 ppb], although neither of these associations remained after adjustment for other pollutants. Other pollutants ($PM_{2.5}$, PM_{10}, and O_3) also demonstrated this inverse association with daytime symptoms, and NO_2 (lag 5) and PM_{10}max (lag 5) were positively related with nighttime symptoms. SO_2 was somewhat correlated with CO, PM_{10}, and NO_2 (correlation coefficients 0.38, 0.23, and 0.23, respectively), but not O_3 or

$PM_{2.5}$ (correlation coefficients −0.04 and −0.07, respectively). This recent study does not offer strong evidence of an association between SO_2 concentration and respiratory symptoms among adults and adds to the inconsistency observed among studies reported in the 2008 SO_X ISA.

Children. The 2008 SO_X ISA (U.S. EPA, 2008b) stated that, "…epidemiologic studies provided evidence for an association between ambient SO_2 exposures and increased respiratory symptoms in children, particularly those with asthma or chronic respiratory symptoms." One study suggested that children with both atopy and asthma were at greater risk of respiratory symptoms in association with short-term SO_2 exposure (Boezen et al., 1999). Recent studies among children with asthma reported some positive associations between SO_2 concentrations and certain respiratory symptoms, although inconsistencies were observed. Concentrations of recent studies were either not reported or were lower than some of the highest quality studies included in the 2008 SO_X ISA (U.S. EPA, 2008b). These recent studies are detailed below and in Table 5-8.

Table 5-8 Summary of recent epidemiologic studies examining associations between SO_2 concentrations and respiratory symptoms among children with asthma.

Study Location and Years	Study Population and N	Measure of SO_2	Mean SO_2 and Upper Concentration Level	Adjusted Effect Estimate
O'Connor et al. (2008) United States 1998−2001	Inner-City Asthma Study Cohort: children (5−12 yr) living in low-income census tracts in big cities across the U.S. with persistent asthma and atopy, N = 861	Fixed site monitors; 24-h mean SO_2 concentrations	Mean and upper level concentration values not reported. The authors stated "SO_2 concentrations were well below the 24-h average NAAQS"	RR (95% CI) for asthma-related symptoms per 10-ppb increase in 5-day average concentration SO_2 *Wheeze-cough, days/2 weeks* 1.05 (0.89, 1.23) *Nighttime asthma, days/2 weeks* 1.11 (0.91, 1.36) *Slow play, days/2 weeks* 1.06 (0.88, 1.27) *Missed school, ≥1 day/2 weeks vs. 0 days/2 weeks* 1.10 (0.82, 1.49)
(Spira-Cohen (2013); Spira-Cohen et al. (2011)) United States 2002−2005	Children (10−12 yr) with asthma attending fifth grade at one of four elementary schools N = 40	Fixed site monitors; 24-h mean SO_2 concentrations	NR	RR (95% CI) per 10-ppb increase in peak morning SO_2 *Cough* 1.12 (1.05, 1.21) *Wheeze* 1.16 (1.04, 1.30) *Shortness of breath* 1.10 (0.98, 1.23)
Dales et al. (2009) Canada 2005	School children (9−14 yr) with asthma and living in a home with no cigarette smoke. N = 182	Fixed site monitors; 24-h mean SO_2 concentrations	SO_2 mean (SD): 6.0 (4.8) ppb 75th percentile: 8.8 ppb	OR (95% CI) for chest tightness for daily SO_2 concentrations of ≥8.8 ppb vs. <2.3 ppb 1.30 (1.06, 1.58) *Note: authors stated that difficulty breathing, cough, and wheeze were not "significant at $p < 0.05$"; no quantitative results were provided

CI = confidence interval; N = population number; NAAQS = National Ambient Air Quality Standards; NR = not reported; OR = odds ratio; ppb = parts per billion; RR = relative risk; SD = standard deviation; SO_2 = sulfur dioxide.

Recent studies in the U.S. have reported some associations between SO_2 concentrations and respiratory symptoms, but the SO_2 concentrations were not reported, making comparisons and interpretations difficult. O'Connor et al. (2008) investigated associations between fluctuations in outdoor air pollution and asthma morbidity among inner-city children with asthma using data collected in seven U.S. urban communities in conjunction with the Inner-City Asthma Study. Central site air pollution measurements were obtained from EPA's AIRS. The authors noted SO_2 concentrations were "well below the 24-hour average National Ambient Air Quality Standards," but exact concentrations were not given. When examining wheeze-cough, nighttime asthma, slow play, and missed school, no positive associations with SO_2 concentrations were observed. Associations were observed with other pollutants, such as CO. SO_2 was not included in any multipollutant models of respiratory symptoms, and the correlation coefficients between SO_2 and other air pollutants were 0.37 for $PM_{2.5}$, −0.43 for O_3, 0.59 for NO_2, and 0.32 for CO. Another study in the United States examined the associations of respiratory health symptoms with increased exposure to air pollution among inner-city children with asthma (Spira-Cohen, 2013; Spira-Cohen et al., 2011). Gaseous pollutants were measured using mobile air monitors located adjacent to the children's schools. Peak morning SO_2 concentrations were associated with increased risk of both cough and wheeze, but not with shortness of breath; however, mean concentrations are not reported. Associations were also present for EC and O_3 concentrations, but not $PM_{2.5}$ nor NO_2 concentrations. No correlation coefficients among the pollutants were reported, and the only mention of copollutant models with SO_2 is in a copollutant model with EC. Thus, recent studies in the United States have reported inconsistency in associations between SO_2 concentration and respiratory symptoms among children with asthma. It is difficult to place these studies in the context of what is known, as no mean SO_2 concentrations are reported.

A study in Windsor, Ontario studied respiratory symptoms among children who were asthmatic and lived in a home without cigarette smoke (Dales et al., 2009). The highest category of SO_2 concentration (≥8.8 ppb) was positively associated with chest tightness compared to the lowest category of SO_2 concentration (<2.3 ppb). SO_2 concentrations were not associated with breathing difficulty, cough, or wheeze. No other pollutants [NO_2, $PM_{2.5}$, O_3 concentrations (correlation coefficients with SO_2: 0.31, 0.43, and −0.02, respectively)] were associated with any respiratory symptoms and copollutant models for respiratory symptoms were not performed. This study demonstrated a positive association between SO_2 concentrations and chest tightness but no other respiratory symptoms.

Summary of Respiratory Symptoms

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. Short-term peak exposures of 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 ranging from 0.4−0.6 ppm SO_2.

Both older epidemiologic studies and a more recent epidemiology study among adults with asthma demonstrate some positive associations between SO_2 concentrations and respiratory symptoms, but there is no overall consistency among the studies. Epidemiologic studies among children with asthma provide stronger evidence for respiratory symptoms in relation to SO_2 concentrations. However, findings of recent studies are more inconsistent than those of older ones among children. A potential reason for the more inconsistent findings is that concentrations of recent studies were either not reported or were lower than some of the highest quality studies included in the 2008 SO_X ISA (U.S. EPA, 2008b).

Airway Responsiveness

The term "airway responsiveness" refers to the ability of the airways to narrow in response to constrictor stimuli. A characteristic feature of individuals with asthma is an increased sensitivity of their airways to respond to this type of stimuli (i.e., AHR). The 2008 SO_X ISA (U.S. EPA, 2008b) provided limited evidence for a relationship between SO_2 concentrations and AHR in asthmatics and in animal models of allergic airway disease. Only a few studies have evaluated this endpoint, and only one new toxicological study is available for review since the last ISA. The following section details the information from all lines of evidence. Additional support for the relationship between allergic responses and AHR is found in Section 4.3.3 (Mode of Action) and Section 5.2.1.2 (Subclinical Effects Underlying Asthma). Furthermore, evidence that repeated SO_2 exposure may induce AHR and allergic responses in naive animals is found in Section 5.2.1.6.

As described in the 2008 SO_X ISA (U.S. EPA, 2008b), two epidemiologic studies provide evidence for a relationship between SO_2 concentrations and AHR. One study, conducted in Norway, reported an association between SO_2 concentration in the previous 24 hours and AHR among children with atopy (Soyseth et al., 1995). The other study found an association between SO_2 concentration and AHR among adult asthmatics in England (Taggart et al., 1996).

The evidence from controlled human exposure studies consists of two studies in adults with asthma. Both of these studies provide evidence for AHR 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 did not affect airway responsiveness to house dust mite allergen immediately after a

6-hour exposure at rest. Because volunteers were exposed at rest, it is unlikely that a high enough concentration of SO_2 or NO_2 reached the airways to cause an effect. However, following exposure to the two pollutants in combination, volunteers demonstrated an increase response to inhaled allergen (Devalia et al., 1994b). Rusznak et al. (1996) confirmed these results in a similar study and found that AHR to dust mites persisted up to 48-hour post-exposure. These results provide further evidence that SO_2 may elicit effects beyond the short time period typically associated with this pollutant.

Animal toxicological studies in several species have shown that a single exposure to SO_2 at a concentration of up to 10 ppm failed to increase airway responsiveness to a challenge agent (U.S. EPA, 2008b) (Section 5.2.1.6). While the majority of these experiments were conducted in naive animals, one study compared effects in naive and allergic animals. Animal models of allergic airway disease share many of the phenotypes associated with asthma. In this study, naive sheep and 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 24 hours, but not immediately, after SO_2 exposure in allergic sheep but not in the naive sheep. These results suggest that the context of allergic inflammation may confer a greater sensitivity to SO_2 effects. Furthermore, the results suggest that AHR may require some time to develop. A recent animal toxicological study in a different model of allergic airway disease also demonstrated AHR following SO_2 exposure (Song et al., 2012). In this study, newborn rats were previously sensitized and challenged with ovalbumin and repeatedly exposed to 2 ppm SO_2 (4 hours/day, 28 days). Results are described below because AHR developed in the context of allergic inflammation.

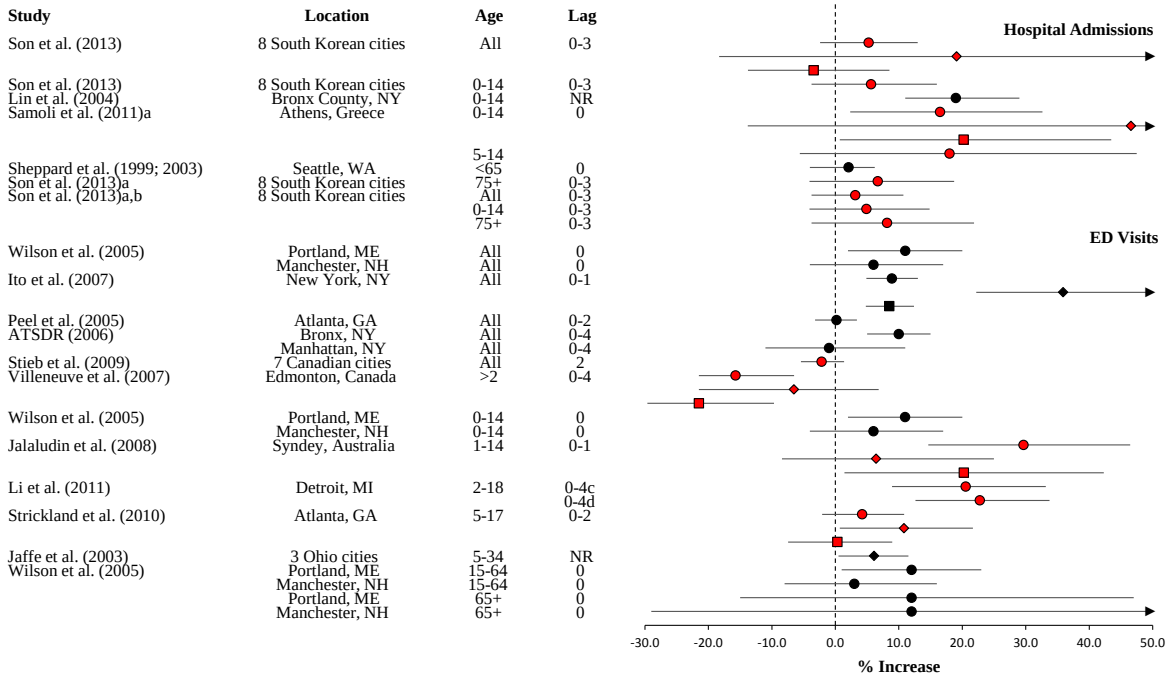
Summary of Airway Responsiveness

In summary, a few studies provide evidence for a relationship between exposure to SO_2 and AHR. This includes a limited number of older epidemiologic studies and a recent toxicological study involving repeated exposure to SO_2 in an animal model of allergic airway disease.

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. As summarized in

Section 5.2.1, the 2008 SO_X ISA (U.S. EPA, 2008b) 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 often larger in magnitude for children (see Figure 5-2, Table 5-9). Additionally, SO_2 associations with asthma hospital admissions and ED visits were found to remain generally robust in copollutant models with PM, NO_2, and O_3.



Note: a = results were presented for four seasons; however the summer and winter estimates represented the largest and smallest estimates across seasons; b = this estimate is for allergic disease, which includes asthma; c = time-series results; d = case-crossover results. Black circles = U.S. and Canadian studies evaluated in the 2008 SO_X Integraged Science Assessment (ISA); red circles = recent asthma hospital admissions and emergency department (ED) visits studies. Circle = all-year; diamond = warm/summer months; square = cool/winter months.

Figure 5-2 Percent increase in asthma hospital admissions and ED 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-hour average or 40-ppb increase in 1-hour maximum sulfur dioxide concentrations.

Table 5-9 Corresponding risk estmates for studies presented in Figure 5-2.

Study	Location	Age (yrs)	Avg Time	Season	Lag (days)	% Increase (95% CI)
Hospital Admissions						
Son et al. (2013)[a]	Eight South Korean cities	All	24-h avg	All	0	5.3 (−0.4, 13.0)
				Summer		19.1 (−18.3, 73.9)
				Winter		−3.4 (−13.8, 8.5)
Son et al. (2013)	Eight South Korean cities	0−14	24-h avg	All	0	5.6 (−3.7, 16.0)
Lin et al. (2004)[b]	Bronx County, NY	0−14	24-h avg	All	NR	19.0 (11.0, 29.0)
Samoli et al. (2011)[a]	Athens, Greece	0−14	24-h avg	All	0	16.5 (2.3, 32.6)
				Summer		46.6 (−13.8, 149.3)
				Winter		20.2 (0.7, 43.5)
Samoli et al. (2011)	Athens, Greece	5−14	24-h avg	All	0	18.0 (−5.6, 47.5)
(Sheppard (2003); Sheppard et al. (1999))[b]	Copenhagen, Denmark	0−18	24-h avg	All	0−4	2.1 (−4.0, 6.2)
Son et al. (2013)	Eight South Korean cities	75+	24-h avg	All	0−3	6.7 (−4.1, 18.7)
Son et al. (2013)[a,c]	Eight South Korean cities	All	24-h avg	All	0−3	3.1 (−3.7, 10.7)
				Summer		4.9 (−4.1, 14.9)
				Winter		8.2 (−3.7, 21.9)
ED Visits						
Wilson et al. (2005)[b]	Portland, ME	All	24-h avg	All	0	11.0 (2.0, 20.0)
	Manchester, NH					6.0 (−4.0, 17.0)
Ito et al. (2007)[b]	New York, NY	All	24-h avg	All	0−1	8.9 (4.9, 13.0)
				Warm		35.9 (22.2, 51.2)
				Cold		8.5 (4.8, 12.4)
Peel et al. (2005)[b]	Atlanta, GA	All	1-h max	All	0−2	0.2 (−3.2, 3.4)
ATSDR (2006)[b]	Bronx, NY	All	24-h avg	All	0−4	10.0 (5.0, 15.0)

Table 5-9 (Continued): Corresponding risk estimates for studies presented in Figure 5-2.

Study	Location	Age (yrs)	Avg Time	Season	Lag (days)	% Increase (95% CI)
	Manhattan, NY					−1.0 (−11.0, 11.0)
Stieb et al. (2009)	Seven Canadian cities	All	24-h avg	All	2	−2.1 (−5.4, 1.4)
Villeneuve et al. (2007)	Edmonton, Canada	>2	24-h avg	All	0−4	−15.7 (−21.5, −6.5)
				Warm		−6.5 (−21.5, 6.8)
				Cold		−21.5 (−29.6, −9.7)
Wilson et al. (2005)[b]	Portland, ME	0−14	24-h avg	All	0	11.0 (2.0, 20.0)
	Manchester, NH					6.0 (−4.0, 17.0)
Jalaludin et al. (2008)	Sydney, Australia	1−14	24-h avg	All	0−1	29.7 (14.7, 46.5)
				Warm		6.4 (−8.4, 25.0)
				Cold		20.3 (1.4, 42.3)
Li et al. (2011)	Detroit, MI	2−18	24-h avg	All	0−4[d]	20.5 (8.9, 33.2)
					0−4[e]	22.8 (12.6, 33.7)
Strickland et al. (2010)	Atlanta, GA	5−17	1-h max	All	0−2	4.2 (−2.1, 10.8)
				Warm		10.8 (0.7, 21.7)
				Cold		0.3 (−7.4, 9.0)
Jaffe et al. (2003)[b]	Three Ohio cities	5−34	24-h avg	Summer	NR	6.1 (0.5, 11.5)
Wilson et al. (2005)[b]	Portland, ME	15−64	24-h avg	All	0	12.0 (1.0, 23.0)
	Manchester, NH					3.0 (−8.0, 16.0)
	Portland, ME	65+				12.0 (−15.0, 47.0)
	Manchester, NH					12.0 (−29.0, 75.0)

avg = average; CI = confidence interval; ED = emergency department; NR = not reported.

[a]Results were presented for four seasons; the summer and winter estimates represented the largest and smallest estimates for each season.

[b]Studies evaluated in the 2008 SO_X Integrated Science Assessment (ISA).

[c]This estimate is for allergic disease, which includes asthma.

[d]Time-series analysis results.

[e]Case-crossover analysis results.

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 often only a small percentage of respiratory-related ED visits will be admitted to the hospital. Therefore, ED visits may represent potentially less serious, but more common, outcomes. Additionally, it is important to note that when focusing on children (i.e., defined age ranges <18 years of age) in the evaluation of asthma hospital admissions and ED visit studies, the results should be viewed with caution if they include children <5 years of age in the study population because of the difficulty in reliably diagnosing asthma within this age range (NAEPP, 2007).

For each of the studies evaluated in this section, Table 5-11 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, and/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-3 (U.S. EPA, 2015h).

Table 5-10 Study-specific details and mean and upper percentile concentrations from asthma hospital admission and ED 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)[a]	Bronx County, NY, U.S. (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))[a]	Seattle, WA, U.S. (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 Two-pollutant models examined: 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 Two-pollutant models examined: 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 Two-pollutant models examined: PM_{10}, SO_2, NO_2, O_3

Table 5-10 (Continued): Study-specific details and mean and upper percentile concentrations from asthma hospital admission and ED 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)[a]	Cincinnati, Cleveland, and Columbus, OH, U.S. (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 Two-pollutant models examined: none
Ito et al. (2007)[a]	New York, NY, U.S. (1999−2002)	Average SO_2 concentrations across 19 monitors	24-h avg	7.8	75th: 10 95th: 17	Correlations (*r*): NR Two-pollutant models examined: $PM_{2.5}$, NO_2, O_3, CO
ATSDR (2006)[a]	Bronx, NY, U.S. Manhattan, NY, U.S. (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 Two-pollutant models: O_3, FRM and Max $PM_{2.5}$, NO_2

Table 5-10 (Continued): Study-specific details and mean and upper percentile concentrations from asthma hospital admission and ED 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)[a]	Atlanta, GA, U.S. (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 Two-pollutant models: none
Wilson et al. (2005)[a]	Portland, ME, U.S. Manchester, NH, U.S. (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 Two-pollutant models examined: 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 Two-pollutant models: none

Table 5-10 (Continued): Study-specific details and mean and upper percentile concentrations from asthma hospital admission and ED 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
Strickland et al. (2010)	Atlanta, GA, U.S. (1993−2004)	Combined daily SO_2 concentrations across monitors using population-weighting	1-h max	All-year: 10.8[a] Warm (May−Oct): 9.6[a] Cold (Nov−Apr): 12.0[a]	NR	Correlations (*r*): NR Two-pollutant models: none
Li et al. (2011)	Detroit, MI, U.S. (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 Two-pollutant models: none
Villeneuve et al. (2007)	Edmonton, Canada (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 Two-pollutant 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 Two-pollutant models: PM_{10}, $PM_{2.5}$, O_3, CO, NO_2

Table 5-10 (Continued): Study-specific details and mean and upper percentile concentrations from asthma hospital admission and ED 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
(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 Two-pollutant models: none
Smargiassi et al. (2009)	Montreal, Canada (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 5-10 (Continued): Study-specific details and mean and upper percentile concentrations from asthma hospital admission and ED 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 of SO_2 concentrations	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 Two-pollutant models: none
Outpatient and Physician Visits						
(Burra et al. (2009))	Toronto, Canada (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 Two-pollutant 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 Two-pollutant models: none

AERMOD = American Meteorological Society/U.S. EPA Regulatory Model; AIRES = Aerosol Research Inhalation Epidemiology Study; avg = average; CO = carbon monoxide; EC = elemental carbon; ED = emergency department; FRM = federal reference method; HCs = hydrocarbons; ISA = Integrated Science Assessment; NO_2 = nitrogen dioxide; NR = not reported; O_3 = ozone; OC = organic carbon; PM = particulate matter; ppb = parts per billion; SEARCH = Southeast Aerosol Research Characterization; SO_2 = sulfur dioxide; UFP = ultrafine particle.

[a]Studies evaluated in 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, but were limited to studies of individual cities, which are sometimes subject to publication bias (Figure 5-2). Additionally, there have been a relative lack of studies that 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-hour average 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 to moderately 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-hour average 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 5-2).

Emergency Department Visits

The majority of studies, both recent and those evaluated in the 2008 SO_X ISA, that have examined the association between short-term SO_2 exposures and 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 5-2). Additionally, there was limited evidence for potential seasonal differences in SO_2 associations with asthma ED visits. Similar to 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 focused on either children or the entire population. (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), that examined all respiratory ED visits. However, unlike Tolbert et al. (2007), which used a single-site centrally located monitor, (Strickland et al. (2010)) used population-weighting, as a more refined exposure assignment approach, to combine daily pollutant concentrations across monitors. As discussed in Section 3.3.5.1, a study by Goldman et al. (2012) demonstrates that the bias in health effect estimates decreases from 76% to 36% when using population-weighted averages instead of a central site monitor when assigning exposure. 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-hour maximum 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 was weakly correlated 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-hour average 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 (see Chapter 5). 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-hour average 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.

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, Alberta, Canada, respectively, did not observe evidence of a positive association between short-term SO_2 exposures and asthma ED visits (Figure 5-2). 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-hour average 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-hour average SO_2 concentrations. Within this study, copollutant analyses or correlations with other pollutants were not presented.

Smargiassi et al. (2009) also informed upon 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 the case of Smargiassi et al. (2009) because the study focuses 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 individuals of older age where 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, Canada 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-hour maximum 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-hour average 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 fixed site monitor located far from a point source may not adequately capture population exposures for residences of interest located closer to that source (see Section 3.3.3.2). 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 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, Canada, 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 5-10, 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-hour average SO_2 concentrations]. Across the eight cities, mean 24-hour average 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-hour average 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-hour maximum SO_2 concentrations], with no evidence of an association during the winter [0.4% (95% CI: −7.5, 9.0)]. 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.

Although there is some evidence for larger associations during the summer, studies conducted by Villeneuve et al. (2007) in Edmonton, Canada 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 5-2).

Overall, the results of Samoli et al. (2011), Son et al. (2013), and Strickland et al. (2010) 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 resulting in some health outcome. Recent studies examined multiple single- and multiday lags in an attempt to identify whether there is a specific exposure window for SO_2 that resulted in the strongest association with 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, through

analyses of 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-hour average 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-hour average 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)].

The aforementioned studies support a rather immediate effect of SO_2 on asthma hospital admissions and ED visits, specifically within the first few days after exposure (i.e., 0−3 days). Controlled human exposure studies demonstrate the rapid onset of bronchoconstriction (i.e., minutes) in exercising asthmatics exposed to SO_2. In addition, one study in asthmatics demonstrated that a 10-minute exposure to SO_2 led to an allergic inflammatory response a few hours later. Studies in allergic animals, which share many of the phenotypic features of asthma, show that repeated SO_2 exposure may exacerbate allergic inflammation over the course of several hours to days. These latter effects are associated with AHR and may lead to bronchoconstriction in response to a trigger (e.g., an allergen).

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 examining 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 depicting the largest association.

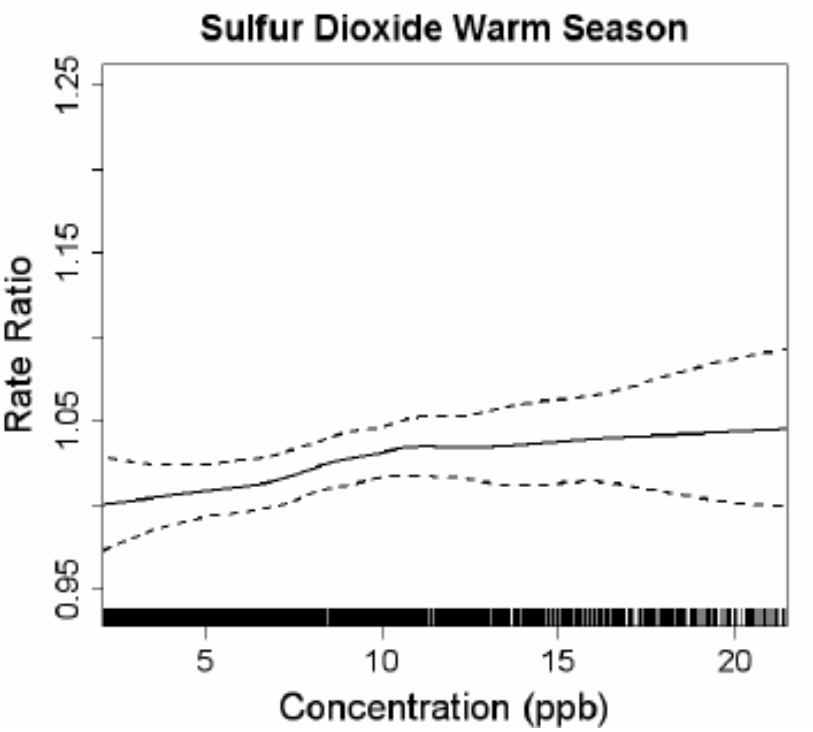
Exposure Assignment

Questions often arise in air pollution epidemiologic studies with regard to the method used to assign exposure (see Section 3.2.3). 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. Within this study, 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 3.3.3.2). 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-hour maximum 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-hour maximum 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-hour maximum 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 indicating 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 5-3). Collectively, these analyses do not provide evidence of a threshold.



Source: Reprinted with permission of the American Thoracic Society. The *American Journal of Respiratory and Critical Care Medicine* is an official journal of the American Thoracic Society. Strickland et al. (2010).

Figure 5-3 Locally weighted scatterplot smoothing concentration-response estimates (solid line) and twice-standard error estimates (dashed lines) from generalized additive models 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 SO_2 concentrations in the Atlanta, GA area.

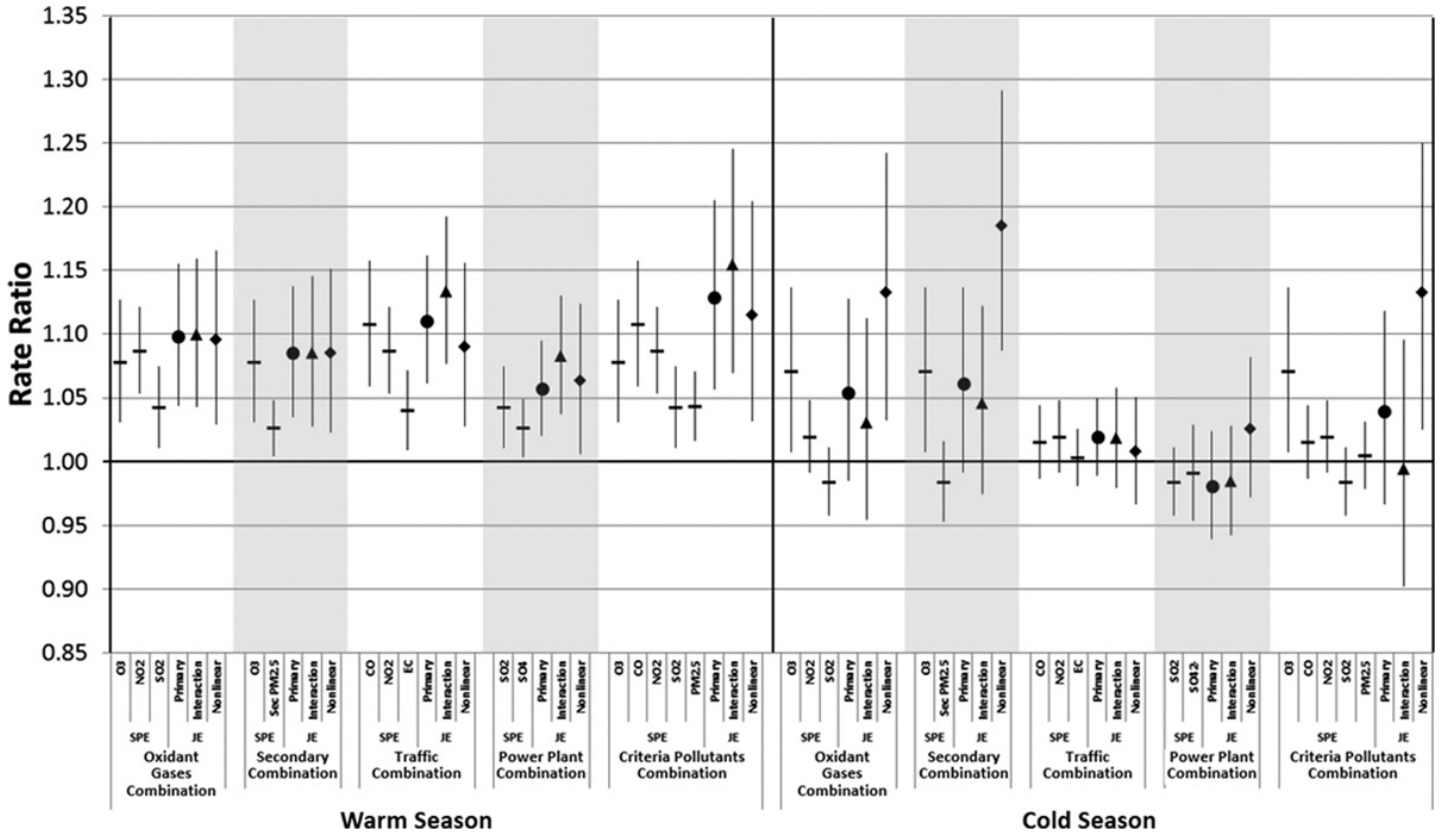
In a study conducted in Detroit, MI, Li et al. (2011) examined whether there is evidence of a nonlinear C-R relationship for air pollutants and pediatric asthma ED visits. Associations with SO_2 were examined in both a time-series and time-stratified case-crossover study design assuming: (1) a linear 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-hour average 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.

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 makes answering this question difficult and primarily limited to examining copollutant models. A recent study conducted by Winquist et al. (2014) 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 this type of study 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 5-4).



SPE = single-pollutant model estimate; JE = joint model estimate.
Source: (Winquist et al., 2014)

Figure 5-4 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 inter-quartile range increase in each pollutant at lag 0−2 days. Inter-quartile range for 1-hour maximum SO_2 concentrations = 10.51 ppb.

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, in the warm season, joint effect models reported consistent positive associations with pediatric asthma ED visits. 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 found to be relatively similar. Overall, the results during the cold season were more variable. The results of Winquist et al. (2014) suggest that SO_2 alone and in combination with other pollutants is associated with asthma ED visits, but also highlights the difficulty in separating out the independent effect of a pollutant that is part of a mixture where multiple pollutants are often highly correlated.

Summary of Asthma Hospital Admission and Emergency Department Visit Studies

Recent studies that examined the association between short-term SO_2 exposure and asthma hospital admissions and ED visits report generally 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 5-2). 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. It is important to note that these studies rely on central site monitors and SO_2 generally has low to moderate spatial correlations across urban geographical scales, which could contribute to some degree of exposure error (Section 3.3.3.2). 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). 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 to moderately correlated with other pollutants examined, which is supported by analyses of NAAQS pollutants at collocated monitors (Section 3.3.4.1). 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 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 5.2.1.5, 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 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). 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 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

Airway inflammation is a key subclinical effect in the pathogenesis of asthma. It consists of both acute and chronic responses, and involves the orchestrated inter-play 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.

The 2008 SO_X ISA (U.S. EPA, 2008b) 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. These studies are discussed below along with a limited number of recent studies.

Controlled Human Exposure Studies

Airway inflammation following peak 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 airway 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 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 4.3.3).

Epidemiologic Studies

As discussed in the 2008 SO_X ISA (U.S. EPA, 2008b), a study among atopic children found an association between SO_2 concentration and capillary blood eosinophil number that was consistent with recruitment of eosinophils to the airways (Soyseth et al., 1995). The 2008 SO_X ISA (U.S. EPA, 2008b) also included an epidemiologic study that evaluated inflammation (measured by eNO) and reported no association with SO_2 concentration. Similarly, a recent study of eNO and SO_2 concentration reported no association (Qian et al., 2009a). However, a recent study performed among children with asthma did indicate that oxidative stress may occur with increased SO_2 concentrations, but no association was reported with fractional exhaled nitric oxide (FeNO) (Liu et al., 2009b). These recent studies are listed in Table 5-11 and described below.

Table 5-11 Summary of recent epidemiologic studies examining associations between SO_2 concentrations and airway inflammation and oxidative stress.

Study	Study Design	Study Population and N	Measure of SO_2	Mean SO_2 and Upper Concentration Level	Adjusted Effect Estimate
Liu et al. (2009b) Canada 2005	Longitudinal repeated measures	School children (9−14 yr) with asthma from a nonsmoking household N = 182	Fixed site monitors; 24-h mean SO_2 concentrations	Median 1-day average: 4.5 ppb 95th percentile: 15.5 ppb Median 2-day average: 5.0 ppb 95th percentile: 13.0 ppb Median 3-day average: 5.6 ppb 95th percentile: 13.8 ppb	Lag 1 [percent change (95% CI) per 10-ppb increase in SO_2] FeNO 2.5 (−13.9, 22.0) TBARS 22.5 (−2.8, 54.3) 8-Isoprostane −3.7 (−17.4, 12.4) 2-day avg [percent change (95% CI) per 10-ppb increase in SO_2] FeNO 10.8 (−16.0, 46.1) TBARS 71.1 (17.6, 149.0) 8-Isoprostane 17.4 (−9.1, 51.6) 3-day avg [percent change (95% CI) per 10-ppb increase in SO_2] FEV_1 −0.6 (−3.5, 2.5) $FEF_{25-75\%}$ −4.2 (−10.0, 1.9) FeNO 3.2 (−24.5, 41.0) TBARS 143.8 (51.0, 293.7) 8-Isoprostane −0.6 (−28.2, 37.8)

Table 5-11 (Continued): Summary of recent epidemiologic studies examining associations between SO_2 concentrations and airway inflammation and oxidative stress.

Study	Study Design	Study Population and N	Measure of SO_2	Mean SO_2 and Upper Concentration Level	Adjusted Effect Estimate
Qian et al. (2009a) United States 1997−1999	Clinical trial/panel study	Patients (12−65 yr) with persistent asthma were recruited from six university-based ambulatory care centers as part of the NHLBI-sponsored Salmeterol Off Corticosteroids Study. N = 119	Fixed site monitors; 24-h mean SO_2 concentrations	Mean (SD): 5.3 (4.4) ppb 75th percentile: 7.6 ppb Max: 27.2 ppb	Change (95% CI) in eNO (ppb) per 10-ppb increase in mean SO_2 *Lag 0:* 0.09 (−0.07, 0.25) *Lag 1:* 0.07 (−0.09, 0.23) *Lag 2:* −0.02 (−0.15, 0.11) *Lag 3:* 0.01 (−0.13, 0.15) *Lag 0−3:* 0.07 (−0.12, 0.26)

CI = confidence interval; eNO = exhaled nitric oxide; $FEF_{25-75\%}$ = forced expiratory flow at 25−75% of forced vital capacity; FeNO = fractional exhaled nitric oxide; FEV_1 = forced expiratory volume in 1 second; N = population number; NHLBI = National Heart, Lung, and Blood Institute; ppb = parts per billion; SO_2 = sulfur dioxide; TBARS = thiobabituric acid reactive substances (species).

Qian et al. (2009a) compared airway inflammation in response to air pollution among a cohort of nonsmoking asthmatics. The participants were randomized into three treatment groups: inhaled corticosteroid (triamcinolone acetonide), inhaled long-acting β2-adrenergic agonist (salmeterol xinafoate), and a placebo. Participant's residential address was used to apply central site air monitoring data from the EPA AQS database. No association was reported between SO_2 concentrations and eNO in any of the treatment groups in both single and copollutant models (models controlled for PM_{10}, O_3, or NO_2; correlations between pollutants not provided). Associations were observed with other pollutants (positive associations with NO_2 and PM_{10} and inverse with O_3). To summarize, this study of individuals with asthma reported no association between SO_2 concentration and eNO.

A study of children with asthma used daily monitoring values from Environment Canada's National Air Pollution Surveillance Network to examine the association between air pollution concentrations and FeNO, oxidative stress [measured by thiobarbituric acid reactive substances (TBARS) and 8-isoprostane], and IL-6 (Liu et al., 2009b). No association was observed between SO_2 concentration and FeNO. Increased SO_2 concentration was associated with increased TBARS (lag 0, 2-day average, and 3-day average) and 8-isoprostane (lag 0). Associations did not vary by corticosteroid use. Other pollutants (NO_2, $PM_{2.5}$) were associated with TBARS but not with 8-isoprostane. The majority of IL-6 levels were under the limit of detection and therefore associations were not analyzed. SO_2 was correlated with NO_2 and $PM_{2.5}$ but not O_3 (correlation coefficients of 0.18, 0.56, and −0.02, respectively). The results for SO_2 concentrations and FeNO and TBARS were not different when copollutants (NO_2, O_3, or $PM_{2.5}$) were included in the models. 8-isoprostane was not examined in copollutant models. Overall, this study reported null associations between SO_2 concentrations and FeNO, but a positive association between SO_2 concentrations and measures of oxidative stress among children with asthma.

Animal Toxicological Studies

The 2008 SO_X ISA (U.S. EPA, 2008b) discussed several studies that investigated the effects of repeated exposure to SO_2 on allergic inflammatory responses. While one study failed to demonstrate inflammation following a single subacute exposure to 1 ppm SO_2 (U.S. EPA, 2008b), other studies found that repeated SO_2 exposure enhanced the development of an allergic phenotype and altered physiologic responses in naive animals. Studies demonstrating effects of repeated SO_2 exposures in naive rats are described below in Section 5.2.1.6. Studies demonstrating effects of repeated SO_2 exposure in models of allergic airway disease are listed in Table 5-12 and described here.

Table 5-12 Study-specific details from animal toxicological studies of subclinical effects underlying asthma.

Study	Species (Strain); n; Sex; Lifestage/Age (mean ± SD)	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 days followed by: (1) Challenge with 1% ovalbumin aerosol for 30 min for 7 days beginning at 15 days, (2) Exposure to 2 ppm SO_2 for 1 h/day for 7 days, or (3) SO_2 exposure followed by ovalbumin aerosol challenge for 7 days	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; 180−200g	Sensitization by i.p. injection of 100 mg ovalbumin followed by booster injection of 10 mg ovalbumin after 7 days followed by: (1) Challenge with 1% ovalbumin aerosol for 30 min for 7 days beginning at 15 days, (2) Exposure to 2 ppm SO_2 for 1 h/day for 7 days, or (3) SO_2 exposure followed by ovalbumin aerosol challenge for 7 days	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 days followed by: (1) Challenge with 1% ovalbumin aerosol for 30 min for 7 days beginning at 15 days, (2) Exposure to 2 ppm SO_2 for 1 h/day for 7 days, or (3) SO_2 exposure followed by ovalbumin aerosol challenge for 7 days	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 5-12 (Continued): Study-specific details from animal toxicological studies of subclinical effects underlying asthma.

Study	Species (Strain); n; Sex; Lifestage/Age (mean ± SD)	Exposure Details (Concentration; Duration)	Endpoints Examined
Song et al. (2012)	Rats (Sprague-Dawley); n = 10/group; M; 4 week-old neonates	Sensitization by i.p. injection of 10 mg ovalbumin followed by booster injection of 10 mg ovalbumin after 7 days followed by: (1) Challenge with 1% ovalbumin aerosol for 30 min daily for 4 weeks beginning at 15 days, and/or (2)Exposure to 2 ppm SO_2 for 4 h/day for 4 weeks beginning at 15 days	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
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 days followed by: (1) Challenge with 1% ovalbumin aerosol for 30 min for 7 days beginning at 15 days, (2) Exposure to 2 ppm SO_2 for 1 h/day for 7 days, or (3) SO_2 exposure followed by ovalbumin aerosol challenge for 7 days	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

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; MCh = methacholine; 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.

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, 2008b), 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 which 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 which 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.

Two other follow-up studies by the same laboratory examined the effects of inhaled SO_2 on the asthma-related genes EGF, EGFR and 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.

Another new toxicological study evaluated the effects of repeated SO_2 exposure on the development of an allergic phenotype and AHR (Song et al., 2012). In this study, both

naive newborn rats and newborn rats that were sensitized and challenged with ovalbumin were exposed to SO_2. Effects in naive rats are described below in Section 5.2.1.6. Effects in allergic rats are described here. Exposure of ovalbumin-treated newborn rats to SO_2 (2 ppm, 4 hours/day for 28 days) resulted in a greater enhancement of lavage fluid IL-4 and an increase in serum IL-4 levels compared with ovalbumin alone. IL-4 is a Th2 cytokine associated with allergic responses; an increase in the ratio of Th2 to Th1 cytokines indicates Th2 polarization, a key step in allergic sensitization. In addition, SO_2 exposure led to increased airway responsiveness and airway remodeling, as indicated by increased content of airway smooth muscle, in the ovalbumin-treated rats. Stiffness and contractility of airway smooth muscle was assessed in vitro using cells from experimentally treated animals. In airway smooth muscle cells from ovalbumin-treated 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 enhanced allergic inflammation, AHR and airway remodeling in SO_2-exposed ovalbumin-treated rats. Further, this study suggests that airway remodeling may contribute to AHR in newborn allergic animals following prolonged exposure to SO_2.

Summary of Subclinical Effects

The available evidence supports a relationship between short-term exposure to SO_2 and allergic responses related to asthma. This includes findings of eosinophilic inflammation in asthmatics exposed acutely to SO_2 and findings of an association between SO_2 exposure and changes in blood eosinophils in atopic children. In addition, enhanced inflammation and allergic responses were demonstrated in animals made allergic to ovalbumin and exposed repeatedly to SO_2. One study suggests that airway remodeling may contribute to AHR in newborn allergic animals following prolonged exposure to SO_2. Recent epidemiologic studies did not specifically evaluate indices of allergic inflammation and found no evidence for a relationship with a nonspecific indicator of inflammation (eNO), although there is some evidence for a relationship between SO_2 exposure and markers of oxidative stress.

5.2.1.3 Chronic Obstructive Pulmonary Disease Exacerbation

COPD is a type of lung disease characterized by deterioration of lung tissue and airflow limitation. Clinical symptoms demonstrating exacerbations of COPD include decrements in lung function and/or symptoms (dyspnea, sputum changes, nasal discharge/congestion, wheeze/tight chest, or upper respiratory symptoms). Severe exacerbations can lead to hospital admissions or ED visits.

Lung Function and Respiratory Symptoms

Only one study investigating the relationship between short-term SO_2 exposure and exacerbation of COPD was described in the 2008 SO_X ISA (U.S. EPA, 2008b). This controlled human exposure study found no evidence of a relationship. A recent epidemiologic study found no association between SO_2 concentration and worsening COPD symptoms.

Controlled Human Exposure Studies

The relationship between individuals with COPD and SO_2-induced respiratory health effects has been examined in only one controlled human exposure study. Linn et al. (1985a) reported no significant effect on lung function following 15-minute exposures to SO_2 at concentrations of 0.4 and 0.8 ppm in a group of older adults with physician-diagnosed COPD. Although it appears that older adults with COPD are less sensitive to SO_2, the authors suggested that the lack of response may be explained by several factors. One apparent difference in this study and those conducted in individuals with asthma is very low levels of exercise (VE = 18 L/minute), which effectively lowers the dose delivered to the lungs (Section 4.2.2).

Epidemiologic Studies

In a recent study, Peacock et al. (2011) investigated air pollution's effect on respiratory symptoms and lung function among adult patients with moderate to severe COPD in east London, England. Outdoor air pollution exposure (lag 1 day) was obtained from local central site monitoring stations from the U.K. National Air Quality Information Archive. Twenty-four-hour means were calculated from hourly measures of SO_2. The year-round mean was 7.5 ppb (SD 6.3 ppb) and the 75th percentile was 9.3 ppb. The mean was higher in the autumn/winter (9.8 ppb) compared to the spring/summer (5.5 ppb) but the maximum concentration was highest in the spring/summer (74 ppb; 42 ppb for autumn/winter). No association was observed between SO_2 concentration and worsening COPD symptoms (dyspnea, sputum changes, nasal discharge/congestion, wheeze/tight chest, or upper respiratory symptoms) or changes in lung function [PEF, FEV_1, forced vital capacity (FVC)]. The odds ratios for a 10 ppb change in SO_2 for each of the symptoms measures were as follows, dyspnoea: 0.96 (95% CI 0.82, 1.13), sputum changes: 1.08 (95% CI 0.89, 1.32), nasal discharge/congestion: 1.12 (95% CI 0.94, 1.32), wheeze/tight chest: 1.02 (95% CI 0.87, 1.20), and upper respiratory symptoms: 0.91 (95% CI 0.75, 1.12). For lung function measures, the change in estimate associated with a 10 ppb change in SO_2 concentration was 0.31 (95% CI −0.10, 0.72) for PEF, −0.35 (95% CI −3.86, 3.16) for FEV_1, and −3.35 (95% CI −11.92, 5.22) for FVC. No association was detected for respiratory symptoms or lung function among other pollutants (NO_2, O_3,

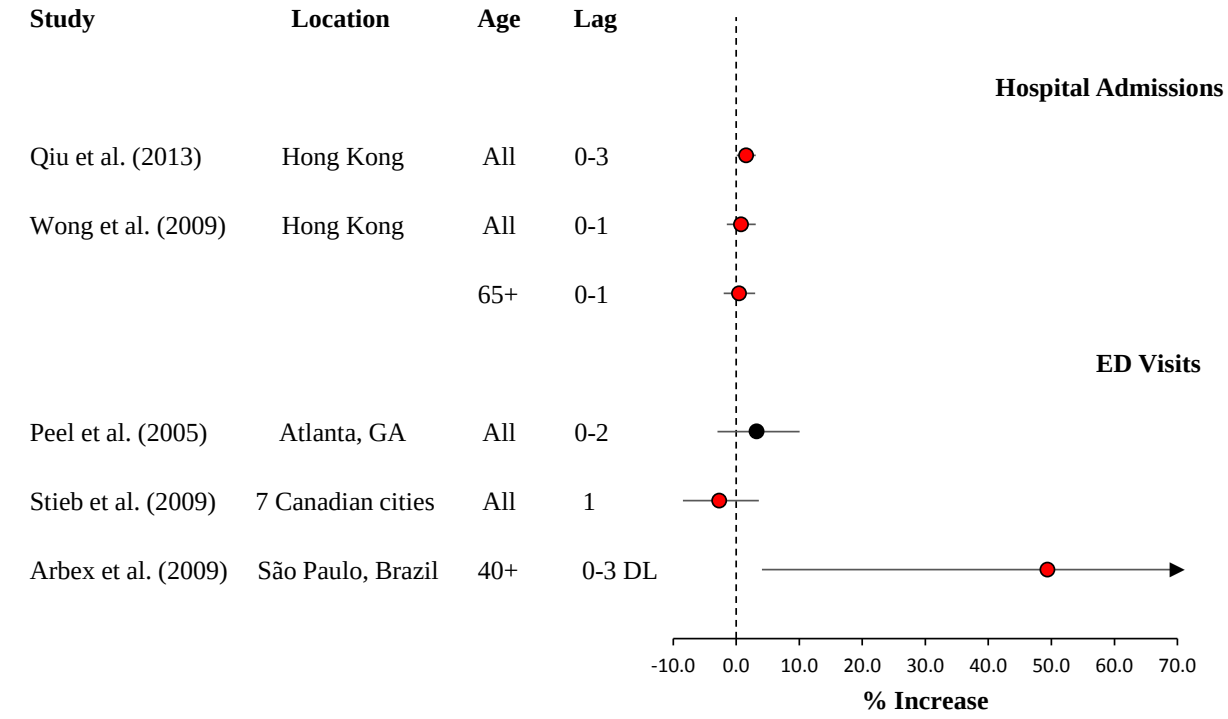
PM_{10}, BS, correlation coefficients with SO_2 not provided). No associations were demonstrated between SO_2 concentrations and COPD exacerbations or symptomatic fall in PEF (PM_{10} and BS were positively associated with the latter). Copollutant models were not examined for SO_2. This study does not support a relationship between SO_2 concentration and COPD symptoms or lung function among adult patients with COPD.

Summary of Lung Function and Respiratory Symptoms

Very few studies have examined a relationship between SO_2 concentrations and lung function or respiratory symptoms among individuals with COPD. The available evidence is not supportive of such a relationship.

Hospital Admissions and Emergency Department Visits for Chronic Obstructive Pulmonary Disease

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 5-5, Table 5-13). 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. 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 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-3 (U.S. EPA, 2015h).



ED = emergency department

Figure 5-5 Percent increase in chronic obstructive pulmonary disease hospital admissions and ED visits from U.S. and Canadian studies evaluated in the 2008 SO_X Integrated Science Assessment (ISA) and recent studies in all-year analyses for a 10-ppb increase in 24-hour average or 40-ppb increase in 1-hour maximum SO_2 concentrations. Note: Black circles = U.S. and Canadian studies evaluated in the 2008 SO_X ISA; red circles = recent chronic obstructive pulmonary disease hospital admission and ED visit studies. a = study evaluated in the 2008 SO_X ISA.

Table 5-13 Corresponding risk estimates for studies presented in Figure 5-5.

Study	Location	Age	Avg Time	Season	Lag	% Increase (95% CI)
Hospital Admissions						
Qiu et al. (2013a)	Hong Kong, China	All	24-h avg	All	0−3	1.6 (0.1, 3.1)
Wong et al. (2009)	Hong Kong, China	All	24-h avg	All	0−1	0.8 (−1.5, 3.1)
		65+				0.5 (−2.0, 3.0)
ED Visits						
Peel et al. (2005)[a]	Atlanta, GA	All	1-h max	All	0−2	3.2 (−3.0, 10.0)
Stieb et al. (2009)	Seven Canadian cities	All	24-h avg	All	1	−2.7 (−8.4, 3.6)
Arbex et al. (2009)	São Paulo, Brazil	40+	24-h avg	All	0−3 DL	49.4 (4.1, 113.7)

Avg = average; CI = confidence interval; DL = distributor lag; ED = emergency department; ISA = Integrated Science Assessment.
[a]Studies evaluated in the 2008 SO_x ISA.

Table 5-14 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. (2013a); 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 Two-pollutant 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 Two-pollutant models: none
ED Visits						
Peel et al. (2005)[a]	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 Two-pollutant models: none

Table 5-14 (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. Two-pollutant 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 Two-pollutant models: none

CO = carbon monoxide; EC = elemental carbon; ED = emergency department; ISA = Integrated Science Assessment; NR = not reported; O_3 = ozone; OC =organic carbon; NO_2 = nitrogen dioxide; PM = particulate matter; ppb = parts per billion; *r* = correlation coefficient; SO_2 = sulfur dioxide; UFP - ultrafine particle.

[a]Studies evaluated in the 2008 SO_X ISA.

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 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 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 for a 10-ppb increase in 24-hour average 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. (2013a) 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. (2013a) 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-hour average SO_2 concentrations. The magnitude of the SO_2 association was found to differ between Qiu et al. (2013a) 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 ISA for SO_X 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, consistent with the asthma ED visits results, Stieb et al. (2009) did not find any evidence of associations between 24-hour average 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-hour average of ED visits versus 3-hour average 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-hour average 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 less 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. (2013a) examined potential seasonal differences in associations by the traditional approach of stratifying by season, but also by examining 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-hour average 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. (2013a) 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-hour average SO_2 concentrations, Qiu et al. (2013a) 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 play 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-hour average SO_2 concentrations]. The results from Qiu et al. (2013a) 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 they 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. (2013a) 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 days) 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 day. Collectively, the results of Qiu et al. (2013a) 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 Hospital Admission and Emergency Department Visit Studies

To date, a relatively limited number of studies have examined the association between short-term SO_2 exposures and COPD hospital admissions and ED visits, and these studies have reported inconsistent evidence of an association (Figure 5-5). Additionally, it is important to note that these studies rely on central site monitors and SO_2 generally has low to moderate spatial correlations across urban geographical scales, which could contribute to some degree of exposure error (Section 3.3.3.2). Although limited in number, studies that examined potential seasonal patterns of associations and the lag structure of associations indicate a potential combined effect of both temperature and humidity on SO_2-COPD hospital admission associations, specifically cool temperatures and low humidity (Qiu et al., 2013a), and provide initial evidence of an immediate effect within the first few days after exposure (i.e., 0−3 days). An examination of potential factors that may modify the SO_2-COPD hospital admission or ED visits relationship finds potential differences by lifestage, sex, and influenza intensity (see Chapter 6. However, similar to studies that have examined other respiratory-related hospital admissions and

ED visits, studies of COPD hospital admissions and ED visits have not conducted extensive analyses to examine potential copollutant confounding. Overall, the limited number of studies that have examined associations between short-term SO_2 exposures and COPD hospital admissions and ED visits complicate the ability to assess whether there is an independent effect of short-term SO_2 concentrations on COPD hospital admissions or ED visits.

5.2.1.4 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, 2008b). 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. Recent contributions to the evidence are limited to epidemiologic studies.

Hospital Admissions and Emergency Department Visits for Respiratory Infections

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. For each of the studies evaluated in this section, Table 5-15 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-3 (U.S. EPA, 2015h).

Table 5-15 Study-specific details and mean and upper percentile concentrations from respiratory infection hospital admission and emergency deparment 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 (ICD9/10)	Exposure Assignment	Metric	Mean Concentra-tion (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 Two-pollutant 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 Two-pollutant models: none

Table 5-15 (Continued): Study-specific details and mean and upper percentile concentrations from respiratory infection hospital admission and emergency deparment 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 (ICD9/10)	Exposure Assignment	Metric	Mean Concentration (ppb)	Upper Percentile of Concentrations ppb	Copollutants Examined
ED Visits							
Peel et al. (2005)[a]	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 Two-pollutant 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. Two-pollutant models: none

Table 5-15 (Continued): Study-specific details and mean and upper percentile concentrations from respiratory infection hospital admission and emergency deparment 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 (ICD9/10)	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 Two-pollutant models: none
Zemek et al. (2010)	Edmonton, Canada (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 Two-pollutant 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 Two-pollutant models: none

AIRES = Aerosol Research Inhalation Epidemiology Study; avg = average; BS = black smoke; CO = carbon monoxide; EC = elemental carbon; ED = emergency department; 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; ppb = parts per billion; *r* = correlation coefficient; SEARCH = Southeast Aerosol Research Characterization; SO_2 = sulfur dioxide; UFP = ultrafine particle.

[a]Study evaluated in 2008 SO_X ISA.

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-hour average SO_2 concentrations]. A larger association was observed in the time-series analysis (HEI, 2012) (Figure 5-6, Table 5-16). 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-hour average SO_2 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-hour average 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 5-6). 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-hour average 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 day. 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-hour average 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, Alberta, Canada, 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-hour average 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-hour average SO_2 concentrations, lag 1−6 day average], 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-hour average SO_2 concentrations, lag 1−6 day average].

Additionally, Zemek et al. (2010) in the study of otitis media ED visits in Alberta, Canada 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-hour average SO_2 concentrations.

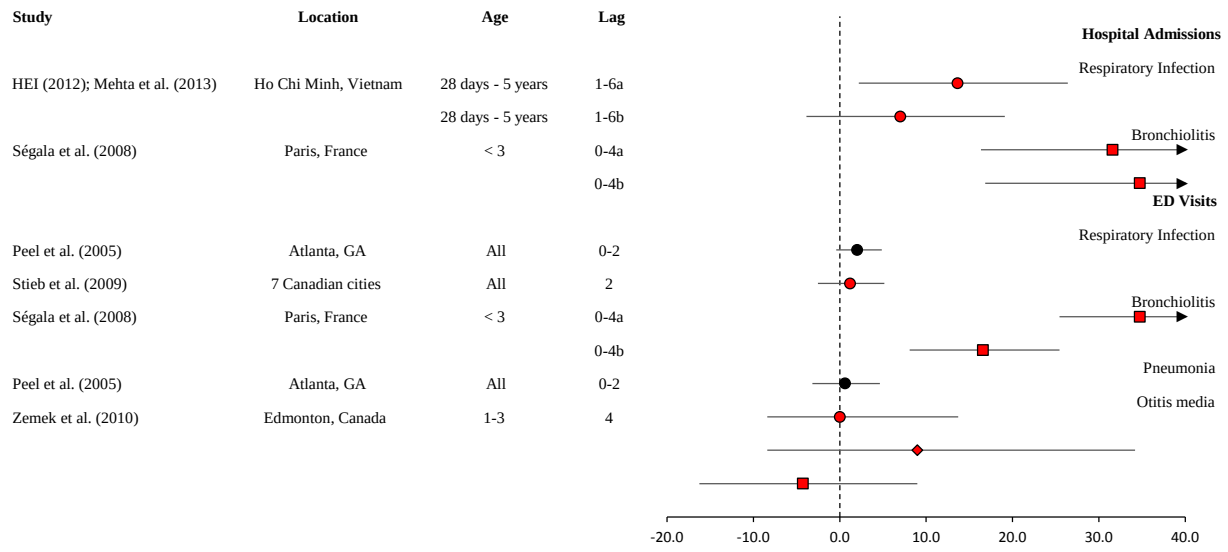
Nonhospital Admissions or Emergency Department Visit Respiratory Infection Studies

Two epidemiologic studies performed among general populations of school children examined respiratory infection as one of the outcomes. These studies reported inconsistent findings. Linares et al. (2010) examined children in Mexico where the mean 24-hour average SO_2 concentration ranged from 8.8 to 13.6 ppb depending on the season

and monitor. A positive association was observed between SO_2 concentration and acute respiratory tract infection [OR 1.14 (95% CI 1.07, 1.22) per 10 ppb], but no association was present for acute respiratory tract infection hospitalization [OR 1.00 (95% CI 0.98, 1.02) per 10 ppb]. Zhao et al. (2008) evaluated children in China where mean ambient SO_2 concentrations were much higher (272.1 ppb) but reported no association with respiratory infection [OR 0.99 (95% CI 0.98, 1.01) per 10 ppb].

Summary of Respiratory Infection Studies

Overall, a relatively limited number of studies have examined the association between short-term SO_2 exposures and respiratory infection hospital admissions and ED visits, specifically with respect to the respiratory infection outcomes examined. Additionally evidence from the few studies that focused on respiratory infections in school children is inconsistent and does not add to understanding the relationship between short-term SO_2 exposures and respiratory infections (Linares et al., 2010; Zhao et al., 2008). Overall, the hospital admission and ED visits studies provide initial evidence of a positive association, but the lack of multiple studies examining the same respiratory infection outcome complicates the interpretation of the collective body of evidence, specifically because the etiology of upper and lower respiratory infections are vastly different (Figure 5-6). Additionally, these studies rely on central site monitors, and SO_2 generally has low to moderate spatial correlations across urban geographical scales, which could contribute to some degree of exposure error (Section 3.3.3.2). Similar to studies that have examined other respiratory-related hospital admissions and ED visits, studies of respiratory infection hospital admissions and ED visits have not conducted extensive analyses to examine potential copollutant confounding. Although the SO_2 correlations with other pollutants were high in some locations outside of the U.S., an examination of correlations between NAAQS pollutants at collocated monitors in the U.S. has demonstrated that SO_2 is low to moderately correlated with other pollutants (Section 3.3.4.1). An examination of potential factors that could modify the SO_2-respiratory infection hospital admission or ED visit association finds potential differences in SO_2 risk estimates by SES with inconsistent evidence for differences in risk estimates by sex (see Chapter 6). Additionally, the relatively small number of studies has resulted in inadequate assessment of issues such as potential seasonal differences in associations or the lag structure of associations.



ED = emergency department.

Figure 5-6 Percent increase in respiratory infection hospital admissions and ED visits from U.S. and Canadian studies evaluated in the 2008 SO_X Integrated Science Assessment (ISA) and recent studies in all-year and seasonal analyses for a 10-ppb increase in 24-hour average or 40-ppb increase in 1-hour maximum SO_2 concentrations. Note: Black circles = U.S. and Canadian studies evaluated in the 2008 SO_X ISA; red circles = recent respiratory infection hospital admissions and ED visits studies.

Table 5-16 Corresponding risk estimates for studies presented in Figure 5-6.

Study	Location	Age	Avg Time	Season	Lag	% Increase (95% CI)
Hospital Admissions						
Respiratory Infection						
HEI (2012); Mehta et al. (2013)	Ho Chi Minh, Vietnam	28 days – 5 years	24-h avg	All	1 – 6[b]	13.6 (2.2, 26.4)
					1 – 6[c]	7.0 (-3.9, 19.1)
Bronchiolitis						
Ségala et al. (2008)	Paris, France	< 3	24-h avg	Winter	0 – 4[b]	31.6 (13.7, 51.2)
					0 – 4[c]	34.8 (19.5, 47.8)

Table 5-16 (Continued): Corresponding risk estimates for studies presented in Figure 5-6.

Study	Location	Age	Avg Time	Season	Lag	% Increase (95% CI)
ED Visits						
Respiratory Infection						
Peel et al. (2005)[a]	Atlanta, GA	All	1-h max	All	0−2	2.0 (−0.4, 4.9)
Stieb et al. (2009)	Seven Canadian cities	All	24-h avg	All	2	1.2 (−2.5, 5.2)
Bronchiolitis						
Ségala et al. (2008)	Paris, France	< 3	24-h avg	Winter	0 – 4[b]	34.7 (25.5, 44.5)
					0 – 4[c]	16.6 (8.1, 25.5)
Pneumonia						
Peel et al. (2005)[a]	Atlanta, GA	All	1-h max	All	0 – 2	0.6 (-3.2, 4.7)
Otitis Media						
Zemek et al. (2010)	Edmonton, Canada	1 – 3	24-h avg	All	4	0.0 (-8.4, 13.7)
				Warm		9.0 (-8.4, 34.2)
				Cold		-4.3 (-16.3, 9.0)

Avg = average; CI = confidence interval; ED = emergency department; ISA = Integrated Science Assessment.

[a]Studies evaluated in the 2008 SO_X ISA.

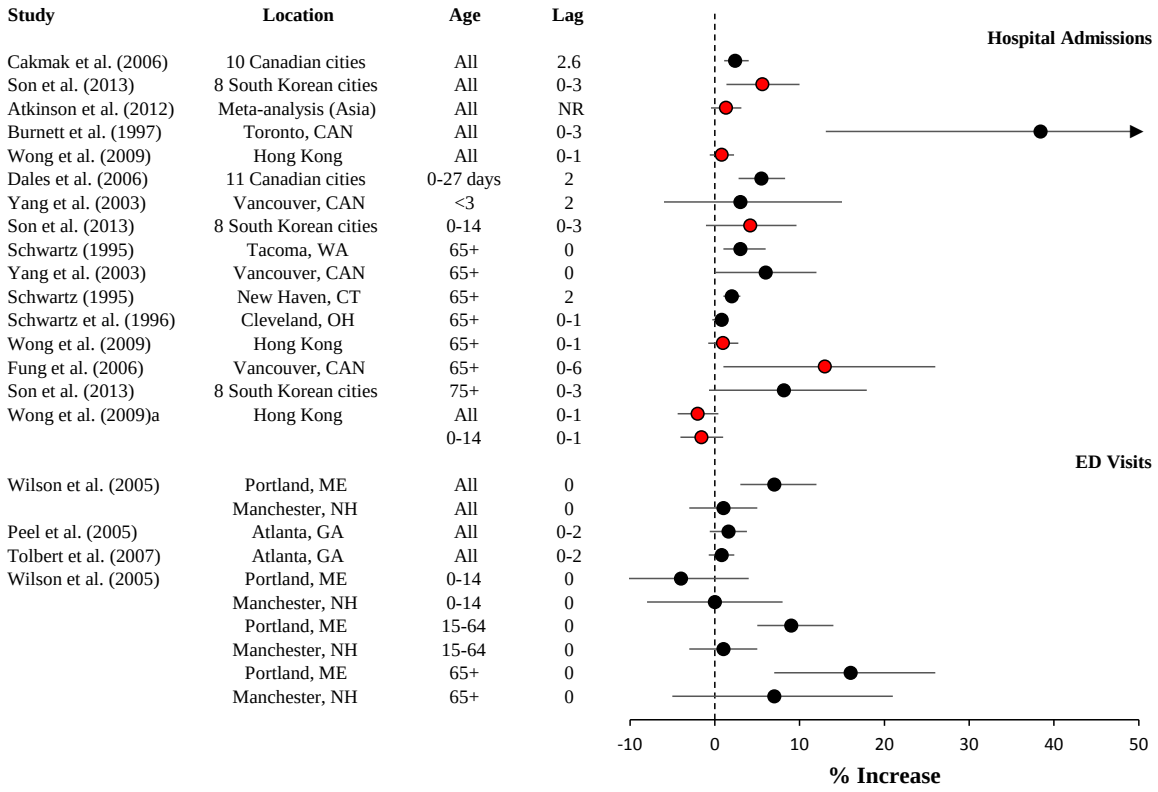
[b] Time-series analysis.

[c] Case-crossover analysis.

5.2.1.5 Respiratory Disease Hospital Admissions and Emergency Department Visits

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 ISA for SO_X (U.S. EPA, 2008b) 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. The studies that examined all respiratory disease hospital admissions and ED visits generally reported positive associations (see Figure 5-7, Table 5-17). 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, 2008b).



Note: Black circles = U.S. and Canadian studies evaluated in the 2008 SO_X Integrated Science Assessment (ISA); red circles = recent respiratory infection hospital admissions and emergency department (ED) visits studies;

a = Wong et al. (2009) also presented results for acute respiratory disease hospital admissions, which is a subset of total respiratory hospital admissions.

Figure 5-7 Percent increase in respiratory disease hospital admissions and ED 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-hour average or 40-ppb increase in 1-hour maximum SO_2 concentrations.

Table 5-17 Corresponding risk estimates for studies presented in Figure 5-7.

Study	Location	Age	Avg Time	Season	Lag	% Increase (95% CI)
Hospital Admissions						
Cakmak et al. (2006)	10 Canadian cities	All	24-h avg	All	2.6	2.4 (1.1, 4.0)
Son et al. (2013)	Eight South Korean cities	All	24-h avg	All	0−3	5.6 (1.4, 10.0)
Atkinson et al. (2012)	Meta-analysis (Asia)	All	24-h avg	All	NR	1.3 (−0.4, 3.2)
Burnett et al. (1997)[a]	Toronto, Canada	All	1-h max	Summer	0−3	38.4 (13.1, 69.2)
Wong et al. (2009)	Hong Kong, China	All	24-h avg	All	0−1	0.8 (−0.6, 2.3)
Dales et al. (2006)[a]	11 Canadian cities	0−27 days	24-h avg	All	2	5.5 (2.8, 8.3)
Yang et al. (2003b)[a]	Vancouver, Canada	<3	24-h avg	All	2	3.0 (−6.0, 15.0)
Son et al. (2013)	Eight South Korean cities	0−14	24-h avg	All	0−3	4.2 (−1.0, 9.6)
Schwartz (1995)[a]	Tacoma, WA	65+	24-h avg	All	0	3.0 (1.0, 6.0)
Yang et al. (2003b)[a]	Vancouver, Canada	65+	24-h avg	All	0	6.0 (0.0, 12.0)
Schwartz (1995)[a]	New Haven, CT	65+	24-h avg	All	2	2.0 (1.0, 3.0)
Schwartz et al. (1996)[a]	Cleveland, OH	65+	24-h avg	All	0−1	0.8 (−0.3, 1.5)
Wong et al. (2009)	Hong Kong, China	65+	24-h avg	All	0−1	1.0 (−0.8, 2.8)
Fung et al. (2006)[a]	Vancouver, Canada	65+	24-h avg	All	0−6	13.0 (1.0, 26.0)
Son et al. (2013)	Eight South Korean cities	75+	24-h avg	All	0−3	8.2 (−0.7, 17.9)
Wong et al. (2009)[b]	Hong Kong, China	All	24-h avg	All	0−1	−2.0 (−4.4, 0.4)
		0−14				−1.6 (−4.1, 1.0)

Table 5-17 (Continued): Corresponding risk estimates for studies presented in Figure 5-7.

Study	Location	Age	Avg Time	Season	Lag	% Increase (95% CI)
ED Visits						
Wilson et al. (2005)[a]	Portland, ME	All	24-h avg	All	0	7.0 (3.0, 12.0)
	Manchester, NH					1.0 (−3.0, 5.0)
Peel et al. (2005)[a]	Atlanta, GA	All	1-h max	All	0−2	1.6 (−0.6, 3.8)
Tolbert et al. (2007)[a]	Atlanta, GA	All	1-h max	All	0−2	0.8 (−0.7, 2.3)
Wilson et al. (2005)[a]	Portland, ME	0−14	24-h avg	All	0	−4.0 (−11.0, 4.0)
	Manchester, NH					0.0 (−8.0, 8.0)
	Portland, ME	15−64				9.0 (5.0, 14.0)
	Manchester, NH					1.0 (−3.0, 5.0)
	Portland, ME	65+				16.0 (7.0, 26.0)
	Manchester, NH					7.0 (−5.0, 21.0)

Avg = average; CI = confidence interval; ED = emergency department; ISA = Integrated Science Assessment; NR = not reported.

[a]Studies evaluated in the 2008 SO_X ISA.

[b]Wong et al. (2009) also presented results for acute respiratory disease hospital admissions, which is a subset of total respiratory hospital admissions.

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 5-18 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-3 (U.S. EPA, 2015h).

Table 5-18 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)[a]	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 Two-pollutant models examined: none
Dales et al. (2006)[a]	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 Two-pollutant models examined: none
Burnett et al. (1997)[a]	Toronto, Canada (1992−1994)	Average of SO_2 concentrations from four to six 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 Two-pollutant models examined: COH, PM_{10}, $PM_{10-2.5}$, $PM_{2.5}$

Table 5-18 (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)[a]	Vancouver, Canada (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 Two-pollutant models examined: none
Schwartz (1995)[a]	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 Two-pollutant models examined: PM_{10}, O_3
Schwartz et al. (1996)[a]	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 Two-pollutant models examined: none
Yang et al. (2003b)a	Vancouver, Canada (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 Two-pollutant models examined: 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 Two-pollutant models examined: none
Atkinson et al. (2012)	Meta-analysis (Asia) (1980−2007)	NR	24-h avg	NR	NR	Correlation (*r*): NR Two-pollutant models examined: none

Table 5-18 (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 Two-pollutant models examined: none
ED Visits						
Peel et al. (2005)[a]	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 Two-pollutant models: none

Table 5-18 (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)[a]	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 $PM_{2.5}$ SO_4: 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 Two-pollutant models examined: none
Wilson et al. (2005)[a]	Portland, ME Manchester, NH (1996−2000)	SO_2 concentrations from a central site monitor	24-h avg	Portland: 11.1 Manchester: 16.5	NR	Correlation (*r*): Portland O_3: 0.05 Manchester O_3: 0.01 Two-pollutant models examined: none

CO = carbon monoxide; COH = coefficient of haze; EC = elemental carbon; ED = emergency department; H^+ = hydrogen ion; ISA = Integrated Science Assessment; OC = organic carbon; NO_2 = nitrogen dioxide; NR = not reported; O_3 = ozone; PM = particulate matter; ppb = parts per billion; *r* = correlation coefficient; SO_2 = sulfur dioxide; SO_4 = sulfate; TC = total hydrocarbon; UFP = ultrafine particle.

[a]Studies evaluated in 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-hour average 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 are observed and the magnitude of the association (Figure 5-7).

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 5-7). 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-hour average 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-hour average 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-hour average 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-hour average 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 5-7, Table 5-17). 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-hour average 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-hour average 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-hour average 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-hour average 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 Hospital Admission and Emergency Department Visit Studies 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 5-7). Note that these studies rely on central site monitors and SO_2 generally has low to moderate spatial correlations across urban geographical scales, which could contribute to some degree of exposure error (Section 3.3.3.2). 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 5-7)]. 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. Although SO_2 correlations with other pollutants in some studies could be considered high, an examination of correlations between NAAQS pollutants at collocated monitors in the U.S. has demonstrated that SO_2 is low to moderately correlated (Section 3.3.4.1). 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.

5.2.1.6 Respiratory Effects in General Populations and Healthy Individuals

The 2008 SO_X ISA (U.S. EPA, 2008b) reported respiratory effects of SO_2 in general populations and healthy individuals but did not make specific conclusions about causal relationships between SO_2 exposure and health effects in these groups. Respiratory effects were demonstrated in healthy individuals following SO_2 exposures ≥1.0 ppm in controlled human exposure studies. Epidemiologic evidence was insufficient to conclude an association between SO_2 and lung function or respiratory symptoms in general populations of children or adults. However, animal toxicological studies demonstrated bronchoconstriction after a single SO_2 exposure and increased airway responsiveness and inflammation after repeated SO_2 exposures.

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, 2008b). Limited epidemiologic studies described in the 2008 SO_X ISA (U.S. EPA, 2008b) provided insufficient evidence to draw conclusions about decrements in lung function and SO_2 exposure in general populations. More recent epidemiologic studies report some positive associations in general populations of adults and children, although evidence is inconsistent. Animal toxicological studies demonstrated SO_2 exposure-induced effects on lung function at concentrations of 2 ppm and lower (U.S. EPA, 2008b).

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 5-19. Andersen et al. (1974) reported that exposures of up to 6 hours to 1.0 ppm SO_2 in resting healthy adults induced a constriction in the upper airways as evidenced by 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.

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 synergistic effect.

Table 5-19 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-day after, and 1 week 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, 75W) two times during each session	Exhaled NO, biomarkers of airway inflammation in EBC and NALF
Tunnicliffe et al. (2003)	Asthma; n = 12 Healthy; n = 12	0 or 0.2 ppm SO_2 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 SO_2 for 4 h with exercise for 15 min (bicycle, 75W) 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 second; 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.

Epidemiologic Studies

Adults. Evidence of an association between ambient SO_2 concentrations and lung function in adults without asthma or chronic respiratory symptoms was limited in the 2008 SO_X ISA (U.S. EPA, 2008b). Recent studies have reported some positive associations although the overall evidence is inconsistent. These recent studies are summarized in the following text and Table 5-20.

Table 5-20 Summary of recent epidemiologic studies examining associations between SO_2 concentrations and lung function among adults.

Study, Location, and Years	Study Design	Study Population and N	Measure of SO_2	Mean SO_2 and Upper Concentration Level	Adjusted Effect Estimate
Dales et al. (2013) Ontario, Canada	Cross-over	Healthy, nonsmoking volunteers (mean age 24.2 yr) not living in a town bordering a steel plant N = 61	Fixed site monitors; 10-h mean SO_2 concentrations	Neighborhood near steel mill: 7.76 (13.21) ppb College campus: 1.59 ppb (4.18) ppb	Percent change per 10 ppb (0−2 days) FEV_1 −0.50 (−1.04, 0.05) FVC −0.45 (−1.09, 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 −2.19 (−4.16, −0.18)

Table 5-20 (Continued): Summary of recent epidemiologic studies examining associations between SO_2 concentrations and lung function among adults.

Study, Location, and Years	Study Design	Study Population and N	Measure of SO_2	Mean SO_2 and Upper Concentration Level	Adjusted Effect Estimate
Steinvil et al. (2009) Tel Aviv, Israel 2002−2007	Cross-sectional	Healthy adult (mean 43 yr), nonsmokers enrolled in the residing within 11 km of monitor N = 2,380	Fixed site monitors; 24-h mean SO_2 concentrations	SO_2 Mean (SD): 2.8 (1.2) ppb 75th percentile: 3.4 ppb Max: 9.4 ppb	Change in FEV_1, expected for a 10-ppb increase in SO_2 Lag 0: 93 (−90, 277) Lag 1: 67 (−117, 250) Lag 2: −60 (−243, 123) Lag 3: −267 (−460, −73) Lag 4: −207 (−387, −27) Lag 5: −300 (−487, −113) Lag 6: −247 (−427, −67) Lag 7: −173 (−353, 7) 7-day avg: −447 (−750, −143) Change in FVC, expected for a 10-ppb increase in SO_2 Lag 0: 53 (−167, 273) Lag 1: 80 (−143, 303) Lag 2: −13 (−237, 210) Lag 3: −313 (−550, −77) Lag 4: −300 (−517, −83) Lag 5: −373 (−600, −147) Lag 6: −327 (−543, −110) Lag 7: −227 (−447, −7) 7-day avg: −560 (−927, −193) Change in FEV_1/FVC, expected for a 1.5-ppb increase in SO_2 Lag 0: 247 (−10, 503) Lag 1: 60 (−203, 323) Lag 2: −100 (−363, 163) Lag 3: 20 (−260, 300) Lag 4: 153 (−50, 357) Lag 5: 133 (−137, 403) Lag 6: 120 (−140, 380) Lag 7: 107 (13, 200) 7-day avg: 220 (−217, 657)
Min et al. (2008a) South Korea 2006	Cross-sectional	Volunteers (20−86 yr) with no serious medical conditions N = 867	Fixed site monitors; 1-h mean SO_2 concentrations	6 ppb	Quantitative effects estimates not reported

Table 5-20 (Continued): Summary of recent epidemiologic studies examining associations between SO_2 concentrations and lung function among adults.

Study, Location, and Years	Study Design	Study Population and N	Measure of SO_2	Mean SO_2 and Upper Concentration Level	Adjusted Effect Estimate
Son et al. (2010) South Korea 2003−2007	Cross-sectional	Participants (7−97 yr) were recruited from a cohort study of residents near the Ulsan petrochemical complex. N = 2,102	Fixed site monitors; 24-h mean SO_2 concentrations	Average across all monitors Mean (SD): 8.60 (4.13) ppb 75th percentile: 10.46 ppb Max: 23.80 ppb Nearest Monitor Mean (SD): 7.25 (5.92) ppb 75th percentile: 9.50 ppb Max: 34.21 ppb IDW Mean (SD): 8.35 (5.26) ppb 75th percentile: 10.81 ppb Max: 29.06 ppb Kriging Mean (SD):8.29 (4.41) ppb 75th percentile: 9.62 ppb Max: 24.78 ppb	Percent change (95% CI) in predicted FVC per 10-ppb increase in SO_2 (Lag 0−2) Average across all monitors −6.96 (−9.04, −4.82) Nearest monitor −5.61 (−7.35, −3.85) IDW −5.31 (−7.07, −3.53) Kriging −6.19 (−8.16, −4.18) Percent change (95% CI) in predicted FEV_1 per 10-ppb increase in SO_2 (Lag 2) Average across all monitors −0.15 (−0.89, 0.58) Nearest monitor 0.35 (−0.21, 0.92) IDW 0.31 (−0.32, 0.95) Kriging −0.08 (−0.76, 0.60)

avg = average ; CI = confidence interval; $FEF_{25–75\%}$ = forced expiratory flow at 25−75% of forced vital capacity; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity ; IDW = inverse distance weighting; N = population number; ppb = parts per billion; SD = standard deviation; SO_2 = sulfur dioxide.

Some studies have reported associations between SO_2 concentration and lung function among healthy adults. A cross-over study in Canada recruited healthy, nonsmoking participants who were assigned to spend five consecutive 8-hour days outside at a neighborhood bordering a steel plant and a college campus, with a wash-out period between the two periods (Dales et al., 2013). Air monitors at each location measured ambient air pollutants. SO_2 concentration was inversely associated with multiple measures of lung function (e.g., $FEF_{25–75}$, total lung capacity, residual volume). Other pollutants examined in the study (NO_2, $PM_{2.5}$, and UFP) were also inversely associated with measures of lung function. Concentrations of O_3 demonstrated some associations, but these were fewer than for the other pollutants. No correlation coefficients or copollutant models were provided. Similarly, inverse associations between SO_2 concentrations and lung function (FEV_1 and FVC for lags of at least 3 days) were

observed among healthy, nonsmoking adults in the Tel Aviv Sourasky Medical Center Inflammation Survey (Steinvil et al., 2009). Some inverse associations were also observed for NO_2 and CO but not PM_{10}. Positive associations were reported for O_3 and both FEV_1 and FVC. None of the air pollutants were associated with the FEV_1/FVC ratio with the exception of CO and O_3 on lag Day 7. Although highly correlated with NO_2 (correlation coefficient 0.70), the inverse association between SO_2 concentration and FEV_1 and FVC were relatively unchanged when adjusted for NO_2, CO (correlation coefficient −0.25), and O_3 (correlation coefficient 0.62) in copollutant models.

Studies in Korea examined the associations between air pollution and lung function using general populations regardless of health status. Son et al. (2010) investigated how different methods of estimating exposure may influence health effect estimates in a case study of FEV_1 and FVC for cohort subjects in Korea chosen based on residence near a petrochemical complex. Age of study participants ranged from 7 to 97 years, with a mean age of 45 years. Measurements from Korea's Department of Environment's air monitors were used to estimate individual-level exposures by averaging across values from all monitors, selecting the value from the nearest monitor, weighting by inverse distance, and kriging. Cross-validation indicated that kriging provided the smallest range of estimated exposures. An inverse association was observed between FVC, but not FEV_1, and SO_2 exposure estimated using all four methods. The same was true of the other pollutants, with the exception of O_3, which was inversely related to both FVC and FEV_1. Copollutant models were run for pollutant pairs that were not highly correlated. Inclusion of CO or O_3 in the models with SO_2 did not affect its association with forced expiratory volume (FEV). The association between SO_2 and FVC did change with adjustment for O_3 concentration, but the association remained when CO concentration was included in the model. Health effect estimates were generally higher using exposures based on averaging across all monitors or kriging than for exposures based on nearest monitor or IDW exposure. Another study of adults in Korea examined the relationship between SO_2 concentration and lung function by smoking status (Min et al., 2008a). One hour lags were examined over a 48-hour period for SO_2 measured from an air monitor. The study population consisted of individuals with no serious medical problems, although having asthma was not an exclusion factor and instead was controlled for in the analysis (proportion of participants with asthma not provided). No association was observed between SO_2 concentration and FVC or FEV_1, among nonsmokers, but among smokers, there was an inverse association starting around 6 hours and lasting until about 20 hours. From the figures presented in the paper, it is difficult to determine whether confidence intervals overlap for the two groups, but the difference appears to be greatest around 11 hours. No other pollutants were examined in this study. In summary, studies from Korea have had mixed findings regarding the association between SO_2 concentration and lung function.

Children. The 2008 SO_X ISA (U.S. EPA, 2008b) stated that there was insufficient evidence to conclude that an association was present between SO_2 and lung function among children. Summarized below and in Table 5-21 are recent studies published since the previous review that examine SO_2 concentrations and lung function in general populations of children. None of these studies were performed in the U.S. or Canada. General populations of children include both healthy children and those with pre-existing disease. Although overall the studies report inconsistent results, some studies report findings that are supportive of an association between SO_2 concentration and lung function in children.

Table 5-21 Summary of recent epidemiologic studies examining associations between SO_2 concentrations and lung function among children.

Study, Location, and Years	Study Design	Study Population and N	Measure of SO_2	Mean SO_2 and Upper Concentration Level	Adjusted Effect Estimate
Linares et al. (2010) Salamanca, Mexico 2004−2005	Longitud-inal repeated measures	Children (6−14 yr) from two schools. N = 464	Fixed site monitors; 24-h mean SO_2 concentrations	Mean (SD) Spring School 1: 11.9 (0.4) ppb School 2: 9.1 (0.4) ppb Summer School 1: 12.3 (0.3) ppb School 2: 8.8 (0.5) ppb Fall School 1: 10.4 (0.3) ppb School 2: 10.2 (0.6) ppb Winter School 1: 9.9 (0.2) ppb School 2: 13.6 (0.7) ppb	Change (95% CI) per 10-ppb increase in SO_2 FVC −0.0649 (−0.1297, −0.0001) FEV_1 −0.0076 (−0.0106, −0.0046) PEF −0.0270 (−0.0539, 0.0000) FEV_1/FVC −0.0728 (−0.1805, 0.0349)

Table 5-21 (Continued): Summary of recent epidemiologic studies examining associations between SO_2 concentrations and lung function among children.

Study, Location, and Years	Study Design	Study Population and N	Measure of SO_2	Mean SO_2 and Upper Concentration Level	Adjusted Effect Estimate
Correia-Deur et al. (2012) Brazil 2004	Panel study	School children (9−11 yr) N = 96	Fixed site monitors; 24-h mean SO_2 concentrations	Mean (SD): 8.78 (3.27) ppb 75th percentile: 11.2 ppb 90th percentile: 13.1 ppb	Estimated change (95% CI) in PEF (L/min) per 0.38-ppb increase in SO_2 2-h avg −2.11 (−3.82, −0.39) 24-h avg −0.79 (−3.03, 1.45) Estimated change (95% CI) in FEV_1 (L) per 0.38-ppb increase in SO_2 2-h avg 0.00 (0.00, 0.00) 24-h avg −0.026 (−0.053, 0.000) Note: authors stated no negative association was demonstrated between SO_2 concentrations and PEF during lag times of 3-, 5-, 7-, and 10-day moving avgs; quantitative results were not provided
Castro et al. (2009) Brazil 2004	Panel study	Random selection of children (6−15 yr) from low-income families attending one public school in a potentially high air pollution area. N = 118	Fixed site monitors; 24-h mean SO_2 concentrations	Mean (SD): 7.10 (6.83) ppb 90th percentile: 15.5 ppb Max: 36.6 ppb	Estimated change (95% CI) in PEF (L/min) per 10-ppb increase in SO_2 Lag 1: −0.73 (−2.46, 0.99) Lag 2: −0.99 (−2.60, 0.61) Lag 3: 0.34 (−1.13, 1.81) 2-day avg; −1.81 (−3.78, 0.17) 3-day avg: −1.47 (−3.39, 0.46)

Table 5-21 (Continued): Summary of recent epidemiologic studies examining associations between SO_2 concentrations and lung function among children.

Study, Location, and Years	Study Design	Study Population and N	Measure of SO_2	Mean SO_2 and Upper Concentration Level	Adjusted Effect Estimate
Altuğ et al. (2013) Eskisehir, Turkey 2008−2009	Cross-sectional	Students (9−13 yr) from public primary schools, located in (1) suburban (2) urban, or (3) urban-traffic regions N = 1,880	Fixed site monitors; weekly mean SO_2 concentrations	Summer period Suburban schools: mean (SD): 8.5 (3.1) ppb Max: 16.1 ppb Urban Schools: Mean (SD): 10.2 (3.9) ppb Max: 16.4 ppb Urban-traffic schools: Mean (SD): 6.3 (2.1) ppb Max: 8.9 ppb Winter period Suburban schools: mean (SD): 21.1 (6.3) ppb Max: 28.9 ppb Urban schools: mean (SD): 29.1 (7.2) ppb Max: 44.2 ppb Urban-traffic schools: mean (SD): 22.0 (7.0) ppb Max: 32.7 ppb	OR (95% CI) per 10-ppb increase in SO_2 Summer Impaired lung function Girls: 1.22 (0.72, 2.09) Boys: 0.83 (0.47, 1.45) Winter Impaired lung function Girls: 1.00 (0.76, 1.32) Boys: 0.83 (0.61, 1.11)

Table 5-21 (Continued): Summary of recent epidemiologic studies examining associations between SO_2 concentrations and lung function among children.

Study, Location, and Years	Study Design	Study Population and N	Measure of SO_2	Mean SO_2 and Upper Concentration Level	Adjusted Effect Estimate
Altuğ et al. (2014) Eskisehir, Turkey	Cross-sectional	4th and 5th grade students (9−13 yr) from public primary Schools located in (1) suburban, (2) urban, or (3) urban-traffic regions. N = 605	Fixed site monitors; weekly mean SO_2 concentrations	Suburban schools: Mean (SD): 21.1 (6.3) ppb Max: 28.9 ppb Urban schools: mean (SD): 29.1 (7.2) ppb max: 44.2 ppb Urban-traffic schools: mean (SD): 22.0 (7.0) ppb Max: 32.7 ppb	OR (95% CI) per 10-ppb increase in SO_2 Subjects with upper respiratory tract symptoms FeNO 1.05 (0.97, 1.14) 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) Subjects without upper respiratory tract symptoms FeNO 0.97 (0.87, 1.09) 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)
Chang et al. (2012) Taipei Taiwan 1996−1997	Cross-sectional	School children (12−16 yr) were randomly selected from 87 junior high schools in 5 districts. (23.8% <14 yr, 33.4% = 14 yr, 42.8% >14 yr) N = 2,919	Fixed site monitors; 4-h, 10-h mean SO_2 concentrations	Six-day median: 2.6 ppb 75th percentile: 5.2 ppb	Estimated change (95% CI) in FVC (mL) per 10-ppb increase in SO_2 Lag 0 Avg: 5.5 (−28.6, 39.6) Peak:6.3 (−18.9, 31.5) Lag 1 Avg: −129.0 (−207.0, −50.9) Peak: −89.6 (−135.1, −44.1) Lag 2 Avg: 32.8 (−36.6, 102.2) Peak: 28.8 (−5.2, 62.8) Estimated change (95% CI) in FEV_1 (mL) per 10-ppb increase in SO_2 Lag 0 Avg: 0.4 (−32.2, 33.0) Peak: 3.6 (−20.8, 27.9) Lag 1 Avg: −117.3 (−193.0, −41.6) Peak: −84.8 (−129.0, −40.6) Lag 2 Avg: 21.2 (−47.0, 89.4) Peak: 25.4 (−7.9, 58.6)

Table 5-21 (Continued): Summary of recent epidemiologic studies examining associations between SO_2 concentrations and lung function among children.

Study, Location, and Years	Study Design	Study Population and N	Measure of SO_2	Mean SO_2 and Upper Concentration Level	Adjusted Effect Estimate
Amadeo et al. (2015) Guadeloupe 2008−2009	Cross-sectional	School children randomly selected from seven elementary schools (8−13 yr) N = 506	Fixed site monitors; max daily 1-h mean SO_2 concentrations	Mean (SD): 1.79 (1.41) ppb Max: 4.85 ppb	β (95% CI) per 10-ppb increase in SO_2 averaged over previous 2 weeks PEF: 30.9 (−69.4, 131.0) Change in PEF: 3.7 (−24.6, 32.0)
Reddy et al. (2012) South Africa 2004−2005	Longitud-inal repeated measures	Indigenous African children from seven primary schools (9−11 yr). N = 129	Fixed site monitors; 24-h mean SO_2 concentrations	Mean (SD): 5.8 (0.2) ppb Max: 40.8 ppb	Percent change in intra-day variability of FEV_1 (95% CI) per 10-ppb increase in SO_2 Lag 1: 1.62 (−0.03, 3.30) Lag 2: 0.27 (−1.28, 1.83) Lag 3: −0.79 (−2.40, 0.85) Lag 4: −0.09 (−1.92, 1.77) Lag 5: −0.08 (−1.64, 1.50) 5-day avg: 0.95 (−3.05, 5.11)

avg = average; CI = confidence interval; FeNO = fractional exhaled nitric oxide; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; MMEF = maximum midexpiratory flow; N = population number; OR = odds ratio; PEF = peak expiratory flow; ppb = parts per billion; SD = standard deviation; SO_2 = sulfur dioxide.

Linares et al. (2010) performed a longitudinal repeated-measures study examining air pollution exposure and lung function among school-aged children in Mexico. SO_2 concentrations were inversely associated with FVC, FEV_1, and PEF, but not FEV_1/FVC. When stratified by sex, the precision decreased and associations were no longer statistically significant. The point estimates were lower among girls but became positive among boys. Additionally, the associations between FEV_1/FVC were positive among both boys and girls. Results were similar in two-pollutant models controlling for O_3 or PM_{10}. Associations were also observed between other air pollutants (O_3, NO_2, and PM_{10}) and lung function, with some of the associations remaining in two-pollutant models stratified by sex. No correlation coefficients between the air pollutants were provided. Similarly, in Brazil a study of school-aged children examined the associations between air pollution and lung function and found an association for SO_2 (Correia-Deur et al., 2012). SO_2 concentration was inversely associated with PEF and FEV_1 when using shorter lag times (2-and 24-hour), but not with longer moving averages (3-, 5-, 7-, and 10-day). Other pollutants were associated with all time periods (PM_{10}, NO_2, and O_3). Results for two-pollutant models with SO_2 were not provided, but SO_2 was positively correlated with CO, PM_{10}, NO, and NO_2 (r = 0.62, 0.75, 0.87, 0.60, respectively) but not

with O_3 (r = 0.07). When stratifying by categories of allergic sensitization, the association between SO_2 concentration and PEF became null among all categories, possibly due to decreased precision. Associations remained for some of the other pollutants. Chang et al. (2012) assessed the association between air pollutants exposure and the lung function of junior high school students in Taiwan and reported an inverse association between SO_2 concentration and lung function. SO_2 concentrations with 1 day lags were inversely associated with FVC and FEV_1. No associations were present with 0 or 2 day lags. Similar associations were detected for O_3, CO, PM_{10}, and NO_2 concentrations. Correlation coefficients and copollutant models were not provided. Other studies did not report an association between SO_2 concentrations and lung function. Castro et al. (2009) examined lung function among school children in another study from Brazil. In this study, no association was observed between SO_2 concentrations and PEF, but there was a large amount of missing data for SO_2 concentrations that could have affected the results. PM_{10} and NO_2 concentrations were inversely associated with lung function, while O_3 concentration showed a positive association and CO demonstrated no association. Correlation coefficients between the pollutants were not provided, and the study did not utilize copollutant models. A study in Turkey observed no association between SO_2 concentration and impaired lung function over two-week periods in either the summer or winter period (Altuğ et al., 2013). This persisted in models adjusted for O_3 and NO_2. Associations with NO_2 and O_3 concentrations also demonstrated no associations with lung function, with the exception of summer O_3 concentrations among girls. Correlation coefficients were not provided, but in two-pollutant models among girls, the lack of association with lung function remained when SO_2 was adjusted for O_3 or NO_2. A subpopulation of this study was re-examined (Altuğ et al., 2014). The association with lung function was assessed by stratifying the population into children who reported upper respiratory tract symptoms and those who did not. No association was observed between SO_2 concentrations and lung function in either group. Similarly, no associations were observed with NO_2 or O_3 concentrations, with the exception of a slight inverse association between O_3 and PEF among those without upper respiratory symptoms. Correlation coefficients with SO_2 were 0.486 and 0.395 for NO_2 and O_3, respectively. No copollutant models were provided. A study in Guadeloupe also reported no associations between SO_2 concentrations and lung function (baseline PEF and after exercise) for any of the time windows examined (lag 0 through 2-week average) (Amadeo et al., 2015). This study examined the potential for an interaction by asthma status in models using the 2-week average of SO_2 concentrations, but none were observed. No associations were found between lung function and O_3 or NO_2, but associations were noted for PM_{10}. No correlations or copollutants models were provided. In summary, although some of these studies reported inverse associations between SO_2 concentration and lung function, many did not and overall the findings are inconsistent among the studies.

South African school children were included in a study of air pollution and lung function that explored differences by glutathione S-transferase mu 1 (GSTM1) and glutathione S-transferase Pi 1 (GSTP1) genes (Reddy et al., 2012). Overall, null associations were observed between SO_2 concentrations and intra-day variability of FEV_1. However, when stratifying by GSTM1 genes, a positive association between SO_2 concentration averaged over 5 days, and FEV_1 intra-day variability was observed among GSTM1 positive children. The association remained null among GSTM1 null children. Conversely, associations with PM_{10} and NO_2 were null overall but demonstrated inverse relationships with FEV_1 among GSTM1 positive individuals. When stratifying the population by GSTP1 genotypes, positive associations were observed for GSTP1 adenine-adenine and guanine-guanine genotype (AA+GG) children at lag Days 1 and 3, with results for children with GSTP1 AA genotypes being null. NO_2 concentrations were positively associated with FEV_1 among GSTP1 AA genotypes and inversely associated with GSTP1 AA+GG genotypes during lag Days 1, 2, and 3, while PM_{10} concentrations were inversely associated with FEV_1 among GSTP1 AA genotypes and positively associated with GSTP1 AA+GG genotypes during lag Days 2 and 3. Correlation coefficients with SO_2 were not provided and no copollutant models were examined. This study suggests that the association between SO_2 concentration and lung function may vary by genotype but the overall evidence base regarding modification of SO_2-related health effects by genotype is limited (see Section 6.4).

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, 2008b). 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, 2008b, 1982a). The 2008 SO_X ISA (U.S. EPA, 2008b) reported a few additional studies conducted at concentrations below 2 ppm. Animal toxicological studies examining lung function changes in naïve animals exposed to SO_2 are summarized in Table 5-22. 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 5-22 Study-specific details from animal toxicological studies of lung function.

Study	Species (Strain); n; Sex; Lifestage/Age (mean ± SD)	Exposure Details (Concentration; Duration)	Endpoints Examined
Amdur et al. (1983)	Hartley guinea pig; male; age NR; 200−300 g; n = 8−23/group	≈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 minute volume
Conner et al. (1985)	Hartley guinea pig; male; age NR; 250−320 g; n ≤ 18/group/time point	1 ppm (2.62 mg/m^3); nose only for 3 h/day for 6 days	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; sex NR; adult; mean 2.0 kg; n = 5−9/group; rabbits were mechanically ventilated	0.5 ppm (1.3 mg/m^3) for 45 min; intra-tracheal	Endpoints examined 5 min before and up to 1 h post-exposure. Lung function—pulmonary resistance

CO = carbon monoxide; n = sample size; NR = not reported; SD = standard deviation.

Summary of Lung Function in General Populations and Healthy Individuals

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. Some epidemiologic studies reported associations between SO_2 exposure and decreases in lung function among general populations of children and adults; however, the evidence is limited and inconsistent. The epidemiologic studies utilized concentration estimates derived from fixed site monitors, which could have issues with exposure measurement error due to spatial variability (Section 3.3.3.2). One study that explored modeling the information from monitors using averages, inverse distance weighting, and kriging reported similar results across the methods.

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, 2008b) 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. There was limited evidence for an association between SO_2 concentrations and respiratory symptoms among adults and children without asthma. A few recent epidemiologic studies have become available for review; studies among children report mixed results.

Controlled Human Exposure Studies

Controlled human exposure studies examining respiratory symptoms in healthy individuals exposed to SO_2 are summarized in Table 5-19. 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). However, Linn et al. (1984a) reported significantly greater clinical scores 1 week post exposure to 2 consecutive days of 0.6 ppm SO_2 exposure for 6 hours.

Epidemiologic Studies

Adults. There was limited evidence in the 2008 SO_X ISA (U.S. EPA, 2008b) for an association between SO_2 concentrations and respiratory symptoms among adults without asthma or other respiratory conditions. Since the previous review, the evidence regarding

an association between SO_2 concentrations and respiratory symptoms among adults without asthma continues to be limited and is described below and in Table 5-23.

Table 5-23 Summary of recent epidemiologic studies examining associations between SO_2 concentrations and respiratory symptoms among adults.

Study Location and Years	Study Design	Study Population and N	Measure of SO_2	Mean SO_2 and Upper Concentration Level	Adjusted Effect Estimate
Ishigami et al. (2008) Japan 2005	Cross-sectional	Healthy volunteers (≥15 yr) working on an active volcanic island after evacuation order was lifted N = 611	Fixed site monitors; 1-h mean and 1-h max SO_2 concentrations	Mean SO_2 levels at monitoring sites ranged from 0 to 3,550 ppb Max range varied by locations from 3,790 to 10,320 ppb	NR
Goldberg et al. (2009) Canada 2002−2003	Panel study	Congestive heart failure patients (50−85 yr) with limitations in physical functioning and an ejection fraction ≤35% N = 31	Fixed site monitors; 24-h mean SO_2 concentrations	Mean: 4.50 ppb Max: 25.1 ppb	Mean difference (95% CI) for shortness of breath at night per 10 ppb SO_2 Lag 0: 0.32 (−1.21,1.85) Lag 1: −0.24 (−1.80, 1.32) Lag 2: 0.68 (−0.84, 2.20) Lag 3: 0.20 (−1.31, 1.72) Lag 4: −0.58 (−2.08, 0.91) Lag 0−2: 0.79 (−1.88, 3.46)

CI = confidence interval.

A study on the Japanese island of Miyakejima, with an active volcano, examined health effects among healthy adults on the island after the evacuation order was lifted (Ishigami et al., 2008). No associations were observed between symptoms and hourly mean SO_2 levels <100 ppb and hourly maximum SO_2 levels <2,900 ppb. At concentrations above these, associations were observed with cough, scratchy throat, sore throat, and breathlessness. When examining rate ratios by sex, higher rates were observed among women compared to men. No associations were found for nasal congestion, eye pain, or skin itching among men or women. No other air pollutants were examined in this study.

A study of patients with congestive heart failure (CHF) in Canada examined the association between air pollution concentrations and shortness of breath at night (Goldberg et al., 2009). No association was observed with SO_2 concentrations. None of the other pollutants examined were associated with shortness of breath at night, including CO (correlation coefficient with SO_2: 0.53), NO_2 (correlation coefficient with SO_2: 0.59), O_3 (correlation coefficient with SO_2: −0.09), and $PM_{2.5}$ (correlation coefficient with SO_2 0.50). Copollutant models were not examined.

Overall, there continues to be limited studies among the general population exposed to average ambient levels that examine the association between SO_2 concentration and respiratory symptoms among adults.

Children. Evidence of an association between SO_2 concentration and respiratory symptoms among children without asthma or in the general population was limited in the 2008 SO_X ISA (U.S. EPA, 2008b), although some studies did report positive associations. Recent studies also demonstrate some positive associations with the overall evidence being mixed among various outcome measures. None of the recent studies were conducted in the U.S. or Canada. Details of these recent studies are described below and in Table 5-24.

Table 5-24 Summary of recent epidemiologic studies examining associations between SO_2 concentrations and respiratory symptoms among children.

Study, Location, and Years	Study Design	Study Population and N	Measure of SO_2	Mean SO_2 and Upper Concentration Level	Adjusted Effect Estimate
Linares et al. (2010) Salamanca, Mexico 2004−2005	Longitudinal repeated measures	Children (6−14 yr) from two schools N = 464	Fixed site monitors; 24-h mean SO_2 concentrations	Mean (SD) Spring School 1: 11.9 (0.4) ppb School 2: 9.1 (0.4) ppb Summer School 1: 12.3 (0.3) ppb School 2: 8.8 (0.5) ppb Fall School 1: 10.4 (0.3) ppb School 2: 10.2 (0.6) ppb Winter School 1: 9.9 (0.2) ppb School 2: 13.6 (0.7) ppb	OR (95% CI) per 10-ppb increase in SO_2 Wheezing 1.0567 (1.0047, 1.1114) Rhinorrhea 0.9815 (0.9171, 1.0504) Eczema 0.9919 (0.9574, 1.0277) Dyspnea 1.0216 (0.9722, 1.0735)

Table 5-24 (Continued): Summary of recent epidemiologic studies examining associations between SO_2 concentrations and respiratory symptoms among children.

Study, Location, and Years	Study Design	Study Population and N	Measure of SO_2	Mean SO_2 and Upper Concentration Level	Adjusted Effect Estimate
Altuğ et al. (2014) Eskisehir, Turkey 2009	Cross-sectional	4th and 5th grade students from public primary schools in (1) suburban, (2) urban, or (3) urban-traffic regions N = 605	Fixed site monitors; weekly mean SO_2 concentrations	Suburban schools: Mean (SD): 21.1 (6.3) ppb Max: 28.9 ppb Urban schools: Mean (SD): 29.1 (7.2) ppb Max: 44.2 ppb Urban-traffic schools: Mean (SD): 22.0 (7.0) ppb Max: 32.7 ppb	OR (95% CI) per 10-ppb increase in SO_2 Cold in the last 7 days 0.74 (0.58, 0.94) Cold at the moment 0.92 (0.67, 1.27) Complaints of the throat in last 7 days 0.83 (0.59, 1.15) Complaints of the throat at the moment 1.03 (0.72, 1.47) Runny nose in the last 7 days 0.95 (0.74, 1.22) Runny nose at the moment 0.92 (0.69, 1.23) Shortness of breath or wheeze in the last 7 days 1.72 (1.05, 2.81) Medication for shortness of breath or wheeze in the last 7 days 1.44 (0.69, 2.99) Shortness of breath or wheeze today 1.79 (0.90, 3.58) Medication for shortness of breath or wheeze today 0.74 (0.16, 3.33)
Moon et al. (2009) South Korea 2003	Cross-sectional	Random selection of primary school children (<13 yr) located near air pollution monitoring stations N = 696	Fixed site monitors; 24-h mean SO_2 concentrations	Mean concentrations NR (majority 24-h avgs were <20 ppb and the max was 38 ppb)	OR (95% CI) per 10-ppb increase in SO_2 Lower respiratory symptoms *Lag 0:* 1.003 (0.931, 1.082) Upper respiratory symptoms *Lag 0:* 1.112 (1.034, 1.196) Irritation symptoms moving avg 0−1: 1.010 (0.918, 1.112)

Table 5-24 (Continued): Summary of recent epidemiologic studies examining associations between SO_2 concentrations and respiratory symptoms among children.

Study, Location, and Years	Study Design	Study Population and N	Measure of SO_2	Mean SO_2 and Upper Concentration Level	Adjusted Effect Estimate
Zhao et al. (2008) Taiyuan City, China 2004	Cross-sectional	Students (11−15 yr) from randomly selected junior high schools N = 1,993	Fixed site monitors; weekly mean SO_2 concentrations (indoor concentrations measured in multiple classrooms; outdoor measured outside of the school)	Indoor Mean (SD): 101.1 (53.1) ppb Max: 244.7 ppb Outdoor Mean (SD): 272.1 (72.3) ppb Max: 387.5 ppb	OR (95% CI) per 10-ppb increase in indoor SO_2 *Cumulative asthma* 1.03 (0.96, 1.12) Wheeze 1.04 (1.01, 1.08) Daytime attacks of breathlessness 1.02 (0.99, 1.04) Nocturnal attacks of breathlessness 1.07 (1.01, 1.13) Furry pet or pollen allergy 1.03 (0.98, 1.08) OR (95% CI) per 10-ppb increase in outdoor SO_2 Cumulative asthma 0.97 (0.92, 1.03) Wheeze 1.01 (0.98, 1.04) Daytime attacks of breathlessness 0.99 (0.97, 1.01) Nocturnal attacks of breathlessness 1.01 (0.96, 1.06) Furry pet or pollen
Farhat et al. (2014) São Paulo, Brazil 2006−2007	Panel study	Cystic fibrosis patients (median 8.9 yr; range 0−15+) at Children's Institute, Clinics Hospital (University of São Paulo) were invited to enroll. N = 103	Fixed site monitors; 24-h mean SO_2 concentrations	SO_2 Mean (SD): 3.78 (1.55) ppb 75th percentile: 4.62 ppb Max: 9.59 ppb	RR (95% CI) of respiratory exacerbation of cystic fibrosis per 10-ppb increase in SO_2 Lag 0: 0.91 (0.07,11.04) Lag 1: 1.51 (0.08, 28.03) Lag 2: 7.58 (0.31, 187.41) Lag 3: 0.52 (0.03, 9.67) Lag 4: 0.31 (0.02, 4.68) Lag 5: 1.38 (0.11, 17.19) Lag 6: 3.24 (0.22, 46.98)

avgs = averages; CI = confidence interval; N = population number; NR = not reported; OR = odds ratio; ppb = parts per billion; RR = relative risk; SD = standard deviation; SO_2 = sulfur dioxide.

A study of children in Mexico used a longitudinal repeated measures design to examine the association between respiratory symptoms and air pollution measurements (Linares et al., 2010). SO_2 concentrations varied by season and school location. Positive associations were observed between SO_2 concentrations and wheezing. Positive associations were also detected for these respiratory symptoms and O_3 and PM_{10}, but not NO_2 concentrations. No associations between SO_2 concentrations and rhinorrhea, eczema, or dyspnea were present. Neither correlation coefficients between the pollutants nor copollutant models between air pollutants and respiratory symptoms were provided. A study in Turkey examined the association between air pollution and respiratory symptoms both in the prior 7 days and at that moment/today and also reported a positive association with wheezing (Altuğ et al., 2014). SO_2 concentrations were positively associated with an attack of shortness of breath or wheeze in the last 7 days, but not the use of medications for shortness of breath or wheeze. An inverse association was observed between SO_2 concentrations and report of a cold in the past week. No association between SO_2 concentrations and other respiratory tract complaints (complaints of the throat and runny nose) were observed. The correlation coefficients between SO_2 and NO_2 and SO_2 and O_3 were 0.486 and 0.395, respectively. NO_2 concentrations were not associated with any respiratory tract complaints and O_3 concentrations were positively associated with having a cold and having a runny nose at the moment. No copollutant models were provided. In summary, these studies reported positive associations between SO_2 concentration and some respiratory symptoms, especially wheezing.

Conversely, Moon et al. (2009) used epidemiologic surveillance data in Korea to investigate the relationship between air pollution and respiratory symptoms among children and reported no association between SO_2 concentrations and lower respiratory symptoms (cough, phlegm, wheezing), both overall and when cities were examined individually. SO_2 concentration was positively associated with upper respiratory symptoms (runny nose, sneezing), although when examining the associations by city, not all cities demonstrated this positive association and one city even had an inverse association. A positive association between SO_2 concentration and allergic symptoms (irritated eyes, itching skin) was demonstrated in a couple of cities, but this association was not observed in the overall analysis. In overall analyses, NO_2 was positively associated with allergic symptoms, whereas O_3 was inversely related to allergic symptoms. CO was positively associated with lower respiratory, upper respiratory, and allergic symptoms. PM_{10} was not associated with any symptoms in the overall analyses. Correlations coefficients between the pollutants were not provided and only single-pollutant models were utilized. Null associations between SO_2 concentrations and respiratory symptoms were also observed in a study in China (Zhao et al., 2008). Mean outdoor SO_2 concentrations were reported as 272.1 ppb, but 3 of the 10 samplers were completely saturated and assigned the saturation concentration, although the actual

concentration of SO_2 could have been higher. No associations were observed between 1-week SO_2 concentrations and cumulative asthma, wheeze/whistling in the chest, daytime attacks of breathlessness, nocturnal attacks of breathlessness, or pet/pollen allergy. Some associations were noted between measured concentrations of SO_2 indoors and respiratory symptoms. Indoor and outdoor SO_2 concentrations were correlated (p-value < 0.01). Although correlation was seen among some of the indoor pollutants, none of the outdoor pollutants were correlated (correlation coefficients not provided). Additionally, none of the outdoor concentrations of NO_2 or O_3 were associated with respiratory symptoms, and copollutant models with outdoor air pollutants were not performed. Some associations were observed with outdoor and indoor concentrations of formaldhyde, as well as some indoor concentrations of NO_2 and O_3. Overall, studies in Asia did not observe associations between SO_2 concentration and wheezing or other lower respiratory symptoms.

A study of respiratory exacerbations among children with cystic fibrosis examined whether risk was associated with air pollution (Farhat et al., 2014). Lag Days 0−6 were examined and SO_2 concentrations were not observed to be associated with cystic fibrosis exacerbations. Similarly, no associations were detected for CO, NO_2, or PM_{10}, although a positive association was found for O_3 and a 2-day lag. Correlation coefficients between SO_2 and the other pollutants were 0.37 for O_3, 0.56 for CO, 0.57 for NO_2, and 0.70 for PM_{10}. Results of copollutant models with SO_2 were not reported.

Summary of Respiratory Symptoms in General Populations and Healthy Individuals

There is limited evidence for an association between SO_2 concentrations and respiratory symptoms in general populations or among individuals without asthma or other respiratory conditions. Controlled human exposure studies of healthy adults exposed to up to 2 ppm SO_2 generally did not find increases in respiratory symptoms. While epidemiologic studies in adults are generally not supportive of a relationship between SO_2 concentrations and respiratory symptoms, some studies in children report positive associations, further supporting the hypothesis that children may be more sensitive to SO_2. The epidemiologic studies utilized pollutant concentrations derived from fixed site monitors, which could have issues with exposure measurement error due to spatial variability (Section 3.3.3.2).

Airway Responsiveness in General Populations and Healthy Individuals

The term “airway responsiveness” refers to the ability of the airways to narrow in response to constrictor stimuli. Studies that examined airway responsiveness in relation to short-term SO_2 exposures are limited to animal toxicological studies in control, or naive,

animals. In several studies, the effects of SO_2 exposure on airway responsiveness was examined in parallel in allergic animals. Results in allergic animals are discussed in Section 5.2.1.2.

The 2008 SO_X ISA (U.S. EPA, 2008b) 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 following 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, and one more recent one (Song et al., 2012), provide evidence that repeated SO_2 exposure in naive animals leads to the development of increased airway responsiveness (AHR). These studies, and others, are summarized in Table 5-25 and are described below because the development of AHR occurred in conjunction with the development of an allergic phenotype following repeated SO_2 exposure.

Table 5-25 Study-specific details from animal toxicological studies of airway responsiveness.

Study	Species (strain); n; Sex; Lifestage/Age (mean ± SD)	Exposure Details (Concentration; Duration)	Endpoints Examined
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/day for 5 days Animals were sensitized to ovalbumin (ovalbumin aerosol) on the last 3 days of exposure Bronchial provocation every other day with aerosolized 0.1% ovalbumin began at 1 week after the last exposure to SO_2 and continued for 14 days 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.
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/day for 5 days Animals were sensitized to ovalbumin (0.1% ovalbumin aerosol) on the last 3 days of exposure Bronchial challenge with 1% ovalbumin aerosol occurred at 1 week after the last exposure to SO_2 4 groups: Control Ovalbumin	Bronchial obstruction—measurement of Penh by whole-body plethysmography

Table 5-25 (Continued): Study-specific details from animal toxicological studies of airway responsiveness.

Study	Species (strain); n; Sex; Lifestage/Age (mean ± SD)	Exposure Details (Concentration; Duration)	Endpoints Examined
Song et al. (2012)	Rats (Sprague-Dawley); N = 40; n = 10 per exposure group; M; 4-week old neonates	SO_2 Ovalbumin/SO_2 Exposure to 2 ppm SO_2 for 4 h/day for 4 weeks beginning at 15 days	Endpoints examined 24 h after challenge Lung function—whole-body plethysmography (MCh challenge) BAL—-IL-4, IFN-γ Serum—IL-4, IFN-γ Lung—histopathology In vitro culture of ASM cells from experimentally treated animals—stiffness and contractility

ASM = airway smooth muscle; BAL = bronchoalveolar lavage; IFN-γ = interferon gamma; IL-4 = interleukin-4; M = male; MCh = methacholine; n = sample size; NR = not reported; Penh = enhanced pause; ppm = parts per million; SD = standard deviation; SO_2 = sulfur dioxide.

Subclinical Respiratory Effects in Healthy Individuals

Controlled Human Exposure Studies

Airway 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.

A recent controlled human exposure study examined eNO and other biomarkers of airway 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 significant changes in eNO; leukotriene B4, prostaglandin E2, and 8-iso-prostaglandin F2 alpha in EBC; and substance P, interleukin-8 (IL-8), and brain derived neurotrophic factor in NALF after exposures compared to air.

Epidemiologic Studies

Since the 2008 SO_X ISA (U.S. EPA, 2008b), recent studies have examined the association between SO_2 concentration and biomarkers among children and young adults in Beijing before, during, and after the 2008 Olympics. A study of elementary school

children reported lower concentrations of SO_2 BC, and $PM_{2.5}$ during the Olympics compared to concentrations prior to the Olympics (Lin et al., 2015). Associations were observed between SO_2 concentration and 8-oxo-7,8-dihydro-2'-deoxyguanosine and malondialdehyde. These two biomarkers were also associated with concentrations of the other pollutants. The associations with SO_2 concentrations generally appeared to be null with the inclusion of copollutants. Additionally, associations were examined stratified by sex and by asthma status, but the results were similar between the respective groups. Nonsmoking, healthy young adults (ages 19−33 years) participated in a study that reported the mean 24-hour average SO_2 concentration measured on the roof of the study hospital to be 6.07 ppb (SD 4.01 ppb) (Roy et al., 2014). While pollutants and biomarkers are grouped together in this study, some individual results for SO_2 demonstrated associations with biomarkers of pulmonary inflammation/oxidative stress and biomarkers of systemic inflammation/oxidative stress. These results were the same as demonstrated for other pollutants [CO, EC, NO_2, organic carbon (OC), sulfate, $PM_{2.5}$], although associations were not as strong for models of systemic inflammation/oxidative stress. In summary, limited evidence is available to demonstrate an independent association between SO_2 concentrations and oxidative stress markers among the available studies.

Animal Toxicological Studies

The 2008 SO_X ISA (U.S. EPA, 2008b) 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 naïve animals exposed to SO_2 are summarized in Table 5-26. 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 antiovalbumin 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.

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, (Li et al., 2007) (Li et al., 2014) 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. Several other indicators of inflammation and immune response were not changed by exposure to SO_2 alone.

Since the 2008 SO_X ISA (U.S. EPA, 2008b), one new toxicological study evaluated the effects of repeated SO_2 exposure on the development of an allergic phenotype and AHR (Song et al., 2012). In this study, both naive newborn rats and rats sensitized and challenged with ovalbumin were exposed to SO_2. Effects in newborn rats sensitized and challenged with ovalbumin are described above in Section 5.2.1.2. Exposure of naive rats to SO_2 (2 ppm, 4 hours/day for 28 days) resulted in hyperemia in lung parenchyma and inflammation in the airways. In addition, SO_2 exposure altered cytokine levels in a way that suggested a shift in Th1/Th2 balance away from Th1 and towards Th2. This is known as Th2 polarization and is one of the steps involved in allergic sensitization. In naive animals exposed to SO_2, levels of IL-4, indicative of a Th2 response, were increased and levels of IFN-γ, indicative of a Th1 response, were decreased in BALF. This study provides additional evidence that repeated exposure to SO_2 promoted allergic sensitization in naive newborn animals.

Summary of Subclinical Respiratory Effects

In summary, there is limited evidence for inflammatory and other subclinical respiratory effects following short-term exposure to SO_2, primarily from animal toxicological studies involving allergen sensitization. In a recent controlled human exposure study, biomarkers of inflammation were unchanged after a single exposure of exercising individuals to 2 ppm SO_2. Recent epidemiologic studies provide limited evidence of an independent association between SO_2 concentrations and oxidative stress markers. 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, SO_2 exposure of guinea pigs to 0.1 ppm SO_2 enhanced allergic sensitization, allergic inflammatory responses, and airway responsiveness to that allergen. In newborn rats, repeated exposure to 2 ppm SO_2 resulted in Th2 polarization and airway inflammation.

Table 5-26 Study-specific details from animal toxicological studies of subclinical effects.

Study	Species (strain); n; Sex; Lifestage/Age (mean ± SD)	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/day for 1−5 days	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/day for 5 days Animals were sensitized to ovalbumin (ovalbumin aerosol) on the last 3 days of exposure Bronchial provocation every other day with 0.1% ovalbumin aerosol began at 1 week after the last exposure to SO_2 and continued for 14 days 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

Table 5-26 (Continued): Study-specific details from animal toxicological studies of subclinical effects.

Study	Species (strain); n; Sex; Lifestage/Age (mean ± SD)	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/day for 5 days Animals were sensitized to ovalbumin (0.1% ovalbumin aerosol) on the last 3 days of exposure Bronchial challenge with 1% ovalbumin aerosol occurred at 1 week 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/day for 7 days	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
Song et al. (2012)	Rats (Sprague-Dawley); n = 40, n = 10 per exposure group; M; 4-week old neonates	Sensitization by i.p. injection of 10 mg OVA followed by booster injection of 10 mg OVA after 7 days Challenge with 1% OVA aerosol for 30 min daily for 4 weeks beginning at 15 days Exposure to 2 ppm SO_2 for 4 h/day for 4 weeks beginning at 15 days	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 ASM cells from experimentally treated animals—stiffness and contractility

Table 5-26 (Continued): Study-specific details from animal toxicological studies of subclinical effects.

Study	Species (strain); n; Sex; Lifestage/Age (mean ± SD)	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/day for 7 days	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

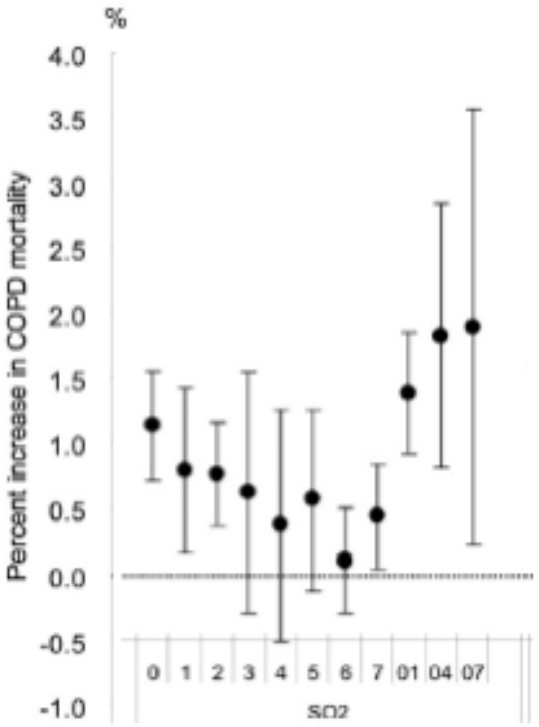
ASM = airway smooth muscle; BAL = bronchoalveolar lavage; BALF = bronchoalveolar lavage fluid; EMSA = electrophoretic mobility shift assay; FOXp3 = forkhead box p3; ICAM-1 = intercellular adhesion molecule 1; IFN-γ = interferon gamma; IgE = immunoglobulin E; IgG = immunoglobulin G; IKKβ = inhibitor of 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; MCh = methacholine; MUC5AC = mucin 5AC glycoprotein; n = sample size; NFκB = nuclear factor kappa−light-chain-enhancer of activated B cells; NR = not reported; OVA = ovalbumin; ppm = parts per million; SD = standard deviation; SO_2 = sulfur dioxide

5.2.1.7 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 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 5-16).

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 with regard to 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-hour average 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-hour average SO_2 concentrations at lag 0−1]. 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 5-17). 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-hour average 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. Additionally, it is important to note that the aforementioned studies relied on central site monitors for estimating exposure. SO_2 is more spatially variable than other pollutants as reflected in the generally low to moderate spatial correlations across urban geographical scales (Section 3.3.3.2); therefore, the attenuation in SO_2 associations may be a reflection of the different degree of exposure error across pollutants. This possibility is further supported by an analysis of correlations between NAAQS pollutants at collocated monitors in the U.S., which demonstrated that SO_2 is low to moderately correlated with other pollutants (Section 3.3.4.1). Overall, the studies that examined the potential confounding effects of copollutants on the SO_2-respiratory mortality relationship report 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.



Source: Adapted from Meng et al. (2013).

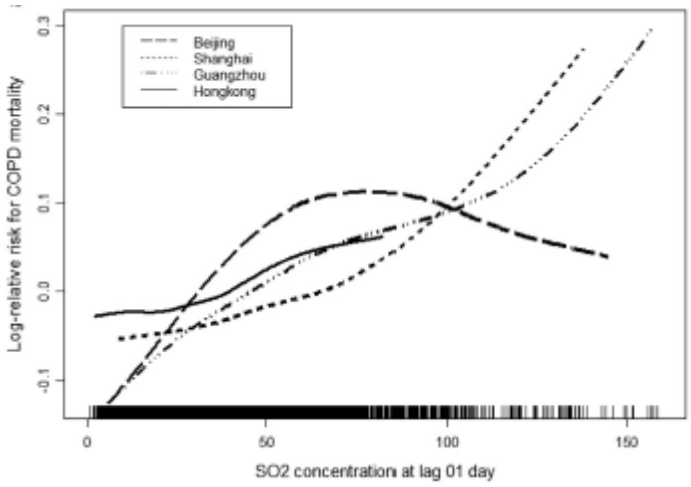
Figure 5-8 Percent increase in chronic obstructive pulmonary disease (COPD) mortality associated with a 10 μg/m^3 (3.62 ppb) increase in 24-hour average SO_2 concentrations at various single and multiday lags.

Of the studies evaluated only Bellini et al. (2007), 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-hour average 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 by 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 5-8). It should be noted 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-hour average SO_2 concentrations] is similar to that reported in Meng et al. (2013) for COPD [3.7% (95% CI: 2.4, 4.9)].

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 5-9, 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.



Source: Adapted from Meng et al. (2013).

Figure 5-9 City-specific concentration-response curves for short-term SO_2 exposures and daily chronic obstructive pulmonary disease (COPD) mortality in four Chinese cities.

Overall, recent multi-city 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 day; and that there is a linear, no threshold C-R relationship, respectively.

5.2.1.8 Summary and Causal Determination

Strong evidence indicates that there is a causal relationship between short-term SO_2 exposure and respiratory morbidity, 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 respiratory effects among multiple lines of evidence, and biological plausibility for effects specifically related to asthma exacerbation. There is some support for other SO_2-related respiratory effects, including exacerbation of COPD in individuals with COPD; respiratory infection and aggregated respiratory conditions, particularly in children; and respiratory mortality in the general population. However, 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 consistent with the conclusions of the 2008 SO_X ISA (U.S. EPA, 2008b). The evidence for this conclusion was heavily based on controlled human exposure studies that showed lung function decrements and respiratory symptoms in adults 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). Numerous epidemiologic studies evaluated in the previous review reported associations between short-term SO_2 exposure and respiratory health effects, ranging from respiratory symptoms to respiratory-related ED visits and hospital admissions. The evidence for a causal relationship is detailed below using the framework described in the Preamble (U.S. EPA, 2015e). 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 related to the causal framework is presented in Table 5-27.

Table 5-27 Summary of evidence for a causal relationship between short-term SO_2 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	Decreased lung function following peak exposures of 5−10 min in exercising individuals with asthma	Section 5.2.1.2 Table 5-2	400−600 ppb
	Increased respiratory symptoms following peak exposure of 5−10 min in exercising individuals with asthma	Section 5.2.1.2 Table 5-2	600−1,000 ppb

Table 5-27 (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]
Consistent evidence from multiple, high-quality epidemiologic studies at relevant SO_2 concentrations	Increase in asthma hospital admissions and ED visits in single- and multicity studies, in studies of 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
	Some supporting epidemiologic evidence of associations with respiratory symptoms among children with asthma	Section 5.2.1.2	2.2−21.7 ppb
Uncertainty regarding exposure measurement error	Exposure assessments in epidemiologic studies of short-term SO_2 exposure using central site monitors may not capture spatial variability of SO_2	Section 3.3.3.2	
Uncertainty regarding potential copollutants confounding	SO_2 associations in copollutant models remained positive, and generally relatively unchanged. Some studies show attenuation of the association in models with NO_2 and PM. Generally SO_2 is low to moderately correlated with other NAAQS pollutants at collocated monitors.	Section 5.2.1.2 Section 3.3.4.1	
Limited and supportive evidence for allergic inflammation, airway remodeling, and AHR	Association with AHR and blood eosinophils among children with atopy Increased airway eosinophils in asthmatics exposed to SO_2 Repeated exposure of allergic animals enhanced inflammation, allergic inflammation, airway remodeling, and airway responsiveness	Soyseth et al. (1995) Gong et al. (2001) Li et al. (2007) Li et al. (2014) Song et al. (2012)	Last 24-h median 7.9 ppb 750 ppb 2,000 ppb 2,000 ppb
Evidence for key events in proposed mode of action	Neural reflexes and/or inflammation lead to bronchoconstriction Allergic inflammation leads to increased airway responsiveness	Section 4.3.6	
Evidence for Other Respiratory Effects			
Limited and inconsistent evidence for COPD, respiratory infection, respiratory diseases hospital admissions and ED visits, and respiratory effects in general populations and healthy individuals		Sections 5.2.1.3, 5.2.1.4, 5.2.1.5, 5.2.1.6	

Table 5-27 (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 Respiratory Mortality			
Consistent epidemiologic evidence from multiple, high-quality studies at relevant SO_2 concentrations	Increases in respiratory mortality in multicity studies conducted in the United States, Canada, Europe, and Asia	Sections 5.2.1.7 and 5.5.1.3 Figures 5-8 and 5-16	Mean 24-h avg: U.S., Canada, Europe: 0.4−28.2[e] ppb Asia: 0.7−>200 ppb Table 5-47
Uncertainty regarding potential confounding by copollutants	The magnitude of SO_2 associations remained positive, but was reduced in copollutant models with PM_{10} and NO_2. No studies examined copollutant models with $PM_{2.5}$. The reduction of SO_2 associations, specifically in models with NO_2 suggest potential copollutant confounding, but studies were limited to areas with relatively high SO_2 concentrations, complicating the interpretation of whether SO_2 is independently associated with total mortality.	Section 5.2.1.7 Section 3.3.4.1	
Uncertainty regarding exposure measurement error	Studies that examine the association between short-term SO_2 exposures and mortality rely on central site monitors.	(Section 3.3.3.2)	

AHR = airway hyperresponsiveness; COPD = chronic obstructive pulmonary disease; ED = emergency department; NAAQS = National Ambient Air Quality Standards; NO_2 = nitrogen dioxide; PM = particulate matter; ppb = parts per billion; SO_2 = sulfur dioxide.

[a]Based on aspects considered in judgments of causality and weight of evidence in causal framework in Tables I and II of the Preamble (U.S. EPA, 2015e).

[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).

Evidence for Asthma Exacerbations

A causal relationship between short-term SO_2 exposure and respiratory effects is primarily based on 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, defined as a ≥100% increase sRaw or ≥15% decrease in FEV_1, decrement in lung function frequently accompanied by

respiratory symptoms, following peak 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 small fraction of the asthmatic population (~5−30%) has also been observed to have decrements in lung function at lower SO_2 concentrations (0.2−0.3 ppm) (Johns et al., 2010; 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). 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.

Epidemiologic evidence also supports a causal relationship. Studies of asthma hospital admissions and ED visits report positive associations with short-term SO_2 exposures when examining all ages, children (i.e., <18 years of age) and older adults (i.e., 65 years of age and older) (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). 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 between respiratory morbidity and respiratory mortality.

Most epidemiologic studies indicating associations between short-term SO_2 exposures and asthma exacerbation assign exposure using SO_2 concentrations measured at central site monitors. The use of central site monitors to assign exposure may introduce exposure measurement error if the spatial variability in SO_2 concentrations is not captured. SO_2 has low to moderate spatial correlations across urban geographical scales (Pearson $r < 0.4$ for 5-minute maximum within an hour, $r < 0.6$ for 24-hour average). Additional uncertainty exists regarding potential copollutant confounding. While some epidemiologic studies reported that associations were relatively unchanged with the inclusion of copollutants in the model, others either failed to examine copollutants or were not robust to their inclusion. However, these inconsistencies could reflect differences in exposure measurement error for SO_2 compared to NO_X, CO, PM, and O_3 when pollutants are simultaneously included in a model.

There is limited, but supportive evidence for a relationship between short-term SO_2 exposure and AHR, airway inflammation, and airway remodeling. Soyseth et al. (1995) demonstrated an association between ambient concentrations of SO_2 and AHR among atopic children. An associations between SO_2 concentrations and blood eosinophils was also observed in this study, suggesting possible recruitment of eosinophils to airways. Controlled human exposure and animal toxicological studies provide coherence and biological plausibility for these relationships. 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 asthmatics (Section 4.2.1). Further support for an important role of airway inflammation, as well as for increased airway responsiveness and remodeling, 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; Song et al., 2012; Li et al., 2007).

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 5-7), suggesting that the respiratory effects of short-term SO_2 exposure may extend beyond exacerbation of asthma. However, from the limited data available for other respiratory conditions, there is uncertainty about relationships with SO_2 and these outcomes because of inconsistency among disciplines and/or lack of biological plausibility. Where epidemiologic associations were found, the studies evaluated were limited by the lack of copollutant analyses, which would support an independent effect of SO_2 on respiratory disease hospital admissions and ED visits. For COPD exacerbation, evidence from controlled human exposure and epidemiologic studies suggests no association between SO_2 exposure and respiratory effects, while evidence of hospital admissions and ED visits was limited and inconsistent. Although there is limited evidence for positive associations between short-term SO_2 exposures and hospital admissions and ED visits due to respiratory infections, the lack of controlled human exposure, animal toxicological, and other epidemiologic studies examining specific outcomes, along with the lack of multiple studies examining the same respiratory infection outcome complicates the interpretation of the collective body of evidence. Controlled human exposure studies in healthy individuals provide evidence for transient decreases in lung function at concentrations $\geq$1 ppm SO_2 under exercising or forced oral breathing condition with no evidence for increased respiratory symptoms. Recent epidemiologic

studies have reported some positive associations at relevant concentrations, but the overall evidence is inconsistent and limited among adults without asthma.

Conclusion

Multiple lines of evidence support a causal relationship between short-term SO_2 exposure and asthma exacerbations in individuals with asthma. This determination is primarily based on respiratory effects observed in controlled human exposure studies in adults with asthma. Epidemiologic studies of asthma hospital admissions and ED visits provide strong support for this conclusion. Limited, but supportive evidence for a relationship between short-term SO_2 exposure and AHR, airway inflammation, and airway remodeling is provided by controlled human exposure, epidemiological, and toxicological studies. While some evidence exists for associations between SO_2 exposure and COPD exacerbation in individuals with COPD and respiratory effects including respiratory infection, aggregated respiratory conditions, and respiratory mortality in the general population, there is inconsistency within disciplines and outcomes and 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.

5.2.2 Long-Term Exposure

The 2008 SO_X ISA (U.S. EPA, 2008b) reviewed the epidemiologic and toxicological evidence of a relationship between 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 respiratory outcomes (i.e., 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-4 (U.S. EPA, 2015i). 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, 2008b), 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 the development of asthma (Section 5.2.2.1), reduced lung function and development in children (Section 5.2.2.2), and other respiratory outcomes (Section 5.2.2.3), including symptoms and markers of respiratory allergy and asthma severity, chronic bronchitis, and respiratory infection are discussed below. Recent longitudinal cohort studies of asthma incidence (Nishimura et al., 2013; Clark et al., 2010) provide some of the strongest results in the evidence base, but uncertainties related to exposure estimates based on IDW-concentrations (see Section 3.2.2.1) may limit the inferences that can be made. The majority of the 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, 2008b) 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 two pollutant analysis. The 2008 SO_X ISA (U.S. EPA, 2008b) 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 animal toxicological study that is discussed in this review found effects of subchronic exposure to SO_2 on airway responsiveness, airway remodeling, and allergic inflammation.

5.2.2.1 Development of Asthma

Epidemiologic Studies

Asthma is a chronic disease characterized by inflammation, AHR, and airway remodeling. In characterizing the epidemiologic evidence for a relationship between long-term SO_2 exposure and asthma, longitudinal studies of asthma incidence and cross-sectional studies of asthma prevalence in children are evaluated. The studies considered in the 2008 SO_X ISA (U.S. EPA, 2008b) were limited to those with cross-sectional designs [Supplemental Table 5S-4 (U.S. EPA, 2015i)]. The majority of these studies reported positive associations of long-term SO_2 exposure with asthma prevalence.

Recent longitudinal studies of asthma incidence add to this evidence base. In a large multicity study (N = 4,320), Nishimura et al. (2013) observed that SO_2 exposures during

the first year of life were not associated with asthma incidence [0.95 (95% CI: 0.59−1.47) per 5 ppb change]. However, SO_2 exposure during the first 3 years of life was associated with asthma incidence [OR = .16 (0.73−1.84) per 5 ppb SO_2]. Pollutant concentrations were estimated using the IDW average of the four fixed site monitors within 50 km of the subject's residence. The cities examined included Chicago, IL, Bronx, NY, Houston, TX, San Francisco Bay Area, CA, and Puerto Rico. In a study of the British Columbia Birth Cohort (n = 2,801), Clark et al. (2010) used IDW estimate-based concentrations from the three closest fixed site 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 during pregnancy and first year of life. Conducted in Southwest British Columbia, there were 14 SO_2 stations 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. The use of questionnaires in both 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 (see Section 3.2.2.1). 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 in both studies were observed with NO_2 concentration. Correlations between pollutant concentrations were not reported by 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.

Several recent studies presented in Table 5-28 also examine the association of long-term exposure to SO_2 with the prevalence of asthma in cross-sectional studies. While these studies are less informative, most (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. An example of a recent source study, Amster et al. (2014), reported an adjusted association between SO_2 as an ambient measure but not for "power plant event or source" exposure and asthma prevalence, COPD, and shortness of breath. The source approach yielded wider 95% CI than the event approach for SO_2. These studies are consistent with similar studies in the 2008 SO_X ISA (U.S. EPA, 2008b). Neither these

recent cross-sectional studies of asthma prevalence nor the recent longitudinal studies of asthma incidence attempt to address the potential for copollutant confounding by conducting a two-pollutant analysis. Thus, within the recent epidemiologic evidence base, no new studies reduce the uncertainty related to whether the effect was from SO_2 or another pollutant. However, the studies of asthma incidence address the temporality of exposure and response and are supportive of this relationship.

Table 5-28 Summary of recent epidemiologic studies examining associations between SO_2 concentrations and the development of asthma.

Study, Location, and Years	Population	Exposure Assessment	Pollutant Correlations	Comment	Results
Longitudinal Asthma Incidence Studies					
Clark et al. (2010), Incident asthma Southwest British Columbia, Canada Births from 1999−2000	British Columbia Birth Cohort (mean age at follow up 48 mo, SD-7 mo) N = 2,801	SO_2, NO_2, CO, PM_{10}, black carbon SO_2 estimated using IDW levels Covariate-adjusted conditional logistic regression	NR	NO_2 effect largest observed using LUR	Adjusted SO_2/IDW per 5 ppb first year exposure OR (95% CI) −1.47 (1.30−1.89) Covariate adjustment: native status, breast-feeding, maternal smoking, income quartile, birth weight, and gestational length

Table 5-28 (Continued): Summary of recent epidemiologic studies examining associations between SO_2 concentrations and the development of asthma.

Study, Location, and Years	Population	Exposure Assessment	Pollutant Correlations	Comment	Results
Nishimura et al. (2013) Incident asthma multicity study Includes: Chicago, IL; Bronx, NY; Houston, TX; San Francisco Bay Area, CA; and Puerto Rico 2006−2011	GALA II and SAGE II cohorts (Latinos and African Americans 8−21 yr) N = 4,320	SO_2, NO_2, O_3, PM_{10}, $PM_{2.5}$ ambient air pollution annually averaged Measurements obtained from fixed monitors. Exposures for the first 3 yr of life were estimated based on residential histories using an inverse distance-squared weighted average from the four closest monitors within 50 km of residence. SO_2 overall mean (SD) ppb 4.0 (3.4) Adjusted logistic regression models	NR	Early life NO_2 exposure was associated with childhood asthma	5 ppb change in SO_2 0.95 (0.59−1.47) First 3 yr of life SO_2 exposures multicity analyses OR (95% CI) for 5 ppb change in SO_2 1.16 (0.74−1.84) Covariate adjustment: age, sex, ethnicity, and composite SES
Cross-Sectional Asthma Prevalence Studies					
Akinbami et al. (2010) Metropolitan areas, United States 2001−2004	National Health Interview Survey, children (3−17 yr) N = 34,073.	SO_2, NO_2, O_3, $PM_{2.5}$ and PM_{10}. SO_2 12 mo average by county Median 3.0 ppb, IQR 1.7−4.8 ppb Exposure estimated with a single pollutant logistic regression	SO_2−N_2: 0.25 SO_2−O_3: −0.38 SO_2−$PM_{2.5}$: 0.12 SO_2−PM_{10}: −0.15	The adjusted current asthma was strongest for ozone	SO_2 per 5-ppb increase positive for both current asthma and asthma attack but CI spanned well below 1. Current asthma adjusted 4th quartile OR 1.15 (0.26−5.01). Covariate adjustment: age, sex, race/ethnicity, and adult smoker in household, single parent, highest level of parental education, poverty status, and region of residence

Table 5-28 (Continued): Summary of recent epidemiologic studies examining associations between SO_2 concentrations and the development of asthma.

Study, Location, and Years	Population	Exposure Assessment	Pollutant Correlations	Comment	Results
Altuğ et al. (2013) Prevalence of asthma symptoms and lung function Eskisehir, Turkey Jan 2008−Mar 2009	ISAAC questionnaire School children (9−13 yr) N = 1,880	Summer (May 27−Jun 13, 2008) and winter (Feb 27−Mar 13, 2009) seasons SO_2, NO_2, O_3 by passive sampling SO_2 range of sampled regions-mean (SD) Summer 16.5(9.3−23.4) to 26.7(10.9−42.9); Winter 55.2(18.4−75.8) to 76.2 (55.5−115.9) µg/m^3 Exposure estimated from measurements taken in the child's primary school garden	SO_2−O_3: −0.395 (winter) SO_2−NO_2: 0.486 (winter)	Association between ozone and impaired lung function only for girls in the summer season Potentially confounding variables included: responder, sex, age, parental smoking habits, coal or wood stove use, maximal parental education of family, domestic pets, and mold in the home	No associations found for SO_2, some positive some negative
Amster et al. (2014) Prevalence of asthma, COPD, and related symptoms Hadera, Israel area 2003 to 2004	Adults in the ECRHS cohort; cross-sectional prevalence design N = 2,244	SO_2 exposures at the residence were determined for an 8 yr avg from 20 monitoring sites based on kriging in relation to emissions from the power plant. Annual SO_2 mean (SD) for total, power plant source, and power plant event in ppb were respectively: 2.52 (0.32); 6.22(2.03); and 16.55 (12.10)	"Source approach" correlated with the "event approach" for SO_2 (Pearson correlation coefficient r = 0.66) but not for NO_X (r = −0.07) Association between NO_X and SO_2 exposure Estimates for both the "source approach" (Pearson correlation coefficient r = 0.62) and the "event approach" (Pearson correlation coefficient r = 0.97)	Prevalence of asthma and history of shortness of breath were statistically associated with total (power plant and nonpower plant) exposures to SO_2. Both source and event approaches of estimating the power plant-specific exposure to SO_2 were not statistically associated with the outcomes of interest. The "source approach" yielded much wider 95% CI than the "event approach"	For the adjusted model for asthma prevalence for a 5-ppb increase for total exposure: 24.11 (1.61, 362.59); for power plant event 1.05 (0.95, 1.16); and for power plant source 1.47 (0.95, 2.19), adjusted for age, sex, smoking history, housing density, proximity to major highways, and level of education Two pollutant models with SO_2 and NO_X did not change the results

Table 5-28 (Continued): Summary of recent epidemiologic studies examining associations between SO_2 concentrations and the development of asthma.

Study, Location, and Years	Population	Exposure Assessment	Pollutant Correlations	Comment	Results
Arnedo-Pena et al. (2009) Prevalence of recent symptoms of asthma Seven centers (Asturias, Barcelona, Bilbao, Cartagena, LA Coruna, Madrid, and Valencia), Spain 2002−2003	ISAAC questionnaire School children (6−7 yr) N = 20,455	SO_2, CO, NO_2, TSP-SO_2 monitoring stations annual concentration mean (SD)—12.4 (4.6) µg/m^3 Cross-sectional, covariate-adjusted multivariate logistic regression	SO_2−CO: 0.6203 SO_2−NO_2: −0.5505 SO_2−TSP: −0.1615	Other pollutants not as strongly or inverse associations	Recent severe asthma-adjusted OR (95% CI) 1.34 (1.01−1.78) between Level 1 and 3 Covariate adjustment: sex, use of paracetamol, maternal smoking, elder siblings cooking with electricity or gas, temperature and humidity
Deger et al. (2012) Prevalence of asthma Montreal, Quebec, Canada 2006	ISAAC questionnaire Children (6 mo−12 yr N = 821	Yearly ambient SO_2 levels from refinery stack emissions were estimated at the locations of the centroid coordinates of the six-digit postal code using dispersion modeling to determine residential exposure estimates Yearly SO_2 level µg/m^3 mean (SD) active asthma—4.75 (3.24); poor asthma control group—5.37 (3.50) Cross-sectional covariate-adjusted log-binomial regression model	NR	No other pollutants considered	PR adjusted—active asthma 1.44 (95% CI 0.84 to 2.48); poor asthma control 1.39 (1.00 to 1.94) Covariate adjustment: child's age, sex, parental history of atopy and tobacco smoke exposure at home

Table 5-28 (Continued): Summary of recent epidemiologic studies examining associations between SO_2 concentrations and the development of asthma.

Study, Location, and Years	Population	Exposure Assessment	Pollutant Correlations	Comment	Results
Dong et al. (2013b) Asthma symptoms 25 districts of seven cites in Northeast China 2006−2008	Children (2−14 yr) Three body weight categories; normal weight, overweight, and obese defined by BMI N = 30,056	Ambient SO_2, PM_{10}, NO_2, O_3 measured at municipal air pollution monitoring stations Annual SO_2 mean (range) 50.3 (20−80) µg/m^3 Three-yr mean SO_2 concentrations used as surrogate of long term exposure Cross-sectional mixed logistic regression model	NR	The association between each pollutants concentrations and the studies respiratory symptoms and asthma was consistently stronger among children with a status of BMI ≥85% than those with normal weight	Doctor-diagnosed asthma in combined overweight and obese population SO_2 IQR 5ppb-OR (95% CI) 1.24 (1.13−1.35) Interaction between overweight and obese with SO_2 *p*-value = 0.011 Covariate adjustment: age, sex, breast feeding habits family history of atopy, passive smoking exposure, study district and parental education level
Dong et al. (2013c) Asthma symptoms 25 districts of seven cites in Northeast China 2008−2009	Children (2−14 yr) Two breast feeding groups; mainly breastfed for greater than 3 mo and not mainly breast-fed for greater than 3 mo N = 31,049	Ambient SO_2, PM_{10}, NO_2, O_3 measured at municipal air pollution monitoring stations taken 2006−2008 Annual SO_2 mean (range) 50.3 (20−80) µg/m^3 Three-yr mean SO_2 concentrations used as surrogate of long-term exposure Cross-sectional mixed logistic regression model	NR	Association of air pollution with respiratory conditions was modified by breastfeeding Breastfeeding is associated with smaller associations between air pollution and respiratory conditions in children but not for doctor-diagnosed asthma	Doctor-diagnosed asthma in breastfed population SO_2 IQR 5 ppb OR 95% CI 1.11 (1.04−1.19) Breastfeeding status test for interaction *p*= 0.70 Covariate adjustment: age, sex, parental education, obesity, family history of atopy, low birth weight, home coal use, home pets, district, passive smoking exposure, and area of residence per person

Table 5-28 (Continued): Summary of recent epidemiologic studies examining associations between SO_2 concentrations and the development of asthma.

Study, Location, and Years	Population	Exposure Assessment	Pollutant Correlations	Comment	Results
Gorai et al. (2014) Asthma emergency department visit rate and asthma discharge rate New York State, United States 2005−2007	Department of Health Asthma Surveillance summary report Asthma hospital discharges visits for 2005, 2006, and 2007 respectively: 39,927, 40,205, and 37,950 Asthma ED visits for 2005, 2006, and 2007 respectively: 59,572, 164,116, and 161,200	Estimated $PM_{2.5}$, SO_2, and O_3 concentrations at centroids of counties using GIS kriging SO_2 mean (SD) ppb for 2005, 2006, and 2007 respectively: 8.46 (2.88), 6.92 (2.31), and 7.18 (2.38) Pearson two-tailed correlation analysis	SO_2−O_3: −0.759 (2005) SO_2−O_3: −0.716 (2006) SO_2−O_3: −0.741 (2007) SO_2−$PM_{2.5}$: 0.868 (2005) SO_2−$PM_{2.5}$: 0.922 (2006) SO_2−$PM_{2.5}$: 0.794 (2007)	A negative association between asthma rate and O_3 observed	Asthma prevalence among the New York residents was associated with exposure to $PM_{2.5}$ followed by SO_2 Correlation coefficients asthma hospital discharges and SO_2 for 2005, 2006, and 2007 respectively: 0.52, 0.38, and 0.41 Correlation coefficients asthma ED visits and SO_2 for 2005, 2006, and 2007 respectively: 0.46, 0.31, and 0.13
Kara et al. (2013) Asthma cases Niğde, Turkey 2006−2010	Asthma hospital admissions determined from the hospital automated diagnosis system (captures >80% of city patients)	Ambient SO_2 and PM_{10} were obtained from the continuous emissions monitoring system. Vehicular SO_2 emissions were estimated using motor vehicle data 9.3% of the daily average SO_2 concentrations were above 60 µg/m^3 Parametric statistical analysis and Mann-Kendall nonparametric evaluation	SO_2-PM_{10}: 0.045 SO_2-O_3: −0.36 SO_2-NO_2: 0.42 SO_2-CO: 0.24	PM_{10} and SO_2 reported to effect asthma cases in Niğde	Total cases of asthma were dependent on ambient SO_2 concentration Pearson correlation coefficient between ambient SO_2 and total monthly asthma cases = 0.4869. Statistically significant at 99% confidence

Table 5-28 (Continued): Summary of recent epidemiologic studies examining associations between SO_2 concentrations and the development of asthma.

Study, Location, and Years	Population	Exposure Assessment	Pollutant Correlations	Comment	Results
Liao et al. (2011) Asthma hospital admission rates and fluctuations in virus respiratory tract infections Taiwan 2001−2008	Asthma admission rate per 100,000 total population extracted from the National Health Insurance Research Database	SO_2, PM_{10}, NO_2, CO, and O_3. Major air monitoring stations in Taipei (five stations) and Kaohsiung (four stations) SO_2 annual means SO_2 for Kaohsiung ~8 ppb and ~4 ppb for Taipei Probabilistic risk assessment based on a DFA to predict future respiratory virus and air pollutant associated asthma incidence Linear and nonlinear autoregression models	PM_{10}: 0.045 O_3: −0.360 NO_2: 0.420 CO: 0.236	No significant correlation found between asthma admission and PM_{10}, O_3, NO_2, and CO. The DFA-based risk model can describe the multiple triggers related to asthma admissions. Frey and Suki (2008) suggest that the fluctuation analysis approach can be used to identify the dynamic patterns of clinical symptoms of complex chronic diseases	The association among influenza (r = 0.80, p < 0.05) and SO_2 level (r = 0.73, p < 0.05) and asthma admission rate was observed to be strong
Liu et al. (2014a) Prevalence of respiratory symptoms and diagnosed asthma China 2006–2008	23,326 Chinese children aged 6 to 13 yr were evaluated using the ATS respiratory questionnaire in a cross-sectional study using a two-stage hierarchical model with logistic and ecologic model analyses	Three-year (2006−2008) average SO_2 concentration, mean (SD): 50.3 (16.8) μg/m^3 Ranges: PM_{10} (79−171 μg/m^3), SO_2 (20−80 μg/m^3), and O_3 (34−89 μg/m^3 calculated from monitoring stations in each of the 25 districts located near schools and near the students' homes	NO_2 with O_3 (0.66) and SO_2 (0.52) tended to be relatively low across the 25 districts, with a higher correlation between PM_{10} and SO_2 (0.78), and between PM_{10} and O_3 (0.74)	Two-pollutant models were not possible due to the high correlation between pollutants; unable to control for weather factors (e.g., temperature or humidity).	Adjusted OR for diagnosed asthma was 1.14 (95% CI, 1.09−1.19) per 5-ppb increase in SO_2 Adjusted for age, sex, house type, smoking, parental atopic disease, breastfeeding, proximity to main roads and factories
Pan et al. (2010) Asthma prevalence 18 districts of six cities in Liaoning Province, northern China 1997−2000	Children (3−12 yr) N = 11,860	SO_2, TSP, NO_2. SO_2 monitored within 1 km of elementary school in each district, annual mean SO_2 (SD) 64 (42) μg/m^3 Cross-sectional two-stage regression	SO_2−TSP: 0.889 SO_2−NO_2: 0.577	Larger effects between cities than within reflecting wider between-city air gradient. Three pollutant analysis OR's for SO_2 decreased	For IQR of 5 ppb for SO_2 OR (95% CI) current asthma—1.09 (1.05,1.15)

Table 5-28 (Continued): Summary of recent epidemiologic studies examining associations between SO_2 concentrations and the development of asthma.

Study, Location, and Years	Population	Exposure Assessment	Pollutant Correlations	Comment	Results
Penard-Morand et al. (2010) Prevalence of asthma and allergies French Cities (Bordeaux, Clermont-Ferrand, Creteil, Marseille, Reims, and Strasbourg) Mar 1999−Oct 2000	ISAAC questionnaire Children (9−11 yr) N = 6,683 Cross-sectional generalized estimating equation adjusted for potential confounders	SO_2, benzene, PM_{10}, NO_2, CO. Mean SO_2 range across the six cites—mean (minimum–maximum) µg/m^3 4.1 (3.1−6.7) to 13.2 (10.7−16.4) Exposure estimated using SO_2 concentrations at the school calculated with a validated dispersion model that integrates background air pollution, traffic emissions, topography and meteorology	SO_2−benzene: 0.70 SO_2−VOC: 0.54 SO_2−CO: 0.60 SO_2−NO_2: 0.58 SO_2−NO_X: 0.51 SO_2−PM_{10}: 0.70	The most robust associations were found for PM_{10} and benzene	SO_2 OR (95% CI) adjusted for lifetime asthma for IQR (5 ppb) 1.83 (1.31−2.51) Covariate adjustment: age, sex, older siblings, family history of allergy, parental education, mother's ethnic origin, and potential sources of indoor pollution at home (smoking; mould or dampness; natural gas used for heating, cooking, or water-heater; and pets)
Portnov et al. (2012) Asthma prevalence Northern Israel 2006−2008	Clalit Health Services Database School children (6−14 yr) [mean age 10.2 yr (SD 2.6 yr)] N = 3,922 Binary logistic regression performed separately for the seven individual townships covered. BMA implemented	SO_2, PM_{10}. SO_2 measured at 14 monitoring stations. The average values of SO_2 were interpolated by kriging providing continuous surfaces and IDW. GIS mapping used home addresses SO_2 mean (SD) 5.4 (1.3) ppb	SO_2−PM_{10}: 0.322	PM_{10} effects observed	SO_2 asthma prevalence IDW OR (95% CI)—0.99 (0.89−1.10) BMA approach estimates the posterior probability for an SO_2 effect to be only 2.8% strengthening the standard logistic regression analysis that SO_2 should not be added to the model when PM_{10} is included Covariate adjustment: sex, age, proximity to main roads, town or residence, and families SES

Table 5-28 (Continued): Summary of recent epidemiologic studies examining associations between SO_2 concentrations and the development of asthma.

Study, Location, and Years	Population	Exposure Assessment	Pollutant Correlations	Comment	Results
Sahsuvaroglu et al. (2009); Asthma prevalence Hamilton, Canada 1994−1995	The ISAAC Phase I questionnaire Children [6−7 yr and 13−14 yr (pre and post-pubescent)] N~1,467	SO_2, ozone, PM NO_2. SO_2 Thiessen polygons, bicubic spline, and IDW interpolation techniques were used to estimate exposure SO_2 3 yr average = 5.82 ppb Adjusted logistic regressions	SO_2-NO_X: −0.165 (Thiessen) SO_2−NO_2: 0.442 (SO_2 Thiessen; NO_2 Kriged) SO_2−NO_2: 0.237 (SO_2 Thiessen; NO_2 LUR)	The most robust effects were observed in NO_2 LUR models in girls for asthma without hay fever	Per 5-ppb increase in SO_2 (Thiessen) controlling for confounding, strongest effect, regression coefficent between nonallergic (without hay fever) asthma and SO_2 in the older children Exp(B) = 1.25) (1.02−1.53). All other SO_2 effects were positive but CI spanned below 1.00 such as all children 1.09 (0.99−1.20). Covariate adjustment: neighborhood proxies for income, dwelling value, female smoking

ATS = American Thoracic Society; BMA = Bayesian Model Averaging; BMI = body mass index; CI = confidence interval; CO = carbon monoxide; COPD = chronic obstructive pulmonary disease; DFA = Detrended Fluctuation Analysis; ECRHS = European Community Respiratory Health Survey; ED = emergency department; Exp(B) = odds ratio of bivariate associations; GALA II = Genes-environments and Admixture in Latino Americans; GIS = geographic information systems; IDW = inverse distance weighting; IQR = interquartile range; ISAAC = International Study of Asthma and Alerrgies in Children; LUR = land use regression; N = population number; N_2 = nitrogen; NO_2 = nitrogen dioxide; NR = not reported; O_3 = ozone; OR = odds ratio; PM = particulate matter; ppb = parts per billion; PR = prevalence ratio; *r* = correlation coefficient; SD = standard deviation; SES = socioeconomic status; SO_2 = sulfur dioxide; TSP = total suspended solids; VOC = volatile organic compound.

Additional epidemiologic evidence for a link between long-term exposure to SO_2 and the development of asthma may come from intervention studies. Physicians, in part, diagnose asthma 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. In an intervention study discussed in the 2008 SO_X ISA (U.S. EPA, 2008b), Peters et al. (1996) observed decreases in respiratory symptoms, including any wheeze or asthmatic symptoms,

wheezing, and cough and sore throat, in association with decreases in SO_2 concentrations due to a government restriction of sulfur content of fuels. In a related study, Wong et al. (1998) examined the effect of the same government intervention in Hong Kong that restricted sulfur content of fuels from July 1990 onwards on BHR in children aged 9−12 who were nonwheezing and nonasthmatic 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. (1996) 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.

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, 2008b). Study characteristics are summarized in Table 5-29. 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.

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, 2008b). One new animal toxicological study of subchronic SO_2 exposure has become available since the last review. This study involves newborn rats and is discussed above in Sections 5.2.1.2, and 5.2.1.6. Key findings are also discussed here; study characteristics are summarized in Table 5-29. 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, 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.

Table 5-29 Study-specific details from animal toxicological studies.

Study	Species (strain); n; Sex; Lifestage/Age (mean ± SD)	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/day, 5 days/week 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 week old neonates	Sensitization by i.p. injection of 10 mg ovalbumin followed by booster injection of 10 mg ovalbumin after 7 days Challenge with 1% ovalbumin aerosol for 30 min daily for 4 weeks beginning at 15 days Exposure to 2 ppm SO_2 for 4 h/day for 4 weeks beginning at 15 days 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; MCh = methacholine; n = sample size; N_2 = nitrogen; NO_X = the sum of nitric oxide and nitrogen dioxide; ppm = parts per million; SD = standard deviation; SO_2 = sulfur dioxide.

Summary of Development of Asthma

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.

5.2.2.2 Lung Function

Epidemiologic Studies

As discussed in the 2008 SO_X ISA (U.S. EPA, 2008b), earlier cross-sectional studies (Dockery et al., 1989; Schwartz, 1989) found no association between long-term SO_2 exposure and lung function in children in the United States. 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 lung function effects 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-4 (U.S. EPA, 2015i).

Recent studies in children and adults add to this evidence base (Table 5-30). 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. (2011b) 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 United Kingdom 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, Ontario using a cross-sectional prevalence design.

In summary, the 2008 SO_X ISA (U.S. EPA, 2008b) concluded that the available evidence from the few epidemiologic studies was inadequate to infer that lung function effects occur as a result of long-term exposure to SO_2 at ambient concentrations. The recent studies add to the database evaluating this relationship. The majority of the recent studies and earlier studies used cross-sectional designs. Some studies took into account potentially confounding covariates. The designs used in most of the recent studies (i.e., ecological, cross-sectional) limit the possible inferences about the causality of 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 two-pollutant analysis found attenuation of the effect. Thus, recent studies do not add information that changes conclusions made in the 2008 SO_X ISA (U.S. EPA, 2008b).

Table 5-30 Summary of recent epidemiologic studies examining associations between SO_2 concentrations and lung function.

Study	Population	Exposure	Pollutant Correlations	Comment	Result
Dales et al. (2008) Examined eNO, FEV_1 and FVC Windsor, Ontario, Canada 2004–2005	In 2,328 elementary school children 9−11 yr of age in a cross-sectional prevalence study	Annual average levels of SO_2, NO_2, and $PM_{2.5}$ were estimated by LUR at the postal-code level. The mean and IQR for SO_2 was 5.39 ppb and 0.94 ppb. (95^{th} percentile: 6.92 ppb)	Wheeler et al. (2008) provides Spearman correlation coefficients: for SO_2 and NO_2, benzene, and toluene of 0.85, 0.82, and 0.61, respectively	eNO was associated with roadway measures.	Adjusted associations between 5 ppb SO_2 and percent predicted FEV_1, percent predicted FVC and ln[eNO] x 10^3 are respectively: −5.45 (−16.6 to 5.7); −1.55 (−7.15 to 4.05); and 3.0 (−273.0 to 274.0).

Table 5-30 (Continued): Summary of recent epidemiologic studies examining associations between SO_2 concentrations and lung function.

Study	Population	Exposure	Pollutant Correlations	Comment	Result
Forbes et al. (2009c), Lung function England 1995, 1996, 1997, and 2001	Health Survey for England Adults from white ethnic groups (≥16 yr) N = 32,712 households	SO_2, PM_{10}, NO_2, and O_3 for each 1 km^2 using air dispersion models. Exposure estimated based on the model value in the participant's post code Median SO_2 (IQR) in $\mu g/m^3$ for the 4 yr respectively 9.3 (7.5); 9.2 (7.6); 9.2 (7.2); and 3.8 (2.7) Cross-sectional, multilevel linear regression	SO_2−PM_{10}: 0.34 (1995) SO_2−PM_{10}: 0.17 (1996) SO_2−PM_{10}: 0.13 (1997) SO_2−PM_{10}: 0.17 (2001) SO_2−O_3: −0.29 (1995) SO_2−O_3: −0.36 (1996) SO_2−O_3: −0.30 (1997) SO_2−O_3: −0.16 (2001) SO_2−NO_2: 0.31 (1995) SO_2−NO_2: 0.31 (1996) SO_2−NO_2: 0.29 (1997) SO_2−NO_2: 0.18 (2001)	Effects also seen for PM_{10} and NO_2 but not for O_3	SO_2 yr-specific estimates were pooled using fixed effects meta-analysis difference (mL) (95% CI): FEV_1 −28.82 (−47.16, −9.17) per 5 ppb adjusted Covariate adjustment: age, sex, height, social class of head of household, smoking, and region
Iwasawa et al. (2010) Miyakejima Island, Japan near the volcano Mt. Ōyama Feb 2005–Nov 2006	Miyake children [mean age (SD)—10.7 yr (4.4 yr)] N = 141	SO_2 monitored at seven sampling points of the residential areas. Mean SO_2 concentration from February 2005 to November 2006 was 31 ppb; range 19 to 45 ppb across areas Inhabitant areas were classified into one lower-SO_2 and three higher-SO_2 areas to gauge exposure.	NR		Percent FVC and FEV_1 in hypersusceptible children were significantly reduced in November 2006 compared to February 2006 (p = 0.047, 0.027) although no reduction observed in normosusceptible children. Covariate adjustment: sex, age, residential area, and hypersusceptiveness

Table 5-30 (Continued): Summary of recent epidemiologic studies examining associations between SO_2 concentrations and lung function.

Study	Population	Exposure	Pollutant Correlations	Comment	Result
Lee et al. (2011b) Lung function 14 Taiwanese communities 2005−2007	Taiwan Children Health Study; Children of Han Chinese ethnic origin (12−13 yr) N = 3,957	SO_2, CO, NO_2, O_3, PM_{10}, $PM_{2.5}$.-air monitoring stations in each community SO_2-chronic monthly average over the time course of the study—mean (SD) 4.68 (2.20) ppb; subchronic average July−September 2007 3.90 (1.48) Cross-sectional, linear regression models	NR	Found greater effects for NO_2 and CO	SO_2 chronic all subjects FEV_1 (95% CI) changes in mL per IQR 5 ppb: −28.91 (−115.65, 58.04) Covariate adjustment: age, sex, height, weight, parental education, mother smoking during pregnancy, dog at home, and visible mould
Linares et al. (2010) Lung function and respiratory symptoms Salamanca, Mexico Mar 2004−Feb 2005	ISAAC questionnaire Children attending two primary schools (6−14 yr). School 1 1,100 m from petrochemical zone. School 2 was 7,300 m away.	SO_2, O_3, NO_2, PM_{10} The two schools were located within 2 km from one of the three monitoring stations. 3-mo levels of SO_2 varied by season and school (23 to 36 µg/m^3) Cross-sectional, longitudinal repeated measures study for pulmonary function generalized linear mixed models for respiratory symptoms multilevel logistic models	NR	Frequency of respiratory symptoms higher in the school closer to the major stationary air pollution sources. PM effects were the most consistent factor. For SO_2, outcomes in one- and two-pollutant analysis of PM_{10} and O_3 by sex were attenuated.	Per 5 ppb SO_2;FEV_1—adjusted beta coefficient −0.004 (−0.005, 0.002) Covariate adjustment: height, BMI, sex, age, fossil fuel, passive smoking and clustering by child

Table 5-30 (Continued): Summary of recent epidemiologic studies examining associations between SO_2 concentrations and lung function.

Study	Population	Exposure	Pollutant Correlations	Comment	Result
Rusconi et al. (2011) Lung function Sarroch and Burcei, Italy Jan 2007−Jun 2007	Schoolchildren (6−14 yr) Sarroch/petrochemical area; Burcei/reference area Sarroch N = 275 Burcei N = 214	SO_2, NO_2, benzene assessed by passive dosimeters from 15 May to 7 Jun 1 week before children examinations SO_2 mean: Sarroch 18.1 µg/m^3; Burcei 3.6 µg/m^3 Ecological cross-sectional study, generalized linear models Estimated logistic regression model coefficients reported as prevalence ratios	NR	Found an increase of markers of bronchial inflammation and oxidative damage in children living near an oil refinery as compared to those in a nonpolluted area	Decrease in FEV_1 reported comparing the two towns. Covariate adjustment: age, sex, parental history of asthma, parental education, passive smoking, and damp in child's bedroom
Tanaka et al. (2013) Chronic bronchitis, asthma, or emphysema Kurashiki and Okayama, Japan 2000−2009	Officially acknowledged victims of pollution-related illnesses (≥65 yr) N = 563 Respiratory symptom questionnaire and yearly spirometry examinations	Mean daily concentrations of SO_2 concentrations were determined at 21 points in Kurashiki starting in 1965. After 1974, SO_2 levels decreased below 40 ppb. Regression coefficients calculated using simple linear regression. Mean annual changes in respiratory function were compared between subjects with and without worsening of dyspnea.	NR	Reduction of air pollution levels may have reduced respiratory disease related to air pollution.	High pollutant concentrations around 1970 resulted in decreases in respiratory function and increased respiratory symptoms. Changes from 2000 to 2009 were in the normal range and were probably due to normal aging

Table 5-30 (Continued): Summary of recent epidemiologic studies examining associations between SO_2 concentrations and lung function.

Study	Population	Exposure	Pollutant Correlations	Comment	Result
Turnovska and Marinov (2009) Lung function Dimitrovgrad, Bulgaria 1985−2003	Children (10 yr). N = 122 Three groups: (1) born and lived in heavy pollution (n = 60); (2) born and lived after the abrupt drop in pollution but pregnancy was during heavy exposure (n = 39); (3) born after the drop, lived in lower pollution levels and mothers had pregnancy in this environment (n = 23)	SO_2, TSP, NO_2, H_2S, HF Average annual mean (SE) µg/m^3 SO_2 dropped from 120 (21) to 30 (4) from 1985 to 2003. Similar drop in TSP but no other pollutants. Regression model		No differences in respiratory diseases observed. The combined impact of additively acting pollutants was suggested as important such as NO_2 + SO_2	The highest values of FEV_1 percent predicted are found among the children in the third group and the lowest values are in the children in the first group Covariate adjustment: sex, home heating fuel type, passive smoking, mother's education, and birthweight included
Wood et al. (2010) Lung function United Kingdom 1997−2006	Patients with α1-antitrypsin deficiency, chronic obstructive pulmonary disease, from the U.K. national registry for α1-antitrypsin deficiency Mean age (SEM) 51.09 (0.70) yr N = 399	SO_2, NO_2, PM_{10} Annual means with validated dispersion model Dispersion kernel approaches and weighted regression analysis were used to map pollutant levels on a 1 × 1 km grid. Exposure estimated from map based on patient's address Mean (SE) per year of decline SO_2 in µg/m^3: 4.12 (0.17) Generalized estimating equations	NR	High PM_{10} exposure predicted more rapid decline of FEV_1	SO_2 change in FEV_1 (mL/yr) mean (95% CI) per increase of 5 ppb −39.3 (−91.7 to 13.1) Covariate adjustment: age, sex, smoke exposure, level of occupational risk, and baseline lung function

Table 5-30 (Continued): Summary of recent epidemiologic studies examining associations between SO_2 concentrations and lung function.

Study	Population	Exposure	Pollutant Correlations	Comment	Result
Yogev-Baggio et al. (2010) Lung function near a coal-fired power plant Hadera district, Israel 1996 and 1999	School children (2nd−5th grade) N = 1,181 Three groups: healthy, chest symptoms, and pulmonary disease	SO_2 and NO_2 from 12 monitoring stations "Event" approach—half-an-hour concentrations of NO_X and SO_2 that simultaneously exceeded predefined air pollution levels were multiplied by the average concentrations during the air pollution events and summed up from 1996 to 1999 Study area divided into three air pollution zones: low pollution ($NO_X \times SO_2$ <312 ppm); medium pollution (312 < $NO_X \times SO_2$ <2,640 ppm), and high pollution ($NO_X \times SO_2$ >2,640 ppm) Exposure estimated at child's home Analysis of variance, multiple regression analysis	NR	The greatest effect was on children with chest symptoms.	Change in FEV_1—the effect of the $NO_X \times SO_2$ interaction term on children's pulmonary function test performance appears to be negative and highly significant in most of the models implying that increasing air pollution levels (ppm) to have a significant and negative effect on the children's pulmonary function growth Covariate adjustment: height, age, sex, parental education, passive smoking, housing density, length of residency in study area, and proximity to the main road

BMI = body mass index; CI = confidence interval; CO = carbon monoxide; eNO = exhaled nitric oxide; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; H_2S = Hydrogen sulfide; HF = high frequency; IQR = interquartile range; ISAAC = International Study of Asthma and Allergies in Children; ln = natural logarithm; LUR = land use regression; N = population number; NO_2 = nitrogen dioxide; NO_X = the sum of nitric oxide and NO_2; NR = not reported; O_3 = ozone; PM = particulate matter; ppb = parts per billion; SD = standard deviation; SE = standard error; SEM = standard error of the mean; SO_2 = sulfur dioxide; TSP = total suspended solids.

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, 2008b). Study characteristics are summarized in Table 5-29. 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 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 of no association between long-term SO_2 exposure and lung function in children made in the 2008 SO_X ISA (U.S. EPA, 2008b).

5.2.2.3 Other Respiratory Outcomes

Severity of Asthma Symptoms

Section 5.2.2.1 discussed studies on the development of asthma (i.e., asthma incidence). However, two studies focused on the relationship between long-term SO_2 exposure and the prevalence of asthma symptoms [Supplemental Table 5S-5 (U.S. EPA, 2015j)]. 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 of age and ≥6 years of age) 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%). 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. The observed associations between asthma severity and air pollution support the notion that air pollutants may increase asthma severity but the uncertainty related to these effects potentially being influenced by short-term exposure is a possibility that needs to be examined.

Respiratory Symptoms

In the 2008 SO_X ISA (U.S. EPA, 2008b), studies examining an array of respiratory symptoms related to SO_2 exposure are presented in in Supplemental Table 5S-5 (U.S. EPA, 2015j; 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 cross-sectional studies of long-term SO_2 exposure estimated at fixed site monitors from volcano emissions in Japan and Hawaii were conducted as shown in Supplemental Table 5S-5 (U.S. EPA, 2015j). Iwasawa et al. (2009) and Iwasawa et al. (2010) 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 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). In other cross-section studies the prevalence of respiratory symptoms was positively associated with long-term exposure to SO_2 (Altuğ et al., 2013; Pan et al., 2010; Arnedo-Pena et al., 2009; Rage et al., 2009; Pino et al., 2004). Although limited by their cross-sectional design, these volcano emission and other studies suggest a potential relationship between long-term SO_2 exposure and the prevalence of respiratory symptoms.

Several studies examine the prevalence of various markers for respiratory allergies including IgE antibodies, rhinitis, eczema, sensitization to pollen, and hay fever related to long-term SO_2 exposure in cross-sectional studies (Bhattacharyya and Shapiro, 2010;

Penard-Morand et al., 2010; Parker et al., 2009; Nordling et al., 2008). Positive results are observed for children using 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.

In summary, some studies examining associations between long-term exposure to SO_2 and respiratory symptoms provide support for a potential relationship between SO_2 exposure and the severity of asthma among asthmatics. Another set of studies provide support for a potential relationship between long-term SO_2 exposure and respiratory symptoms among children and adults living near active volcanoes. Furthermore, there is some evidence for a potential relationship between long-term SO_2 exposure and indicators or respiratory allergies and inflammation among children.

Chronic Bronchitis and Chronic Obstructive Pulmonary Disease

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, 2008b), 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-5 (U.S. EPA, 2015j) 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-5 (U.S. EPA, 2015j), 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.

Respiratory Infection

Studies also examine 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-5 (U.S. EPA, 2015j)]. The strongest

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 United States National Health Interview Survey of 126,060 children age 3−6 years. Lu et al. (2014) observed that the prevalence of pneumonia in children 3 to 6 years old was related to long-term SO_2 exposure. 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-year average 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). 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. 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, 2008b). 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 Other Respiratory Outcomes

A limited number of cross-sectional analyses of prevalence demonstrate increases in respiratory symptoms among children in relation to long-term SO_2 exposure. Associations were observed with SO_2 concentrations estimated from central site monitors. These studies are supportive of the development of asthma; however they may also reflect other respiratory conditions. Evidence for prevalence of bronchitis and/or respiratory infections consists of generally positive associations found in cross-sectional studies. In other cross-sectional studies, limited findings suggest associations between long-term SO_2 exposure and respiratory infection. 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.

5.2.2.4 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, Table 5-54, Figure 5-25). 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 not adequate for study of 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 mortality among adults.

5.2.2.5 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, 2008b).

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 1 of the Preamble to this ISA (U.S. EPA, 2015e) and is presented in Table 5-31.

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 (Clark et al., 2010); (Nishimura et al., 2013) (Section 5.2.2.1). Results are fairly consistent between these studies with one based on several different locations across the United States and the other on a large area in Canada; both with a large number of participants. Uncertainties and the potential for measurement error related to the use of IDW in these studies may limit inferences that can be made (Section 3.2.2.1). 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.

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 to help reduce this uncertainty. No studies of asthma incidence or prevalence evaluated copollutant models to address copollutant confounding, making it difficult to evaluate the independent effect of SO_2 within the epidemiologic evidence base. 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 compared to those for SO_2 (Clark et al., 2010); (Nishimura et al., 2013). 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, important steps in allergic sensitization (Song et al., 2012) (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 5.2.1.6). 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 5.2.1.6). Similarly, SO_2 exposure enhanced airway inflammation in rats previously sensitized with an allergen (Section 5.2.1.2).

Epidemiologic evidence from a few long-term studies provides a link between SO_2 exposure and respiratory allergies among children. 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.

Evidence for Lung Function

Several studies evaluated the relationship between long-term SO_2 exposure and decrements in lung function (Section 5.2.2.2). 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 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, 2008b) 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 Other Respiratory Outcomes

Other respiratory outcomes related to long-term SO_2 exposure are discussed in Section 5.2.2.3. A limited number of cross-sectional analyses of prevalence demonstrate increases in respiratory symptoms among children in relation to long-term SO_2 exposure. Associations were observed with SO_2 concentrations estimated from central sites. These studies are supportive of the development of asthma; however they may also reflect other respiratory conditions. A limited number of 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 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 5.2.2.4). 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. The strongest evidence of long-term SO_2-related respiratory effects is in morbidity studies among children. However, there is no evidence for a relationship between long-term exposure to SO_2 and respiratory mortality in children.

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 5-31). 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 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.

Table 5-31 Summary of evidence for a suggestive of, but not sufficient to infer, a causal relationship between long-term SO_2 exposure and respiratory effects.

Rationale for Causal Determination[a]	Key Evidence[b]	Key References[b]	SO_2 Concentrations Associated with Effects[c]
Asthma Development			
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. 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
	Cross-sectional studies of asthma prevalence among children provide support, although there is uncertainty regarding the temporal sequence between exposure and the development of asthma	Section 5.2.2.1	
	Supporting evidence for respiratory symptoms among children in cross-sectional studies	Section 5.2.2.3	
	Supporting evidence for markers of respiratory allergies among children in cross-sectional studies	Section 5.2.2.3	
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 3.2.2.1	
Uncertainty regarding potential confounding by copollutants	No copollutant models analyzed in asthma incidence studies	Section 3.3.4	
Limited animal toxicological evidence provides coherence and biological plausibility	Evidence for Th2 polarization and airway inflammation following repeated exposure of naive newborn rats for 28 days Evidence for enhanced inflammation, airway remodeling and AHR following repeated exposure of allergic newborn rats for 28 days	Song et al. (2012)	2,000 ppb

Table 5-31 (Continued): Summary of evidence for a suggestive of, but not sufficient to infer, a causal relationship between long-term SO_2 exposure and respiratory effects.

Rationale for Causal Determination[a]	Key Evidence[b]	Key References[b]	SO_2 Concentrations Associated with Effects[c]
Coherence with evidence from short-term animal toxicological studies	Evidence for inflammation and morphologic responses indicative of airway remodeling following repeated exposures of naive rats over several days	Li et al. (2007)	2,000 ppb
	Evidence for 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
	Evidence for 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	
Lung Function			
Epidemiologic evidence of decrements in lung function among children from quality studies but uncertainty regarding SO_2 independent effects	In two cohort studies, associations inconsistent with adjustment for PM and by season	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)	
Other Respiratory Outcomes			
Limited epidemiologic evidence for respiratory symptoms and markers of respiratory allergies among children but uncertainty regarding SO_2 independent effects	Generally positive associations in cross-sectional studies; fixed site monitors	Section 5.2.2.3	
Limited epidemiologic evidence for chronic bronchitis but uncertainty regarding SO_2 independent effects		Section 5.2.2.3	

Table 5-31 (Continued): Summary of evidence for a suggestive of, but not sufficient to infer, a causal relationship between long-term SO_2 exposure and respiratory effects.

Rationale for Causal Determination[a]	Key Evidence[b]	Key References[b]	SO_2 Concentrations Associated with Effects[c]
Limited evidence for respiratory infection, primarily in children; uncertainty regarding SO_2 independent effects	Generally positive associations in cross-sectional studies; fixed site monitors	Section 5.2.2.3	
Limited animal toxicological evidence			
Lack of evidence for key events in proposed mode of action	Changes in specific host defense mechanisms but no evidence of greater infectivity		
Respiratory Mortality			
Epidemiologic studies report generally consistent, positive associations with respiratory mortality	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)	4.8
		Nafstad et al. (2004)	3.6
		Elliott et al. (2007)	12.2−41.4
		Cao et al. (2011)	27.7
		Carey et al. (2013)	1.5
		Dong et al. (2012)	23.9
		Katanoda et al. (2011)	2.4−19.0
No coherence between respiratory morbidity in children and respiratory mortality in adults	No evidence for a relationship between long-term exposure and respiratory mortality among children to support the observed associations with respiratory morbidity among children	Section 5.5.2.5	

AHR = airway hyperresponsiveness; IDW = inverse distance weighting; PM = particulate matter; ppb = parts per billion; SD = standard deviation; SO_2 = sulfur dioxide.

[a]Based on aspects considered in judgments of causality and weight of evidence in causal framework in Tables I and II of the Preamble (U.S. EPA, 2015e).

[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 (for experimental studies, ≤2,000 ppb).

5.3 Cardiovascular Effects

5.3.1 Short-Term Exposure

5.3.1.1 Introduction

The 2008 ISA for Sulfur Oxides (U.S. EPA, 2008b) 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 to SO_2 in humans, animals, and cells. 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, 2008b).

When considered with the evidence reviewed in to 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, and the lack of mechanistic evidence to describe a role for SO_2 in the manifestation of cardiovascular diseases, including key events in the proposed mode of action, and potential confounding by copollutants. The majority of the recent evidence is from epidemiologic studies, which suggest that exposure to SO_2 may result in the triggering of MI. To clearly characterize the evidence underlying causality, the discussion of the evidence is organized into groups of related outcomes (e.g., ischemic heart disease and myocardial infarction, arrhythmia, and cardiac arrest). 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.

The previous ISA included a small number of animal toxicological and controlled human exposure studies that examined cardiovascular effects from short-term exposure to SO_2. Since the 2008 ISA for Sulfur Oxides (U.S. EPA, 2008b), no controlled human exposure

studies and one animal toxicological study have investigated the effects of short-term SO_2 exposure on the cardiovascular system. Study details for the animal toxicological and controlled human exposure studies from the current and past review that evaluated cardiovascular effects of short-term SO_2 exposures of less than 2,000 ppb are summarized in Supplemental Table 5S-3 (U.S. EPA, 2015h). Some studies using higher (5,000−20,000 ppb) inhaled concentrations of SO_2 reported measurable changes in the concentrations of sulfite and sulfonates in plasma and tissues. A recent report in mice exposed to 5,000−20,000 ppb SO_2 for 7 days found an increase in sulfite + sulfonate levels in lung, heart, and brain compared to controls (Meng et al., 2005b). At ambient relevant concentrations these changes would be expected to be far less. The literature discussing the distribution and metabolism of sulfite is discussed in Section 4.2.4.

5.3.1.2 Myocardial Infarction and Ischemic Heart Disease

Several lines of evidence are discussed in support of a 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 where 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, 2008b) 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 (Table 5-33, and Figure 5-10). 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 5-32. 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, all of the studies in this section use central site monitors to estimate ambient SO_2 exposure, which may result in exposure error due to time-activity patterns and spatial variation of SO_2 (Section 3.3.3). This exposure error is likely to lead to attenuation and loss of precision of the effect estimates (Section 3.3.5.1).

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-hour average 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.

One prominent study from the previous 2008 ISA for Sulfur Oxides (U.S. EPA, 2008b) was a study conducted in 14 cities across Spain, which 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-hour average 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 (Qiu et al., 2013b; 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 3.3.3.2).

Table 5-32 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

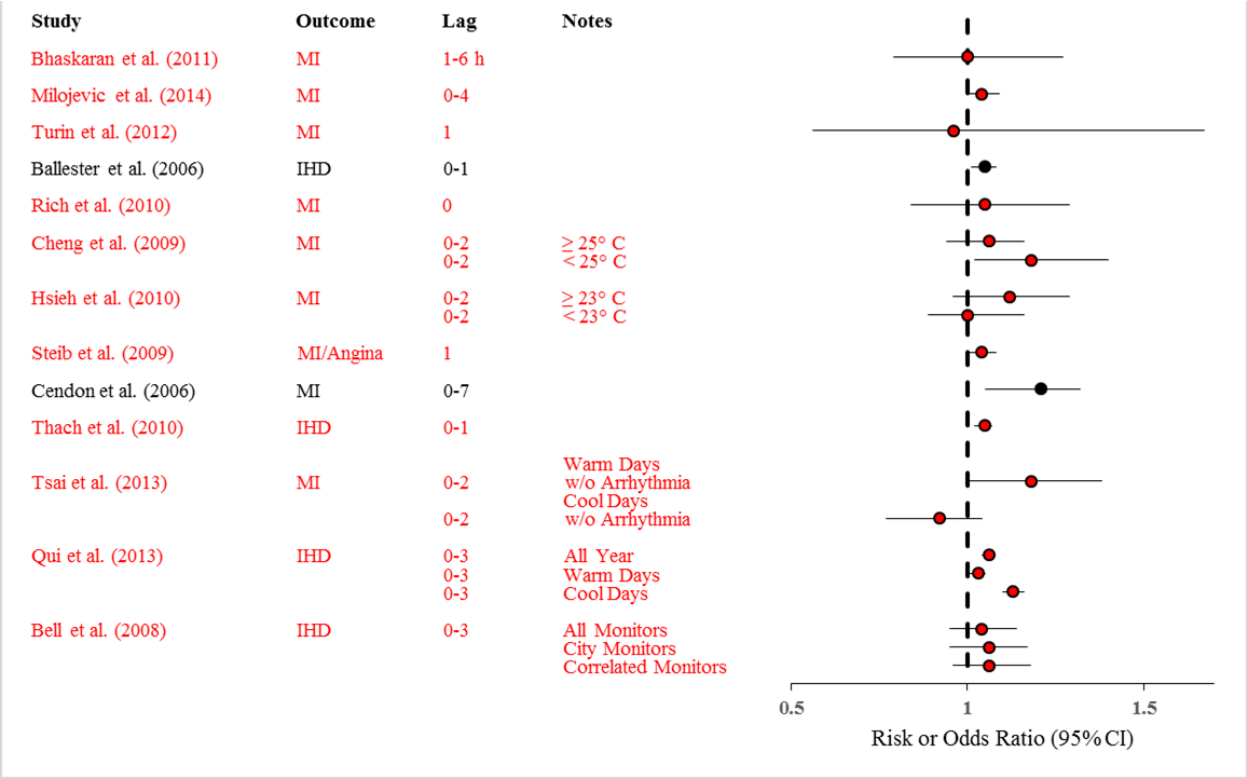
Table 5-32 (Continued): Mean and upper percentile concentrations of sulfur dioxide from ischemic heart disease hospital admission and emergency department visit studies.

Study	Location years	Exposure Assignment	Metric	Mean/Median Concentration ppb	Upper Percentile of Concentrations ppb
†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
†Qiu et al. (2013b)	Hong Kong, China (1998, 2007)	Average across 14 monitoring stations	24-h avg	Mean: 7.4	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

ISA = Integrated Science Assessment; NR = not reported; SO_2 = sulfur dioxide.

†Studies published since the 2008 ISA for Sulfur Oxides.

Note: Studies are listed in the order that they are discussed in the text.



Note: Studies in red are recent studies. Studies in black were included in the 2008 Integrated Science Assesment (ISA) for Sulfur Oxides. Relative risks are standardized to a 10-ppb or 40-ppb increase in SO_2 for 24-hour average and 1-hour max metrics, respectively.

Figure 5-10 Results of studies of short-term sulfur dioxide exposure and hospital admissions for ischemic heart disease.

Table 5-33 Corresponding risk estimates for hospital admissions for ischemic heart disease for studies presented in Figure 5-10.

Study	Location	Health Effect	Risk or Odds Ratio[a] (95% CI)	Copollutant Examination[b]
†Bhaskaran et al. (2011)	15 conurbations in England and Wales	MI	Lag 1−6 h: 1.00 (0.79, 1.27)	No copollutant models examined SO_2 correlations: O_3: −0.14; PM_{10}: 0.26; NO_2: 0.31; CO: 0.30
†Milojevic et al. (2014)	15 conurbations in England and Wales	MI	Lag 0−4: 1.04 (1.00, 1.09)	No copollutant models examined No correlations provided

Table 5-33 (Continued): Corresponding risk estimates for hospital admissions for ischemic heart disease for studies presented in Figure 5-10.

Study	Location	Health Effect	Risk or Odds Ratio[a] (95% CI)	Copollutant Examination[b]
†Turin et al. (2012)	Takashima County, Japan	MI	Lag 1: 0.96 (0.56, 1.67)	No copollutant models examined SO_2 correlations: SPM: 0.54; NO_2: 0.23
Ballester et al. (2006)	14 Spanish cities	IHD	Lag 0−1: 1.05 (1.01, 1.08)	SO_2: attenuated after adjustment for CO or NO_2, and lessened in magnitude, but more precise with adjustment for TSP or O_3 Copollutants: PM_{10} and NO_2 attenuated but still positive after SO_2 adjustment. CO and O_3 robust to SO_2 adjustment, BS and TSP less precise after SO_2 adjustment SO_2 correlations: BS: 0.24; NO_2: 0.46; CO: 0.51; O_3: −0.03; TSP: 0.31; PM_{10}: 0.46
†Rich et al. (2010)	New Jersey	MI	Lag 0: 1.05 (0.84, 1.29)	SO_2: attenuated and no longer positive after $PM_{2.5}$ adjustment Copollutants: $PM_{2.5}$ robust to SO_2 adjustment SO_2 correlations: O_3: −0.32; $PM_{2.5}$: 0.44; NO_2: 0.56; CO: 0.42
†Cheng et al. (2009)	Kaohsiung, Taiwan	MI	≥25°C Lag 0−2: 1.06 (0.94, 1.16) <25°C Lag 0−2: 1.18 (1.02, 1.40)	SO_2: associations attenuated and no longer positive after adjustment for PM_{10}, NO_2, or CO. Robust to O_3 adjustment Copollutants: PM_{10}, NO_2, CO, and O_3 associations robust to adjustment for SO_2 SO_2 correlations: O_3: −0.09; PM_{10}: 0.33; NO_2: 0.53; CO: 0.52
†Hsieh et al. (2010)	Taipei, Taiwan	MI	≥23°C Lag 0−2: 1.12 (0.96, 1.29) <23°C Lag 0−2: 1.00 (0.89, 1.16)	SO_2: associations attenuated and no longer positive after adjustment for PM_{10}, NO_2, CO, or O_3 Copollutants: PM_{10}, NO_2, CO, and O_3 associations robust to adjustment for SO_2 SO_2 correlations: O_3: −0.01; PM_{10}: 0.51; NO_2: 0.51; CO: 0.47

Table 5-33 (Continued): Corresponding risk estimates for hospital admissions for ischemic heart disease for studies presented in Figure 5-10.

Study	Location	Health Effect	Risk or Odds Ratio[a] (95% CI)	Copollutant Examination[b]
†Stieb et al. (2009)	Seven Canadian cities	MI/ Angina	Lag 1: 1.04 (1.00, 1.08)	No copollutant models examined Warm season SO_2 correlations (Pearson *r*): NO_2: 0.05 to 0.69; CO: −0.06 to 0.75; O_3: −0.24 to 0.21; $PM_{2.5}$: 0.01 to 0.55; PM_{10}: 0.25 to 0.60 Cool season SO_2 correlations: NO_2: 0.23 to 0.64; CO: 0.00 to 0.71; O_3: −0.18 to −0.52; $PM_{2.5}$: 0.01 to 0.67; PM_{10}: 0.23 to 0.64
Cendon et al. (2006)	São Paulo, Brazil	MI	Lag 0−7: 1.21 (1.05, 1.32)	No copollutant models examined SO_2 correlations: O_3: 0.31; PM_{10}: 0.77; NO_2: 0.70
†Thach et al. (2010)	Hong Kong, China	IHD	Lag 0−1: 1.05 (1.02, 1.07)	No copollutant models examined No correlations provided
†Tsai et al. (2012)	Taipei, Taiwan	MI	Lag 0−2 Warm days w/o arrhythmia: 1.18 (1.00, 1.38) Cool days w/o arrhythmia: 0.92 (0.77, 1.04)	No copollutant models examined SO_2 correlations (Pearson *r*): O_3: 0.06; PM_{10}: 0.52; NO_2: 0.48; CO: 0.29
†Qiu et al. (2013b)	Hong Kong, China	IHD	Lag 0−3 All yr: 1.06 (1.04, 1.07) Warm: 1.03 (1.00, 1.05) Cool: 1.13 (1.10, 1.16)	No copollutant models examined No correlations provided

Table 5-33 (Continued): Corresponding risk estimates for hospital admissions for ischemic heart disease for studies presented in Figure 5-10.

Study	Location	Health Effect	Risk or Odds Ratio[a] (95% CI)	Copollutant Examination[b]
†Bell et al. (2008)	Taipei, Taiwan	IHD	Lag 0−3 All Taipei monitors: 1.04 (0.95, 1.14) City monitors only: 1.06 (0.95, 1.17) Correlated monitors: 1.06 (0.96, 1.18)	No copollutant models examined No correlations provided

BS = black smoke; CI = confidence interval; CO = carbon monoxide; IHD = ischemic heart disease; ISA = Integrated Science Assessment; MI = myocardial infarction; NO_2 = nitrogen dioxide; O_3 = ozone; PM = particulate matter; *r* = correlation coefficient; SO_2 = sulfur dioxide; SPM = suspended particulate matter; TSP = total suspended particulate.

†Studies published since the 2008 ISA for Sulfur Oxides.

Note: Studies are listed in the order that they are discussed in the text. 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 24-h avg and 1-h max metrics, respectively.

[b]Relevant relative risks for copollutant models can be found in Supplemental Figures 5S-1 (U.S. EPA, 2015a), 5S-2 (U.S. EPA, 2015b), and 5S-3 (U.S. EPA, 2015c) and corresponding Supplemental Tables 5S-7 (U.S. EPA, 2015l), 5S-8 (U.S. EPA, 2015m) and 5S-9 (U.S. EPA, 2015n).

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 ≥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. However, exposure to SO_2 was assigned using fixed site monitors, which have limitations in capturing spatial variation in SO_2 (Section 3.3.3.2). These limitations are likely to lead to attenuation and loss of precision of the effect estimates (Section 3.3.5.1).

Summary of Ischemic Heart Disease and Myocardial Infarction

In summary, evidence from epidemiologic studies suggests that there may be an association between ambient SO_2 concentrations and rates of hospital admissions or ED visits for MI or ischemic heart diseases in single-pollutant models, but this association

may be at least partly due to 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. All of the studies in this section used fixed site monitors to measure ambient SO_2, which have noted limitations in capturing spatial variation in SO_2, which typically leads to attenuation and loss of precision in the effect estimates (Section 3.3.3.2). No experimental studies have been conducted to evaluate measures of ischemic heart disease or MI following short-term SO_2 exposure. Overall, there is limited, but generally consistent, evidence to suggest that short-term exposure to SO_2 in adults may lead to increases in ischemic heart disease and MI from epidemiologic studies of hospital admissions and ED visits and ST-segment changes.

5.3.1.3 Arrhythmias and Cardiac Arrest

The 2008 ISA for Sulfur Oxides (U.S. EPA, 2008b) 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 5-34). 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.

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) using 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.

One animal toxicological study evaluated arrhythmia frequency in rats following short-term SO_2 exposure and reported no significant changes in spontaneous arrhythmias (irregular, delayed, or premature beats) Nadziejko et al. (2004).

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 3.3.3.2). One toxicological study also found no evidence for arrhythmias following short-term SO_2 exposure.

Table 5-34 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: PM10: 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, PM10: 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
†Dennekamp et al. (2010)	Melbourne, Australia 2003−2006 (n = 8,434)	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)

Table 5-34 (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)
†Silverman et al. (2010)	New York City, NY 2003−2006 (n = 8,216)	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)	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)	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)

CI = confidence interval; ED = emergency department; ICD = implantable cardioverter defibrillators; ISA = Integrated Science Assessment; 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 arrhthymias; OR = odds ratio; SO_2 = sulfur dioxide.

†Studies published since the 2008 ISA for Sulfur Oxides.

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.

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). Eleven additional studies are now available for consideration (study details and results presented in Tables 5-35, 5-36, and Figure 5-11). In Edmonton, Canada, 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, Canada, 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, Canada. 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-hour average 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-hour average SO_2 at lag 2] in Lanzhou, a heavily polluted city in China with a high observed mean daily concentration of SO_2 over the 5 year study period (30.19 ppb). 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 no association was seen with other types of stroke. However, the 95% CI for the hemorrhagic stroke association was wide, indicating an imprecise association and co-pollutant 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, Canada. 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 5-35 Mean and upper percentile concentrations of sulfur dioxide from cerebrovascular disease and stroke-related hospital admission and emergency department visit studies.

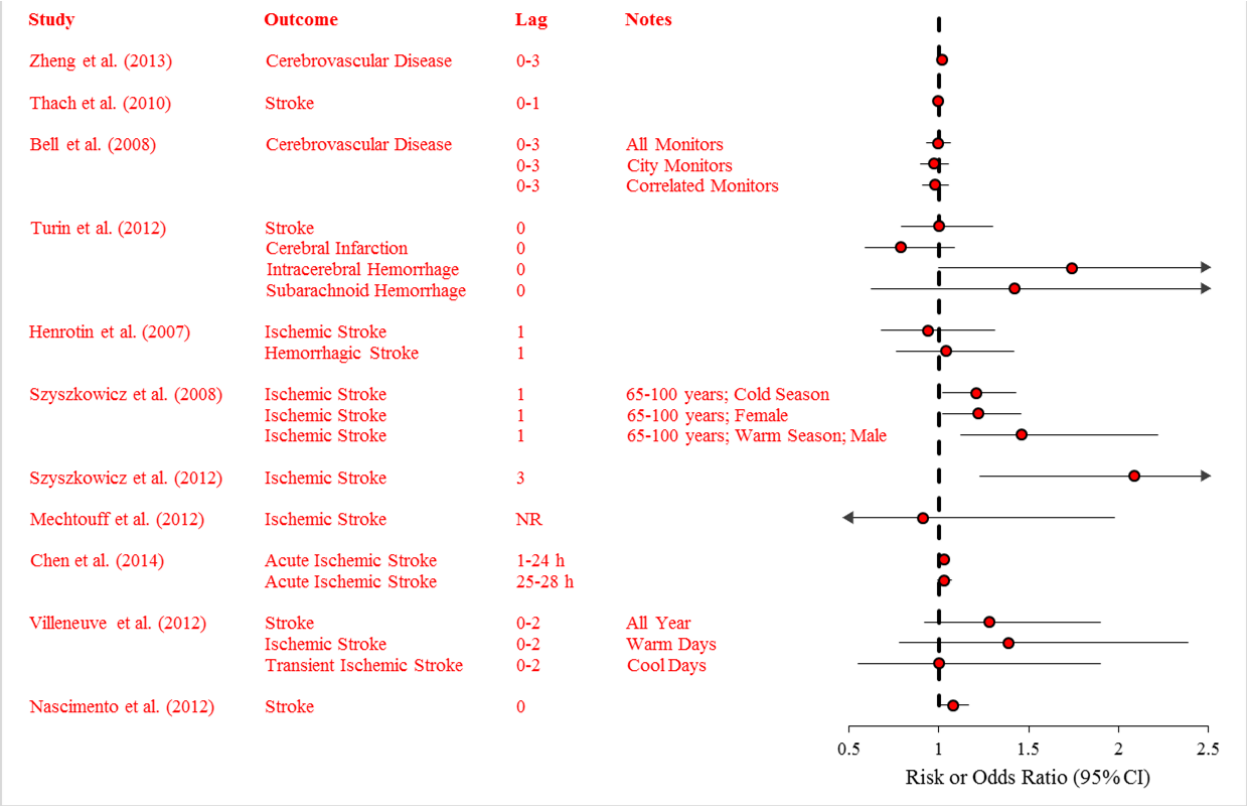
Study	Location years	Exposure Assignment	Metric	Mean/Median Concentration ppb	Upper Percentile of Concentrations ppb
†Zheng et al. (2013)	Lanzhou, China (2001−2005)	Average across four monitoring stations	24-h avg	Mean: 30.19	75th: 40.46 Max: 141.60
†Thach et al. (2010)	Hong Kong, China (1996−2002)	Average 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, Canada (1992−2002)	Average across three monitoring stations	24-h avg	Mean: 2.6	NR
†Szyszkowicz et al. (2012a)	Vancouver, Canada (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, Canada (1998−2002)	Average across three monitoring stations	1-h avg	Mean: 2.0	95th: 6.7

Table 5-35 (Continued): 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
†Villeneuve et al. (2012)	Edmonton, Canada (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

avg = average; ISA = Integrated Science Assessment; NR = not reported; ppb = parts per billion.

†Studies published since the 2008 ISA for Sulfur Oxides.



Note: Studies in red are recent studies not included in the 2008 Integrated Science Assessment (ISA) for Sulfur Oxides. Effect estimates are standardized to a 10-ppb increase in sulfur dioxide 24-hour average metric, but not standardized for other metrics (e.g., Chen et al., 2014b).

Figure 5-11 Results of studies of short-term sulfur dioxide exposure and hospital admissions for cerebrovascular disease and stroke.

Table 5-36 Corresponding risk estimates for hospital admissions or emergency department visits for cerebrovascular disease and stroke for studies presented in Figure 5-11.

Study	Location Years	Health Effect	Risk or Odds Ratio[a] (95% CI)	Copollutant Examination[b]
†Zheng et al. (2013)	Lanzhou, China 2001-2005	Cerebrovascular disease	Lag 0−3: 1.017 (1.005, 1.029)	SO_2: robust after adjustment for PM_{10} or NO_2 in copollutant models Copollutants: NO_2 association attenuated in magnitude and precision, but still positive after adjustment for SO_2 SO_2 correlations: NO_2: 0.64; PM_{10}: 0.62
†Thach et al. (2010)	Hong Kong, China 1996-2002	Stroke	Lag 0−1: 0.996 (0.979, 1.012)	No copollutant models examined No correlations provided
†Bell et al. (2008)	Taipei, Taiwan 1995-2002	Cerebrovascular disease	Lag 0−3 All Taipei monitors: 0.997 (0.930, 1.068) City monitors only: 0.972 (0.898, 1.053) Correlated monitors: 0.979 (0.907, 1.056)	No copollutant models examined No correlations provided
†Turin et al. (2012)	Takashima County, Japan 1988-2004	Stroke Cerebral infarction Hemorrhagic stroke	Lag 0 All stroke: 1.00 (0.79, 1.30) Cerebral infarction: 0.79 (0.59, 1.09) Intra-cerebral hemorrhage: 1.74 (1.00, 3.18) Subarachnoid hemorrhage: 1.42 (0.62, 3.41)	No copollutant models examined SO_2 correlations: Suspended PM: 0.54; NO_2: 0.23
Henrotin et al. (2007)	Dijon, France 1994-2004	Ischemic stroke Hemorrhagic stroke	Lag 1 Ischemic stroke: 0.94 (0.68, 1.31) Hemorrhagic stroke: 1.04 (0.76, 1.42)	No copollutant models examined No correlations provided
†Szyszkowicz (2008)	Edmonton, Canada 1992-2002	Ischemic stroke	Lag 1 Adults 65−100 yr old Cold season: 1.21 (1.02, 1.43)	No copollutant models examined No correlations provided

Table 5-36 (Continued): Corresponding risk estimates for hospital admissions or emergency department visits for cerebrovascular disease and stroke for studies presented in Figure 5-11.

Study	Location Years	Health Effect	Risk or Odds Ratio[a] (95% CI)	Copollutant Examination[b]
			Females: 1.22 (1.02, 1.46) Males and warm season: 1.46 (1.12, 2.22)	
†Szyszkowicz et al. (2012a)	Vancouver, Canada 1999-2003	Ischemic stroke	Lag 3: 2.09 (1.23, 3.52)	SO_2: robust to adjustment for O_3 in a copollutant model, and attenuated, although still positive after adjustment for CO Copollutants: O_3 association robust to adjustment for SO_2 in a copollutant model; CO association attenuated, although still positive after adjustment for SO_2 No correlations provided
†Mechtouff et al. (2012)	Lyon, France 2006-2007	Ischemic stroke	Lag NR: 0.91 (0.41, 1.98)	No copollutant models examined No correlations provided
†Chen et al. (2014b)	Edmonton, Canada 1998-2002	Acute ischemic stroke	Lag 1−24 h: 1.03 (0.99, 1.06) Lag 25−48 h: 1.03 (0.99, 1.07)	No copollutant models examined SO_2 correlations: NO_2: 0.18; O_3: −0.02; PM_{10}: 0.14; $PM_{2.5}$: 0.15
†Villeneuve et al. (2012)	Edmonton, Canada 2003-2009	Stroke Ischemic stroke Transient ischemic stroke	Lag 0−2 All stroke: 1.28 (0.92, 1.90) Ischemic stroke: 1.39 (0.78, 2.39) Transient ischemic stroke: 1.00 (0.55, 1.90)	Copollutants: O_3, CO, NO_2, and $PM_{2.5}$ associations with ischemic stroke in the warm season robust to adjustment for SO_2 No correlations provided
†Costa Nascimento et al. (2012)	São Paulo, Brazil 2007-2008	Stroke	Lag 0: 1.078 (1.000, 1.165)	No copollutant models examined SO_2 correlations: O_3: 0.26; PM_{10}: 0.48

CI = confidence interval; CO = carbon monoxide; ISA = Integrated Science Assessment; NO_2 = nitrogen dioxide; NR = not reported; O_3 = ozone; PM = particulate matter; *r* = correlation coefficient; SO_2 = sulfur dioxide.

†Studies published since the 2008 ISA for Sulfur Oxides.

All Lag times are in days, unless otherwise noted.

[a]Effect estimates are standardized to a 10-ppb increase in SO_2 24-h avg metric, but not standardized for other metrics (e.g., Chen et al., 2014b).

[b]Relevant relative risks for copollutant models can be found in Supplemental Figures 5S-1 (U.S. EPA, 2015a), 5S-2 (U.S. EPA, 2015b), and 5S-3 (U.S. EPA, 2015c) and corresponding Supplemental Tables 5S-7 (U.S. EPA, 2015l), 5S-8 (U.S. EPA, 2015m) and 5S-9 (U.S. EPA, 2015n).

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, 2008b) concluded that the overall evidence was insufficient to conclude 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. (2013a) 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. (2013a) and Rich et al. (2012) observed a positive association between 24-hour average SO_2 and systolic blood pressure, but an inverse association between 24-hour average 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. (2013a).

A pair of cross-sectional studies also reported contrasting 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, there were also three new studies examining 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-hour average 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-hour average 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-6 (U.S. EPA, 2015k). 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 intra-tracheally 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 if 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 co-pollutant 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 or insulin deficiency 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-hour average 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, 2008b) were inconsistent with regard to the association between ambient SO_2 concentrations and hospital admissions or ED visits for heart failure. Three 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-hour average 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-hour average 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 5-37 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 5-37 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 (ICD9/10)	Metric	Mean Concentration ppb	Upper Percentile of Concentrations ppb
United States					
Gwynn et al. (2000)	Buffalo and Rochester, NY (1988-1990)	Hospital admissions: Circulatory (401−405, 410−417)	24-h avg	12.2	Range: 1.63, 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 5-37 (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 (ICD9/10)	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)	10th−90th range: 2.0 to 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: 0.010 (0.005) Chicago: 0.025 (0.011) Philadelphia: 0.029 (0.015) New York City: 0.032 (0.015) Detroit: 0.025 (0.013) Houston: 0.018 (0.009) Milwaukee: 0.017 (0.013)	NR

Table 5-37 (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 (ICD9/10)	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	Range: 1.0, 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 intra-cerebral hemorrhage. (ICD codes not provided)	24-h avg	6.22 (median)	90th: 16.17

Table 5-37 (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 (ICD9/10)	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), Canada (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), Canada (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, Ontario, Canada (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, New Brunswick, Canada (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, Canada (1992-2002)	ED visits: acute ischemic stroke (434 and 436)	24-h avg	2.6	NR
†Szyszkowicz et al. (2012a)	Vancouver, Canada (1999-2003)	ED visits (discharge diagnosis): Transient ischemic attack, cerebrovascular incident, seizure	24-h avg	2.5	NR

Table 5-37 (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 (ICD9/10)	Metric	Mean Concentration ppb	Upper Percentile of Concentrations ppb
†Szyszkowicz et al. (2012b)	Edmonton, Canada (1992-2002)	ED visits: hypertension (401.9)	24 h avg	2.6	Max: 16.3
Villeneuve et al. (2006)	Edmonton, Canada (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; ISA = Integrated Science Assessment; MI = myocardial infarction; NR = not reported; ppb = parts per billion; 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, 2008b) 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 study and other studies in this section are presented in Tables 5-38, 5-39, and Figure 5-12]. 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. 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-hour average 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. 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-hour average 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 per IQR increase in 24-hour average 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-hour average SO_2.

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, all of the studies in this section used fixed site monitors to measure ambient SO_2, which have noted limitations in capturing spatial variation in SO_2, which generally lead to attenuation and loss of precision of the effect estimates (Sections 3.3.3.2 and 3.3.5.1).

Table 5-38 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, Canada (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)	Fixed site monitors in each city	24-h avg	Median: 1.9−8.0 across cities	90th: 5.3−29.4 across cities

Table 5-38 (Continued: Mean and upper percentile concentrations of sulfur dioxide from cardiovascular-related hospital admission and emergency department visit studies.

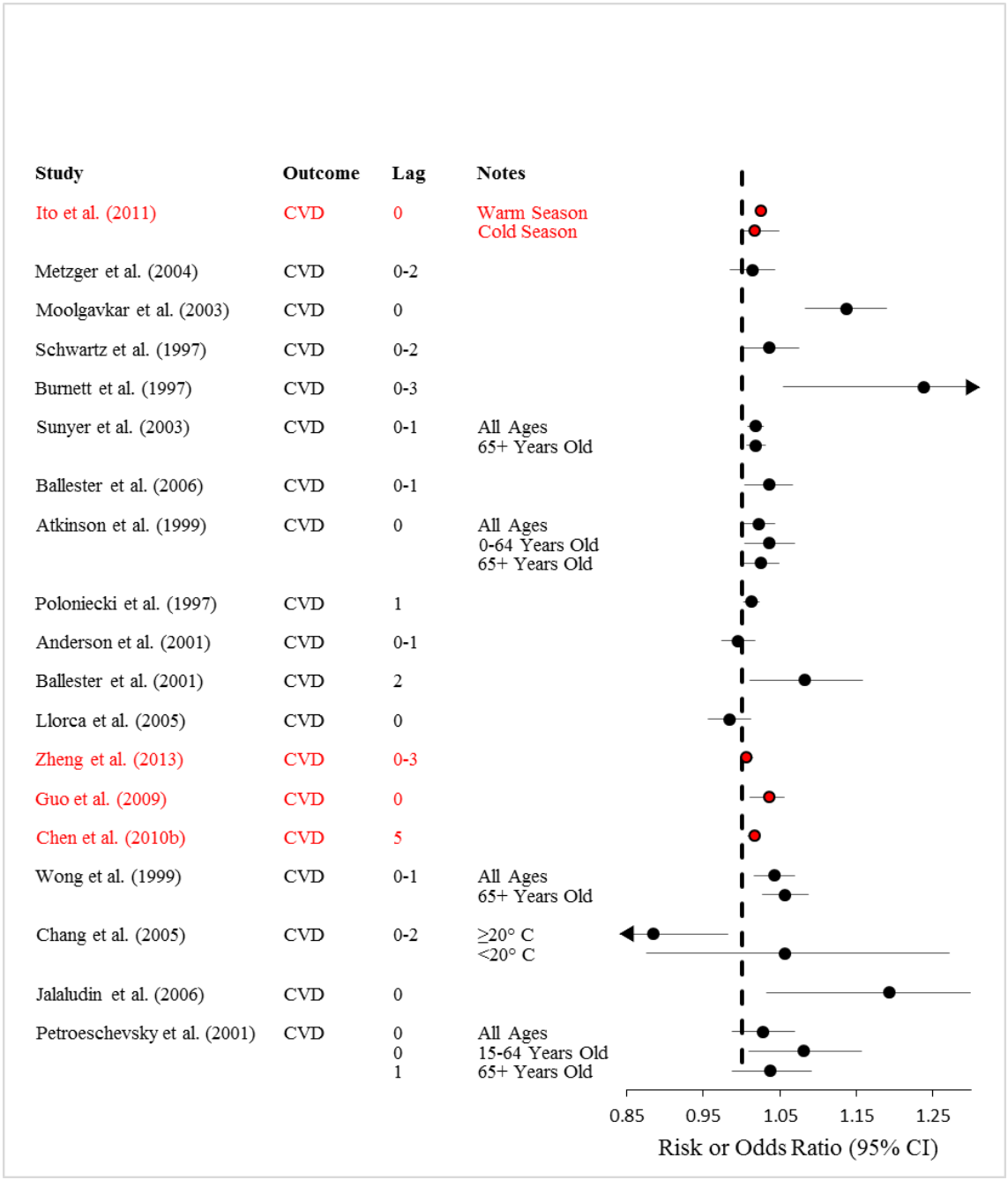
Study	Location (years)	Exposure Assignment	Metric	Mean/Median Concentration ppb	Upper Percentile of Concentrations ppb
Ballester et al. (2006)	14 Spanish cities (1995−1999)	Citywide average for each city	24-h avg	Mean: 2.9−15.6 across cities	90th: 4.8−28.8 across cities
Atkinson et al. (1999)	London, 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
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
†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

Table 5-38 (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
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

avg = average; ISA = Integrated Science Assessment; NR = not reported; ppb = parts per billion; SO_2 = sulfur dioxide.

†Studies published since the 2008 ISA for Sulfur Oxides.



Note: red indicates new studies since the 2008 SO_X Integrated Science Assessment (ISA).

Figure 5-12 Studies of hospital admissions and emergency department visits for all cardiovascular disease (CVD).

Table 5-39 Corresponding relative risk (95% CI) for hospital admissions and emergency department visits for all CVD for studies presented in Figure 5-12.

Study	Location	Risk or Odds Ratio[a] 95% CI	Copollutant Examination[b]
†Ito et al. (2011)	New York City, NY	Lag 0 Warm season: 1.026 (1.021, 1.031) Cold season: 1.018 (0.998, 1.49)	No copollutant models examined Warm season: $PM_{2.5}$: 0.66; EC: 0.60; OC: 0.71; SO_4^{2-}: 0.44; NO_3^-: 0.71; NO_2: 0.68; CO: 0.50 Cold season: $PM_{2.5}$: 0.57; EC: 0.53; OC: 0.52; SO_4^{2-}: 0.53; NO_3^-: 0.43; NO_2: 0.67; CO: 0.34
Metzger et al. (2004)	Atlanta, GA	Lag 0−2: 1.014 (0.985, 1.044)	No copollutant models examined SO_2 correlations: PM_{10}: 0.20; O_3: 0.19; NO_2: 0.34; CO: 0.26;$PM_{2.5}$: 0.17; UFP: 0.24
Moolgavkar (2003)	Los Angeles, CA	Lag 0: 1.137 (1.083, 1.190)	No copollutant models examined No correlations provided
Schwartz (1997)	Tuscon, AZ	Lag 0−2: 1.036 (0.999, 1.075)	No copollutant models examined SO_2 correlations: PM_{10}: 0.10; NO_2: 0.48; O_3: −0.27; CO: 0.40
Burnett et al. (1997)	Toronto, Canada	Lag 0−3: 1.238 (1.055, 1.452)	No copollutant models examined SO_2 correlations: O_3: 0.18; NO_2: 0.46; CO: 0.37
Sunyer et al. (2003)	Seven European cities	Lag 0−1 All ages: 1.019 (1.008, 1.029) 65+ yr old: 1.019 (1.007, 1.031)	No copollutant models examined No correlations provided

Table 5-39 (Continued): Corresponding relative risk (95% CI) for hospital admissions and emergency department visits for all CVD for studies presented in Figure 5-12.

Study	Location	Risk or Odds Ratio[a] 95% CI	Copollutant Examination[b]
Ballester et al. (2006)	14 Spanish cities	Lag 0−1: 1.036 (1.004, 1.067)	SO_2: attenuated after adjustment for CO or NO_2, and lessened in magnitude, but more precise with adjustment for TSP or O_3 Copollutants: PM_{10} and NO_2 attenuated but still positive after SO_2 adjustment. CO and O_3 robust to SO_2 adjustment, BS and TSP less precise after SO_2 adjustment SO_2 correlations: BS: 0.24; PM_{10}: 0.46; TSP: 0.31; NO_2: 0.46; CO: 0.51; O_3: −0.03
Atkinson et al. (1999)	London, England	Lag 0 All ages: 1.023 (1.003, 1.043) 0−64 yr old: 1.036 (1.004, 1.069) 65+ yr old: 1.025 (1.002, 1.049)	No copollutant models examined No correlations provided
Poloniecki et al. (1997)	London, England	Lag 1: 1.013 (1.003, 1.023)	No copollutant models examined No correlations provided
Anderson et al. (2001)	Birmingham, England	Lag 0−1: 0.995 (0.974, 1.017)	No copollutant models examined SO_2 correlations: PM_{10}: 0.55; $PM_{2.5}$: 0.52; $PM_{2.5-10}$: 0.31; BS: 0.50; NO_2: 0.52; O_3: −0.22; CO: 0.49
Ballester et al. (2001)	Valencia, Spain	Lag 2: 1.082 (1.011, 1.158)	SO_2: slightly attenuated, but still positive after adjustment for BS; robust to adjustment for CO Copollutants: BS attenuated but still positive after SO_2 adjustment. CO attenuated and null after SO_2 adjustment SO_2 correlations (Pearson *r*): BS: 0.63; NO_2: 0.22; CO: 0.74; O_3: −0.35
Llorca et al. (2005)	Torrelavega, Spain	Lag 0: 0.984 (0.956, 1.012)	No copollutant models examined SO_2 correlations: NO_2: 0.59; TSP: −0.40

Table 5-39 (Continued): Corresponding relative risk (95% CI) for hospital admissions and emergency department visits for all CVD for studies presented in Figure 5-12.

Study	Location	Risk or Odds Ratio[a] 95% CI	Copollutant Examination[b]
†Zheng et al. (2013)	Lanzhou, China	Lag 0−3: 1.007 (0.999, 1.015)	SO_2: small, precise association robust to NO_2 adjustment; attenuated and null after adjustment for PM_{10} Copollutants: PM_{10} and NO_2 robust to SO_2 adjustment SO_2 correlations: NO_2: 0.64; PM_{10}: 0.62
†Guo et al. (2009)	Beijing, China	Lag 0 1.037 (1.011, 1.056)	SO_2: association robust to NO_2 or $PM_{2.5}$ adjustment SO_2 correlations: NO_2: 0.53; $PM_{2.5}$: 0.42
†Chen et al. (2010b)	Shanghai, China	Lag 5: 1.017 (1.008, 1.025)	SO_2: association robust to NO_2 or PM_{10} adjustment Copollutants: PM_{10} attenuated and no longer positive after SO_2 adjustment. NO_2 attenuated in strength and precision, but still positive SO_2 correlations: NO_2: 0.76; PM_{10}: 0.72
Wong et al. (1999)	Hong Kong, China	Lag 0−1 All ages: 1.043 (1.016, 1.070) 65+ yr old: 1.056 (1.027, 1.087)	No copollutant models examined No correlations provided
Chang et al. (2005)	Taipei, Taiwan	Lag 0−2 ≥20°C: 0.885 (0.798, 0.982) <20°C: 1.056 (0.876, 1.272)	No association between SO_2 and CVD hospitalizations. Copollutant models did not change results No correlations provided
Jalaludin et al. (2006)	Sydney, Australia	Lag 0 65+ yr old: 1.193 (1.033, 1.377)	SO_2: attenuated, but still positive after adjustment for BS, $PM_{2.5}$, NO_2, or CO; robust to adjustment for O_3 or PM_{10} Copollutants: PM_{10} attenuated but still positive after SO_2 adjustment. BS, $PM_{2.5}$, NO_2, and CO robust to SO_2 adjustment SO_2 correlations: BS: 0.21; PM_{10}: 0.37; $PM_{2.5}$: 0.27; O_3: 0.45; NO_2: 0.52; CO: 0.46

Table 5-39 (Continued): Corresponding relative risk (95% CI) for hospital admissions and emergency department visits for all CVD for studies presented in Figure 5-12.

Study	Location	Risk or Odds Ratio[a] 95% CI	Copollutant Examination[b]
Petroeschevsky et al. (2001)	Brisbane, Australia	Lag 0: All ages 1.028 (0.987, 1.070) Lag 0: 15−64 yr old 1.081 (1.010, 1.157 Lag 1: 65+ yr old 1.038 (0.988, 1.091)	No copollutant models examined No correlations provided

BS = black smoke; CI = confidence interval; CO = carbon monoxide; CVD = cardiovascular disease; EC = elemental carbon; ISA = Integrated Science Assessment; PM = particulate matter; O_3 = ozone; OC = organic carbon; SO_4^{2-} = sulfate; NO_2 = nitrogen dioxide; NO_3^- = nitrate; *r* = correlation coefficient; SO_2 = sulfur dioxide; TSP = total suspended particulates; UFP = ultrafine particle.

†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 24-h avg and 1-h max metrics, respectively.

[b]Relevant relative risks for copollutant models can be found in Supplemental Figures 5S-1 (U.S. EPA, 2015a), 5S-2 (U.S. EPA, 2015b), and 5S-3 (U.S. EPA, 2015c) and corresponding Supplemental Tables 5S-7 (U.S. EPA, 2015l), 5S-8 (U.S. EPA, 2015m) and 5S-9 (U.S. EPA, 2015n).

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. 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 (Section5.5.1.3, Figure 5-16). 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 5-16). 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-hour average 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 5-47).

Previous studies evaluated in and prior to the 2008 SO_X ISA, which 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 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-hour average 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 more so in models with NO_2 (Figure 5-17). In an analysis of stroke mortality in eight of the CAPES cities, Chen et al. (2013) reported a similar pattern of associations as 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-hour average 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)]. Additionally, it is important to note that the aforementioned studies rely on central site monitors for estimating exposure. SO_2 is more spatially variable than other pollutants as reflected in the generally low to moderate spatial correlations across urban

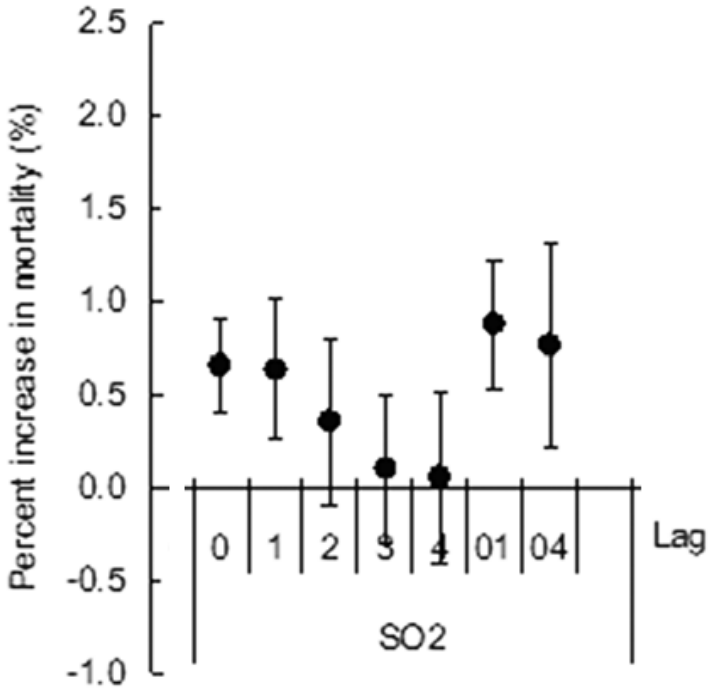
geographical scales (Section 3.3.3.2); therefore, the attenuation in SO_2 associations may be a reflection of the different degree of exposure error across pollutants (Section 3.3.5.1). Overall, the studies that examined potential copollutant confounding on the SO_2-cardiovascular mortality relationship report results consist with what has been 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, 2.9% increase, which is 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, which found 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) report 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 (Sections 3.3.3.2, 3.3.5.1). 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 it remains unclear if 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.

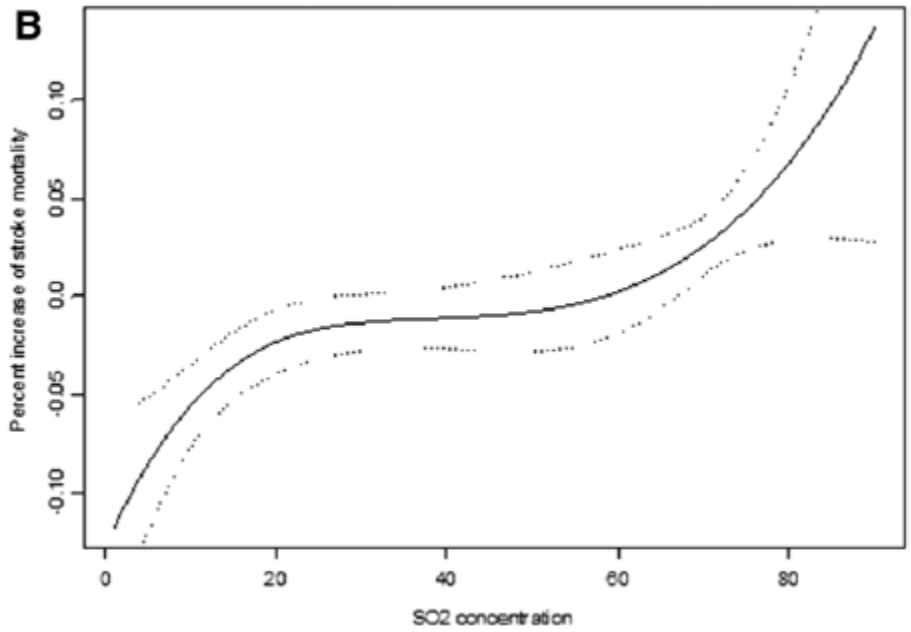
When examining the lag structure of associations, Chen et al. (2013) reported results for stroke mortality that are consistent with those observed for all cardiovascular mortality. As depicted in Figure 5-13 there is evidence of a steady decline in the SO_2-stroke mortality association at longer individual 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 5-18), as well as the PAPA study (Kan et al., 2010b) (Figure 5-19). 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.



Adapted from Chen et al. (2013).

Figure 5-13 Percent increase in stroke mortality associated with a 10 μg/m^3 (3.62 ppb) increase in SO_2 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 if there was 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 5-14).



Adapted from Chen et al. (2013).

Figure 5-14 Pooled concentration-response curves for SO_2 and daily stroke mortality in eight Chinese cities for a 10 μg/m^3 (3.62 ppb) increase in 24-hour average concentrations at lag 0−1 day. Note: The black line represents the mean estimate and the dotted lines are 95% confidence intervals.

Overall, recent multi-city 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-cardiovascualr 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 associations: remain robust when alternating the df used to control for seasonality; associations are larger and

more precise within the first few days after exposure in the range of 0 and 1 day; and that there is a linear, no threshold C-R relationship, respectively.

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 (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 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) (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 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

Six 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-hour average 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 inter-quartile 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. (2013a) 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. (2013a) 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-6. (U.S. EPA, 2015k) 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 (pNN50), 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 and largely inconsistent.

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, 2008b) 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-hour average SO_2] (Henneberger et al., 2005). There was little variability between daily measured SO_2 concentrations, therefore 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. Contrary to what the limited findings of these studies may suggest, epidemiologic and experimental evidence is not suggestive of an association between SO_2 exposure and arrhythmias (Section 5.3.1.3).

Insulin Resistance

There were no epidemiologic studies of diabetes or insulin deficiency available for the 2008 ISA for Sulfur Oxides. Two recent studies reported contrasting findings regarding short-term associations between air pollutants and measures of insulin resistance, which plays a key role 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-hour average 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. Conversely, Kelishadi et al. (2009) reported a lack of an association between 24-hour average SO_2 and insulin resistance in a study of 374 Iranian children aged 10−18 years. Both of the recent studies relied on central site monitoring for exposure estimation, and neither evaluated potential confounding by other pollutants.

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.

Blood Markers 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, 2008b) (Table 5-40). 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.

Epidemiologic Studies

The epidemiologic data available for review by the 2008 ISA for Sulfur Oxides (U.S. EPA, 2008b) did not suggest a consistent link between SO_2 and blood markers 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 5-40). Similarly, during the Beijing Olympics, SO_2 was inversely associated with white blood cell counts, although positively associated with fibrinogen (Zhang et al., 2013a). 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. 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., 2011a), 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.

Table 5-40 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, Canada 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-day moving average 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	
†Lee et al. (2011a)	Allegheny County, PA 1997–2001 (n = 1,696)	7-day 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."	

Table 5-40 (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)
†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 days: 0.2 (−4.3, 4.7) Homocysteine difference, postmethionine-load (percent change) Lag 24 h: 2.6 (−3.2, 8.6) Lag 0−6 days: 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, Canada 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.
†Zhang et al. (2013a)	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).

Table 5-40 (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)
†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.

avg = average; AT = atascadero; CI = confidence interval; CRP = C-reactive protein; IL-6 = interleukin-;6; Lp-PLA_2 = lipoprotein-associated phospholipase A;2n = sample size; ISA = Integrated Science Assessment; mg/cL = milligrams per distributed lag; NO = nitric oxide; NO_2 = nitrogen dioxide; NR = not reported; PNC = particle number concentration; ppb = parts per billion; 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.

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 blood markers of cardiovascular risk following SO_2 exposure. Study characteristics are summarized in Supplemental Table 5S-6 (U.S. EPA, 2015k). 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 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 (Baskurt, 1988). These results indicate a systemic effect of inhaled SO_2 and are consistent with an oxidative injury to red blood cells.

Summary of Subclinical Effects Underlying Cardiovascular Disease

There is inconsistent evidence regarding any potential link between SO_2 and other circulating markers of cardiovascular risk. Studies of markers of inflammation 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 suggestive of, but not sufficient to infer, a causal relationship between short-term exposure to SO_2 and cardiovascular health effects. Associations of short-term exposure to SO_2 with the triggering of an MI have been observed in epidemiologic studies. Epidemiologic studies have also reported SO_2-associated hospitalizations and ED visits for MI, IHD, and aggregated CVD, ST-segment alterations, and mortality from cardiovascular disease. In general, studies used fixed-site monitors to measure ambient SO_2 concentrations. This approach has noted limitations in capturing spatial variation in SO_2 and typically leads to attenuation and loss of precision of the effect estimates (Sections 3.3.3.2 and 3.3.5.1). There is also uncertainty regarding the influence of confounding by copollutants. Experimental studies examining the direct effect of SO_2 exposure on cardiovascular outcomes, which would allow a complete evaluation of coherence across disciplines, are lacking. The limited evidence from the available experimental studies is inconsistent and does not demonstrate potentially biologically plausible mechanisms for cardiovascular effects.

This conclusion represents a change from the 2008 ISA for Sulfur Oxides that concluded the "the evidence as a whole is inadequate to infer a causal relationship" (U.S. EPA, 2008b). Specifically, the epidemiologic and experimental studies available at the time of the last review were inconsistent, lacked coherence across and within disciplines, and were limited by inadequate control for potential confounding. Despite some positive findings, a limited number of controlled human exposure and epidemiologic studies reviewed in the 2008 ISA for Sulfur Oxides provided inconsistent evidence to support an effect of SO_2 on the autonomic nervous system. Some epidemiologic studies found positive associations between ambient SO_2 concentrations and risk of hospital admissions or ED visits for all cardiovascular diseases. However, it was unclear at that time whether these results supported a direct effect of short-term SO_2 exposure on cardiovascular morbidity or were confounded by other correlated pollutants. Recent epidemiologic studies have further evaluated this uncertainty using copollutant models and comparing associations of SO_2 with those of other criteria pollutants. While the recently reviewed studies provide some evidence for independent associations of SO_2 with cardiovascular effects after adjusting for some pollutants, uncertainties still remain regarding the independent effect of SO_2 after adjustment for copollutants [Supplemental Figures 5S-1−5S-3 (U.S. EPA, 2015a, b, c) and corresponding Supplemental Tables 5S-

7–5S-9 (U.S. EPA, 2015l, m, n)]. Moreover, there continues to be a lack of experimental evidence in coherence with the epidemiologic studies to strengthen the inference of causality for SO_2-related cardiovascular effects, including MI. Although spillover of sulfite into the circulation could possibly lead to redox stress and inflammation, there is no evidence that this occurs at relevant concentrations (Section 4.3). Thus, the limited and inconsistent mechanistic evidence, including key events in the proposed mode of action, fails to describe a role for SO_2 in the triggering of cardiovascular diseases; an uncertainty that remains from the 2008 ISA for Sulfur Oxides.

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 [(U.S. EPA, 2015e), Tables I and II]. The key evidence, supporting or contradicting, as it relates to the causal framework is summarized in Table 5-41. The causal determination between short-term SO_2 exposure and cardiovascular effects is primarily based on the evidence for effects related to triggering an MI. The evaluation of evidence supporting the occurrence of an MI includes hospital admissions and ED visits for IHD or MI and ST-segment amplitude changes. Time-series studies of adults in the general population generally report seasonal or year-round associations between 24-hour average and 1-hour maximum SO_2 concentrations and hospital admissions and ED visits for IHD and MI in single-pollutant models (Figure 5-10, Section 5.3.1.2). Although the majority of the reported relative risks were above 1.0, the risk estimates ranged from 0.92 to 1.21 per 10-ppb increase in SO_2, depending on whether stratified analyses were conducted. The small number of epidemiologic studies based on clinical data report inconsistent evidence regarding associations between ambient SO_2 concentrations and risk of MI. However, one of the studies reviewed that observed a null association was likely underpowered to detect an association of the expected magnitude. Once hospitalized, ST-segment decreases are considered a nonspecific marker of myocardial ischemia. A single study reported an association between short-term SO_2 exposure and ST-segment changes 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 (Chuang et al., 2008).

The evidence for IHD and MI hospital admissions and ED visits is coherent with the positive associations reported in epidemiologic studies of short-term SO_2 exposure and stroke 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.

Controlled human exposure and animal toxicological studies have reported limited and inconsistent results for effects on the cardiovascular system, including heart rate, HRV,

arrhythmia frequency, blood pressure, and biomarkers of cardiovascular risk. Studies have not evaluated SO_2 exposure and measures of atherosclerotic plaque instability or rupture that could provide coherence with epidemiologic studies reporting associations with triggering an MI. Additionally, experimental studies do not provide convincing evidence to support a plausible biological mechanism leading to cardiovascular effects such as triggering an MI following SO_2 exposure. There is the potential that cardiovascular effects following SO_2 exposure could be mediated through activation of neural reflexes or oxidative stress (Section 4.3.1); however, uncertainty remains.

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 moderately to highly correlated with SO_2. Generally, SO_2 has low to moderate correlations with other NAAQS pollutants with the highest correlations for primary pollutants (i.e., CO and NO_2) (Section 3.3.4.1). 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-1, (U.S. EPA, 2015a)], NO_2 [Figure 5S-2, (U.S. EPA, 2015b)], or other correlated pollutants [Figure 5S-3; (U.S. EPA, 2015c)] 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 CVD outcomes or if SO_2 is a marker for the effects of another correlated pollutant or mix of pollutants.

There is inconclusive evidence from epidemiologic, controlled human exposure, and animal toxicological studies for other cardiovascular effects from short-term exposure to SO_2. Studies of patients with implantable cardioverter defibrillators, hospital admissions for arrhythmias, and out-of-hospital cardiac arrest do not provide evidence for a relationship between ambient SO_2 concentrations and arrhythmias (Section 5.3.1.3). Epidemiologic and experimental studies provide inconsistent evidence for a potential association between ambient SO_2 concentrations and risk of cerebrovascular disease and

stroke (Section 5.3.1.4) and increased BP (Section 5.3.1.5). Other outcomes have an insufficient quantity of studies to evaluate the effects, including venous thromboembolism (Section 5.3.1.6) and heart failure (Section 5.3.1.7).

In conclusion, epidemiologic evidence from multiple studies at relevant SO_2 concentrations is suggestive of, but not sufficient to infer, a causal relationship between short-term SO_2 exposure and cardiovascular health effects. The strongest evidence supporting this determination comes from epidemiologic studies of varying quality that are generally supportive of an association between ambient SO_2 and triggering an MI. This evidence is supported by findings from epidemiologic studies of cardiovascular and stroke mortality. The use fixed-site monitors to measure ambient SO_2 in the epidemiologic studies, has limitations in capturing spatial variation in SO_2, which generally lead to attenuation and loss of precision of the effect estimates. Additionally, the majority of the studies did not include analyses to determine whether SO_2 is independently associated with these cardiovascular outcomes; thus, uncertainty remains regarding copollutant confounding. Generally, there is a lack of experimental studies in human and animal studies evaluating exposure to SO_2; their findings are inconsistent and do not provide evidence to support the epidemiologic studies and the lack of studies. Thus, the combined evidence from epidemiologic and experimental studies is suggestive of, but not sufficient to infer, a causal relationship between short-term SO_2 exposure and cardiovascular effects.

Table 5-41 Summary of evidence, which is suggestive of, but not sufficient to infer, a causal relationship between short-term SO_2 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			
Generally supportive but not entirely consistent evidence from multiple, high-quality epidemiologic studies at relevant SO_2 concentrations	Increases in hospital admissions and ED visits for IHD and MI in adults in multiple studies, including multicity studies, in diverse locations	Section 5.3.1.2	24-h avg: 1.2−15.6 ppb
	Increases in hospital admissions and ED visits for all CVD in adults in multiple studies, including multicity studies, in diverse locations	Section 5.3.1.8	24-h avg: 1.9−30.2 ppb
	Coherence with ST-segment depression in adults with pre-existing coronary heart disease in association with SO_2	Chuang et al. (2008)	24-h avg: 4.6 ppb (median)
	Consistent evidence for increased risk of cardiovascular mortality in adults applying differing model specifications in diverse locations	Section 5.3.1.9	
Uncertainty regarding potential confounding by copollutants	A number of studies report associations with ED visits and hospital admissions were attenuated after adjustment with CO, NO_2, or PM_{10}	Supplemental Figures 5S-1, 5S-2, and 5S-3 (U.S. EPA, 2015a, b, c)	
Uncertainty regarding exposure measurement error	Majority of evidence from time-series studies that rely on exposure estimates from central site monitors	Sections 3.3.3.2 and 3.3.5.1	
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	

Table 5-41 (Continued): Summary of evidence, which is suggestive of, but not sufficient to infer, a causal relationship between short-term SO_2 exposure and cardiovascular effects.

Rationale for Causal Determination[a]	Key Evidence[b]	Key References[b]	SO_2 Concentrations Associated with Effects[c]
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	Sections 5.3.1.4 and 5.3.1.5	
	Insufficient quantity of studies evaluating decompensation of heart failure and venous thrombosis and pulmonary embolism	Sections 5.3.1.6 and 5.3.1.7	
	Inconsistent evidence for changes in HR and HRV in controlled human exposure and epidemiologic studies	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 4-3	

Table 5-41 (Continued): Summary of evidence, which is suggestive of, but not sufficient to infer, a causal relationship between short-term SO_2 exposure and cardiovascular effects.

Rationale for Causal Determination[a]	Key Evidence[b]	Key References[b]	SO_2 Concentrations Associated with Effects[c]
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 days. Results based on SO_2 averaged across central site monitors. 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
Uncertainty due to limited coherence with cardiovascular 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		

avg = average; 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; ppb = parts per billion; PM = particulate matter; SO_2 = sulfur dioxide; ST-segment = segment of the electrocardiograph between the end of the S wave and beginning of the T wave.

[a]Based on aspects considered in judgments of causality and weight of evidence in causal framework in Tables I and II of the Preamble (U.S. EPA, 2015e).

[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.

5.3.2 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, 2008b)(U.S. EPA, 2008) reviewed a limited body of toxicological and

epidemiologic studies published through 2006 and concluded that the available evidence was inadequate to determine a causal relationship between the effects of long-term exposure to SO_2 on cardiovascular health. New studies do not change this conclusion.

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 postmenopausal 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 3.3.5.2). Consequently, the extent to which this study supports an independent effect of SO_2 on the cardiovascular system is limited.

Experimental animal studies with long-term exposures below 5,000 ppb were not available for inclusion in the 2008 ISA for Sulfur Oxides. Although a small number of studies using exposures above 5,000 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. Several recent epidemiologic studies of the association of long term SO_2 exposure with preclinical and clinical cardiovascular outcomes add to the available body of evidence. These studies do not change the conclusion from the 2008 ISA for Sulfur Oxides. 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. To clearly characterize the evidence underlying causality, the discussion of the evidence is organized into groups of related outcomes (e.g., ischemic heart disease and myocardial infarction, cerebrovascular disease and stroke). Evidence for subclinical effects (e.g., blood biomarkers of cardiovascular effects) of long-term exposure to SO_2 are discussed in Section 5.3.2.5, and serve to inform biological plausibility across multiple clinical cardiovascular events and outcomes.

5.3.2.2 Myocardial Infarction and Ischemic Heart Disease

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 5-42). However, uncertainty remains regarding the influence of exposure measurement error on the effect estimates observed in epidemiologic studies (Section 3.3.3.2) 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 3.3.4).

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. An increased risk of 1.20 (1.02, 1.41) was observed per 10 µg/m^3 per $PM_{2.5}$. An imprecise association between SO_2 and incident MI was observed (see Table 5-42). 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).

Table 5-42 Epidemiologic studies of long-term exposure to SO_2 and effects on the cardiovascular system.

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, U.S. 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) Stroke incidence SO_2: HR 6.21 (0.4, 88) per 5 ppb SO_2 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) Stroke incidence HR: 1.13 (1.00, 1.34) Arrhythmia incidence HR: 1.13 (1.00, 1.27) Heart failure incidence HR: 1.27 (1.06, 1.59) per 5 ppb Covariates: age, sex, smoking BMI, diabetes, hypertension, and index of multiple deprivation Copollutant adjustment: none
Rosenlund et al. (2006)	n = 1,397 cases and 1,870 controls SHEEP cohort 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

Table 5-42 (Continued): Epidemiologic studies of long-term exposure to SO_2 and effects on the cardiovascular system.

Study	Cohort, Location, and Study Period	Mean (ppb)	Exposure Assessment	Effect Estimates (95% CI)
Miller et al. (2007)	WHI Cohort United States 1994−1998	NR	Annual avg (2000): nearest monitor to residence zip code centroid	Cardiovascular events HR: 1.07 (0.95, 1.20) per 5 ppb 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
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 Correlations between PM_{10}, ozone, and SO_2 characterized as "high" NO_2, r = 0.38 O_3, r = 0.87 PM_{10}, r = 0.70	Stroke OR: 1.21 (1.01, 1.46) per 5 ppb CHD, MI, or CHF OR: 1.18 (0.86, 1.66) per 5 ppb 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
Dong et al. (2014)	n = 9,354 Children (5−17 yr) Seven cities northeastern China 2012−2013	Mean: 18. SD: 20	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 Diastolic blood pressure (all children) 0.43 (0.26, 0.61) SBP (all children 0.71 (0.50, 0.91) per 5 ppb Covariates adjustment: age, sex, BMI, parental education, low birth weight, premature birth, income, passive smoking exposure, home coal use, exercise time, area residence per person, family history of hypertension, and district

Table 5-42 (Continued): Epidemiologic studies of long-term exposure to SO_2 and effects on the cardiovascular system.

Study	Cohort, Location, and Study Period	Mean (ppb)	Exposure Assessment	Effect Estimates (95% CI)
Johnson et al. (2010)	Edmonton, 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; CHF = congestive heart failure; CHD = coronary heart disease; 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; med = median; MI = myocardial infarction; N = population number; NO_2 = nitrogen dioxide; non-HS = non-hemhorragic stroke; NR = not reported; Q1 = 1st quartile; Q2 = 2nd quartile; Q3 = 3rd quartile; Q4 = 4th quartile; Q5 = 5th quartile; OR = odds ratio; O_3 = ozone; PM = particulate matter; ppb = parts per billion; r = correlation coefficient; RR = relative risk; SBP = systolic blood pressure; SD = standard deviation; SES = socioeconomic status; SHEEP = Stockholm Heart Epidemiology Programme; SO_2 = sulfur dioxide; TIA = transient ischemic attack;WHI = Women's Health Initiative.

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 away from the null (Section 3.3.5.2). Associations of other pollutants (i.e., PM_{10}, NO_2 ozone) with MI in this study were also observed.

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-year average 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 observed. 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. Weak or inverse associations of cardiovascular and ischemic heart disease were reported in a study relying on a particle dispersion model to estimate SO_X emissions (gaseous and particulate component) from a refinery (Ancona et al., 2015). Null associations with PM_{10}, which was highly correlated with SO_X (r = 0.81) in this study, were also observed.

Overall, these epidemiologic data do not provide support for an association of long-term SO_2 exposure with MI. Correlations between SO_2 concentration and other pollutants are generally moderate to high introducing uncertainty regarding the independent effect of SO_2 on the cardiovascular system. Further, the exposure assessment may be subject to some degree of error depending on the method (Sections 3.3.3.2).

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, O_3) and PM (Table 5-42). 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 O_3) 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. 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, Canada (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).

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 and in Table 5-42. 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 were 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).

Blood Pressure and Hypertension

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-year average SO_2 concentration. Associations of hypertension with the other pollutants examined (i.e. PM_{10}, Ozone, CO, NO_2) were also reported in these studies.

5.3.2.4 Cardiovascular Mortality

The recent evidence for associations between long-term SO_2 exposure and total mortality is generally consistent with the evidence in the 2008 ISA for Sulfur Oxides (Section 5.5.2). Several studies report associations between long-term SO_2 exposure and cardiovascular mortality (Figure 5-25); 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 3.3.4) and uncertainties remain regarding the influence of exposure measurement error (Sections 3.3.3.2 and 3.3.5.2). Together, these uncertainties limit the interpretation of the causal nature of the associations observed in the available epidemiologic studies of long-term mortality.

5.3.2.5 Subclinical Effects Underlying Cardiovascular Diseases

Markers of Cardiovascular Disease Risk

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, weak imprecise increases in pulse wave velocity and augmentation index were observed in association with SO_2 concentration. Other pollutants examined (NO_2, $PM_{2.5}$, black smoke) were not associated cIMT although associations between NO_2 concentration and pulse wave velocity/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).

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-year average 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).

Markers of Inotropic Change in the Rodent Heart

Ion channels in the heart including the adenosine triphosphate (ATP)-sensitive potassium (K_{ATP}) channels are important for cardiac force conduction and heart rate. Pathophysiologically, the K_{ATP} channels are thought to play an important role in

myocardial ischemia reperfusion injury and ischemic preconditioning (Backx, 2008). These ion channels were examined in adult male mice that had been exposed to 1.24 and 2.48 ppm SO_2 for 4 hours/day for 30 days and the two K_{ATP} channel subunits, sulfonylurea receptor 2A (SUR2A) and the inward-rectifier potassium ion channel $K_{ir}6.2$, in rat hearts were shown to have significantly higher message (mRNA) levels after SO_2 exposure versus air control males (Zhang et al., 2014). Protein levels of these subunits reflected the same trend, albeit not significant. Earlier studies are consistent with these findings (Zhang and Meng, 2012; Nie and Meng, 2005; Du and Meng, 2004). Message levels of cardiac ion channels, which contribute to inotropic potential of rat hearts, is significantly altered by exposure to inhaled SO_2.

Overall, there is no consistent positive trend in the associations observed between SO_2 and markers of cardiovascular risk, most notably 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.

5.3.2.6 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. This conclusion is consistent with the conclusion of the 2008 ISA for Sulfur Oxides (U.S. EPA, 2008b). The available evidence examining the relationship between long-term exposure to SO_2 and cardiovascular effects was evaluated using the framework described in Tables I and II of the Preamble (U.S. EPA, 2015e). The key evidence, supporting or contradicting, as it relates to the causal framework is summarized in Table 5-43.

Table 5-43 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 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 5-42	
Uncertainty due to exposure measurement error	Central site monitors may not capture spatial variability of SO_2 concentrations. SO_2 estimates from dispersion model show poor to moderate agreement with measured concentrations.	Miller et al. (2007) Section 3.3.3.2 Atkinson et al. (2013) Forbes et al. (2009a)	
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	Backx (2008) Section 5.3.2.5	1.24 or 2.48 ppm SO_2 4 h/day for 30 days

Table 5-43 (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 systemic inflammation (e.g. cIMT, IL-6, CRP) in epidemiologic studies	Section 4.3	

cIMT = carotid intima-media thickness; CO = carbon monoxide; CRP = C-reactive protein; CVD = cardiovascular disease; IL-6 = interleukin-;6; med = median; MI = myocardial infarction; NO_2 = nitrogen dioxide; NR = not reported; ppb = parts per billion; SO_2 = sulful dioxide.

[a]Based on aspects considered in judgments of causality and weight of evidence in causal framework in Tables I and II of the Preamble (U.S. EPA, 2015e).

[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.

Although a number of epidemiologic studies report positive associations between long-term exposure to SO_2 concentrations and cardiovascular disease and stroke (Section 5.3.2.5), the evidence for any one endpoint is limited and inconsistent. The animal toxicological literature shows evidence for negative inotropic changes in the rodent heart after chronic SO_2 exposure. Exposure measurement error is an uncertainty in the interpretation of the evidence. As discussed in Section 3.3.3.2, short-term metrics of SO_2 concentration typically have low to moderate spatial correlations across urban geographical scales and thus, studies using central site monitors for exposure assessment are subject to some degree of exposure error. Dispersion models generally capture SO_2 variability on near-source spatial scales (up to tens of km), but are subject to uncertainty under specific meteorological conditions (Section 3.2.2.1). There is additional uncertainty regarding the potential for copollutant confounding (Section 3.3.4). Primary pollutants such as NO_2 and CO typically show moderate to high correlations with SO_2 (Table 5-42) and there is a lack of experimental evidence to provide coherence or biological plausibility for an independent effect of SO_2 on cardiovascular health. In conclusion, 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.

5.4 Reproductive and Developmental Effects

5.4.1 Introduction

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, 2008b), with over 40 recent epidemiologic studies. However, the number of studies for any particular outcome remains limited. Among the recent epidemiologic studies, outcomes of fetal growth (e.g., small for gestational age, preterm birth, and birth weight) predominate. Several new studies of congenital anomalies have been added 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.

At present, one of the challenges to reproductive health research is selecting the appropriate exposure windows to study, as biological modes of action leading to adverse reproductive outcomes are not well understood. While some outcomes (e.g., cardiac birth defects) have a known risk period, many outcomes do not, or have multiple possibilities for risk periods and modes of action. Due to this, many epidemiologic studies will examine multiple exposure windows, including both long-term (months to years; i.e., trimesters or entire pregnancy) and short-term (days to weeks; i.e., days or weeks immediately preceding birth) periods. Animal toxicological studies will investigate short-term air pollution exposure windows that are equivalent to human pregnancy in lifestage but not in absolute time (e.g., entire pregnancy of a rodent is typically 18−24 days). In order to characterize the weight of evidence for the effects of SO_2 on reproductive and developmental effects in a consistent, cohesive, and integrated manner, results from both short-term and long-term exposure periods are included in this section and are identified accordingly in the text and tables throughout this section.

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), but also 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.

Epidemiologic studies included in the 2008 SO_X ISA (U.S. EPA, 2008b) examined impacts on reproductive outcomes including: preterm birth; birth weight; intra-uterine growth retardation; birth defects; infant mortality; and neonatal respiratory hospitalizations. Possible modes of action follow those proposed for other air pollutants

including: oxidative stress, systemic inflammation, vascular dysfunction, and impaired immune function. While positive associations were observed in the previous SO_X ISA (U.S. EPA, 2008b), 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.

In toxicological research, only a single study has been published at relevant exposure levels (2,000 ppb or lower) for this ISA. This study investigated reproductive changes in exposed females and their offspring, altered birth outcomes, and developmental effects. 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: the difficulty in assessing exposure as most studies use existing monitoring networks to estimate individual exposure to ambient air pollution, the need for detailed exposure data and potential residential movement of mothers during pregnancy, 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 limited evidence on the physiological modes of action for these effects (Ritz and Wilhelm, 2008; Slama et al., 2008). 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.

An ongoing limitation of many air pollution studies is adjustment for copollutants; in studies of reproductive and developmental outcomes, copollutants often are not adjusted for. Three recent studies across reproductive and developmental health outcomes examine effects of SO_2 adjusted for copollutants (Faiz et al., 2013; Slama et al., 2013; Le et al., 2012). No clear trends are observed in copollutant models. 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.

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.

Table 5-44 Key reproductive and developmental epidemiologic studies for SO_2.

Study	Location sample size	Mean SO_2 ppb	Exposure Assessment	Selected Effect Estimates* 95% CI
Fetal Growth				
Liu et al. (2003)	Vancouver, Canada (n = 229,085)	4.9	Monitors at census subdivision level	IUGR (those with birth weight falls 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, Canada (n = 70,249)	5.3	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, U.S. (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)
Le et al. (2012)	Detroit, MI, U.S. (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)

Table 5-44 (Continued): Key reproductive and developmental epidemiologic studies for SO_2.

Study	Location sample size	Mean SO_2 ppb	Exposure Assessment	Selected Effect Estimates* 95% CI
Preterm Birth				
Liu et al. (2003)	Vancouver, Canada (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 U.S. (n = 187,997)	7.9	Monitors at county level	Last 6 weeks: 1.05 (1.00, 1.10) 3 day 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 day lag: 1.01 (0.99, 1.04) 2 day lag: 1.02 (0.99, 1.04) 3 day lag: 1.02 (0.99, 1.04)
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, Canada (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, Canada (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, U.S. (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, U.S. (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)

Table 5-44 (Continued): Key reproductive and developmental epidemiologic studies for SO_2.

Study	Location sample size	Mean SO_2 ppb	Exposure Assessment	Selected Effect Estimates* 95% CI
Birth Weight				**Δg**
Darrow et al. (2011) Distributed lag, 1-h max SO_2	Atlanta, GA, U.S. (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, U.S. (n = 1,548,904)	2.3	County average from monitors	EP: −15.594 (−25.344, −5.844)
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, U.S. (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, U.S. (n = 1,277)	5.8	Nearest monitor (within 10 km, 1 of 16 monitors)	2 day 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)	United States (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 5-44 (Continued): Key reproductive and developmental epidemiologic studies for SO_2.

Study	Location sample size	Mean SO_2 ppb	Exposure Assessment	Selected Effect Estimates* 95% CI
Developmental				
Dales et al. (2006)	Atlanta, Georgia, U.S. (n = 8,586 cases)	4.3	Monitors, averaged to city	Neonatal hospitalization for respiratory disease 2 day 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, Canada (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; CO = carbon monoxide; EP = entire pregnancy; IUGR = intrauterine growth restriction; M1 = month 1; M2 = month 2; M3 = month ;3; n = sample size; NO_2 = nitrogen dioxide; O_3 = ozone; PM = particulate matter; 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.

*Relative risk per 5 ppb change in SO_2, unless otherwise noted

5.4.1.1 Fertility, Reproduction, and Pregnancy

Infertility affects approximately 11% of all women ages 15−44 in the United States (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 often 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).

5.4.1.2 Effects on Reproduction (Fertility) and Pregnancy

Three recent studies have examined the effects of SO_2 on measures of fertility; all use different populations and outcomes and observed null effects for SO_2 exposures. One study examined semen quality parameters in a cohort of men from Chongqing, China and observed decreases in normal morphology with increases in SO_2 exposure; however, all other quality metrics showed null associations (Zhou et al., 2014). 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. Three recent studies examined increased blood pressure during pregnancy or

pre-eclampsia. The studies in an Alleghany County, PA population found no associations between SO_2 exposure during the first trimester and changes in late pregnancy blood pressure (Lee et al., 2012); however, a study in Florida observed increased hypertension with higher SO_2 exposure during the 1st trimester (Xu et al., 2014). A small Iranian study found no association between pre-eclampsia and SO_2 above versus below median concentrations (Nahidi et al., 2014). In other pregnancy-related outcomes, no associations were observed in the Alleghany 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., 2011a). Increases in SO_2 exposure during the preconception period and the 1st trimester were associated with increased odds of gestational diabetes mellitus (Robledo et al., 2015).

No recent animal studies evaluating fertility and pregnancy were identified. An older study in laboratory animals exposed to sulfur dioxide 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, significant alterations in stages of the estrus cycle were seen including significant decreases in duration of diestrus and metastrus. During the 2nd and 3rd months 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, 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 study in this area is limited, currently SO_2 exposures appear to have no association with fertility, or effects on pregnancy. Studies are summarized in Supplemental Table 5S-11 (U.S. EPA, 2015o).

5.4.1.3 Birth Outcomes

Fetal growth

Fetal growth can be difficult to quantify; typically, small-for-gestational age (SGA) or intrauterine 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. Another issue is that SGA/IUGR is based only on weight distribution at birth, so only infants born are accounted for, fetal weight of continuing pregnancies is not considered, although those fetuses are part of the population at risk (Ritz and Wilhelm, 2008). 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 although may be updated with 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 single 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]. Three Canadian studies using the traditional definition of SGA/IUGR had mixed results. In Vancouver populations, increases in ORs were observed with entire pregnancy exposures (Brauer et al., 2008) and with 1st month and 1st trimester exposures (Liu et al., 2003). Whereas in a study over Calgary, Edmonton, and Montreal, Liu et al. (2007) found lowered ORs with exposures in Months 1 to 5 of pregnancy and no associations in Months 6 to 9. Of the two recent studies in the United States, Le et al. (2012) observed generally null associations for 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}. 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.

No recent animal studies evaluating fertility and pregnancy were identified.

In summary, there is some evidence for increased odds of fetal growth restriction with exposure to SO_2 during pregnancy, but 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 rather than peak concentrations. Studies examining the association between SO_2 and fetal growth can be found in Supplemental Table 5S-12 (U.S. EPA, 2015p).

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. Studies in Europe and Asia report increased ORs/RRs of PTB with exposures across pregnancy, although not consistently between studies (Zhao et al., 2011; Leem et al., 2006; Bobak, 2000; Xu et al., 1995). However, mean SO_2 concentrations and exposure contrasts are high for these studies. In the more recent study, a 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. In the United States and Canada, older 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 weeks

pre-birth 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). A recent time-series study in Atlanta, GA observed null associations for both 1st month and near-birth exposures using 1-hour maximum SO_2 [exposure during last week of pregnancy RR per 5-ppb increase = 0.99 (0.98, 1.01)] (Darrow et al., 2009). Finally, a cross-sectional study of PTB across the U.S. reported only that SO_2 showed "nonsignificant" effects with PTB for exposures during the month of birth (Trasande et al., 2013).

No recent animal studies evaluating birth outcomes 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-hour maximum SO_2 found no associations for PTB. Studies are characterized in Supplemental Table 5S-13 (U.S. EPA, 2015q).

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 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 (Yorifuji et al., 2015; 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) in the United States have inconsistent results. In a northeast population, Bell et al. (2007) observed no association with change in birth weight for entire pregnancy exposure [−2.711g (−13.253g, 7.831g) 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 [−15.594g (−25.344g, −5.844g)] (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-hour maximum 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 outcomes were identified.

In summary, LBW may be associated with SO_2, while evidence for an association with change in birth weight is inconsistent. Studies for both LBW and change in birth weight can be found in Supplemental Table 5S-14 (U.S. EPA, 2015r).

Litter Size

No recent animal studies evaluating birth outcomes were identified. In laboratory animals from an older study, exposure to sulfur dioxide has been shown to affect 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 5-45).

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 United States. 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 (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 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 outcomes 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-15 (U.S. EPA, 2015s).

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 Enkhmaa et al. (2014)'s study, other pollutants also showed very strong correlations and were highly correlated with one another.

No recent animal studies evaluating birth outcomes 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. Studies are characterized in Supplemental Table 5S-16 (U.S. EPA, 2015t).

Infant Mortality

Studies of infant mortality and SO_2 are limited in number. In a study across the U.S. Woodruff et al. (2008) observed increased ORs for respiratory-related post-neonatal infant mortality with long-term (2 month) exposure increases in county-level SO_2 concentrations [OR = 1.09 (0.89, 1.36) per 5-ppb increase]. This held 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). Studies are characterized in Supplemental Table 5S-16 (U.S. EPA, 2015t).

5.4.1.4 Developmental Outcomes

Respiratory Outcomes

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, gaseous copollutants and PM_{10} confidence intervals were very large, but effect estimates remained elevated. Hospitalizations due to respiratory causes are covered in Section 5.2.1.5.

Two recent studies examined asthma onset in association with early life exposure to SO_2. Clark et al. (2010) observed elevated ORs for asthma with SO_2 exposure in pregnancy and the 1st year of life. While Nishimura et al. (2013) observed elevated ORs for asthma with SO_2 exposure in the 1st 3 years of life, but not the 1st year of life alone. Asthma onset is covered in further detail in Section 5.2.1.2.

In summary, there is some evidence for an association between pregnancy and early life exposure to SO_2 and respiratory health effects after birth, although evidence is limited and exposure windows are uncertain. Key studies are summarized in Table 5-44.

Table 5-45 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 days	Estrus cyclicity duration (F0 and F1), litter size, offspring growth (body weight)

ppm = parts per million; SO_2 = sulfur dioxide.

Other Developmental Effects

Studies examining other developmental exposures are limited in number. A single recent study has examined SO_2 exposure with apnea and bradycardia in a vulnerable subpopulation of infants in Atlanta, and found no association for either health outcome (Peel et al., 2011). 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 growth or body weight over time were reported with 1.5 ppm exposure.

5.4.2 Summary and Causal Determination

Overall the evidence is suggestive of, but not sufficient to infer, a causal relationship between exposure to SO_2 and reproductive and developmental outcomes. The 2008 ISA for Sulfur Oxides 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 35 recent studies, examining the relationship between exposure to SO_2 and reproductive and developmental effects was evaluated using the framework described in the ISA Preamble (U.S. EPA, 2015e). The key evidence as it relates to the causal framework is summarized in Table 5-46.

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 (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, there are a number of uncertainties connected with the associations observed between exposure to SO_2 and birth outcomes.

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) (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 (Chapter 3). 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.

Again, 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 adjustment emerge (Faiz et al., 2013; Slama et al., 2013; Le et al., 2012).

There is also little 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., preeclampsia, 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, even if the literature was more extensive.

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 reproductive toxicity based on evidence from laboratory animal studies and epidemiologic studies. However, 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.

Other U.S. regulatory agencies have addressed the reproductive and developmental toxicology of sulfur dioxide. Although the body of evidence is relatively small, multiple high-quality (Chapter 5 Annex) studies observe association between SO_2 and birth outcomes. The strongest evidence is for near-birth exposures and preterm birth. Preterm birth is a marker for immediate fetal underdevelopment, and is linked to many later health outcomes, including: infant mortality, infant rehospitalizations,

neurodevelopmental problems, and growth issues. The associations with preterm birth and near-birth SO_2 exposures are coherent with the strongest evidence for SO_2, which indicates short-term effects. Other reproductive health outcomes also show positive associations with SO_2; however they may lack consistency in timing of exposure or in definition of outcome, and as such present weaker evidence for causal association. Although there is only a single toxicological study at relevant dose ranges of SO_2, this study offers supportive evidence for health outcomes of altered menstrual function with prolonged estrus cycles in exposed rodents that return to normal cycling after a SO_2 exposure is stopped (Mamatsashvili, 1970a). Many uncertainties remain when evaluating the evidence for these health endpoints; therefore, the evidence is suggestive of, but not sufficient to infer, a causal relationship between exposure to SO_2 and reproductive and developmental outcomes.

Table 5-46 Summary of evidence supporting suggestive of a causal relationship between SO_2 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—Suggestive of, but Not Sufficient to Infer, a Causal Relationship			
Evidence from multiple epidemiologic studies of preterm birth is generally supportive but 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) (Le et al. (2012); Sagiv et al. (2005)) Section 5.4.1.3	Mean: 4.9 ppb Mean: 5.8 ppb Mean: 7.9 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.	Section 5.4.1.3	Means: 4.9−5.8 ppb
	Several high quality studies show associations between SO_2 exposure and low birth weight or change in birth weight. Timing of exposure is inconsistent across studies. Only one study uses 1-h max for exposure determination.	Section 5.4.1.3	Means: 2.1−13.2 ppb
	Limited and inconsistent epidemiologic evidence for associations with various birth defects	Section 5.4.1.3	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 5.4.1.3	Mean: 5.7 ppb Mean: 5.8 ppb Mean: 5.9 ppb Mean: 3 ppb
	Limited evidence for positive associations between prenatal/early life exposures and childhood respiratory outcomes	Section 5.4.1.4	Means: 2−4.3 ppb

Table 5-46 (Continued): Summary of evidence supporting suggestive of a causal relationship between SO_2 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 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 5.4.1.1	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.	Chapter 3	
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.		

ISA = Integrated Science Assessment; ppb = parts per billion; SO_2 = sulfur dioxide.

[a]Based on aspects considered in judgments of causality and weight of evidence in causal framework in the ISA Preamble (U.S. EPA, 2015e).

[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).

5.5 Mortality

5.5.1 Short-Term Mortality

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, 2008b), 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-hour average SO_2 concentrations. These associations were primarily observed at mean 24-hour average 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, 2008b).

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 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.

5.5.1.2 Evaluation of Short-Term Sulfur Dioxide Exposure and Mortality Studies

Since the completion of the 2008 SO_X ISA (U.S. EPA, 2008b), 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, 2008b), 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., 2008) 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 (2013b)], 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, 2008b). 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-17 (U.S. EPA, 2015u). Overall this section evaluates studies that examined the association between short-term SO_2 exposure and mortality, and addresses 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, 2008b). Specifically, this section evaluates whether there is evidence of: confounding (i.e., copollutants and seasonal/temporal), effect modification (i.e., sources of heterogeneity in risk estimates across cities or within a population), and seasonal heterogeneity in SO_2-mortality associations. Additionally, the section assesses the SO_2-mortality C-R relationship and related issues, such as the lag structure of associations.

5.5.1.3 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, 2008b). 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 5-15; Table 5-48). Air quality characteristics and study specific details for the studies evaluated in this section are provided in Table 5-47.

Table 5-47 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)[a]	72 U.S. cities (NMMAPS)[b]	1987–1994	Total	24-h avg	0.4−14.2	---
Burnett et al. (2004)a	12 Canadian cities	1981–1999	Total Cardiovascular Respiratory	24-h avg	0.9−9.6	---

Table 5-47 (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)
Moolgavkar et al. (2013)	85 U.S. cities (NMMAPS)[f]	1987–2000	Total	24-h avg	---	---
Europe						
Katsouyanni et al. (1997)[a]	12 European cities (APHEA-1)	1980–1992	Total	24-h avg	5.0−28.2[c]	90th: 17.2−111.8
Biggeri et al. (2005)[a]	Eight Italian cities (MISA-1)	1990–1999	Total Cardiovascular Respiratory	24-h avg	2.5−15.6	95th: 6.0−50.1 Max: 7.1−111.0
Hoek (2003)[a]	Netherlands	1986–1994	Total Cardiovascular Respiratory	24-h avg	3.5−5.6	---
Berglind et al. (2009)	Five European cities[g]	1992–2002	Total	24-h avg	1.0−1.6[h]	---
Bellini et al. (2007)	15 Italian cities (MISA-2)	1996–2002	Total Cardiovascular Respiratory	24-h avg	---	---
Asia						
Kan et al. (2010b); Wong et al. (2008); Wong et al. (2010)	Four Asian cities (PAPA)	1996–2004[i]	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[j]	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[j]	Stroke	24-h avg	6.1−32.1	---
Meng et al. (2013)	Four Chinese cities	1996–2008[l]	COPD	24-h avg	6.8−19.1	---
Meta-analyses						
Stieb et al. (2003)[a]	Meta-analysis	1958–1999[d]	Total	24-h avg	0.7−75.2	---

Table 5-47 (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)
HEI (2004)[a]	Meta-analysis (South Korea, China, Taiwan, India, Singapore, Thailand, Japan)	1980–2003[e]	Total	24-h avg	~10−>200	---
Atkinson et al. (2012)	Meta-analysis (Asia)	1980–2007[k]	Total Cardiovascular Respiratory COPD	24-h avg	---	---
Shah et al. (2015)	Meta-analysis	1948−Jan 2014	Stroke	NR	6.2[c]	Max: 30.2
Yang et al. (2014b)	Meta-analysis (Asia, Europe, and North America)	1996–2013	Stroke	24-h avg	Asia: 11.4[c] Europe: 5.2[c] North America: 4.2[c]	75th: Asia: 18.6 Europe: 2.3 North America: 7.6

APHEA = Air Pollution and Health: A European Approach study; avg = average; 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; ppb = parts per billion; SO_X = Sulfur Oxides.

[a]Multicity studies and meta-analyses evaluated in the 2008 SO_X ISA.

[b]Of the 90 cities included in the NMMAPS analysis only 72 had SO_2 data.

[c]Median concentration.

[d]The mortality time-series of studies included in the meta-analysis spanned these years.

[e]Studies included within this meta-analysis were published during this time period.

[f]Of the 108 cities included in the analyses using NMMAPS data only 85 had SO_2 data.

[g]SO_2 data was not available for Barcelona, therefore the SO_2 results only encompass four cities.

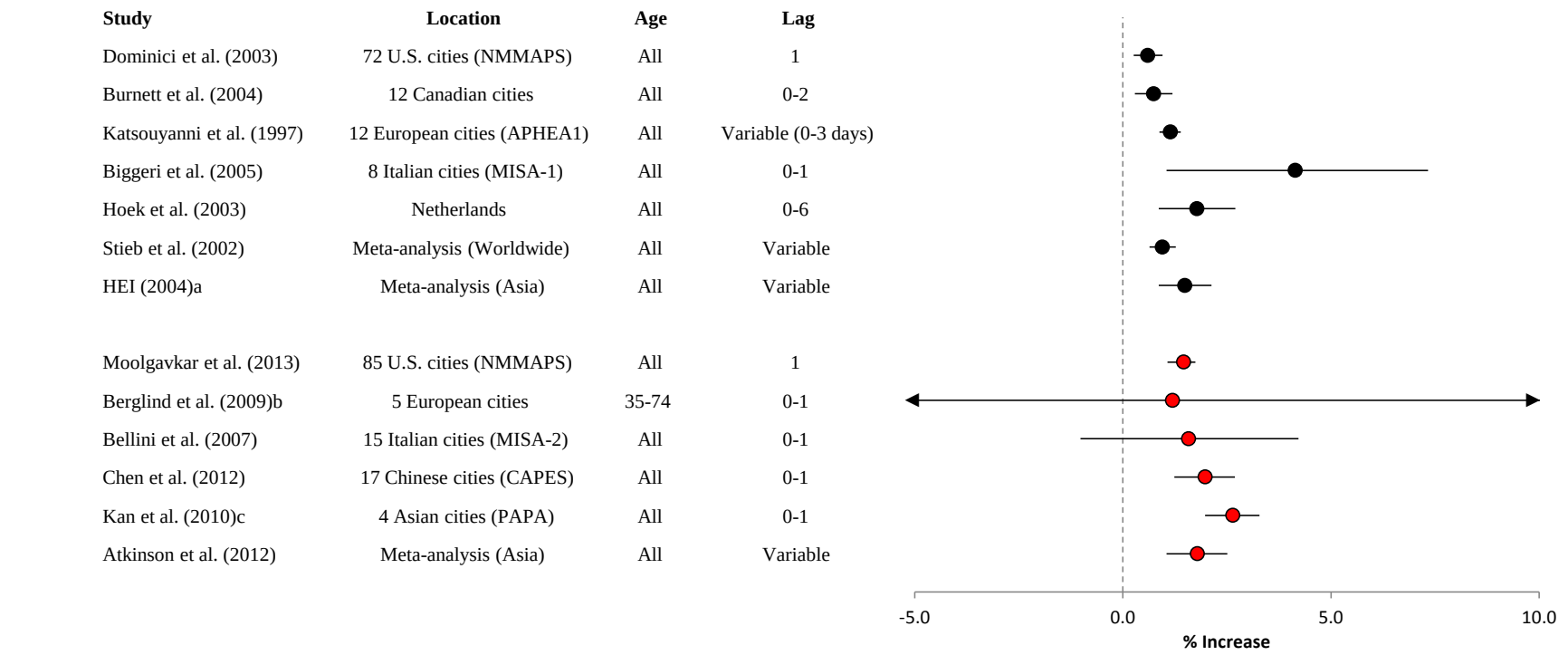
[h]Median concentrations.

[i]The study period varied for each city, Bangkok: 1999−2003, Hong Kong: 1996−2002, and Shanghai and Wuhan: 2001−2004.

[j]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.

[k]Yr defined represent the yr in which studies were published that were included in the meta-analysis.

[l]Study period varied from 2 to 7 yr. Hong Kong was the only city that had air quality data prior to 2001.



Note: a = Meta-analysis of Asian cities: South Korea, China, Hong Kong, Taipei, India, Singapore, Thailand, Japan; b = Study was of MI survivors therefore only included individuals 35+; c = Kan et al. (2010b) reported results that were also found in (Wong et al., 2010; Wong et al. (2008)).

Figure 5-15 Percent increase in total mortality from multi-city studies and meta-analyses evaluated in the 2008 SO_X Integrated Science Assessment (black circles) and recently published multi-city studies (red circles) for a 10-ppb increase in 24-hour average SO_2 concentrations.

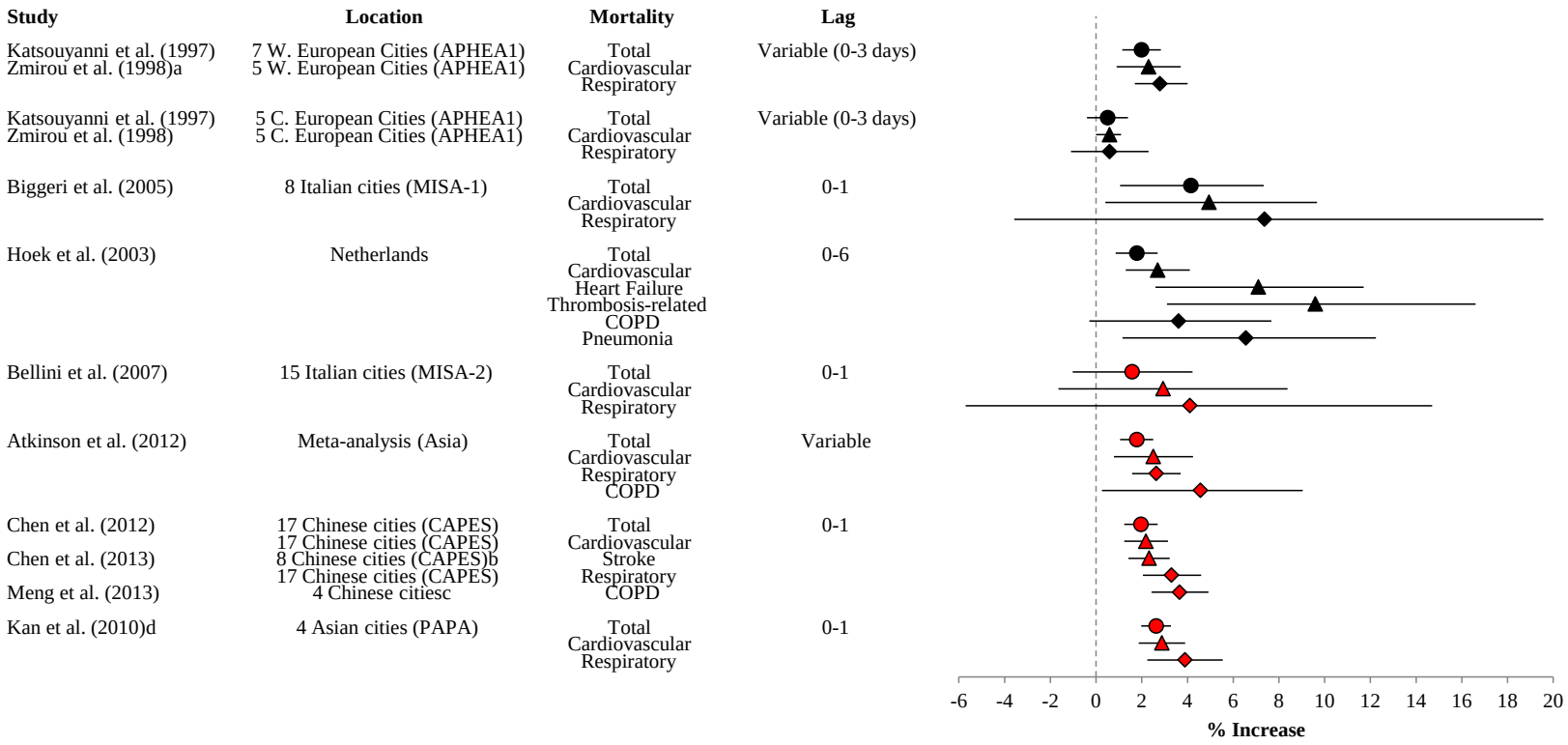
Table 5-48 Corresponding excess risk estimates for Figure 5-15.

Study	Location	Age	Lag	Averaging Time	% Increase (95% CI)
Studies Evaluated in 2008 ISA for Sulfur Oxides					
Dominici et al. (2003)	72 U.S. cities (NMMAPS)	All	1	24-h avg	0.60 (0.26, 0.95)
Burnett et al. (2004)	12 Canadian cities	All	0−2	24-h avg	0.74 (0.29, 1.19)
Katsouyanni et al. (1997)	12 European cities (APHEA-1)	All	Variable (0−3 days)	24-h avg	1.14 (0.88, 1.39)
Biggeri et al. (2005)	Eight Italian cities (MISA-1)	All	0−1	24-h avg	4.14 (1.05, 7.33)
Hoek (2003)	Netherlands	All	0−6	24-h avg	1.78 (0.86, 2.70)
Stieb et al. (2002)	Meta-analysis	All	Variable	24-h avg	0.95 (0.64, 1.27)
HEI (2004)	Meta-analysis	All	Variable	24-h avg	1.49 (0.86, 2.13)
Recent Multicity Studies					
Moolgavkar et al. (2013)	85 U.S. cities	All	1	24-h avg	1.5 (1.1, 1.7)
Berglind et al. (2009)	Five European cities	35−74	0−1	24-h avg	1.2 (−25.7, 37.7)
Bellini et al. (2007)	15 Italian cities (MISA-2)	All	0−1	24-h avg	1.6 (−1.0, 4.2)
Chen et al. (2012b)	17 Chinese cities (CAPES)	All	0−1	24-h avg	2.0 (1.2, 2.7)
Kan et al. (2010b)[a]	Four Asian cities (PAPA)	All	0−1	24-h avg	2.6 (2.0, 3.3)
Atkinson et al. (2012)	Meta-analysis (Asia)	All	Variable	24-h avg	1.8 (1.1, 2.5)

APHEA = Air Pollution and Health: A European Approach study; avg = average; CAPES = China Air Pollution and Health Effects Study; CI = confidence interval; 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; PAPA = Public Health and Air Pollution in Asia.

[a]These results were also presented in Wong et al. (2008) and Wong et al. (2010).

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 5-16). 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 5-16 and corresponding Table 5-49 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.



Note: Total mortality = circle; cardiovascular-related mortality = triangle; and respiratory-related mortality = diamond. a = Only five of the seven cities included in Katsouyanni et al. (1997) 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 (CAPES) 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 = These results were also presented in Wong et al. (2008) and Wong et al. (2010).

Figure 5-16 Percent increase in total, cardiovascular, and respiratory mortality from multi-city studies evaluated in the 2008 SO_X Integrated Science Assessment (black circles) and recently published multi-city studies (red circles) for a 10-ppb increase in 24-hour average SO_2 concentrations.

Table 5-49 Corresponding excess risk estimates for Figure 5-16.

Study	Location	Age	Lag	Averaging Time	Mortality	% Increase (95% CI)
Studies Evaluated in 2008 SO_X ISA						
Katsouyanni et al. (1997)	Seven Western European cities (APHEA-1)	All	Variable (0−3 days)	24-h avg	Total	2.0 (1.2, 2.8)
Zmirou et al. (1998)	Five Western European cities (APHEA-1)[a]	All			Cardiovascular Respiratory	2.3 (0.9, 3.7) 2.8 (1.7, 4.0)
Katsouyanni et al. (1997)	Five Central European cities (APHEA-1)	All	Variable (0−3 days)	24-h avg	Total	0.5 (−0.4, 1.4)
Zmirou et al. (1998)	Five Central European cities (APHEA-1)	All			Cardiovascular Respiratory	0.6 (0.0, 1.1) 0.6 (−1.1, 2.3)
Biggeri et al. (2005)	Eight Italian cities (MISA-1)	All	0−1	24-h avg	Total Cardiovascular Respiratory	4.1 (1.1, 7.3) 4.9 (0.4, 9.7) 7.4 (−3.6, 19.6)
Hoek (2003)	Netherlands	All	0−6	24-h avg	Total Cardiovascular Heart failure Thrombosis-related COPD Pneumonia	1.8 (0.9, 2.7) 2.7 (1.3, 4.1) 7.1 (2.6, 11.7) 9.6 (3.1, 16.6) 3.6 (−0.3, 7.7) 6.6 (1.2, 12.2)
Recent Multicity Studies						
Bellini et al. (2007)	15 Italian cities (MISA-2)	All	0−1	24-h avg	Total Cardiovascular Respiratory	1.6 (−1.0, 4.2) 2.9 (−1.6, 8.4) 4.1 (−5.7, 14.7)
Atkinson et al. (2012)	Meta-analysis (Asia)	All	Variable	24-h avg	Total Cardiovascular Respiratory COPD	1.8 (1.1, 2.5) 2.5 (0.8, 4.2) 2.6 (1.6, 3.7) 4.6 (0.3, 9.0)
Chen et al. (2012b)	17 Chinese cities (CAPES) 17 Chinese cities (CAPES)	All	0−1	24-h avg	Total Cardiovascular Stroke Respiratory COPD	2.0 (1.2, 2.7) 2.2 (1.2, 3.1) 2.3 (1.4, 3.2) 3.3 (2.1, 4.6) 3.7 (2.4, 4.9)
Chen et al. (2012b)	Eight Chinese cities (CAPES)[b] 17 Chinese cities (CAPES)					

Table 5-49 (Continued): Corresponding excess risk estimates for Figure 5-16.

Study	Location	Age	Lag	Averaging Time	Mortality	% Increase (95% CI)
Meng et al. (2013)	Four Chinese cities[c]					
Kan et al. (2010b)[d]	Four Asian cities (PAPA)	All	0−1	24-h avg	Total Cardiovascular Respiratory	2.6 (2.0, 3.3) 2.9 (1.9, 3.9) 3.9 (2.2, 5.5)

APHEA-1 = Air Pollution and Health: A European Approach study; avg = average; CAPES = China Air Pollution and Health Effects Study; CI = confidence interval; COPD = chronic obstructive pulmonary disease; ISA = Integrated Science Assessment; MISA = Meta-analysis of the Italian studies on short-term effects of air pollution; PAPA = Public Health and Air Pollution in Asia.

[a]Only five of the seven cities included in Katsouyanni et al. (1997) had cause-specific mortality data and were included in the analysis.

[b]Chen et al. (2012b) examined stroke only in the CAPES cities that had stroke data.

[c]Meng et al. (2013) was not considered an analysis based out of CAPES, but the four cities included had data for the same yr as was included in CAPES.

[d]These results were also presented in Wong et al. (2008) and Wong et al. (2010).

5.5.1.4 Potential Confounding of the Sulfur Dioxide-Mortality Relationship

A limitation of the studies evaluated in the 2008 SO_X ISA, was the relatively limited analyses of the potential confounding effects of copollutants on the SO_2-mortality relationship (U.S. EPA, 2008b). 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.

Modeling Approaches to Control for Copollutant Confounding

In the 2008 SO_X ISA (U.S. EPA, 2008b), 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 study (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, 2008b), 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-hour average 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 and highly correlated with PM_{10} (r = 0.49) and NO_2 (r = 0.65), respectively. The results from copollutant models (Table 5-50) indicate that SO_2 mortality associations within these cities may be confounded by PM_{10} and NO_2. 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

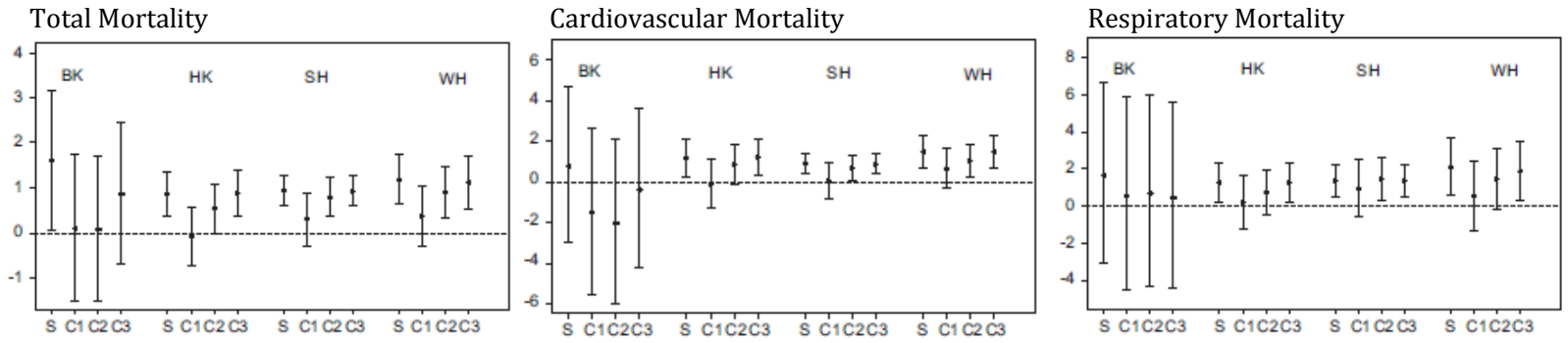
NO_2. These results are consistent with those observed in Chen et al. (2013), which focused on stroke mortality in a subset of the CAPES cities (i.e., eight cities) and also found a similar reduction in SO_2 risk estimates in models with PM_{10} and NO_2.

Table 5-50 Percent increase in total, cardiovascular, and respiratory mortality for a 10-ppb increase in 24-hour average 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 = particulate matter.
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 5-17). 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 was SO_2 found to be highly correlated with NO_2 (r = 0.64 and 0.76, respectively). Similarly, SO_2 was also found to be highly correlated with PM_{10} in Shanghai and Wuhan, 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.



BK = Bangkok; HK = Hong Kong; SH = Shanghai; WH = Wuhan.
S = single-pollutant model; C1 = sulfur dioxide + nitrogen dioxide; C2 = sulfur dioxide + PM_{10}; C3 = sulfur dioxide + ozone.
Figure adapted from Kan et al. (2010b).

Figure 5-17 Percent increase in total, cardiovascular, and respiratory mortality associated with a 10 µg/m^3 (3.62 ppb) increase in 24-hour average SO_2 concentrations, lag 0−1, in single and copollutants models in Public Health and Air Pollution in Asia cities.

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. It is important to note that the aforementioned studies rely on central site monitors for estimating exposure to SO_2. SO_2 is more spatially variable than other pollutants as reflected in the generally low to moderate spatial correlations across urban geographical scales (Section 3.3.3.2); therefore, the attenuation in SO_2 associations may be a reflection of the different degree of exposure error across pollutants. This is further supported by an analysis of correlations between NAAQS pollutants at collocated monitors in the U.S., which demonstrated that SO_2 is low to moderately correlated with other pollutants (Section 3.3.4.1). 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

Weather

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.

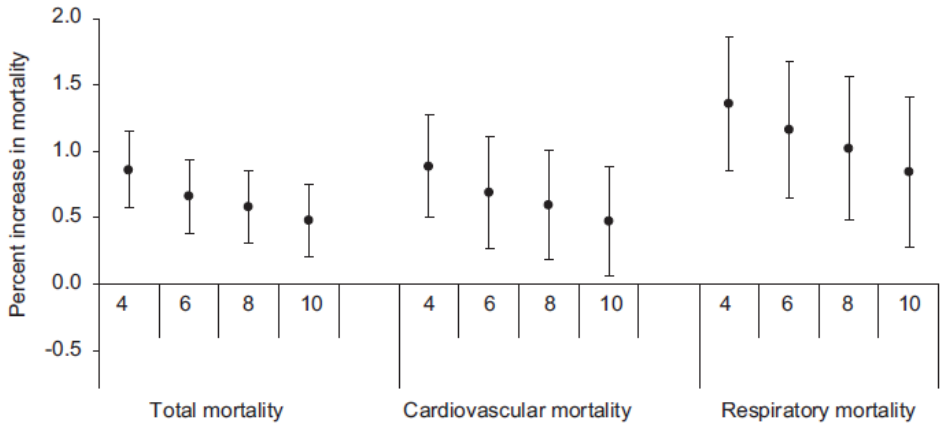
As part of the CAPES study, Chen et al. (2012b) examined the influence of alternative lag structures for controlling the potential confounding effects of temperature on the SO_2-mortality relationship by varying the lag structure of the temperature variable (i.e., lag 0, lag 0−3, or lag 0−7). The authors found that although the SO_2-mortality associations remained positive and 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.

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 5-18).

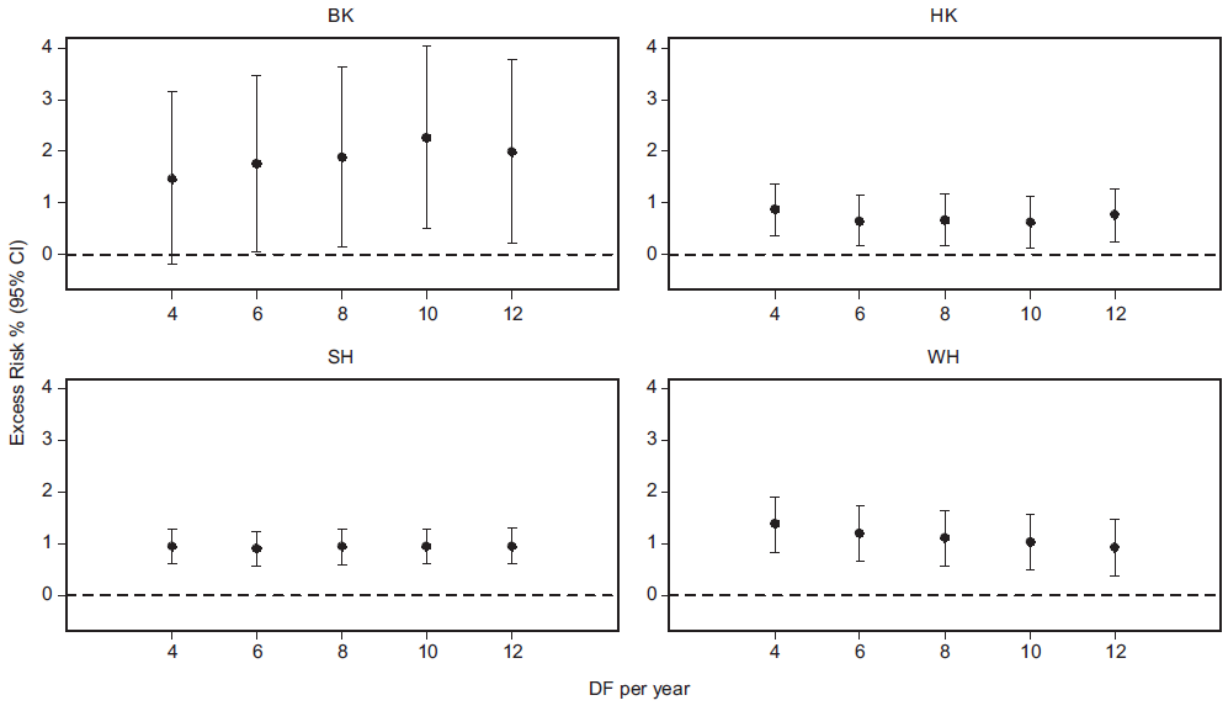


Source: (Chen et al., 2012b).

Figure 5-18 Percent increase in daily mortality associated with a 10 μg/m³ (3.62 ppb) increase in 24-hour average SO_2 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 5-18, and in some cities in Figure 5-19, 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.



Source: (Kan et al., 2010b).

Figure 5-19 Percent increase in total mortality associated with a 10 μg/m^3 (3.62 ppb) increase in 24-hour average SO_2 concentrations at lag 0−1 in Public Health and Air Pollution in Asia cities, using different degrees of freedom/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-hour average 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 have 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.

5.5.1.5 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, 2008b), 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. (2008))] conducted extensive analyses of potential effect measure modifiers of the SO_2-mortality relationship as detailed in Chapter 6. These studies provided limited evidence for potential differences in the risk of SO_2-related mortality by lifestage, sex, and socioeconomic status (SES).

Season

A limited number of studies have examined whether there is evidence of seasonal differences 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

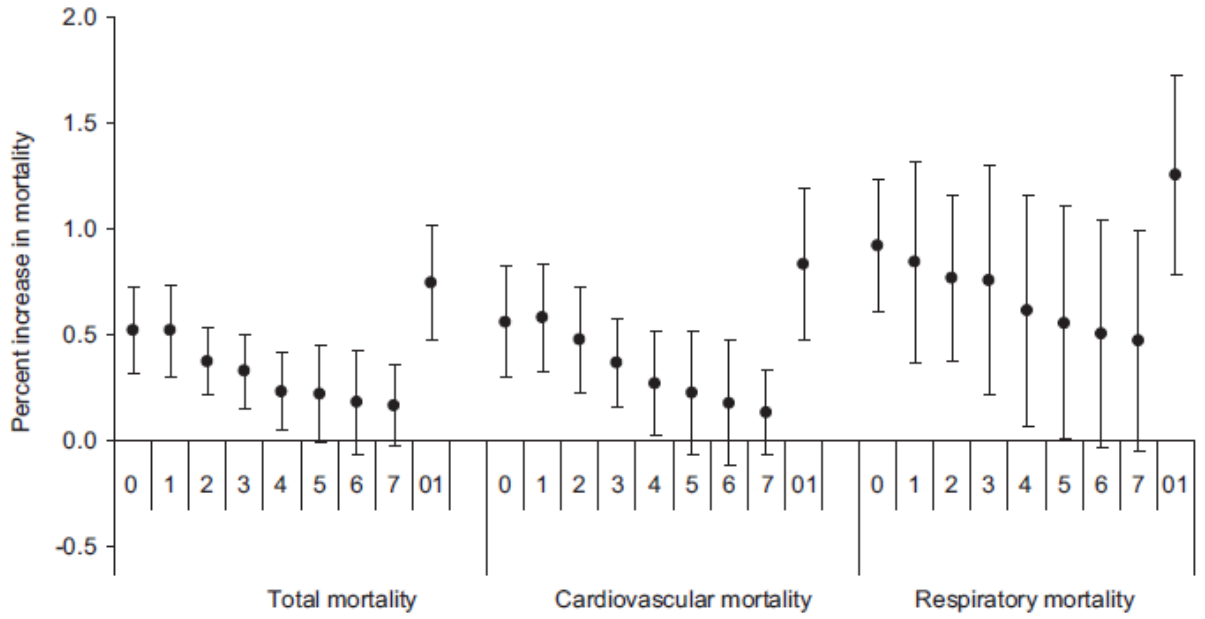
reported results consistent with Zmirou et al. (1998). In a study of 15 Italian cities (MISA-2), Bellini et al. (2007) is the only multicity study that examined whether there were seasonal differences in SO_2-mortality risk estimates. The authors found a similar pattern of associations across mortality 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-hour average SO_2 concentrations. Overall, the limited number of studies that conducted seasonal analyses reported initial evidence indicating larger SO_2-mortality associations during the summer season.

5.5.1.6 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.

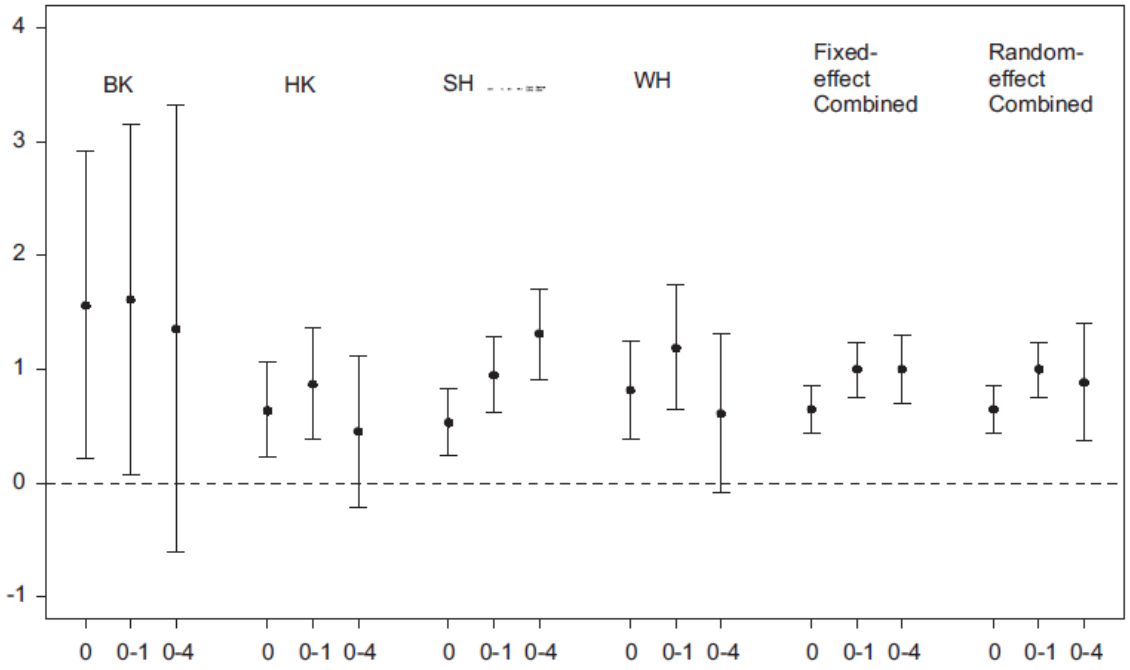
Chen et al. (2012b), within the CAPES study, examined individual lag days (Lag Day 0 to 7) and a multiday lag of 0−1 days. As depicted in Figure 5-20, the authors found evidence of immediate SO_2 effects on mortality that slowly declined over time with the multiday lag of 0−1 days exhibiting the largest risk estimate across mortality outcomes.



Source: (Chen et al., 2012b).

Figure 5-20 Percent increase in daily mortality associated with a 10 ug/m^3 (3.62 ppb) increase in 24-hour average SO_2 concentrations, using various lag structures for SO_2 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 5-21). 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 5-20).



Source: Kan et al. (2010b).

Figure 5-21 Percent increase in total mortality associated with a 10 µg/m³ (3.62 ppb) increase in 24-hour average SO_2 concentrations for different lag structures in individual Public Health and Air Pollution in Asia cities and in combined four city analyses. BK = Bangkok; HK = Hong Kong; SH = Shanghai; WH = Wuhan.

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-hour average 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 5-20). 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.

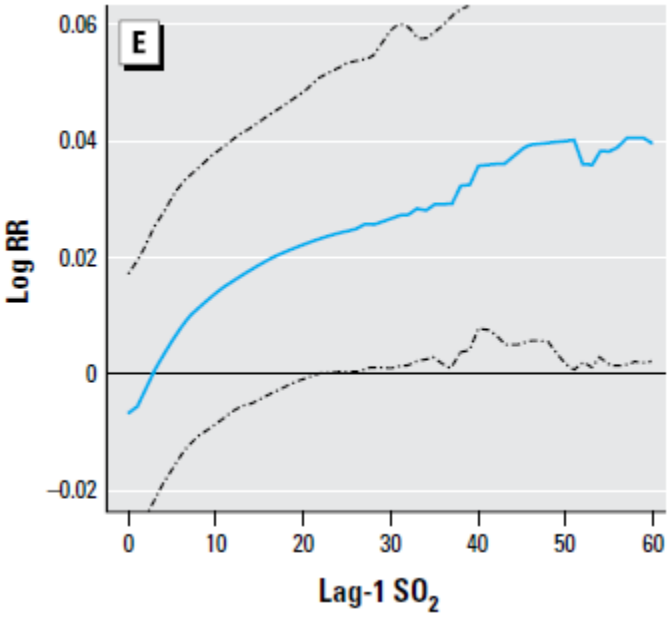
Overall, the limited analyses that have examined the lag structure of associations for short-term SO_2 exposures and mortality suggest that the greatest effects occur within the

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, 2008b), 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. These studies have conducted analyses focusing on the combined C-R relationship across multiple cities, or an evaluation of single-city C-R relationships in the context of a multicity study.

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 5-22, 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.

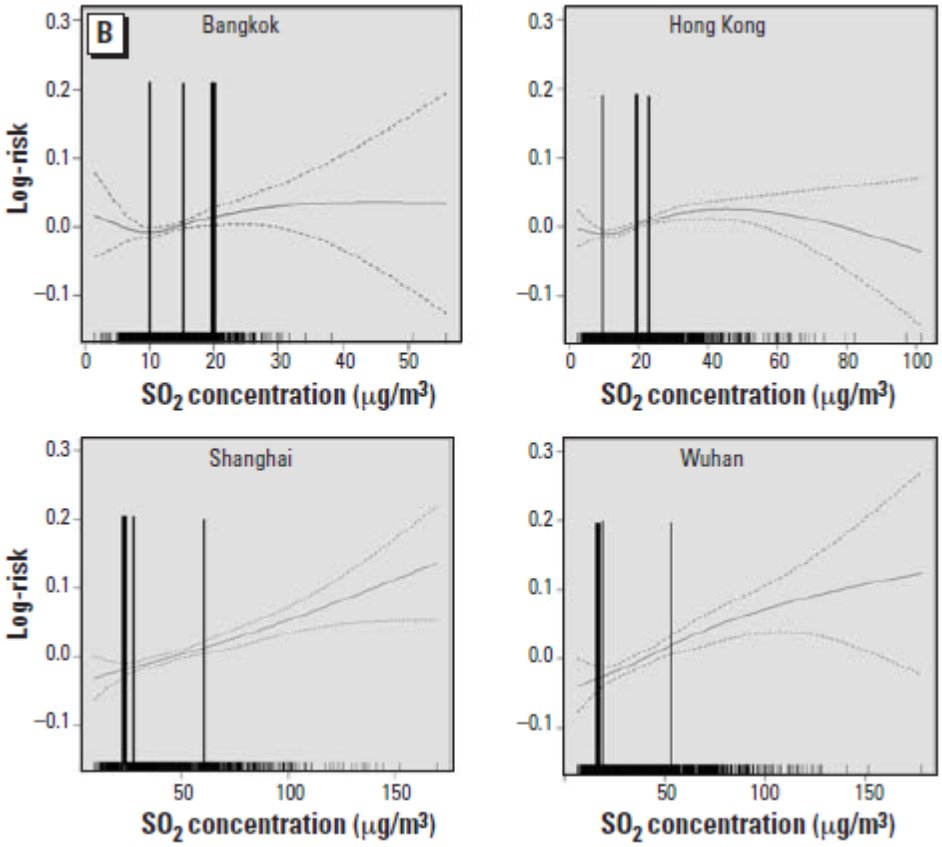


Source: Moolgavkar et al. (2013).

Figure 5-22 Flexible ambient concentration-response relationship between short-term SO_2 (ppb) exposure (24-hour average concentrations) and total mortality at lag 1. Note: Pointwise means and 95% confidence intervals adjusted for size of the bootstrap sample (d = 4).

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 5-23). 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.



Source: (Wong et al., 2008).

Figure 5-23 Concentration-response curves for total mortality (degrees of freedom = 3) for SO_2 in each of the four Public Health and Air Pollution in Asia cities. Note: *x*-axis is the average of lag 0−1 24-hour average 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 inter-quartile 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-hour averaging time of SO_2.

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 Sections 5.2.1.7 (respiratory mortality) and 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 (Figures 5-9 and 5-14).

Collectively across studies, specifically within the range of SO_2 concentrations where the data density is highest, evidence supports a linear, no threshold relationship between short-term SO_2 concentrations and mortality. Although, some differences in the shape of the curve were observed on a city-to-city basis, these results are consistent with what has been reported for other criteria air pollutants.

5.5.1.7 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, 2008b). 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}. 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 (U.S. EPA, 2015e). The key evidence, as it relates to the causal framework, is summarized in Table 5-51.

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. Although SO_2-mortality associations remain positive in copollutant models with PM_{10} and NO_2 they are 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 3.3.3.2); therefore, the attenuation in SO_2 associations in copollutant models may be a reflection of the different degree of exposure error across pollutants (Section 3.3.5.1). 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. However, 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 day) 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 Sections 5.2.1.7 (respiratory mortality) and 5.3.1.9 (cardiovascular).

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 suggestive of, but not sufficient 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 generally supportive, but not entirely consistent evidence for ischemic events such as triggering a myocardial infarction. Additionally, there is inconclusive epidemiologic and experimental evidence for other cardiovascular endpoints. 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 provides limited coherence and biological plausibility for SO_2-related 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 peak (generally 5−10-minute) 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 central site monitors 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 3.3.3.2). 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 central site monitors in capturing exposure to SO_2, and the uncertainty in the biological mechanism that could lead to SO_2-induced mortality (Section 3.3.5.1). 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.

Table 5-51 Summary of evidence, which is suggestive of, but not sufficient to infer, a causal relationship between short-term SO_2 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 5.5.1.3 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 5-47
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 5.5.1.4 Section 3.3.4.1	
Uncertainty regarding exposure measurement error	U.S. Studies that examine the association between short-term SO_2 exposures and mortality rely on central site monitors and SO_2 generally has low to moderate spatial correlations across urban geographical scales.	Section 3.3.3.2 Section 3.3.5.1	

Table 5-51 (Continued): Summary of evidence, which is suggestive of, but not sufficient to infer, a causal relationship between short-term SO_2 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 5-41	
	Consistent evidence of asthma exacerbations from controlled human exposure studies demonstrating respiratory effects (i.e. respiratory symptoms and decreased lung function) in response to peak SO_2 exposures, generally 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 5-27	

avg = average; ED = emergency department; NAAQS = National Ambient Air Quality Standards; NO_2 = nitrogen dioxide; PM = particulate matter; ppb = parts per billion; SO_2 = sulfur dioxide.

[a]Based on aspects considered in judgments of causality and weight of evidence in causal framework in Tables I and II of the Preamble (U.S. EPA, 2015e).

[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).

5.5.2 Long-Term Mortality

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, 2008b). 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. A brief summary of the studies included in this section can be found in Table 5-52.

Table 5-52 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)	United States (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)[b]	United States 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)

Table 5-52 (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]
Pope et al. (2002) [b]	United States (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)	United States (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)	United States (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)
Lipfert et al. (2006a) [b]	United States (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)[b]	United States (SO_2: 1966−1992; follow-up: 1977−1992)	5.6 IQR: 3.7	ZIP-code level monthly 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)[b]	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)

Table 5-52 (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]
Nafstad et al. (2004)[b]	Norway (SO_2: 1974−1995; follow-up: 1972−1998)	3.6	Model results (per square kilometer) for some yr/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)[b]	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)
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 5-52 (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]
Dong et al. (2012)	China (SO_2: 1998−2009; follow-up: 1998−2009)	23.9 SD: 5.7	1-yr average of from five fixed site 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 average 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) [b]	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)
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)

Table 5-52 (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. (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; CI = condifence interval; 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; ISA = Integrated Science Assessment; NO = nitric oxide; NO_2 = nitrogen dioxide; NO_X = the sum of NO and NO_2; O_3 = ozone; OC = organic carbon; PM = particulate matter; SD = standard deviation; SO_2 = sulfur dioxide; SO_4 = 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.

[b]Included in 2008 SO_X ISA.

[c]Effect estimate per 2.88 μg/m^3 increase in SO_X concentration (as reported by author in original publication).

5.5.2.1 United States 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) utilizes 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 reanalyses 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% 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 EPA's Speciation Trends Network (STN) data, which collected chemical components of $PM_{2.5}$. They analyzed the STN data for year 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 3.2.2.1 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 utilized 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

Three recent cohort studies have been conducted in China to examine the association between long-term exposure to SO_2 and mortality (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 5-52). Cao et al. (2011) observed generally modest positive associations with all-cause, respiratory and lung cancer mortality. 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 United States 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 populations, 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.

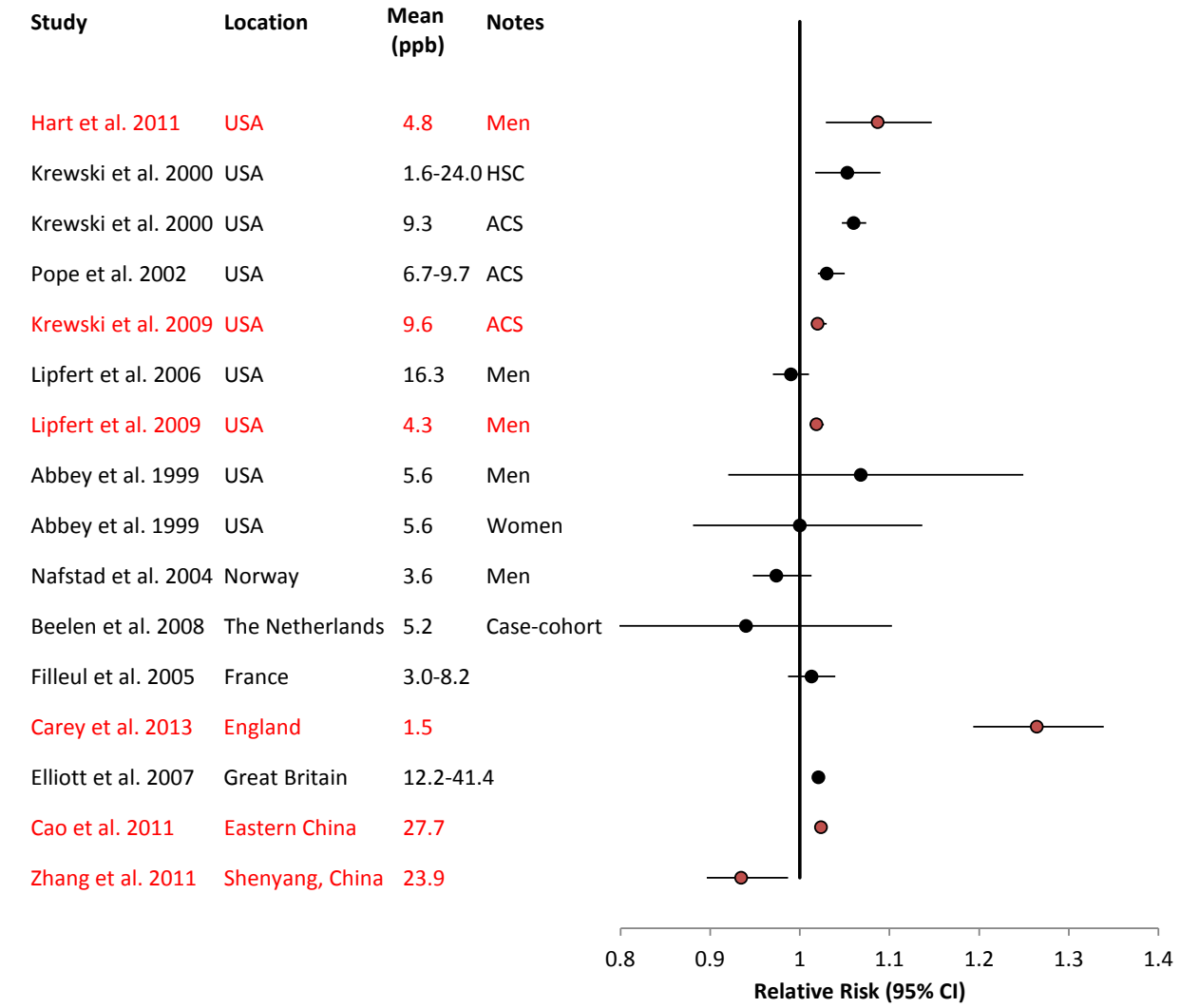
In a recent cross-sectional analysis, Wang et al. (2009) examined the long-term exposure to gaseous air pollutants (i.e., NO_2, O_3, and SO_2) and cardio-respiratory mortality in Brisbane, Australia. Pollutant concentrations were estimated for small geographic units, statistical local areas, using IDW. 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 of Evidence on the Effect of Long-Term Exposure on Mortality

Figure 5-24 and Table 5-53 present 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 United States, 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 5-25 and Table 5-54 present 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.



CI = confidence interval; HSC = Harvard Six Cities Study; ACS = American Cancer Society Study.

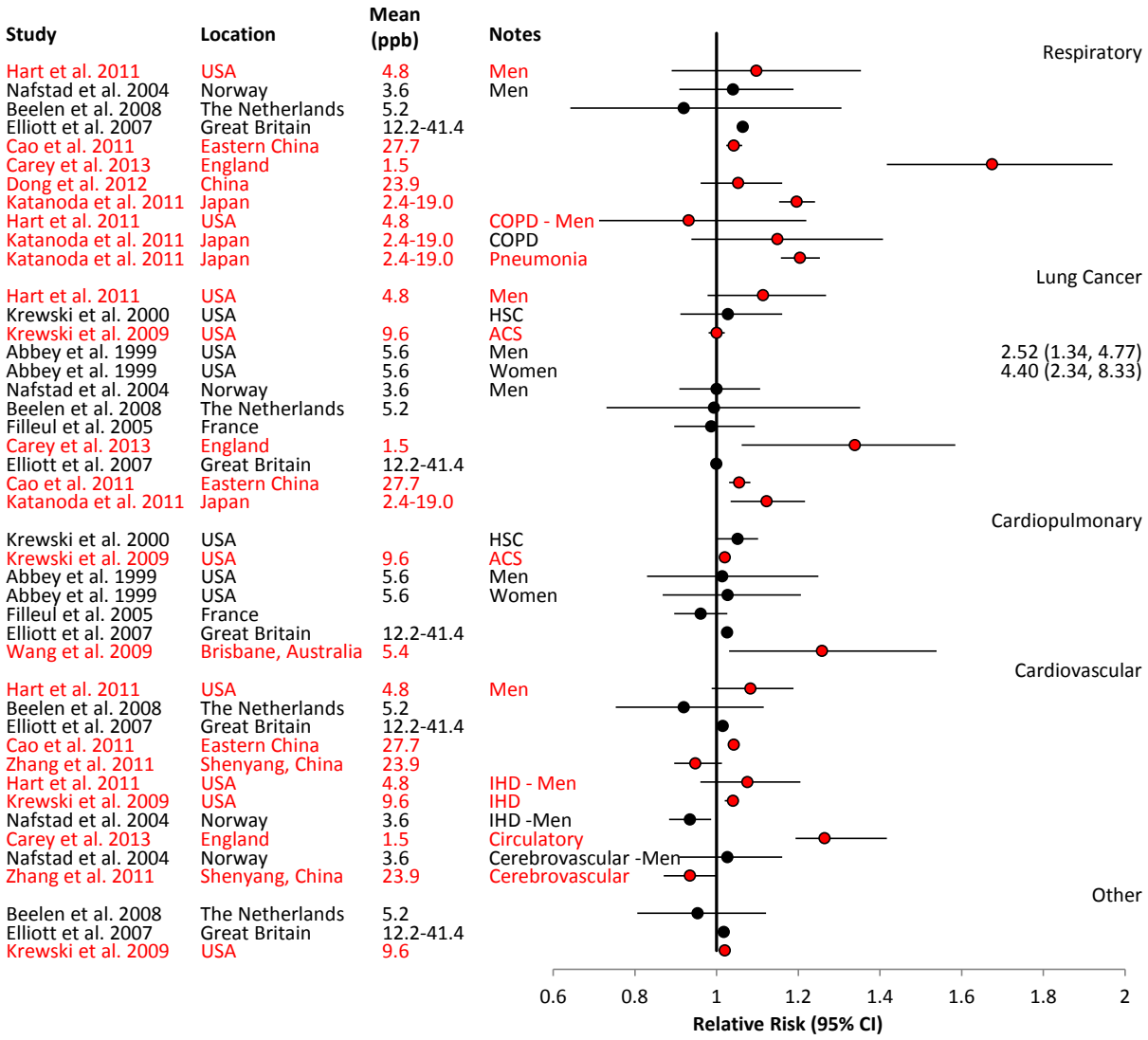
Figure 5-24 Relative risks (95% CI) of sulfur dioxide-associated total mortality. Effect estimates are standardized per 5-ppb increase in sulfur dioxide concentrations.

Table 5-53 Corresponding risk estimates for Figure 5-24.

Study	Location	Notes	Relative Risk[a] (95% CI)
Hart et al. (2011)	United States	Men	1.09 (1.03, 1.15)
Krewski et al. (2000)	United States	HSC	1.05 (1.02, 1.09)
Krewski et al. (2000)	United States	ACS	1.06 (1.05, 1.07)
Pope et al. (2002)	United States	ACS	1.03 (1.02, 1.05)
Krewski et al. (2009)	United States	ACS	1.02 (1.02, 1.03)
Lipfert et al. (2006a)	United States	Men	0.99 (0.97, 1.01)
Lipfert et al. (2009)	United States	Men	1.02 (1.01, 1.03)
Abbey et al. (1999)	United States	Men	1.07 (0.92, 1.25)
Abbey et al. (1999)	United States	Women	1.00 (0.88, 1.14)
Nafstad et al. (2004)	Norway	Men	0.97 (0.95, 1.01)
Beelen et al. (2008b)	Netherlands	Case-cohort	0.94 (0.80, 1.10)
Filleul et al. (2005)	France		1.01 (0.99, 1.04)
Carey et al. (2013)	England		1.26 (1.19, 1.34)
Elliott et al. (2007)	Great Britain		1.02 (1.02, 1.02)
Cao et al. (2011)	Eastern China		1.02 (1.02, 1.03)
Zhang et al. (2011)	Shenyang, China		0.93 (0.90, 0.99)

ACS = American Cancer Society; CI = confidence interval; HSC = Harvard Six Cities.

[a]Effect estimates are standardized to a 5-ppb increase in SO_2 concentration.



CI = confidence interval; COPD = chronic obstructive pulmonary disease; HSC = Harvard Six Cities Study; ACS = American Cancer Society Study; IHD = ischemic heart disease

Figure 5-25 Relative risks (95% CI) of sulfur dioxide-associated cause-specific mortality. Effect estimates are standardized per 5-ppb increase in sulfur dioxide concentrations.

Table 5-54 Corresponding risk estimates for Figure 5-25.

Study	Location	Notes	Relative Risk[a] (95% CI)
Respiratory			
Hart et al. (2011)	United States	Men	1.10 (0.89, 1.35)
Nafstad et al. (2004)	Norway	Men	1.04 (0.91, 1.19)
Beelen et al. (2008b)	Netherlands		0.92 (0.64, 1.31)
Elliott et al. (2007)	Great Britain		1.06 (1.06, 1.07)
Cao et al. (2011)	Eastern China		1.04 (1.02, 1.06)
Carey et al. (2013)	England		1.67 (1.42, 1.97)
Dong et al. (2012)	China		1.05 (0.96, 1.16)
Katanoda et al. (2011)	Japan		1.20 (1.15, 1.24)
Hart et al. (2011)	United States	COPD—men	0.93 (0.71, 1.22)
Katanoda et al. (2011)	Japan	COPD	1.15 (0.94, 1.41)
Katanoda et al. (2011)	Japan	Pneumonia	1.20 (1.16, 1.25)
Lung Cancer			
Hart et al. (2011)	United States	Men	1.11 (0.98, 1.11)
Krewski et al. (2000)	United States	HSC	1.03 (0.91, 1.16)
Krewski et al. (2009)	United States	ACS	1.00 (0.98, 1.02)
Abbey et al. (1999)	United States	Men	2.52 (1.34, 4.77)
Abbey et al. (1999)	United States	Women	4.40 (2.34, 8.33)
Nafstad et al. (2004)	Norway	Men	1.00 (0.91, 1.11)
Beelen et al. (2008b)	Netherlands		0.99 (0.73, 1.35)
Filleul et al. (2005)	France		0.99 (0.90, 1.09}
Carey et al. (2013)	England		1.34 (1.06, 1.58)
Elliott et al. (2007)	Great Britain		1.00 (0.99, 1.01)
Cao et al. (2011)	Eastern China		1.06 (1.03, 1.08)
Katanoda et al. (2011)	Japan		1.12 (1.03, 1.22)

Table 5-54 (Continued): Corresponding risk estimates for Figure 5-25.

Study	Location	Notes	Relative Risk[a] (95% CI)
Cardiopulmonary			
Krewski et al. (2000)	United States	HSC	1.05 (1.00, 1.10}
Krewski et al. (2009)	United States	ACS	1.02 (1.01, 1.03}
Abbey et al. (1999)	United States	Men	1.01 (0.83, 1.25}
Abbey et al. (1999)	United States	Women	1.03 (0.87, 1.21)
Filleul et al. (2005)	France		0.96 (0.90, 1.03)
Elliott et al. (2007)	Great Britain		1.03 (1.02, 1.03)
Wang et al. (2009)	Brisbane, Australia		1.26 (1.03, 1.54}
Cardiovascular			
Hart et al. (2011)	United States	Men	1.08 (0.99, 1.19}
Beelen et al. (2008b)	Netherlands		0.92 (0.75. 1.12)
Elliott et al. (2007)	Great Britain		1.01 (1.01, 1.02)
Cao et al. (2011)	Eastern China		1.04 (1.03, 1.05)
Zhang et al. (2011)	Shenyang, China		0.95 (0.90, 1.01)
Hart et al. (2011)	United States	IHD—men	1.08 (0.96, 1.21)
Krewski et al. (2009)	United States	IHD	1.04 (1.02, 1.05)
Nafstad et al. (2004)	Norway	IHD—men	0.93 (0.88, 0.99)
Carey et al. (2013)	England	Circulatory	1.26 (1.19, 1.42)
Nafstad et al. (2004)	Norway	Cerebrovascular	1.03 (0.91, 1.16)
Zhang et al. (2011)	Shenyang, China	Cerebrovascular	0.93 (0.87, 1.00)
Other			
Beelen et al. (2008b)	Netherlands		0.95 (0.81, 1.12)
Elliott et al. (2007)	Great Britain		1.02 (1.01, 1.02)
Krewski et al. (2009)	United States		1.02 (1.02, 1.03)

ACS = American Cancer Society; CI = confidence interval; COPD = chronic obstructive pulmonary disease; HSC = Harvard Six Cities; IHD = ischemic heart disease.

[a]Effect estimates are standardized to a 5-ppb increase in SO_2 concentration.

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, 2008 SO_X ISA noted 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.

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 (U.S. EPA, 2015e). The key evidence as it relates to the causal framework is summarized in Table 5-55. The overall evidence is suggestive of, but not sufficient to infer, a causal relationship between long-term exposure to SO_2 and total mortality among adults. The strongest evidence supporting this conclusion comes from increased consistency in the results of cohort studies that evaluate respiratory and total mortality.

Table 5-55 Summary of evidence, which is suggestive of, but not sufficient to infer, a causal relationship between long-term SO_2 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)	

Table 5-55 (Continued): Summary of evidence, which is suggestive of, but not sufficient to infer, a causal relationship between long-term SO_2 exposure and total mortality.

Rationale for Causal Determination[a]	Key Evidence[b]	Key References[b]	SO_2 Concentrations Associated with Effects[c]
		Lipfert et al. (2009)	County-level mean from air quality model: 4.3 ppb
	Recent cohort studies in the United States 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 to high.	Table 5-52	
Uncertainty regarding how exposure measurement error may influence the results	SO_2 has low to moderate 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 3.3.3.2	
	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	
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; ppb = parts per billion; SO_2 = sulfur dioxide.

[a]Based on aspects considered in judgments of causality and weight of evidence in causal framework in Tables I and II of the Preamble (U.S. EPA, 2015e).

[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).

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, 2008b). 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 and laboratory studies of mutagenicity or genotoxicity. The 2008 SO_X ISA summarized the literature on SO_2 concentrations and lung cancer as "inconclusive" (U.S. EPA, 2008b). Multiple studies across the United States and Europe investigated the relationship between SO_2 concentrations and lung cancer incidence and mortality. Many studies reported no association present, 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-18 (U.S. EPA, 2015v)] and genotoxic/mutagenic [Table 5S-19 (U.S. EPA, 2015w)] 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.

5.6.1.1 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 were 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 association was apparent 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.

Studies in the United States have reported inconsistent findings for the association between SO_2 concentrations and lung cancer mortality. 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 (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, like studies conducted in the United States examining SO_2 concentrations and cancer mortality, recent studies performed in Asia and Europe also had inconsistent findings.

Finally, a study in Italy used a Lagrangian dispersion model to estimate SO_X concentrations as a marker for refinery plant emissions (exposure information in Section 3.2.2.1 (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.

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 a significant increase in the number of lung tumors subgrouped as (1) adenomas and (2) primary carcinomas versus controls. Males also had a nonsignificant 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 intra-tracheal injection. Thus, 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 intra-tracheally 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. Thus, SO_2 acted as a tumor promoted 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) 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).

5.6.1.2 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, 2008b). 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). No association was observed among men or 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 association 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-18, (U.S. EPA, 2015v), 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 3.2.2.1) and high correlation with PM_{10} and H_2S.

5.6.1.3 Incidence of Other Cancers

Recent studies of SO_2 concentrations and other cancer types have also been published since the 2008 ISA for Sulfur Oxides (U.S. EPA, 2008b), but provided limited information on associations with SO_2. An ecological study in southern France also investigated the relationships between SO_2 and hospitalizations for breast cancer, acute leukemia, myeloma, and non-Hodgkin's lymphoma (Pascal et al., 2013). No associations were observed in sex-stratified analyses among men or 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 utilized 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 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.

5.6.1.4 Summary

Similar to studies of SO_2 concentrations and lung cancer in the previous ISA (U.S. EPA, 2008b), 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.

5.6.2 Genotoxicity and Mutagenicity

Multiple studies of genotoxicity or mutagenesis with SO_2 in vivo or in vitro exposure have been reported in the literature and are detailed below in Supplemental Table 5S-19 (U.S. EPA, 2015w).

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 days, 6 hours/day) 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 SO_2 in vivo or in vitro exposure have been reported in the literature and are summarized in Supplemental Table 5S-19 (U.S. EPA, 2015w). 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.

5.6.3 Summary and Causal Determination

The overall evidence for long-term SO_2 exposure and cancer is suggestive of, but not sufficient to infer, a causal relationship. This conclusion is based on evidence from some epidemiologic studies, as well as some evidence within the 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, 2008b). Recent studies include evidence on lung cancer as well as new types of cancer, evaluating both incidence and mortality. All available evidence for cancer due to long-term SO_2 concentrations was evaluated using the framework described in Table II of the Preamble (U.S. EPA, 2015e). The key evidence as it relates to the causal framework is summarized in Table 5-56.

Some of the epidemiologic studies provide support for the suggestive relationship between SO_2 concentrations and cancer. Although some studies of SO_2 concentrations and lung cancer mortality have reported null results, other studies have reported positive associations. Some of these studies with positive associations were relatively unchanged with the inclusion of various cofounders and copollutants. Cohort studies have reported no association 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.

Animal toxicological studies employing SO_2 exposure with other known carcinogens provide further supporting evidence, showing that inhaled SO_2 can increase tumor load in laboratory rodents. Nonetheless, toxicological data provide no clear evidence of SO_2 acting as a complete carcinogen and not all epidemiologic studies report positive associations.

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.

American Conference of Governmental Industrial Hygienists has rated sulfur dioxide as A4. 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.

However, in some animal toxicological models SO_2 may act as a tumor promoter. Genotoxic and mutagenic studies with SO_2 have mixed results. Some studies with coexposure to other known carcinogens demonstrated that inhaled SO_2 can increase tumor burden in rodents. Collectively, while some studies observed no associations, the evidence from several toxicological and epidemiologic studies is suggestive of, but not sufficient to infer, a causal relationship between long-term exposure to SO_2 and cancer incidence and mortality.

Table 5-56 Summary of evidence, which is suggestive of, but not sufficient to infer, a causal relationship between long-term SO_2 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, some epidemiologic studies show an association.	Increases in lung cancer and bladder cancer mortality in studies conducted in the United States, Europe, and Asia.	Section 5.6.1	Means varied with studies of lung cancer mortality 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.
Uncertainty due to exposure measurement error	Central site monitors used in cancer studies may not capture spatial variability of SO_2 concentrations	Section 3.3.3.2	
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 3.3.4.1	
		Peacock and Spence (1967)	500,000 ppb

Table 5-56 (Continued): Summary of evidence, which is suggestive of, but not sufficient to infer, a causal relationship between long-term SO_2 exposure and cancer.

Rationale for Causal Determination[a]	Key Evidence[b]	Key References[b]	SO_2 Concentrations Associated with Effects[c]
Uncertainty due to limited coherence with toxicological evidence	Studies in a tumor-susceptible mouse model, females had increased numbers of lung adenomas and carcinomas. Studies of facilitation of metastasis and coexposures with known carcinogens show mixed SO_2 related effects.	Laskin et al. (1976)	10,000 ppb
		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 5.6.1.1	
Some evidence to identify 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 5.6.2	5,000, 10,700, 21,400, 32,100 ppb

ppb = parts per billion; MOA = mode of action; NO_2 = nitrogen dioxide; SO_2 = sulfur dioxide.

[a]Based on aspects considered in judgments of causality and weight of evidence in causal framework in Tables I and II of the Preamble (U.S. EPA, 2015e).

[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 Sufur Oxides

Table A-1 Scientific considerations for evaluating the strength of inference from studies on the health effects of sulfur oxides.

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.

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 report 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.a 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.

Exposure Assessment or Assignment
Controlled Human Exposure:
For this assessment, the focus will be on studies that utilize SO_2 concentrations less than or equal to 2 ppm (Section 1.2). Studies that utilize 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 peak exposures, defined here as exposures from 5−10 minutes, 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 utilize SO_2 concentrations less than or equal to 2,000 ppb (Section 1.2). Studies that utilize 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 (Sections 3.3.2 and 3.3.3.1), 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 3.3.5.1). 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.

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 report, 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.

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 2.5.5), 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[e]
Controlled Human Exposure:
Preference is given to studies utilizing 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 utilizing 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.

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; ppb = parts per billion; ppm = parts per million; 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).

References for Chapter 5

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

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

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

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 2: 758-759.

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).

Amster, ED; Haim, M; Dubnov, J; Broday, DM. (2014). Contribution of nitrogen oxide and sulfur dioxide exposure from power plant emissions on respiratory symptom and disease prevalence. Environ Pollut 186: 20-28. http://dx.doi.org/10.1016/j.envpol.2013.10.032

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.

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

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

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

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

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

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

Backx, PH. (2008). Sulfonylurea receptor expression heterogeneity suggests chamber-specific roles for sarcolemmal KATP channels in heart [Editorial]. Circ Res 103: 1345-1347. http://dx.doi.org/10.1161/CIRCRESAHA.108.189738

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

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

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.

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

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.

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

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

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

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

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

Bobak, M. (2000). Outdoor air pollution, low birth weight, and prematurity. Environ Health Perspect 108: 173-176.

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

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

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 pii: hpu302 [Epub ahead of print]: 1-6. http://dx.doi.org/10.1093/ajh/hpu302

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. Res Rep Health Eff Inst5-71; discussion 73-89.

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

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.

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

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

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

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

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.

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//S0034-89102006000300008

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, YK; Wu, CC; Lee, LT; Lin, RS; Yu, YH; Chen, YC. (2012). 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.

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, 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. (2012a). 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; 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. (2012b). Short-term effects of air pollution on pulse pressure among nonsmoking adults. Epidemiology 23: 341-348. http://dx.doi.org/10.1097/EDE.0b013e3182452f1d

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

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: 1-6. http://dx.doi.org/10.3109/14767058.2014.924104

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

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

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. http://dx.doi.org/10.1289/ehp.9044

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.

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 sulphur dioxide on airway response of mild asthmatic patients to allergen inhalation. Lancet 344: 1668-1671.

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.

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

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; 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

Du, Z; Meng, Z. (2004). Effects of derivatives of sulfur dioxide on transient outward potassium currents in acutely isolated hippocampal neurons. Food Chem Toxicol 42: 1211-1216. http://dx.doi.org/10.1016/j.fct.2004.02.016

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

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

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

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

Farhat, SC; Almeida, MB; Silva-Filho, LV; Farhat, J; Rodrigues, JC; Braga, AL. (2014). Ozone is associated with an increased risk of respiratory exacerbations in cystic fibrosis patients. Chest 144: 1186-1192. http://dx.doi.org/10.1378/chest.12-2414

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

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.

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

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

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.

Frey, U; Suki, B. (2008). Complexity of chronic asthma and chronic obstructive pulmonary disease: implications for risk assessment, and disease progression and control. Lancet 372: 1088-1099.

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

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.

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

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

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

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

Goldberg, MS; Giannetti, N; Burnett, RT; Mayo, NE; Valois, MF; Brophy, JM. (2009). Shortness of breath at night and health status in congestive heart failure: Effects of environmental conditions and health-related and dietary factors. Environ Res 109: 166-174. http://dx.doi.org/10.1016/j.envres.2008.10.007

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

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

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? 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

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.

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

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

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.

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 (pp. 5-72; discussion 73-83). (Research Report 169). Boston, MA: Health Effects Institute, HEI Collaborative Working Group on Air Pollutino, Poverty, and Health in Ho Chi Minh City. http://pubs.healtheffects.org/view.php?id=380

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

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

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

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

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, 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

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, 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. 29: 183-190. http://dx.doi.org/10.3904/kjim.2014.29.2.183

IOM (Institute of Medicine). (2007). Preterm birth: Causes, consequences, and prevention. Washington, DC: National Academies Press (US). http://www.nap.edu/catalog.php?record_id=11622

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.

Iwasawa, S; Michikawa, T; Nakano, M; Nishiwaki, Y; Tsuboi, T; Tanaka, S; Uemura, T; Milojevic, A; Nakashima, H; Takebayashi, T; Morikawa, A; Maruyama, K; Kudo, S; Uchiyama, I; Omae, K. (2010). [Nine-month observation of effects of SO2 on the respiratory system in child Miyakejima citizens]. Nippon Koshu Eisei Zasshi 57: 39-43.

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. 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

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; 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

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; 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, 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

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. http://pubs.healtheffects.org/view.php?id=348

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

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

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

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

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, 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

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

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

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.

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.

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. http://dx.doi.org/10.1289/ehp.5957

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 AC, I; 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.

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.

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.

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

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, 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. (2011a). 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. (2011b). 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

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

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

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, 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

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

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; 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 132C: 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 Occup Health 39: 313-319.

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.

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.

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.

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; 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. http://dx.doi.org/10.3155/1047-3289.59.4.473

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, 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; 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.

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.

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, ei. (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

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

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

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.

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.

Martins, LC; Pereira, LAA; Lin, CA; Santos, UP; Prioli, G; Luiz Odo, C; Saldiva, PHN; Braga, ALF. (2006). The effects of air pollution on cardiovascular diseases: lag structures. Rev Saude Publica 40: 677-683.

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

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

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

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. (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, DCE, H. (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

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.

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

Moolgavkar, SH. (2000). Air pollution and hospital admissions for diseases of the circulatory system in three US 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

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

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.

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.

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: guidelines for the diagnosis and management of asthma. J Allergy Clin Immunol 120: S93. http://dx.doi.org/10.1016/j.jaci.2007.09.043

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: 610-605.

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.

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

Nie, A; Meng, Z. (2005). Study of the interaction of sulfur dioxide derivative with cardiac sodium channel. Biochim Biophys Acta 1718: 67-73. http://dx.doi.org/10.1016/j.bbamem.2005.09.020

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, J. R.; 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

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

O'Byrne, PM. (2007). How much is too much? The treatment of mild asthma. Eur Respir J 30: 403-406. http://dx.doi.org/10.1183/09031936.00084107

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. http://dx.doi.org/10.1016/j.jaci.2008.02.020

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

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

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

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

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

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

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

Peters, J; Hedley, AJ; Wong, CM; Lam, TH; Ong, SG; Liu, J; Spiegelhalter, DJ. (1996). 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.

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

Pino, P; Walter, T; Oyarzun, M; Villegas, R; Romieu, I. (2004). Fine particulate matter and wheezing illnesses in the first year of life. Epidemiology 15: 702-708. http://dx.doi.org/10.1097/01.ede.0000142153.28496.d0

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.

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.

Pool, BL; Janowsky, I; Klein, P; Klein, RG; Schmezer, P; Vogtleucht, G; Zeller, WJ. (1988b). Effects of SO2 or NOx on toxic and genotoxic properties of chemical carcinogens .1. Invitro studies. Carcinogenesis 9: 1237-1245.

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.

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

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

Qiu, H; Yu, I; Wang, X; Tian, L; Tse, L; Wong, T. (2013a). 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

Qiu, H; Yu, IT; Wang, X; Tian, L; Tse, LA; Wong, TW. (2013b). 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

Rabe, KF; Adachi, M; Lai, CK; Soriano, JB; Vermeire, PA; Weiss, KB; Weiss, ST. (2004). Worldwide severity and control of asthma in children and adults: the global asthma insights and reality surveys. J Allergy Clin Immunol 114: 40-47. http://dx.doi.org/10.1016/j.jaci.2004.04.042

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

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

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. 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

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

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.

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

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

Rusconi, F; Catelan, D; Accetta, G; Peluso, M; Pistelli, R; Barbone, F; Di Felice, E; Munnia, A; Murgia, P; Paladini, L; Serci, A; Biggeri, A. (2011). Asthma symptoms, lung function, and markers of oxidative stress and inflammation in children exposed to oil refinery pollution. J Asthma 48: 84-90. http://dx.doi.org/10.3109/02770903.2010.538106

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, 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

Sacks, S. (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

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

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.

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.

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

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

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; 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

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.

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

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, LG; Busch, RH; Buschbom, RL; Cannon, WC; Loscutoff, SM; MorrisJE. (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

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.

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

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.

Spira-Cohen, A. (2013). Email from Dr. Spira-Cohen to Dr. Patel; Response to data request. Available online

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

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. (2002). Meta-analysis of time-series studies of air pollution and mortality: Effects of gases and particles and the influence of cause of death, age, and season. J Air Waste Manag Assoc 52: 470-484. http://dx.doi.org/10.1080/10473289.2002.10470794

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.

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: 25. 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

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

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

Tanaka, T; Asai, M; Yanagita, Y; Nishinakagawa, T; Miyamoto, N; Kotaki, K; Yano, Y; Kozu, R; Honda, S; Senjyu, H. (2013). Longitudinal study of respiratory function and symptoms in a non-smoking group of long-term officially-acknowledged victims of pollution-related illness. BMC Public Health 13: 766. http://dx.doi.org/10.1186/1471-2458-13-766

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

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.

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

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/doi: 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.

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.

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.

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

Turnovska, TH; Marinov, BI. (2009). The influence of air pollution during intrauterine development and early childhood on respiratory functions at later age. Int J Hyg Environ Health 212: 519-532. http://dx.doi.org/10.1016/j.ijheh.2009.03.002

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). Research Triangle Park: Environmental Criteria and Assessment Office. http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=46205

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. (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). (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). (1996). Guidelines for reproductive toxicity risk assessment. (EPA/630/R-96/009). Washington, DC: U.S. Environmental Protection Agency, Risk Assessment Forum. http://www.epa.gov/raf/publications/guidelines-reproductive-tox-risk-assessment.htm

U.S. EPA (U.S. Environmental Protection Agency). (1998). Guidelines for neurotoxicity risk assessment [EPA Report]. (EPA/630/R-95/001F). Washington, DC: U.S. Environmental Protection Agency, Risk Assessment Forum. http://www.epa.gov/raf/publications/guidelines-neurotoxicity-risk-assessment.htm

U.S. EPA (U.S. Environmental Protection Agency). (2005a). Guidelines for carcinogen risk assessment. (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). (2008b). Integrated science assessment for sulfur oxides: Health criteria [EPA Report]. (EPA/600/R-08/047F). Research Triangle Park, NC: U.S. Environmental Protection Agency, National Center for Environmental Assessment. 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, National Center for Environmental Assessment. http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=216546

U.S. EPA (U.S. Environmental Protection Agency). (2013b). 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). (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/b5d8a1ce9b0729348525737500 7012b7/ee1e280e77586de985257b65005d37e7!OpenDocument

U.S. EPA (U.S. Environmental Protection Agency). (2015a). Figure 5S-1. 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). (2015b). Figure 5S-2. 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). (2015c). Figure 5S-3. 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). (2015e). 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.

U.S. EPA (U.S. Environmental Protection Agency). (2015f). 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). (2015g). 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). (2015h). Table 5S-3. Summary of additional respiratory hospital admission and emergency department visit studies.

U.S. EPA (U.S. Environmental Protection Agency). (2015i). Table 5S-4. Summary of epidemiologic studies of long-term exposure to SO2 and respiratory morbidity.

U.S. EPA (U.S. Environmental Protection Agency). (2015j). Table 5S-5. Summary of cross-sectional epidemiologic studies examining associations between SO2 and other respiratory effects.

U.S. EPA (U.S. Environmental Protection Agency). (2015k). Table 5S-6. Study-specific details of experimental studies of SO2 and cardiovascular effects.

U.S. EPA (U.S. Environmental Protection Agency). (2015l). Table 5S-7. 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-1.

U.S. EPA (U.S. Environmental Protection Agency). (2015m). Table 5S-8. Corresponding risk estimates of ambient sulfur dioxide for hospital admissions for cardiovascular disease in studies conducting copollutants models with NO2 presented in Figure 5S-2.

U.S. EPA (U.S. Environmental Protection Agency). (2015n). Table 5S-9. Corresponding risk estimates of ambient sulfur dioxide for hospital admissions for cardiovascular disease in studies conducting copollutants models with PM presented in Figure 5S-3.

U.S. EPA (U.S. Environmental Protection Agency). (2015o). Table 5S-11. Summary of epidemiologic studies of exposure to sulfur dioxide and fertility/pregnancy effects.

U.S. EPA (U.S. Environmental Protection Agency). (2015p). Table 5S-12. Summary of epidemiologic studies of exposure to sulfur dioxide and fetal growth.

U.S. EPA (U.S. Environmental Protection Agency). (2015q). Table 5S-13. Summary of epidemiologic studies of exposure to sulfur dioxide and preterm birth.

U.S. EPA (U.S. Environmental Protection Agency). (2015r). Table 5S-14. Summary of epidemiologic studies of exposure to sulfur dioxide and birth weight.

U.S. EPA (U.S. Environmental Protection Agency). (2015s). Table 5S-15. Summary of epidemiologic studies of exposure to sulfur dioxide and birth defects.

U.S. EPA (U.S. Environmental Protection Agency). (2015t). Table 5S-16. Summary of epidemiologic studies of exposure to sulfur dioxide and fetal and infant mortality.

U.S. EPA (U.S. Environmental Protection Agency). (2015u). Table 5S-17. Summary of additional epidemiologic studies of short-term sulfur dioxide exposure and mortality.

U.S. EPA (U.S. Environmental Protection Agency). (2015v). Table 5S-18. Summary of epidemiologic studies of SO2 concentration and cancer incidence and mortality.

U.S. EPA (U.S. Environmental Protection Agency). (2015w). Table 5S-19. Study-specific details of experimental studies of SO2 exposure and genotoxicity.

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

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

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. (2006). 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; 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

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

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, 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.

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.

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

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: 26. http://dx.doi.org/10.1186/1476-069X-6-26

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

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

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

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

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.

Wong, CM; Vichit-Vadakan, N; Kan, H; Qian, Z. (2008). 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, 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.

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

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; 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

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: 52. 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, 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

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

Yorifuji, T; Kashima, S; Doi, H. (2015). 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

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. (2013a). Cardiorespiratory biomarker responses in healthy young adults to drastic air quality changes surrounding the 2008 Beijing Olympics. Res Rep Health Eff Inst Feb: 5-174.

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: e20827. http://dx.doi.org/10.1371/journal.pone.0020827

Zhang, Q; Meng, Z. (2012). The negative inotropic effects of gaseous sulfur dioxide and its derivatives in the isolated perfused rat heart. Environ Toxicol 27: 175-184. http://dx.doi.org/10.1002/tox.20628

Zhang, Q; Tian, J; Bai, Y; Lei, X; Li, M; Yang, Z; Meng, Z. (2014). Effects of gaseous sulfur dioxide and its derivatives on the expression of KATP, BKCa and L-Ca(2+) channels in rat aortas in vitro. Eur J Pharmacol 742: 31-41. http://dx.doi.org/10.1016/j.ejphar.2014.08.025

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: 2. 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

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

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.

CHAPTER 6 POPULATIONS AND LIFESTAGES POTENTIALLY AT 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 detrimental 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 ISA (U.S. EPA, 2015e)]. 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 ISA (U.S. EPA, 2015e)]. 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 ISA (U.S. EPA, 2015e), 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, could be at increased risk of an air pollutant-related health effect via multiple avenues. As discussed in the Preamble (U.S. EPA, 2015e), there are many avenues by which risk may be modified, including intrinsic or extrinsic factors, differences in internal dose, or differences in exposure to air pollutant 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 multiple 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 ISA (U.S. EPA, 2015e)].

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 (U.S. EPA, 2015e). 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, 2008b). Based on the approach developed in previous ISAs (U.S. EPA, 2015d, 2013a, b), evidence is integrated across scientific disciplines, across health effects, and where available, with information on exposure and dosimetry (Chapters 3 and 4). 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 (U.S. EPA, 2015e), 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, those that include stratified analyses to compare populations or lifestages exposed to similar air pollutant concentrations within the same study design provide the most relevant evidence with consideration of their strengths and limitations. Other epidemiologic studies that do not stratify results but instead examine a specific population or lifestage can provide further evidence, particularly when these studies are similar enough to allow comparison. Experimental studies in human subjects or animal models that focus on factors, such as genetic background or health status, are also important lines of evidence to evaluate because they inform the independent effects of SO_2 as well as coherence and biological plausibility of effects observed in epidemiologic studies. Additionally, studies examining whether factors may result in differential exposure to SO_2 and subsequent increased risk of SO_2-related health effects are also included.

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 (Section 6.3), genetic background (Section 6.4), sociodemographic (Section 6.5), and behavioral and other factors (see Section 6.6). The classifications of evidence are characterized in Table 6-1, and a summary of the characterization of the evidence for each factor considered is presented in Section 6.7.

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/Conditions

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, 2008b) 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 by pre-existing disease, most focused on asthma (Section 6.3.1), though other studies examined effect modification by pre-existing CVD (Section 6.3.2), diabetes (Section 6.3.3), and obesity (Section 6.3.4). Table 6-2 presents the prevalence of these 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, including various cardiovascular 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, cardiovascular diseases, diabetes, and obesity among adults by age and region in the U.S. in 2012.

	Adults (18+)	Age (%)[a]				Region (%)[b]			
Chronic Disease/Condition	**N (in thousands)**	**18−44**	**45−64**	**65−74**	**75+**	**North-east**	**Midwest**	**South**	**West**
All (N, in thousands)	234,921	111,034	82,038	23,760	18,089	42,760	53,378	85,578	53,205
Selected respiratory diseases									
Asthma[c]	18,719	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
Selected cardiovascular diseases/conditions									
All heart disease	26,561	3.8	12.1	24.4	36.9	10.0	11.6	11.6	9.3
Coronary heart disease	15,281	0.9	7.1	16.2	25.8	5.3	6.5	7.0	5.1
Hypertension	59,830	8.3	33.7	52.3	59.2	21.4	24.1	26.6	21.5
Stroke	6,370	0.6	2.8	6.3	10.7	1.8	2.5	3.0	2.5

Table 6-2 (Continued): Prevalence of respiratory diseases, cardiovascular diseases, and diabetes among adults by age and region in the U.S. in 2010.

Chronic Disease/Condition	Adults (18+)	Age (%)[a]				Region (%)[b]			
	N (in thousands)	18−44	45−64	65−74	75+	North-east	Midwest	South	West
Metabolic disorders/conditions									
Diabetes	21,391	2.4	12.7	21.1	19.8	7.6	8.4	10.0	7.3
Obesity (BMI ≥30 kg/m^2)	64,117	26	33.7	29.7	18	25.1	29.9	29.9	25.2
Overweight (BMI 25−30 kg/m^2)	78,455	31.4	36.8	40.7	38.6	34.3	34.1	34.2	35.3

BMI = body mass index; COPD = chronic obstructive pulmonary disease.

[a]Percentage of individual adults 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]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 9.3% 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. Based on evidence from the 2008 ISA for Sulfur Oxides (U.S. EPA, 2008b) 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 (Sections 5.2.1.2 and 5.2.1.8). This is nearly the same body of evidence evaluated in the 2008 SO_X ISA (U.S. EPA, 2008b), which also concluded that individuals with asthma were more sensitive to exposures to ambient SO_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 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, 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, 21 atopic; mild asthma n = 16 moderate/ severe asthma n = 24	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 bronchial asthma, 12 healthy	0.5 ppm SO_2 for 10 min tidal breathing, 10 min of isocapnic hyperventilation (30 L/min); Histamine challenge	Magnussen et al. (1990)
Asthma	Healthy	−	Lung function (FEV_1, FVC, MMEF)	n = 12 asthma, 12 healthy	0.2 ppm SO_2 for 1 h at rest	Tunnicliffe et al. (2003)

Table 6 3 (Continued): Controlled human exposure 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
Mild asthma n = 12, 34.5 yr	Healthy n = 12, 35.7 yr	–	Heart rate	n = 24	0.2 ppm SO_2 for 1 h at rest; ECG during exposure	Tunnicliffe et al. (2001)
		↓	HRV			
Asthmatic rat model (OVA sensitization)	Normal rats	↑	AHR (methach-oline)	Rats (Sprague-Dawley), n = 10 males/group (4 weeks)	2 ppm SO_2 for 4 h/day for 4 weeks beginning at 15 days	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; ECG = electrocardiogram; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; HRV = heart rate variability; IFN-γ = interferon gamma; IL-4 = interleukin 4; MMEF = maximum midexpiraotry flow; NaCl = sodium chloride; OVA = ovalbumin; 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 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, subjects 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 at SO_2 concentrations ranging from 0.2 ppm 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, mild asthmatic, atopic asthmatic, and moderate/severe asthmatic individuals 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 subjects with asthma relative to healthy controls when exposed at rest (Tunnicliffe et al., 2003; Koenig et al., 1980). It is

important to note though that these studies were limited by exposure design and small sample sizes. In addition to controlled human exposure studies, a long-term study conducted in ovalbumin (OVA)-sensitized rats as an asthmatic 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, only two studies included stratification by asthma status but did not find differences for short-term exposure to ambient SO_2 with respiratory outcomes (Table 6-4) (Amadeo et al., 2015; Lin et al., 2015). However, evidence presented in Section 5.2.1.2 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 older studies reviewed in the 2008 ISA for Sulfur Oxides (U.S. EPA, 2008b) indicates that children with asthma experience respiratory symptoms associated with exposure to ambient SO_2.

In conclusion, there is consistent evidence from controlled human exposure studies and animal toxicology studies demonstrating decrements in lung function with SO_2 exposures. In addition, there is clear biological plausibility (Section 4.3) supporting the observed effects as well as epidemiologic evidence suggesting individuals with asthma experience respiratory symptoms associated with exposure to ambient SO_2. Overall, there is adequate evidence from experimental studies to conclude that people with pre-existing asthma are at increased risk of SO_2-induced respiratory effects.

Table 6-4 Epidemiologic studies evaluating pre-existing asthma.

Factor Evaluated	Reference Category	Direction of Effect Modification[a]	Outcome	Study Population	Study Details	Study
Short-term exposure						
Asthmatic n = 16.6%	Nonasthmatic n = 83.4%	–	Lung function (PEF)	n = 506 elementary school children ages 8−13 yr	Guadeloupe (French West Indies) December 2008–December 2009	Amadeo et al. (2015)
Asthmatic n = 8	Nonasthmatic n = 28	–	Oxidative stress (8-oxo-7,8-dihydro-2´-deoxyguano-sine and malondial-dehyde)	n = 36 elementary school children (fourth grade, mean age 10.6 yr)	Beijing, China June 2007–September 2008	Lin et al. (2015)

n = sample size; PEF = peak expiratory flow; yr = year.

[a]A dash indicates no difference in SO_2-related health effect between groups.

6.3.2 Cardiovascular Disease

Cardiovascular disease is the primary cause of death in the U.S., and approximately 12% of adults report a diagnosis of heart disease [Table 6-2; (Schiller et al., 2012)]. The evidence on SO_2-related health effects in individuals with pre-existing cardiovascular disease evaluated in the 2008 ISA for Sulfur Oxides (U.S. EPA, 2008b) was found to be limited and inconsistent. Recent evidence reviewed in this ISA adds two epidemiologic studies evaluating effects of SO_2 exposure on individuals with pre-existing cardiovascular disease, but does not provide any more clarity regarding whether or not these individuals may be at greater risk for SO_2-related health effects compared to individuals without cardiovascular disease (Table 6-5).

Table 6-5 Epidemiologic studies evaluating pre-existing cardiovascular disease and sulfur dioxide exposure.

Factor Evaluated	Reference Category	Direction of Effect Modification[a]	Outcome	Study Population	Study Details	Study
Short-term exposure						
Hypertension n = 40% visits	No hypertension n = 60% visits	–	Hospital admissions, myocardial infarction	n = 27,563 admissions	Taipei, Taiwan 1999–2009	Tsai et al. (2012)
CHF n = 15% visits	No CHF n = 85% visits	–				
Cardiac arrhythmia n = 11% visits	No cardiac arrhythmia n = 89% visits					
Cardiovascular disease n = 535	No cardiovascular disease n = 956	↑	Hospital admissions, stroke	n = 1,491 admissions for stroke	Tehran, Iran 2004	Nabavi et al. (2012)
Hypertension n = 955	No hypertension n = 536	–				

CHF = congestive heart failure; n = sample size.

[a]Up facing arrow indicates that the effect of SO_2 is greater (e.g., larger forced expiratory volume in 1 second 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 difference in SO_2-related health effect between groups.

Tsai et al. (2012) and Nabavi et al. (2012) reported weak associations between short-term ambient SO_2 exposure and hospital admissions for myocardial infarction and stroke, respectively, and those associations remained weak for individuals with various pre-existing cardiovascular conditions. Similarly, Routledge et al. (2006) compared cardiovascular outcomes in older adults with and without pre-existing cardiovascular disease during exposure to 200 ppb SO_2 and found that only individuals without pre-existing disease had significant responses to SO_2 (Table 6-6). Additionally, biological plausibility for the outcomes examined remains unclear (Section A.B.C).

Table 6-6 Controlled human exposure evaluating pre-existing cardiovascular disease and sulfur dioxide exposure.

Factor Evaluated	Reference Category	Direction of Effect[a]	Outcome	Study Population/ Animal Model	Study Details	Study
Older adults with pre-existing cardiovascular disease n = 20	Healthy older adults n = 20	↑	Heart rate	Adults 5−75 yr	200 ppb SO_2 for 1 h at rest; ECG 4 h after exposure	Routledge et al. (2006)
		↓	Decrements in HRV			
		–	Blood pressure			

ECG = electrocardiogram; HRV = heart rate variability.

[a]A dash indicates that SO_2 was not observed to induce an effect in the group with cardiovascular disease evaluated relative to the reference group. An up-facing arrow indicates that effect measured after SO_2 exposure was reduced in the group of healthy, older adults and exposure did not affect response in older adults with cardiovascular disease. Down facing arrow indicates that the effect of SO_2 is smaller in the group.

Overall, the limited and inconsistent evidence and lack of biological plausibility is inadequate to determine if individuals with pre-existing cardiovascular disease may be at increased risk for SO_2-related health outcomes.

6.3.3 Diabetes

Diabetes mellitus is a group of diseases characterized by high blood glucose levels which affected an estimated 20 million Americans in 2012 or approximately 8.6% of the adult population (Blackwell et al., 2014). High blood glucose levels have adverse effects on the cardiovascular system, and diabetes and cardiovascular disease are linked by common risk factors such as hypertension and obesity. These relationships provide support for diabetes influencing the risk of cardiovascular disease; however, diabetes has not consistently been observed to modify epidemiologic associations in studies of short-term SO_2 exposure and cardiovascular effects (Table 6-7). Filho et al. (2008) found stronger

associations between SO_2 exposures and emergency department visits for hypertension or ischemic heart disease among individuals with diabetes compared to those without, but no difference by diabetic status was observed in studies examining SO_2-related hospital admissions for MI (Tsai et al., 2012; Filho et al., 2008). Huang et al. (2012) found SO_2-associated decrements in HRV in a panel study of individuals with cardiovascular disease, and decrements were greater in individuals with diabetes compared to those without; however, the sample sizes were small. Given the limited number of studies evaluating diabetes as a risk factor, the evidence is inadequate to determine whether people with diabetes are at increased risk for SO_2-associated health outcomes.

Table 6-7 Epidemiologic studies evaluating pre-existing diabetes and sulfur dioxide exposure.

Factor Evaluated	Reference Category	Direction of Effect Modification[a]	Outcome	Study Population	Study Details	Study
Short-term exposure						
Diabetes n = 700 ED visits	No diabetes n = 44,300 ED visits	↑	ED visits for hypertension and cardiac ischemic disease	N = 45,000 ED visits	Sao Paulo Hospital, Brazil January 2001–July 2003	Filho et al. (2008)
Diabetes n = 29.6%	No diabetes n = 70.4%	–	Hospital admissions, myocardial infarction	N = 27,563 admissions	Taipei, Taiwan 1999−2009	Tsai et al. (2012)
Diabetes n = 9	No diabetes n = 31	↑	HRV decrements (SDNN)	N = 40 with CVD Mean age 66 yr	Beijing, China 2008	Huang et al. (2012)

CVD = cardiovascular disease; ED = emergency department; HRV = heart rate variability; SDNN = standard deviation of normal RR intervals.

[a]Up facing arrow indicates that the effect of SO_2 is greater (e.g., larger risk of ED visit, larger decrement in HRV) 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 difference in SO_2-related health effect between groups.

6.3.4 Obesity

In the U.S., obesity is defined as a BMI of 30 kg/m^2 or greater, with a BMI between 25 and 30 kg/m^2 indicating an overweight individual. It is a public health issue of increasing importance as obesity rates in adults have continually increased over several decades in the U.S., reaching an estimated 28% in 2012 (Blackwell et al., 2014). Furthermore,

34.5% of adults in the U.S. are considered overweight while only 28.9% are at a healthy weight (BMI 18.5−25 kg/m^2) (Blackwell et al., 2014). Obesity or high BMI could increase the risk of SO_2-related health effects through multiple mechanisms, including persistent low-grade inflammation, and may act in combination with other risk factors such as poor diet or chronic disease that commonly occur with obesity.

The 2008 ISA for Sulfur Oxides (U.S. EPA, 2008b) did not evaluate obesity as a potential factor that could increase the risk of SO_2-related health effects, but recent literature includes obesity or BMI as a potential effect measure modifier (Table 6-8). Across cardiovascular outcomes, including decrements in heart rate variability, blood pressure, and levels of lipoprotein-associated phospholipase 2 (an indicator of vascular inflammation), associations with short-term exposure to ambient SO_2 were not consistently greater in obese or overweight individuals compared to those of healthy weight (Sun et al., 2015; Huang et al., 2012; Brüske et al., 2011; Longo et al., 2008). Studies of long-term SO_2 exposure examined associations with cardiovascular mortality, heart failure, and respiratory mortality, but reported mixed results (Atkinson et al., 2013; Dong et al., 2013b; Dong et al., 2012; Cao et al., 2011; Zhang et al., 2011). In addition, there is a lack of biological plausibility and uncertainty in the causality of cardiovascular effects related to SO_2 exposure (Sections 4.2.6, 5.3.1.11, and 5.3.2.6). Thus, the limited and inconsistent evidence is inadequate to determine whether obese or overweight individuals are at greater risk for SO_2-associated health outcomes than nonobese individuals.

Table 6-8 Epidemiologic studies evaluating pre-existing obesity and sulfur dioxide exposure.

Factor Evaluated	Reference Category	Direction of Effect Modification[a]	Outcome	Study Population	Study Details	Study
Short-term exposure						
High BMI (≥25) n = 16	Low BMI (<25) n = 24	↓	HRV decrements (SDNN)	n = 40 nonsmoking adults with CVD Mean age: 66 yr	Beijing, China 2007−2008	Huang et al. (2012)
High BMI (25<BMI <28)[b]	Low BMI (<25)[b]	↑	HRV decrements (SDNN)	n = 53 adults ages 51−68 with Type-2 diabetes or impaired glucose tolerance	Shanghai, China April, June, and September 2010	Sun et al. (2015)
High BMI (25<BMI <28)[b]	Low BMI (<25)[b]	↑				

Table 6-8 (Continued): Epidemiologic studies evaluating pre-existing obesity and sulfur dioxide exposure.

Factor Evaluated	Reference Category	Direction of Effect Modification[a]	Outcome	Study Population	Study Details	Study
High BMI (>28)[b]	Low BMI (<25) (kg/m^2)[b]	↑	Blood pressure, systolic	n = 335 adults >20 yr, residing downwind from volcano	Hawaii April-June 2004	Longo et al. (2008)
High BMI (>25) n = 168	Low BMI (≤25) n = 31	–	Lipoprotein-associated phospholipase A2 in plasma (marker for vascular inflammation related to atherosclerosis)	n = 200 post-MI patients Mean age: 61.9±9.0 yr	Augsburg, Germany May 2003–March 2004	Brüske et al. (2011)
Long-term exposure						
High BMI (>30) n = 2,570	Lower BMI (25−30) n = 4,194	↓	Heart failure	n = 12,851 Ages 40−89 yr in 2003	England 2003−2007	Atkinson et al. (2013)
High BMI (≥25) n = 73	Low BMI (<18.5) n = 21	–	Cardiovascular mortality	n = 9,941 subjects ≥25 yr at study enrollment and living at residence ≥10 yr; 256 cardiovascular deaths	Shenyang, China 1998−2009	Zhang et al. (2011)
High BMI (≥25)[b]	Low BMI (<25)[b]	↑	Cardiovascular mortality	n = 70,947 study participants, 8,319 deaths	China 1991−2000	Cao et al. (2011)
High BMI (≥25) n = 10	Low BMI (<18.5) n = 12	↑	Respiratory mortality	n = 9,441 residents ≥35 yr living at residence ≥10 yr; 72 deaths due to respiratory disease	Shenyang, China 1998−2009	Dong et al. (2012)

Table 6-8 (Continued): Epidemiologic studies evaluating pre-existing obesity and sulfur dioxide exposure.

Factor Evaluated	Reference Category	Direction of Effect Modification[a]	Outcome	Study Population	Study Details	Study
Overweight/obese children n = 7,937	Normal weight children n = 22,119	↑	Doctor-diagnosed asthma	n = 30,056 children ages 2−14 yr; weight categories determined according to CDC standards	Seven northeastern cities study, Liaoning Provence, northeast China 2006−2008	Dong et al. (2013b)
		↑	Respiratory symptoms (cough, phlegm, wheeze)			

BMI = body mass index in kg/m^2; CDC = Centers for Disease Control and Prevention; CVD = cardiovascular disease; HRV = heart rate variability.

[a]Up facing arrow indicates that the effect of SO_2 is greater (e.g., larger change in ventricular repolarization) 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 evaluated factor than in the reference group. A dash indicates no difference in SO_2-related health effect between groups.

[b]Sample size not reported.

6.4 Genetic Factors

Genetic variation in the human population is known to contribute to numerous diseases and differential physiologic responses. The 2008 SO_X ISA (U.S. EPA, 2008b) 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. Only one recently conducted study reviewed in this ISA examined effect measure modification by genotype [(Reddy et al., 2012); Table 6-9] 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 genotype 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 evidence base is inadequate to determine whether genetic background contributes to increased risk for SO_2-associated health outcomes.

Table 6-9 Epidemiologic studies evaluating genetic factors and sulfur dioxide exposure.

Factor Evaluated/Gene Function	Reference Category	Direction of Effect Modification[a]	Outcome	Study Population	Study Details	Study
GSTM1 null n = 33 Null oxidant metabolizing capacity	GSTM1 positive n = 89	↓	Lung function (FEV_1,intraday variability)	n = 129 indigenous African children, 9−11 yr	Durban, South Africa 2004−2005	Reddy et al. (2012)
GSTP Ile/Val + Val/Val (AG + GG) n = 91 Reduced oxidant metabolizing capacity (Val/Val)	GSTP1 Ile/Ile (AA) n = 21	↑				

AA = adenine-adenine genotype; AG = adenine-guanine genotype; FEV_1 = forced expiratory volume in 1 second; GG = guanine-guanine genotype; GSTM1 = glutathione s-transferase mu 1; GSTP = glutathione s-transferase P; GSTP1 = glutathione S-transferase pi 1; Ile = isoleucine; Val = valine.

[a]Up facing arrow indicates that the effect of SO_2 is greater (e.g., larger change in ventricular repolarization) 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 evaluated factor than in the reference group. A dash indicates no difference in SO_2-related health effect between groups.

6.5 Sociodemographic Factors

6.5.1 Lifestage

The 2008 ISA for Sulfur Oxides (U.S. EPA, 2008b) 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 and/or physiological characteristics that are associated with development and growth (U.S. EPA, 2014c). 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, it is plausible to consider children to have intrinsic risk for respiratory effects due to potential perturbations in normal lung development. 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 (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 SO_X ISA (U.S. EPA, 2008b).

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. supports the public health significance of characterizing the risk of SO_2-related health effects among children, especially because there is a causal relationship between ambient SO_2 exposure and lung function decrements in individuals with asthma, which affects approximately 10.5−11% of children 5 years and older. The 2008 ISA for Sulfur Oxides (U.S. EPA, 2008b) presented evidence demonstrating increased risk of SO_2-related respiratory outcomes in children compared to adults; however, recent evidence is not entirely consistent with the discussion presented previously (Table 6-10). Although Son et al. (2013) found children (0−14 years) to be at greater risk for SO_2-related asthma hospital admissions, several studies did not observe differences between children and adults when examining associations of ambient SO_2 and asthma hospitalizations or emergency department visits (Samoli et al., 2011; Ko et al., 2007b; Villeneuve et al., 2007). Jalaludin et al. (2008) compared associations of short-term SO_2 exposure and respiratory-related ED visits among different age groups of children and found those of ages 1−4 years to have greater associations than those of ages 10−14 years. However, Dong et al. (2013c) and Nishimura et al. (2013) 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.

Table 6-10 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						
Childhood Ages 0−14 yr n = 60.1/day	All ages n = 104.9/day	↓	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/day	Adulthood Ages 15−64 yr n = 4.3/day	↑	Asthma hospital admissions	Database accounting for 48% of Korean population n = 19/day	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/day	Childhood Ages 10−14 yr n = 25/day	↑	Respiratory-related ED visits	Daily number of ED visits in metropolitan Sydney from the New South Wales Health Department n = 174/day	Sydney, Australia 1997−2001	Jalaludin et al. (2008)

Table 6-10 (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
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)			
First year of life exposure n = 2,876	First three years of life exposure n = 2,512	−	Physician-diagnosed asthma plus two or more symptoms of coughing, wheezing or shortness of breath	n = 4,320 GALA II and SAGE II cohorts (Latinos and African-Americans ages 8−21 yr)	Chicago, IL; Bronx, NY; Houston, TX; San Francisco Bay Area, CA and Puerto Rico 2006−2011	Nishimura et al. (2013)
Younger children Ages 6−7 yr n = 918	Older children Ages 13−14 yr n = 549	↓	Non-allergic asthma	n ~1,467 Children grades one (ages 6−7 yr) and eight (ages 13−14 yr)	Hamilton, Canada 1994−1995	Sahsuvaroglu et al. (2009)

ED = emergency department; GALA II = Genes-environments and Admixture in Latino Americans; SAGE II = Study of African Americans, Asthma, Genes and Environments.

[a]Up facing arrow indicates that the effect of SO_2 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 SO_2 is smaller in the group with the factor evaluated than in the reference group. A dash indicates no difference in SO_2-related health effect between groups.

Overall, the combined evidence from the previous and current ISA examining respiratory outcomes across lifestages is only suggestive of increased risk in children, given the inconsistencies across epidemiologic studies and limited toxicological evidence to inform plausibility.

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, 2008b) 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 mortality, respiratory, or cardiovascular effects. Recently published studies evaluating risk in older adults compared to younger adults are shown in Table 6-11, and generally support conclusions from the 2008 ISA for Sulfur Oxides (U.S. EPA, 2008b). 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 respiratory admissions or ED visits in adults greater than 65 years of age reported mixed results compared to the earlier literature (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 years and older than 75 years) to have larger decrements in lung function compared to adults aged 16−44.

Table 6-11 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
Short-term exposure						
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		↑				

Table 6-11 (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 ≥65 yr n = 789	Younger adulthood Ages 40−64 yr n = 980	↑	COPD ED visits	Sao Paulo Hospital, daily records for patients >40 yr n = 1,769	Sao Paulo, Brazil 2001−2003	Arbex et al. (2009)
Older adulthood Ages 65−74 yr n = 5.8/day	Younger adulthood Ages 15−64 yr n = 8.8/day	−	Asthma and allergic disease hospital admissions	Hospital admission database accounting for 48% of Korean population n = 37.7/day	Eight South Korean cities 2003−2008	Son et al. (2013)
Older adulthood Ages ≥75 yr n = 5.8/day	Younger adulthood Ages 15−64 yr n = 8.8/day	↑				
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 n = 130.8	All ages n = 203.5	−	Cardiovascular hospital admissions			
Older adulthood Ages 65−100 yr n = 8,008	Younger adulthood Ages 20−64 yr n = 2,873	−	Ischemic stroke (ED visit)	Five hospitals from the metropolitan area n = 10,881	Edmonton, Canada 1992−2002	Szyszkowicz (2008)
Older adulthood Ages ≥65 yr n = 87	Younger adulthood Ages <65 yr n = 248	−	Blood pressure, systolic	n = 335 adults ≥20 yr, residing downwind from volcano for ≥7 yr	Big Island, Hawaii	Longo et al. (2008)
Older adulthood Ages 65−74 yr	Younger adulthood Ages ≤64 yr	−	Diabetes (hospital-izations)		Santiago, Chile 2001−2008	Dales et al. (2012)
Older adulthood Ages 75−84 yr		−				

Table 6-11 (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 ≥85 yr		−		Ministry of Health statistics for hospitalizations for acute serious complications of diabetes		
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, Wuhan Centre for Disease Prevention and Control, Wuhan	Bangkok, Thailand; Hong Kong, Shanghai, and Wuhan, China1996−2004	Wong et al. (2008)
Long-term exposure						
Older adulthood Ages ≥65 yr n = 2,234	Younger adulthood Ages <55 yr n = 18,698	−	Blood pressure (hyper-tension)	n = 24,845 subject from different households at residence for ≥5 yr	Shenyang, Anshan and Jinzhou, China 2006−2008	Dong et al. (2013d)
Older adulthood Ages 55−64 yr n = 3,913	Younger adulthood Ages <55 yr n = 18,698	−				

Table 6-11 (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 >40 yr n = 1,404	Younger adulthood Ages <40 yr n = 45	−	Stroke (hospital admissions)	n = 1,491 patients admitted with the diagnosis of stroke in eight referral hospitals in Tehran	Tehran, Iran 2004	Nabavi et al. (2012)
Older adulthood Ages ≥65 yr n = 5.50 admissions/day	Younger adulthood Ages <65 yr n = 4.15 admissions/day	↑	Cerebro-vascular disease (hospital admissions)	Records obtained from four largest hospitals	Lanzhou, China 2001−2005	Zheng et al. (2013)
Older adulthood Ages 65−89 yr n ~ 2,213	Younger adulthood Ages 40−64 yr n = 10,638	−	Heart failure (hospital admissions)	n = 12,851 Ages 40−89 yr at baseline	England 2003−2007	Atkinson et al. (2013)
Older adulthood Ages ≥60 yr	Younger adulthood Ages <60 yr	↓	Respiratory mortality	n = 9,441 residents ≥35 yr living at residence ≥10 yr; 72 deaths due to respiratory disease	Shenyang, China 1998−2009	Dong et al. (2012)
Older adulthood Ages ≥65 yr	Younger adulthood Ages 30−65 yr	−	All-cause mortality	n = 420,776 deaths	Great Britain 1982−1986, 1986−1990, 1990−1994, 1994−1998	Elliott et al. (2007)
Older adulthood Ages >60 yr n = 4,061	Younger adulthood Ages ≤60 yr n = 5,880	−	Cardio-vascular mortality	n = 9,941 subjects ≥25 years at study enrollment and living at residence ≥10 yr; 256 cardio-vascular deaths	Shenyang, China 1998−2009	Zhang et al. (2011)

Table 6-11 (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 45−74 yr[b]	Younger adulthood Ages 16−44 yr[b]	↑	Decrements in lung function (FEV_1)	n = 32,712 households. adults from white ethnic groups (≥16 yr)	Health Survey for England; Lung function in England 1995, 1996, 1997, and 2001	Forbes et al. (2009c)
Older adulthood Ages ≥75 yr[b]	Younger adulthood Ages 16−44 yr[b]	↑				

COPD = chronic obstructive pulmonary disease; ED = emergency department; FEV_1 = forced expiratory volume in 1 second.

[a]Up facing arrow indicates that the effect of SO_2 is greater (e.g., larger risk of hospital admission, larger decrement in heart rate vatiability) 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 difference in SO_2-related health effect between groups.

[b]Sample size not reported.

Other recent studies comparing results in older and younger adults evaluated cardiovascular outcomes and mortality and generally found associations between outcomes and short or long-term SO_2 exposures to be the same (Atkinson et al., 2013; Dong et al., 2013d; Dales et al., 2012; Nabavi et al., 2012; Zhang et al., 2011; Longo et al., 2008; Szyszkowicz, 2008; Elliott et al., 2007). However, Chen et al. (2012c) and Wong et al. (2008) both 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.

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. Although the evidence from cardiovascular studies is generally the same in comparisons of age, there is uncertainty in the relationship between ambient SO_2 and cardiovascular outcomes in general. The evidence from the current and previous ISA related to respiratory hospitalizations and ED visits as well as mortality, consistently suggest that older adults, particularly those older than 75 years, may be at increased risk for SO_2-related health effects.

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.

There are a number of studies evaluating sex-based differences in SO_2-associated health effects, details for which are shown in Table 6-12. 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 men compared to women. No differences were found between men and women for 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 significantly stronger associations between ambient SO_2 exposure and asthma hospital admissions.

Table 6-12 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, Ontario, Canada October–December 2005	Dales et al. (2009)

Table 6 12 (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 = 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	Sao Paulo Hospital, daily records for patients > 40 yr n = 1,769	Sao Paulo, Brazil 2001−2003	Arbex et al. (2009)
Female n = 7.4 admissions/ day	Male n = 8 admissions/ day	↓	Asthma hospital admissions	Database accounting for 48% of Korean population n = 19/day	Eight South Korean cities 2003−2008	Son et al. (2013)
Female n = 7.1 admissions/ day	Male n = 8 admissions/ day	↓	Allergic disease hospital admissions			
Female[b]	Male[b]	↓	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)
Female n = 36	Male n = 164	–	Lipoprotein-associated phospholipase A2 in plasma (marker for vascular inflammation related to atherosclerosis)	Post-MI patients Mean age: 61.9±9.0 yr n = 200	Augsburg, Germany May 2003–March 2004	Brüske et al. (2011)
Female n = 24	Male n = 16	↑	Reductions in HRV (SDNN)	n = 40 nonsmoking adults with CVD Mean age: 65.6 yr	Beijing, China 2007−2008	Huang et al. (2012)

Table 6 12 (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 = 22.04 admissions/day	Male n = 22.39 admissions/day	↑	CHF, Cardiovascular disease (measured by hospital admissions)	Healthy older adults (≥64 yr)	Sao Paulo, Brazil 1996−2001	Martins et al. (2006)
Female n = 5,250	Male n = 5,680	↑	Ischemic stroke (ED visit)	Five hospitals from the metropolitan area n = 10,881	Edmonton, Canada 1992−2002	Szyszkowicz (2008)
Female[b]	Male[b]	–	Diabetes (hospitalizations)	Ministry of Health statistics for hospitalizations for acute serious complications of diabetes	Santiago, Chile 2001−2008	Dales et al. (2012)
Long-term exposure						
Female 53%	Male 47%	–	Carotid intima-media thickness (preclinical atherosclerosis)	n = 745 Ages 26−30 yr	Utrecht, Netherlands 1999−2000	Lenters et al. (2010)
		↓	Pulse wave index (measure of arterial stiffness, marker for CHD)			
Female n = 12,184	Male n = 12,661	↓	Blood pressure (hypertension)	n = 24,845 subject from different households at residence for ≥5 yr Mean age: 41.7 ± 13.7 yr	Shenyang, Anshan, and Jinzhou, China 2006−2008	Dong et al. (2013d)
Female n = 12,184	Male n = 12,661	↓	Incident cardiovascular disease (hospital admissions)	n = 24,845 subject from different households at residence for ≥5 yr Mean age: 41.7±13.7 yr	Shenyang, Anshan, and Jinzhou, China 2006−2008	Dong et al. (2013a)
		↓	Incident stroke (hospital admissions)			
Female n = 727	Male n = 764	–	Hospital admissions, stroke	n = 1,491 admissions for stroke	Tehran, Iran 2004	Nabavi et al. (2012)

Table 6 12 (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 = 6,139	Male n = 6,712	–	Heart failure (hospital admissions)	n = 12,851 Ages 40−89 yr in 2003	England 2003−2007	Atkinson et al. (2013)
Female n = 3.71 admissions/ day	Male n = 5.94 admissions/ day	↓	Cerebrovascular disease (hospital admissions)	Records obtained from four largest hospitals	Lanzhou, China 2001−2005	Zheng et al. (2013)
Female 43.5%	Male 56.5%	↑	Cardiovascular mortality	n = 70,947 study participants; 8,319 deaths	China 1991−2000	Cao et al. (2011)
Female n = 69	Male n = 187	–	Cardiovascular mortality	n = 9,941 subjects ≥25 yr at study enrollment and living at residence ≥10 yr; 256 cardio-vascular deaths	Shenyang, China 1998−2009	Zhang et al. (2011)
Female n = 18	Male n = 54	–	Respiratory mortality	n = 9,441 residents ≥35 yr living at residence ≥10 yr; 72 deaths due to respiratory cause	Shenyang, China 1998−2009	Dong et al. (2012)
Female[b]	Male[b]	–	Hospitalizations for cancer (lung, myeloma, and non-Hodgkin lymphoma)	Hospitalization records obtained from database used in public and private hospitals	Etang-de-Berre, France 2004−2007	Pascal et al. (2013)
		↓	Hospitalizations (acute leukemia)			

Table 6 12 (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[b]	Male[b]	–	Cancer incidence (bladder, lung, non-Hodgkin lymphoma)	Records obtained from national database; patients had to reside in Jewish communities in study area >10 yr n = 1,452 cases	Haifa, Israel 1995−1999	Eitan et al. (2010)
Female[b]	Male[b]	↓	Decrements in lung function (FEV_1)	N = 32,712 households adults from white ethnic groups (≥16 yr)	Health Survey for England. Lung function in England 1995, 1996, 1997, and 2001	Forbes et al. (2009c)
Female n = 1,968	Male n = 1,989	–	Decrements in lung function (FEV_1, FVC, MMEF, PEFR)	n = 3,957 seventh grade children Ages 12−13 yr from 14 Taiwanese communities	Taiwan Children Health Study 2005−2007	Lee et al. (2011b)
Female n = 235	Male n = 229	–	Decrements in lung function (FVC, FEV_1, PEF, FEV_1/FVC)	n = 464 children from two schools Ages 6−14 yr	Salamanca, Mexico March 2004–February 2005	Linares et al. (2010)
Female n = 155	Male n = 244	–	Decrements in lung function (FEV_1)	n = 399 COPD patients with severe α-1-antitrypsin deficiency	United Kingdom 1997−2006	Wood et al. (2010)
Female n = 731	Male n = 649	–	Impaired lung function (FEV_1, FVC, PEF, MMEF) (summer)	n = 1,880 students Ages 9-13 yr	Eskisehir, Turkey January 2008–March 2009	Altuğ et al. (2013)
Female n = 588	Male n = 530	–	Impaired lung function (FEV_1, FVC, PEF, MMEF) (winter)			

Table 6 12 (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[b]	Male[b]	↑	Asthma diagnosis	n = 20,364 children diagnosed with asthma at up to 3−4 yr of age, mean age at follow up 48 ± 7 mo	Southwestern British Columbia Births from 1999−2000	Clark et al. (2010)
Female[b]	Male[b]	−	Respiratory symptoms (cough, phlegm, current wheeze) and 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)
Female n = 2,826	Male n = 2,561	−	Physician-diagnosed asthma plus two or more symptoms of coughing, wheezing, or shortness of breath	n = 4,320 GALA II and SAGE II cohorts (Latinos and African-Americans ages 8−21 yr)	Chicago, IL; Bronx, NY; Houston, TX; San Francisco Bay Area, CA and Puerto Rico 2006−2011	Nishimura et al. (2013)
Female n = 2,458	Male n = 2,449	↓	Lifetime asthma	n = 6,683 children Ages 9−11 yr (mean age = 10.4 yr)	French Six Cities study (Bordeaux, Clermont-Ferrand, Creteil, Marseille, Strasbourg, Reims) March 1999–October 2000	Penard-Morand et al. (2010)
		−	Past year asthma			
		↓	Exercise-induced asthma			
Female n = 729	Male n = 738	−	Nonallergic asthma	n ~1,467 children grades one (ages 6−7 yr) and eight (ages 13−14 yr)	Hamilton, Canada 1994−1995	Sahsuvaroglu et al. (2009)
Female n = 19	Male n = 17	−	Oxidative stress (8-oxo-7,8-dihydro-2′-deoxyguanosine and malondialdehyde)	n = 36 elementary school children (fourth grade, mean age 10.6 yr)	China June 2007–September 2008	Lin et al. (2015)

Table 6 12 (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 = 4,583	Male n = 4,771	−	Hypertension and arterial blood pressure (diastolic and systolic)	n = 9,354 elementary and middle school children Ages 5−17 yr	Seven Northeastern Cities study, Liaoning Provence, northeast China 2012−2013	Dong et al. (2014)
Female n = 27	Male n = 26	↑	Autonomic dysfunction—changes in heart rate variability (changes in SDNN)	N = 53 adults ages 51−68 yr with Type-2 diabetes or impaired glucose tolerance	Shanghai, China April, June, and September 2010	Sun et al. (2015)
Female n = 44,181	Male n = 41,378	−	Mortality Natural causes, cardiovascular diseases, cancers (stomach, colon and rectum, liver, pancreas, lung, bladder, kidney, brain, lymphatic, and hematopoietic tissue)	n = 85,559 Ages 5−106 yr	Rome Longitudinal Study, suburb of Rome (Italy) 2001−2010	Ancona et al. (2015)
		↑	Mortality Cancer (larynx)			
		↓	Mortality Respiratory diseases			

Table 6 12 (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 = 44,181	Male N = 41,378	–	Hospital admissions All causes, cardiovascular diseases, and cancer (stomach, colon and rectum, pancreas, lung, bladder, kidney, brain, lymphatic, and hematopoietic tissue)	N = 85,559 Ages 5−106 yr	Rome Longitudinal Study, suburb of Rome (Italy) 2001−2010	Ancona et al. (2015)
		↑	Hospital admissions Cancer (liver, larynx)			
		↓	Hospital admissions Respiratory diseases			

CHD = coronary heart disease; CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease; CVD = cardiovascular disease; ED = emergency department; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; GALA II = Genes-environments and Admixture in Latino Americans; HRV = heart rate variability; MI = myocardial infarction; MMEF = maximum midexpiratory flow; PEF = peak expiratory flow; PEFR = peak expiratory flow rate; SDNN = standard deviation of RR intervals.

[a]Up facing arrow indicates that the effect of SO_2 is greater (e.g., larger risk of hospital admission, larger decrement in HRV) 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 difference in SO_2-related health effect between groups.

[b]Sample size not reported.

Cardiovascular outcomes associated with both short- and long-term SO_2 exposures also evaluated sex-specific differences, though results varied across studies. In short- and long-term studies of SO_2 exposure, there was no consistent pattern of risk for men or women for the various subclinical markers of cardiovascular outcomes that were examined, including lipo-protein-associated phospholipase A2, heart rate variability, carotid intima-media thickness, pulse wave index, and blood pressure (Dong et al., 2013d; Huang et al., 2012; Brüske et al., 2011; Lenters et al., 2010). There was some evidence that females had stronger associations for cardiovascular hospitalizations or ED visits than men relative to short-term SO_2 levels (Szyszkowicz, 2008; Martins et al., 2006), but long-term exposures resulted in the same or smaller associations for hospital admissions for cardiovascular codes when comparing females to males (Dong et al., 2013a; Zheng et al., 2013; Nabavi et al., 2012). Evidence for cardiovascular-specific mortality in long-term studies did not indicate consistent sex-specific differences (Cao et al., 2011; Zhang et al., 2011), which is also true for respiratory mortality (Dong et al., 2012) and cancer outcomes (Pascal et al., 2013; Eitan et al., 2010).

The collective body of evidence does not clearly indicate that SO_2-related health effects differ between males and females. Several different outcomes were evaluated in studies looking at effect modification by sex, including a wide range of cardiovascular outcomes in short- and long-term studies. Due to the wide range of outcomes examined and inconsistent results demonstrated across studies, 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. Persons with lower SES have been generally 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 this population's risk to SO_2-related health effects. 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 challenge the synthesis of findings, which is also complicated by variations in definitions of SES across countries based on population demographics, bureaucracy, and the local economy, which can contribute to varying degrees of deprivation or inequities. 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.

Although there is evidence demonstrating differential exposures to air pollution based on SES, no studies have investigated SO_2-specific exposure. However, a handful of studies in this ISA evaluated effect modification by income and education on SO_2-associated health outcomes (Table 6-13). The majority of evidence on effect modification is for mortality, but results across studies are inconsistent. Chen et al. (2012c) found low education to increase risk for mortality with short-term SO_2 exposure, but in a study of long-term SO_2 exposure, Krewski et al. (2009) did not find low education to increase risk for mortality. Dong et al. (2012) and Zhang et al. (2011) looked at associations between long-term SO_2 and respiratory and cardiovascular mortality, respectively, in the same cohort and generally did not find low SES (education and income) to increase risk, with the exception of an increase in risk of respiratory mortality for low education, although only a small number of deaths in the study were due to respiratory causes.

Table 6-13 Epidemiologic studies evaluating socioeconomic status and sulfur dioxide exposure.

Factor Evaluated	Reference Category	Direction of Effect Modification[a]	Outcome	Study Population	Study Details	Study
Short-term exposure						
Low education (illiterate/ primary school)[b]	High education (middle school and above)[b]	↑	Total mortality	Data from Municipal Centers for Disease Control and Prevention	17 Chinese cities	Chen et al. (2012c)
Long-term exposure						
Low education n = 13%	Medium or high education n = 87%	↑	Carotid intima-media thickness (preclinical atherosclerosis)	n = 745 Ages 26−30 yr	Utrecht, Netherlands 1999−2000	Lenters et al. (2010)
		–	Pulse wave index (measure of arterial stiffness, marker for CHD)			
Lowest deprivation index n = 2,109	Highest deprivation index n = 2,327	↓	Heart failure (hospital admissions)	n = 12,851 Ages 40−89 yr in 2003	England 2003−2007	Atkinson et al. (2013)
Low education (< grade 12) n = 4,026	High education (> grade 12) n = 76,685	–	Mortality (all cause, lung cancer, cardiopulmonary)	American Cancer Society cohort	United States 1982−2000	Krewski et al. (2009)
Low education n = 76.4%	High education n = 23.6%	↓	Cardiovascular mortality	N = 70,947 study participants; 8,319 deaths	China 1991−2000	Cao et al. (2011)
Low income (<200 RMB/mo) n = 48	High income (≥800 RMB/mo) n = 75	–	Cardiovascular mortality	n = 9,941 subjects ≥25 yr at study enrollment and living at residence ≥10 yr; 256 cardiovascular deaths	Shenyang, China 1998−2009	Zhang et al. (2011)
Low education n = 183	High education n = 72	–				
Low income (<200 RMB/mo) n = 14	High income (≥800 RMB/mo) n = 20	–	Respiratory mortality		Shenyang, China 1998−2009	Dong et al. (2012)

Table 6-13 (Continued): Epidemiologic studies evaluating socioeconomic status and sulfur dioxide exposure.

Factor Evaluated	Reference Category	Direction of Effect Modification[a]	Outcome	Study Population	Study Details	Study
Low education n = 47	High education n = 25	↑		n = 9,441 residents ≥35 yr living at residence ≥10 yr; 72 deaths due to respiratory disease		

CHD = coronary heart disease; RMB = renminbi.

[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 SO_2 is smaller in the group with the factor evaluated than in the reference group. A dash indicates no difference in SO_2-related health effect between groups.

Lenters et al. (2010) and Atkinson et al. (2013) evaluated SO_2-associated cardiovascular outcomes with long-term exposure but did not report consistent evidence related to effect modification by education level or a deprivation index, respectively.

Overall, the evidence for effect modification by SES is inconsistent for a limited number of health outcomes. In addition, various SES factors were used across studies that were conducted in a wide variety of countries. Due to these limitations and complexities, the evidence is inadequate to determine whether low SES increases risk for SO_2-related health effects.

6.5.4 Race/Ethnicity

Based on the 2010 census, 63.7% of the U.S. population identified themselves as non-Hispanic whites, 12.6% reported their race as non-Hispanic black, and 16.3% reported being Hispanic (Humes et al., 2011). Race and ethnicity are complex factors that are often closely correlated with other factors including particular genetics, diet, and socioeconomic status. Therefore, race and ethnicity may influence any potential differences in SO_2-related health effects through both intrinsic and extrinsic mechanisms.

Despite our understanding of disproportionate health effects experienced across race or ethnicity, only two epidemiologic studies evaluating associations between long-term ambient SO_2 exposure and birth weight decrements have considered effect modification by race (Table 6-14). Neither Bell et al. (2007) nor Darrow et al. (2011) found any indication of greater SO_2-associated decrements in birth weight for mothers of black or Hispanic infants compared to white infants. In addition, there is uncertainty regarding the relationship between ambient SO_2 exposures and birth outcomes in the general population, including associations with birth weight (Section 5.4.1.3). Overall, this

limited evidence is inadequate to determine whether individuals of a certain race or ethnicity are at increased risk for SO_2-associated health effects.

Table 6-14 Epidemiologic studies evaluating race/ethnicity and sulfur dioxide exposure.

Factor Evaluated	Reference Category	Direction of Effect Modification[a]	Outcome	Study Population	Study Details	Study
Long-term exposure						
Black maternal race n = 10.7%	White maternal race n = 83.4%	–	Birth weight decrements	n = 358,504 births (all registered births)	Massachusetts, Connecticut 1999−2002	Bell et al. (2007)
Hispanic maternal race n = 14.3%	White maternal race n = 45.2%	–	Birth weight decrements	N = 406,627 full-term, singleton births	Atlanta, GA 1994−2004	Darrow et al. (2011)
Non-Hispanic black maternal race n = 40.5%		–				

[a]Up facing arrow indicates that the effect of SO_2 is greater (e.g., larger risk of hospital admission, larger decrement in birth weight) 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 difference in SO_2-related health effect between groups.

6.6 Behavioral and Other Factors

6.6.1 Smoking

Smoking is a common behavior as indicated by the 2010 National Health Interview Survey which estimated that within the U.S. adult population approximately 19.2% of individuals report being current smokers and 21.5% report being a former smoker (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.

Of the epidemiologic studies included in this ISA that evaluate effect modification by smoking status, the majority focused on cardiovascular outcomes (Table 6-15). Min et al. (2009) and Lenters et al. (2010) found stronger associations between subclinical cardiovascular outcomes with short- or long-term SO_2 exposures, respectively, in individuals who smoke compared to those that do not. Further, Atkinson et al. (2013) found current or former smoking to increase risk for SO_2-associated hospital admissions for heart failure; however, Cao et al. (2011) and Zhang et al. (2011) did not find increased risk for cardiovascular mortality associated with long-term ambient SO_2 exposures in individuals with smoking.

Dong et al. (2012) and Forbes et al. (2009c) were the only other studies that investigated effect modification in respiratory endpoints by smoking status. Dong et al. (2012) found that of the few number of respiratory deaths included in their retrospective cohort study, associations with long-term ambient SO_2 were only present with smoking. 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 no smoking; however, former smoking did appear to increase risk in this study.

Overall, the collective evidence is suggestive of increased risk for SO_2-associated health effects in individuals who smoke, particularly for cardiovascular outcomes. There is consistency among cohort studies showing stronger associations between subclinical cardiovascular outcomes and SO_2 exposure with smoking, which is strengthened by evidence for hospital admissions. There are limitations in that evidence does not show that associations with cardiovascular mortality are modified by smoking status in addition to the uncertainties related to the overall strength of the relationship between SO_2 and cardiovascular effects (Sections 5.3.1.11 and 5.3.2.6).

Table 6-15 Epidemiologic studies evaluating smoking status and sulfur dioxide exposure.

Factor Evaluated	Reference Category	Direction of Effect Modification[a]	Outcome	Study Population	Study Details	Study
Short-term exposure						
Smoking n = 256	No smoking n = 767	↑	Reductions in HRV (SDNN, LF, HF)	n = 1,023 adults	Taein Island, Korea	Min et al. (2009)
Long-term exposure						
Current smoking n = 31%	Never smoking n = 55%	↑	Carotid intima-media thickness (preclinical atherosclerosis) Pulse wave index (measure of arterial stiffness, marker for CHD)	n = 745 Ages 26−30 yr	Utrecht, Netherlands 1999−2000	Lenters et al. (2010)
Current or former smoking n = 2,310	Never smoking n = 5,329	↑	Heart failure (hospital admissions)	n = 12,851 Ages 40−89 yr in 2003	England 2003−2007	Atkinson et al. (2013)
Current smoking n = 37.1%	Never smoking n = 58.2%	↓	Cardiovascular mortality	N = 70,947 study participants; 8,319 deaths	China 1991−2000	Cao et al. (2011)
Current smoking n = 2,850	Never smoking n = 4,359	–	Cardiovascular mortality	n = 9,941 subjects ≥25 yr at study enrollment and living at residence ≥10 yr; 256 cardiovascular deaths	Shenyang, China 1998−2009	Zhang et al. (2011)
Smoking (yes) n = 37	Smoking (no) n = 35	↑	Respiratory mortality	n = 9,441 residents ≥35 yr living at residence ≥10 yr; 72 deaths due to respiratory cause	Shenyang, China 1998−2009	Dong et al. (2012)

Table 6-15 (Continued) Epidemiologic studies evaluating smoking status and sulfur dioxide exposure

Factor Evaluated	Reference Category	Direction of Effect Modification[a]	Outcome	Study Population	Study Details	Study
Current smoking[b]	Never smoking[b]	–	Decrements in lung function (FEV_1)	n = 32,712 households. Adults from white ethnic groups (≥16 yr)	Health Survey for England. Lung function in England 1995, 1996, 1997, and 2001	Forbes et al. (2009c)
Former smoking[b]	Never smoking[b]	↑				

CHD = coronary heart disease; FEV_1 = forced expiratory volume in 1 second; HF = high frequency; HRV = heart rate variability; LF = low frequency; SDNN = standard deviation of RR intervals.

[a]Up facing arrow indicates that the effect of SO_2 is greater (e.g., larger risk hypertension) 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 difference in SO_2-related health effect between groups.

6.7 Conclusions

This chapter characterized factors that may result in populations and lifestages being at increased risk for SO_2-related health effects (Table 6-16). 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 that related to exposure, dosimetry, modes of action, and/or the independence of relationships of SO_2 exposure with health effects; however, this information was particularly limited for literature on ambient SO_2.

Table 6-16 Summary of evidence for potential increased SO_2 exposure and increased risk of SO_2-related health effects.

Evidence Classification	Factor Evaluated	Rationale for Classification
Adequate evidence	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	Children (Section 6.5.1.1) Older adults (Section 6.5.1.2) Smoking (Section 6.6.1)	Each factor: evidence for increased risk provided in previous ISA; lack of toxicology studies Children: mixed results in studies for respiratory-related outcomes Older adults: mixed results in studies for respiratory-related outcomes and mortality Smoking: evidence primarily for cardiovascular morbidity
Inadequate evidence	Pre-existing cardiovascular disease (Section 6.3.2) Pre-existing diabetes (Section 6.3.3) Pre-existing obesity (Section 6.3.4) Genetic background (Section 6.4) Sex (Section 6.5.2) Socioeconomic status (Section 6.5.3) Race/ethnicity (Section 6.5.4)	Epidemiologic findings inconsistently show differences in SO_2-related health effects, show no difference, or are limited in quantity. Findings based primarily on cardiovascular effects, diabetes, birth outcomes, and mortality. Uncertainty in independent relationships with SO_2 provides limited basis for inferences about differential risk.
Evidence of no effect	None	

ED = emergency department; ISA = Integrated Science Assessment.

Consistent with observations made in the 2008 ISA for Sulfur Oxides (U.S. EPA, 2008b), there is adequate evidence to conclude that people with asthma are at increased risk for SO_2-related health effects. The majority of evidence was presented in the previous ISA as well, 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 5.2.1.8). 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.

Evidence for age-related risk of SO_2-related respiratory effects is suggestive of increased risk for children and older adults. Although the 2008 ISA for Sulfur Oxides (U.S. EPA, 2008b) 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 evidence generally found 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.

The evidence is suggestive that smoking increases risk for SO_2-associated health effects, particularly cardiovascular outcomes. Cohort and hospital admissions studies show stronger associations between cardiovascular outcomes and SO_2 with smoking, although uncertainties remain regarding the overall strength of the relationship between SO_2 and cardiovascular effects in addition to inconsistencies related to respiratory outcomes associated with long-term SO_2 exposure.

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 were a limited number of studies available to inform risk for individuals with pre-existing cardiovascular disease, diabetes, or obesity as well as those evaluating SES, genetic background, and race/ethnicity. 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 for Chapter 6

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

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

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

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

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

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

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

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

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

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

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

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, RE; Cakmak, S; Vidal, CB; Rubio, MA. (2012). Air pollution and hospitalization for acute complications of diabetes in Chile. Environ Int 46: 1-5. http://dx.doi.org/10.1016/j.envint.2012.05.002

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

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; 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

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

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

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

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

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

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

Humes, KR; Jones, NA; Ramirez, RR. (2011). Overview of race and Hispanic origin: 2010. (2010 Census Briefs, C2010BR-02). Washington, DC: U.S. Department of Commerce, Economics and Statistics Administration, U.S. Census Bureau. http://www.census.gov/prod/cen2010/briefs/c2010br-02.pdf

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

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

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; 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.

Krewski, D; Jerrett, M; Burnett, RT; Ma, R; Hughes, E; Shi, Y; Turner, MC; Pope AC, I; 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

Lee, YL; Wang, WH; Lu, CW; Lin, YH; Hwang, BF. (2011b). 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

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

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

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

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

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

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.

Martins, LC; Pereira, LAA; Lin, CA; Santos, UP; Prioli, G; Luiz Odo, C; Saldiva, PHN; Braga, ALF. (2006). The effects of air pollution on cardiovascular diseases: lag structures. Rev Saude Publica 40: 677-683.

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

Nabavi, SM; Jafari, B; Jalali, MS; Nedjat, S; Ashrafi, K; Salahesh, A. (2012). Environmental air pollution and acute cerebrovascular complications: An ecologic study in Tehran, Iran. IJPM 3: 723-729.

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, J. R.; 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

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

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

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

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

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

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

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

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

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

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

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/doi: 10.1080/15287394.2012.641202

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.

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.

U.S. EPA (U.S. Environmental Protection Agency). (2008b). Integrated science assessment for sulfur oxides: Health criteria [EPA Report]. (EPA/600/R-08/047F). Research Triangle Park, NC: U.S. Environmental Protection Agency, National Center for Environmental Assessment. http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=198843

U.S. EPA (U.S. Environmental Protection Agency). (2013a). 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). (2013b). 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). (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). (2015d). Integrated science assessment for oxides of nitrogen health criteria. Second external review draft. (EPA/600/R-14/006). Research Triangle Park, NC: National Center for Environmental Assessment. http://nepis.epa.gov/exe/ZyPURL.cgi?Dockey=P100LTRO.txt

U.S. EPA (U.S. Environmental Protection Agency). (2015e). 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.

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

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

Wong, CM; Vichit-Vadakan, N; Kan, H; Qian, Z. (2008). 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; 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

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

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: e20827. http://dx.doi.org/10.1371/journal.pone.0020827

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