United States Environmental Protection Agency

September 2007
EPA/600/R-07/108A

Annexes for the Integrated Science Assessment for Sulfur Oxides – Health Criteria

(First External Review Draft)

EPA/600/R-07/108A
September 2007

Annexes for the Integrated Science Assessment for Sulfur Oxides – Health Criteria

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

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PREFACE

Legislative Requirements

Two sections of the Clean Air Act (CAA) govern the establishment and revision of the national ambient air quality standards (NAAQS). Section 108 (U.S. Code, 2003a) directs the Administrator to identify and list "air pollutants" that "in his judgment, may reasonably be anticipated to endanger public health and welfare" and whose "presence … in the ambient air results from numerous or diverse mobile or stationary sources" and to issue air quality criteria for those that are listed. Air quality criteria are intended to "accurately reflect the latest scientific knowledge useful in indicating the kind and extent of identifiable effects on public health or welfare which may be expected from the presence of [a] pollutant in ambient air …."

Section 109 (U.S. Code, 2003b) directs the Administrator to propose and promulgate "primary" and "secondary" NAAQS for pollutants listed under section 108. 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 required to protect the public welfare from any known or anticipated adverse effects associated with the presence of [the] pollutant in the ambient air."[2]

[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" [U.S. Senate (1970)].

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

The requirement that primary standards include 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 reasonable degree of protection against hazards that research has not yet identified. See *Lead Industries Association v. EPA*, 647 F.2d 1130, 1154 (D.C. Cir 1980), cert. denied, 449 U.S. 1042 (1980); *American Petroleum Institute v. Costle*, 665 F.2d 1176, 1186 (D.C. Cir. 1981), cert. denied, 455 U.S. 1034 (1982). Both kinds of uncertainties 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 include 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.

In selecting a 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 sensitive population(s) at risk, and the kind and degree of the uncertainties that must be addressed. The selection of any particular approach to providing an adequate margin of safety is a policy choice left specifically to the Administrator's judgment. See *Lead Industries Association v. EPA*, supra, 647 F.2d at 1161-62.

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. See generally *Whitman v. American Trucking Associations*, 531 U.S. 457, 465-472, 475-76 (2001).

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 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) of EPA's Science Advisory Board.

History of Reviews of the Primary NAAQS for Sulfur Dioxide

On April 30, 1971, the EPA promulgated primary NAAQS for sulfur dioxide (SO_2). These primary standards, which were based on the findings outlined in the original 1969 Air Quality Criteria (hereafter "AQCD") for Sulfur Oxides (U.S. DHEW, 1969), were set at 0.14 parts per million (ppm) averaged over a 24-hour period, not to be exceeded more than once per year, and 0.030 ppm annual arithmetic mean. In 1982, EPA published the AQCD for Particulate Matter (PM) and Sulfur Oxides along with an addendum of newly published controlled human exposure studies (U.S. Environmental Protection Agency, 1982), which updated the scientific criteria upon which the initial standards were based. In 1986, a second addendum was published presenting newly available evidence from epidemiologic and controlled human exposure studies (U.S. Environmental Protection Agency, 1986). In 1988, EPA reviewed and revised the health criteria upon which the SO_2 standards were based. As a result of that review, EPA published a proposed decision not to revise the existing standards (Federal Register, 1988). However, EPA specifically requested public comment on the alternative of revising the current standards and adding a new 1-h primary standard of 0.4 ppm.

As a result of public comments on the 1988 proposal and other post-proposal developments, EPA published a second proposal on November 15, 1994 (Federal Register, 1994). The 1994 re-proposal 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. Environmental Protection Agency, 1994). As in the 1988 proposal, EPA proposed to retain the existing 24-h and annual standards. The EPA also solicited comment on three regulatory alternatives to further reduce the health risk posed by exposure to high 5-min peaks of SO_2 if additional protection were judged to be necessary. The three alternatives included (1) revising the existing primary SO_2 NAAQS by adding a new 5-min 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; and (3) augmenting implementation of existing standards by focusing on those sources or source types likely to produce high 5-min peak concentrations of SO_2. On May 22, 1996, EPA's final decision, that revisions of the NAAQS for sulfur oxides were not appropriate at that time, was announced in

the Federal Register (Federal Register, 1996). In that decision, EPA announced an intention to propose guidance, under section 303 of the Act, to assist states in responding to short-term peak levels of SO_2.

Annexes for the Integrated Science Assessment for Sulfur Oxides – Health Criteria

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Authors, Contributors, and Reviewers

Authors

Dr. Jee Young Kim (SO_x Team Leader)—National Center for Environmental Assessment (B243-01), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. Jeffrey Arnold—National Center for Environmental Assessment (B243-01), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. James S. Brown—National Center for Environmental Assessment (B243-01), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. Douglas Bryant—Intrinsik Science, 1900 Minnesota Court, Mississauga, Ontario L8S 1P5

Dr. Ila Cote—National Center for Environmental Assessment (B243-01), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. Arlene Fiore—Geophysical Fluid Dynamics Laboratory/National Oceanographic & Atmospheric Administration, 201 Forrestal Rd., Princeton, NJ 08542-0308

Dr. Panos Georgopoulos—Computational Chemodynamics Laboratory, EOHSI Room 308, 170 Frelinghuysen Road, Piscataway, New Jersey 08854

Dr. Brett Grover—National Exposure Research Laboratory (D205-03), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. Vic Hasselblad—Duke University Medical Center, Box 17969, Durham, NC 27715

Dr. Larry Horowitz—Geophysical Fluid Dynamics Laboratory/National Oceanographic & Atmospheric Administration, Princeton University Forrestal Campus, 201 Forrestal Road, Princeton, NJ 08540-5063

Dr. Annette Ianucci—Sciences International, 1800 Diagonal Road, Suite 500, Alexandria, VA 22314

Dr. Kazuhiko Ito—New York University School of Medicine, 57 Old Forge Road, Tuxedo, NY 10987

Dr. Doug Johns—National Center for Environmental Assessment (B243-01), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. Ellen Kirrane—National Center for Environmental Assessment (B243-01), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Authors, Contributors, and Reviewers

(cont'd)

Authors

Dr. Jane Koenig—University of Washington, Department of Environmental and Occupational Health Sciences, Box 357234, Seattle, WA 98195-7234

Dr. Thomas Long—National Center for Environmental Assessment (B243-01), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. Thomas Luben—National Center for Environmental Assessment (B243-01), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. Therese Mar—University of Washington, Department of Environmental and Occupational Health Sciences, Box 357234, Seattle, WA 98195-7234

Dr. Qingyu Meng—National Center for Environmental Assessment (B243-01), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. Anu Mudipalli—National Center for Environmental Assessment (B243-01), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. Joseph Pinto—National Center for Environmental Assessment (B243-01), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. Mary Ross—National Center for Environmental Assessment (B243-01), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. David Svendsgaard—National Center for Environmental Assessment (B243-01), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. Lori White—National Center for Environmental Assessment (B243-01), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. William Wilson—National Center for Environmental Assessment (B243-01), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Authors, Contributors, and Reviewers

(cont'd)

Contributors

Dr. Dale Allen, University of Maryland, College Park, MD

Ms. Louise Camalier, U.S. EPA, OAQPS, Research Triangle Park, NC

Dr. Russell Dickerson, University of Maryland, College Park, MD

Dr. Tina Fan, EOHSI/UMDNJ, Piscataway, NJ

Dr. William Keene, University of Virginia, Charlottesville, VA

Dr. Randall Martin, Dalhousie University, Halifax, Nova Scotia

Dr. Maria Morandi, University of Texas, Houston, TX

Dr. William Munger, Harvard University, Cambridge, MA

Mr. Charles Piety, University of Maryland, College Park, MD

Dr. Sandy Sillman, University of Michigan, Ann Arbor, MI

Dr. Helen Suh, Harvard University, Boston, MA

Dr. Charles Wechsler, EOHSI/UMDNJ, Piscataway, NJ

Dr. Clifford Weisel, EOHSI/UMDNJ, Piscataway, NJ

Dr. Jim Zhang, EOHSI/UMDNJ, Piscataway, NJ

Reviewers

Dr. Tina Bahadori—American Chemistry Council, 1300 Wilson Boulevard, Arlington, VA 22209

Dr. Tim Benner—Office of Science Policy, Office of Research and Development, Washington, DC 20004

Dr. Daniel Costa—National Program Director for Air, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Authors, Contributors, and Reviewers

(cont'd)

Reviewers

Dr. Robert Devlin—National Health and Environmental Effects Research Laboratory, Office of Research and Development, U.S. Environmental Protection Agency, Chapel Hill, NC

Dr. Judy Graham—American Chemistry Council, LRI, 1300 Wilson Boulevard, Arlington, VA 22209

Dr. Stephen Graham—Office of Air Quality Planning and Standards (C504-06), Office of Air and Radiation, U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Ms. Beth Hassett-Sipple—Office of Air Quality Planning and Standards (C504-06), Office of Air and Radiation, U.S. Environmental Protection Agency (C504-06), Research Triangle Park, NC 27711

Dr. Gary Hatch—National Health and Environmental Effects Research Laboratory, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. Scott Jenkins—Office of Air Quality Planning and Standards (C504-06), Office of Air and Radiation, U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. David Kryak—National Exposure Research Laboratory, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Mr. John Langstaff—Office of Air Quality Planning and Standards (C504-06), Office of Air and Radiation, U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. Morton Lippmann—NYU School of Medicine, 57 Old Forge Road, Tuxedo, NY 10987

Dr. Karen Martin—Office of Air Quality Planning and Standards (C504-06), Office of Air and Radiation, U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. William McDonnell—William F. McDonnell Consulting, 1207 Hillview Road, Chapel Hill, NC 27514

Dr. Dave McKee—Office of Air Quality Planning and Standards (C504-06), Office of Air and Radiation, U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. Lucas Neas—National Health and Environmental Effects Research Laboratory, Office of Research and Development, U.S. Environmental Protection Agency, Chapel Hill, NC 27711

Authors, Contributors, and Reviewers

(cont'd)

Reviewers

Dr. Russell Owen—National Health and Environmental Effects Research Laboratory, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. Haluk Ozkaynak—National Exposure Research Laboratory, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. Jennifer Peel—Colorado State University, 1681 Campus Delivery, Fort Collins, CO 80523-1681

Mr. Harvey Richmond—Office of Air Quality Planning and Standards (C504-06), Office of Air and Radiation, U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Mr. Steven Silverman—Office of General Counsel, U.S. Environmental Protection Agency, Washington, DC 20460

Dr. Michael Stewart—Office of Air Quality Planning and Standards (C504-06), Office of Air and Radiation, U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Ms. Susan Stone—Office of Air Quality Planning and Standards (C504-06), Office of Air and Radiation, U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Ms. Chris Trent—Office of Air Quality Planning and Standards (C504-06), Office of Air and Radiation, U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. John Vandenberg—National Center for Environmental Assessment (B243-01), Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. Alan Vette—National Exposure Research Laboratory, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Mr. Ron Williams— National Exposure Research Laboratory, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

U.S. Environmental Protection Agency Project Team for Development of Integrated Scientific Assessment for Sulfur Oxide

Executive Direction

Dr. Ila Cote (Acting Director)—National Center for Environmental Assessment-RTP Division, (B243-01), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Scientific Staff

Dr. Jee Young Kim (SO_x Team Leader)—National Center for Environmental Assessment (B243-01), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. Jeff Arnold—National Center for Environmental Assessment (B243-01), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. James S. Brown—National Center for Environmental Assessment (B243-01), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. Ellen Kirrane—National Center for Environmental Assessment (B243-01), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. Dennis Kotchmar—National Center for Environmental Assessment (B243-01), Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. Tom Long—National Center for Environmental Assessment (B243-01), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. Thomas Luben—National Center for Environmental Assessment (B243-01), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. Quingyu Meng—National Center for Environmental Assessment (B243-01), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. Joseph Pinto—National Center for Environmental Assessment (B243-01), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. Paul Reinhart—National Center for Environmental Assessment (B243-01), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

U.S. Environmental Protection Agency Project Team for Development of Integrated Scientific Assessment for Sulfur Oxide

(cont'd)

Scientific Staff
(cont'd)

Dr. Mary Ross—National Center for Environmental Assessment (B243-01),
U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. David Svendsgaard—National Center for Environmental Assessment (B243-01),
U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. Lori White—National Center for Environmental Assessment (B243-01),
U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. William Wilson—National Center for Environmental Assessment (B243-01),
U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Technical Support Staff

Ms. Emily R. Lee—Management Analyst, National Center for Environmental Assessment (B243-01), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Ms. Christine Searles—Management Analyst, National Center for Environmental Assessment (B243-01), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Ms. Debra Walsh—Program Analyst, National Center for Environmental Assessment (B243-01),
U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Mr. Richard Wilson—Clerk, National Center for Environmental Assessment (B243-01),
U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Document Production Staff

Ms. Barbra H. Schwartz—Task Order Manager, Computer Sciences Corporation,
2803 Slater Road, Suite 220, Morrisville, NC 27560

Mr. John A. Bennett—Technical Information Specialist, Library Associates of Maryland,
11820 Parklawn Drive, Suite 400, Rockville, MD 20852

U.S. Environmental Protection Agency Project Team for Development of Integrated Scientific Assessment for Sulfur Oxide

(cont'd)

Document Production Staff
(cont'd)

Mrs. Melissa Cesar—Publication/Graphics Specialist, Computer Sciences Corporation, 2803 Slater Road, Suite 220, Morrisville, NC 27560

Mrs. Rebecca Early—Publication/Graphics Specialist, TekSystems, 1201 Edwards Mill Road, Suite 201, Raleigh, NC 27607

Mr. Eric Ellis—Records Management Technician, InfoPro, Inc., 8200 Greensboro Drive, Suite 1450, McLean, VA 22102

Ms. Stephanie Harper—Publication/Graphics Specialist, TekSystems, 1201 Edwards Mill Road, Suite 201, Raleigh, NC 27607

Ms. Sandra L. Hughey—Technical Information Specialist, Library Associates of Maryland, 11820 Parklawn Drive, Suite 400, Rockville, MD 20852

Dr. Barbara Liljequist—Technical Editor, Computer Sciences Corporation, 2803 Slater Road, Suite 220, Morrisville, NC 27560

Ms. Molly Windsor—Graphic Artist, Computer Sciences Corporation, 2803 Slater Road, Suite 220, Morrisville, NC 27560

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(cont'd)

Members
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Dr. Kent Pinkerton, Professor, Regents of the University of California, Center for Health and the Environment, University of California, Davis, CA

Mr. Richard L. Poirot*, Environmental Analyst, Air Pollution Control Division, Department of Environmental Conservation, Vermont Agency of Natural Resources, Waterbury, VT

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Dr. Armistead (Ted) Russell*, Georgia Power Distinguished Professor of Environmental Engineering, Environmental Engineering Group, School of Civil and Environmental Engineering, Georgia Institute of Technology, Atlanta, GA

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Dr. Frank Speizer [M.D.]*, Edward Kass Professor of Medicine, Channing Laboratory, Harvard Medical School, Boston, MA

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Dr. James Ultman, Professor, Chemical Engineering, Bioengineering Program, Pennsylvania State University, University Park, PA

Dr. Ronald Wyzga, Technical Executive, Air Quality Health and Risk, Electric Power Research Institute, P.O. Box 10412, Palo Alto, CA

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Science Advisory Board (SAB)
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CASAC NO_x and SO_x Primary NAAQS Review Panel
(cont'd)

SCIENCE ADVISORY BOARD STAFF

Mr. Fred Butterfield, CASAC Designated Federal Officer, 1200 Pennsylvania Avenue, N.W., Washington, DC, 20460, Phone: 202-343-9994, Fax: 202-233-0643 (butterfield.fred@epa.gov) (Physical/Courier/FedEx Address: Fred A. Butterfield, III, EPA Science Advisory Board Staff Office (Mail Code 1400F), Woodies Building, 1025 F Street, N.W., Room 3604, Washington, DC 20004, Telephone: 202-343-9994)

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

Abbreviations and Acronyms

ACCENT	European Union project Atmospheric Composition Change: the European Network of Excellence
ADS	annular denuder system
AHH	aryl hydrocarbon hydroxylase
AHR	airways hyperreactiveness
AIRPEX	Air Pollution Exposure (model)
AIRQUIS	Air Quality Information System (model)
ALT	alanine-amino-transferase
AM	alveolar or pulmonary macrophages
AMF	air mass factor
AMI	acute myocardial infarction
AMMN	*N*-nitroso-acetoxymethylmethylamine
ANOVA	analysis of variance
AP	alkaline phosphatase
API	air pollution index
AOR	adjusted odds ratio
APEX	Air Pollution Exposure (model)
APHEA	Air Pollution on Health: a European Approach (study)
APIMS	atmospheric pressure ionization mass spectrometer
AQCD	Air Quality Criteria Document
AQEG	Air Quality Expert Group
ARIC	Atherosclerosis Risk in Communities (study)
ARIMA	Autoregressive Integrated Moving Average (model)
ARR	arrhythmia
ATP	adenosine triphosphate
ATTILA	type of Lagrangian model
asl	above sea level
AST	aspartate-amino-transferase
β	beta; slope
BAL	bronchoalveolar lavage
B[*a*]P	benzo[*a*]pyrene
BC	black carbon
BERLIOZ	Berlin Ozone Experiment
BHPN	*N*-bis(2-hydroxypropyl)nitrosamine
BHR	bronchial hyperresponsiveness
BME	Bayesian Maxim Eutropy
BMI	body mass index

bpm	beats per minute
Br	bromine
Br^-	bromine ion
BrO	bromine oxide
bw	body weight
C	carbon or carbon black particles
CA	chromosome aberrations
CAMP	Childhood Asthma Management Program
CAMx	Comprehensive Air-Quality Model
CAT	catalase
CB4, CB-IV	Carbon Bond 4 (chemical mechanism)
CCN	cyanomethylidyne radical
CD	criteria document
Cd	cadmium
CEPEX	Central Equatorial Pacific Experiment
CFD	Computational Fluid Dynamics
CG	cloud-to-ground (flash)
CH_4	methane
C_2H_4	ethene
C_2H_6	ethane
C_5H_8	isoprene
CHAD	Consolidated Human Activities Database
CH_3-CHO	acetaldehyde
$CH_3CH(O)OONO_2$	peroxyacetyl nitrate
$CH_3C(O)O$	peroxyacetyl radical
CH_3-$C(O)O_2$, CH_3-C(O)OO	acetyl peroxy, peroxyacetyl
CHF	congestive heart failure
CH_2I_2	diiodomethane
Chol	cholesterol
CH_3OOH	methyl hydroperoxide
$(CH_3)_2S$, CH_3-S-CH_3	dimethylsulfide
CH_3-S-H	methyl mercaptan
$(CH_3)_2SO$	dimethylsulfoxide
CH_3SO_3H	methanesulfonic acid
CH_3-S-S-CH_3	dimethyl disulfide
CI	confidence interval
CIMS	chemical ionization mass spectroscopy

CL	chemiluminescence
Cl	chorine
Cl^-	chorine ion
CLRD	chronic lower respiratory disease
CMAQ	Community Multiscale Air Quality (model)
CMD	count median diameter
CO	carbon monoxide
CoH	coefficient of haze
COPD	chronic obstructive pulmonary disease
CP	coarse particulate
Cr	chromium
CS_2	carbon disulfide
CTM	chemistry transport model
Cu	copper
CVD	cardiovascular disease
CYP	cytochrome P450
D_{ae}	aerodynamic diameter
DEcCBP	diesel exhaust particulates extract-coated carbon black particles
DEN	diethylnitrosamine
DEP	diesel exhaust particles
DEP+C	diesel exhaust particle extract adsorbed to C
dG	2′-deoxyguanosine
DL	detection limit
DMBA	7, 12-dimethylbenzanthracene
DMS	dimethylsulfide
DMSO	dimethylsulfoxide
DNA	deoxyribonucleic acid
DNS	Direct Numerical Simulation
DOAS	differential optical absorption spectroscopy
EC	elemental carbon
ECG	electrocardiogram
ED	emergency department
EDMAS	Exposure and Dose Modeling and Analysis System
EDXRF	energy dispersive X-ray fluorescence
EE	energy expenditure
EIB	exercise-linked bronchial reactivity
EMECAM	Spanish Multicentre Study on Air Pollution
EPA	U.S. Environmental Protection Agency

ER	emergency room
ESR	electron spin resonance (spectroscopy)
F344	Fischer 344 (rat)
Fe	iron
FEF_{25-75}	forced expiratory flow between 25 and 75% of vital capacity
FEM	Federal Equivalent Method
FEV_1	forced expiratory volume in 1 second
FHLC	fetal hamster lung cells
FL	fluoranthene
FLEXPART	type of Lagrangian model
FP	fine particulate
FPD	flame photometric detection
FRM	Federal Reference Method
FTIR	Fourier Transform Infrared Spectroscopy
FVC	forced vital capacity
FW2	black carbon soot model
γN_2O_5	uptake coefficient for N_2O_5
GAM	Generalized Additive Model(s)
GCE	Goddard Cumulus Ensemble (model)
GC/ECD	gas chromatography-electron capture detection
GCS	γ-glutamylcysteine synthetase
GEE	Generalized Estimating Equations
GEOS-Chem	three-dimensional model of atmospheric composition driven by assimilated Goddard Earth Orbiting System observations
GEOS-1 DAS	NASA Goddard Earth Orbiting System Data Assimilation System
GFED	Global Fire Emissions Database
GIS	Geographic Information System
GLM	Generalized Linear Model(s)
GMP	guanosine-3',5'-monophosphate
GOME	Global Ozone Monitoring Instrument
GP	general practitioner physician
GPx	glutathione peroxidase
GRed	glutathione reductase
GSD	geometric standard deviation
GSH	glutathione
GSH-Px	glutathione peroxidase
GSSG	oxidized glutathione; glutathione disulfide
$GSSO_3H$	glutathione *S*-sulfonate

GST	glutathione *S*-transferase (e.g., GSTM1, GSTP1, GSTT1)
GT	γ-glutamyltransferase
^{3}H	hydrogen-3 radionuclide; tritium
H^{+}	hydrogen ion
HA	hospital admissions
HAPEM	Hazardous Air Pollutant Exposure Model
HCHO	formaldehyde
HCl	hydrochloric acid
HC	hydrocarbon
$HCOO^{-}$	formate
HEADS	Harvard-EPA Annular Denuder System
HEI	Health Effects Institute
HES	hospital episode statistics
HF	high frequency
Hg	mercury
HNO_3	nitric acid
HNO_4	pernitric acid
HO_2	hydroperoxyl; hydroperoxy radical
H_2O_2	hydrogen peroxide
HOBr	hypobromous acid
HOCl	hypochlorous acid
HONO, HNO_2	nitrous acid
HO_2NO_2	peroxynitric acid
HOONO	pernitrous acid
HOX	hypohalous acid
HO_x	oxides of hydrogen
HP	hydrolyzed protein
HRV	heart rate variability
HS	hemorrhagic stroke
H_2S	hydrogen sulfide
HSO_3^{-}	hydrogen sulfite
H_2SO_4	sulfuric acid
h*v*	solar ultraviolet photon
HVA-I_{Ca}	high-voltage activated calcium currents
I	iodine
IARC	International Agency for Research on Cancer
IBEM	Individual Based Exposure Models
IC	intracloud (flash); ion chromatography

ICARTT	International Consortium for Atmospheric Research on Transport and Transformation
ICD, ICD9	International Classification of Disease, 9th Revision
Ig	immunoglobulin (e.g., IgA, IgE, IgG)
IHD	ischemic heart disease
IIASA	International Institute for Applied Systems Analysis
IMPROVE	Interagency Monitoring of Protected Visual Environments
INDOEX	Indian Ocean Experiment
INO_3	iodine nitrate
INTEX-NA	NASA Intercontinental Chemical Transport Experiment - North America
IO	iodine oxide
IPCC-AR4	Intergovernmental Panel on Climate Change-Fourth Assessment Report
IPCC-TAR	Intergovernmental Panel on Climate Change-Third Assessment Report
IQR	interquartile range
IS	ischemic stroke
IUGR	intrauterine growth retardation
JPL	Jet Propulsion Laboratory
K_a	acid dissociation constant in M
K_H	Henry's Law constant in M atm^{-1}
^{85}Kr	krypton-85 radionuclide
K_w	ion product of water
LBW	low birth weight
LDH	lacticate dehydrogenase
LES	Large Eddy Simulation
LF	low frequency
LFHFR	low frequency/high frequency ratio
LIF	laser-induced fluorescence
LOESS	locally estimated smoothing splines
LP	long-path
LRD	lower respiratory disease
LRI	lower respiratory illness
LRS	lower respiratory symptoms
LWC	liquid water content
M	air molecule
MAD	median aerodynamic diameter
MAP	mean arterial pressure
MAQSIP	Multiscale Air Quality Simulation Platform

MAX	multi axis
MBL	marine boundary layer
MCM	master chemical mechanism
MDA	malondialdehyde
MEF_{50}	maximal midexpiratory flow at 50% of forced vital capacity
MEM	model ensemble mean
MENTOR-1A	Modeling Environment for Total Risk for One-Atmosphere studies
MET	metabolic equivalent of work
MgO	magnesium oxide
MI	myocardial infarction
MIESR	matrix isolation electron spin resonance (spectroscopy)
MM5	National Center for Atmospheric Research/Penn State Mesoscale Model
MMAD	mass median aerodynamic diameter
MMEF	maximal midexpiratory flow
MN	micronuclei
MNPCE	micronucleated polychromatic erythrocytes
Mo	molybdenum
MOBILE6	Highway Vehicle Emission Factor Model
MONICA	Monitoring Trend and Determinants in Cardiovascular Disease (registry)
MOZART-2	(model)
MPAN	peroxymethacryloyl nitrate; peroxy-methacrylic nitric anhydride
MPP	multi-phase process
mRNA	messenger ribonucleic acid
MSA	metropolitan statistical area
^{15}N	nitrogen-15 radionuclide
N	nitrogen
N, n	number of observations
N_2	molecular nitrogen, nitrogen gas
NA	not available
NAAQS	National Ambient Air Quality Standards
NaCl	sodium chloride
Na_2CO_3	sodium carbonate
NADP	National Atmospheric Deposition Program
$NaHCO_3$	sodium bicarbonate
NARSTO	North American Regional Strategy for Atmospheric Ozone
NASA	National Aeronautics and Space Administration
NBS	National Bureau of Standards

NCAR	National Center for Atmospheric Research
NCICAS	National Cooperative Inner-City Asthma Study
NDMA	*N*-nitrosodimethylamine
NDMA-D	*N*-nitrosodimethylamine demethylase
NMBzA	*N*-nitrosomethylbenzylamine
NEM	National Ambient Exposure Model
NEM/pNEM	National Ambient Exposure Model and Probabilistic National Exposure Model
NERL	National Exposure Research Laboratory
NF	nitrofluoranthene (e.g., 3- or 8-nitrofluoranthene)
NH_2	amino
NH_3	ammonia
NH_4^+	ammonium ion
NH_4Cl	ammonium chloride
NH_4NO_3	ammonium nitrate?
$(NH_4)_2SO_4$	ammonium sulfate
NIST	National Institute of Standards and Technology
NMHC	nonmethane hydrocarbon
NMOC	nonmethane organic compound
NN	nitronaphthalene (e.g., 1- or 2-nitronaphthalene)
NO	nitric oxide
NO_2	nitrogen dioxide
NO_2^+	nitronium ion
NO_2^-	nitrite
NO_3	nitrate (radical)
NO_3^-	nitrate
N_2O_5	dinitrogen pentoxide
NO_x	nitrogen oxides; oxides of nitrogen
NO_y	sum of NO_x and NO_z; odd nitrogen species
NO_z	oxides of nitrogen and nitrates; difference between NO_y and NO_x
NP	nitropyrene (e.g., 1- or 2-nitropyrene)
NPAHs	nitro polycyclic aromatic hydrocarbons
NR	not reported; data not relevant
NRC	National Research Council
NS	nonsignificant
NSA	nitrosating agent
nss	non-sea-salt
NTRMs	NIST Traceable Reference Materials

^{16}O	oxygen-16 radionuclide
O_2	molecular oxygen
O_3	ozone
OAQPS	Office of Air Quality Planning and Standards
OC	organic carbon
OCS	carbonyl sulfide
$O(^1D)$	electronically excited oxygen atom
OH	hydroxyl radical
OHC	oxygenated hydrocarbons
8-OHdG	8-hydroxy-2′-deoxyguanosine
OMI	Ozone Monitoring Instrument
$O(^3P)$	ground-state oxygen atom
OPE	ozone production efficiency
OPSIS	Open Path Ambient Air Monitoring Systems for SO_2
OR	odds ratio
OSPM	Danish Operational Street Pollution Model
P, p	probability value
PAHs	polycyclic aromatic hydrocarbons
PAMS, PAMs	Photochemical Aerometric Monitoring System
PAN	peroxyacetyl nitrate; peroxyacyl nitrate
Pb	lead
PBEM	Population Based Exposure Models
PCA	principal component analysis
PCE	polychromatic erythrocytes
PE	parameter estimates
PEC	pulmonary endocrine cells
PEF	peak expiratory flow
PEFR	peak expiratory flow rate
PERI	peripheral vascular and cerebrovascular disease
$P(HNO_3)$	particulate nitrate
PIH	primary intracerebral hemorrhage
PIXE	particle induced X-ray emission
PKA	cyclic AMP-dependent protein kinase A
PKI	synthetic peptide inhibitor of PKA
PL	phospholipids
PM	particulate matter
$PM_{2.5}$	particulate matter with 50% upper cut point aerodynamic diameter of 2.5 μm for sample collection; surrogate for fine PM

PM_{10}	particulate matter with 50% upper cut point aerodynamic diameter of 10 µm for sample collection
$PM_{10-2.5}$	particulate matter with 10 µm as upper cut point aerodynamic diameter and 2.5 µm as lower cut point for sample collection; surrogate for thoracic coarse PM (does not include fine PM)
PM_{13}	particulate matter with 50% upper cut point aerodynamic diameter of 13 µm for sample collection
PM-CAMx	Particulate Matter Comprehensive Air Quality Model with Extensions
PMN	polymorphonuclear leukocytes
PNC	particle number concentration
PNN50	percentage of differences between adjacent NN intervals
PMT	photomultiplier tube
pNEM	Probabilistic National Exposure Model
$P(O_3)$	ozone precursor
POM	particulate organic matter
ppb	parts per billion
ppbv	parts per billion by volume
ppm	parts per million
PPN	peroxypropionyl nitrate; peroxypropionic nitric anhydride
ppt	parts per trillion
pptv	parts per trillion by volume
PRB	policy relevant background
Pt	platinum
PSA	particle strong acidity
psi	pounds per square inch
PTEP	PM_{10} Technical Enhancement Program
PTFE	polytetrafluoroethylene (Teflon)
PY	pyrene
r	correlation coefficient
R^2	coefficient of determination
RACM	Regional Air Chemistry Mechanism
RADM	Regional Acid Deposition Model
RANS	Reynolds Averaged Numerical Simulation
RBC	red blood cell or erythrocyte
RDBMS	Relational Database Management Systems
REHEX	Regional Human Exposure Model
RH	relative humidity
RMR	resting metabolic rate
r-MSSD	root mean square of successive differences in R-R intervals.

RO_2	organic peroxyl; organic peroxy
$RONO_2$	organic nitrate
$ROONO_2$, RO_2NO_2	peroxy nitrate
RR	relative risk
^{34}S	sulfur-34 radionuclide
S	sulfur
S_2^-	sulfide
S_2*	electronically excited sulfur molecules
S_2O	disulfur monoxide
SCAQS	Southern California Air Quality Study
SCE	sister chromatid exchange
SCIAMACHY	Scanning Imaging Absorption Spectrometer for Atmospheric Chartography
SCOS97	1997 Southern California Ozone Study
SD	standard deviation
SDNN	standard deviation of normal R-R intervals
SE	standard error
SEPs	somatosensory-evoked potentials
SGV	subgrid variability
SHEDS	Simulation of Human Exposure and Dose System
SHS	subarachnoid hemorrhagic stroke
SIDS	sudden infant death syndrome
SMOKE	Spare-Matrix Operator Kernel Emissions (system)
SO	sulfur monoxide
SO_2	sulfur dioxide
SO_2*	electronically excited sulfur dioxide molecules
SO_3	sulfur trioxide
SO_3^{2-}	sulfite ion
SO_4^{2-}	sulfate ion
SOD	superoxide dismutase
SONEX	Subsonic Assessment Ozone and Nitrogen Oxides Experiment
SO_x	oxides of sulfur
SPF	specific pathogen free
SPM	suspended particulate matter
SQCA	squamous cell carcinoma
SRM	standard reference material; suspended particulate matter extract
SSO	seabuckthorn seed oil
STE	stratospheric-tropospheric exchange

STEP	Stratospheric-Tropospheric-Exchange Project
STN	Speciation Trends Network
STPD	standard temperature and pressure, dry
STRF	Spatio-Temporal Random Field (theory)
SV40	simian virus 40
τ	tau; atmospheric lifetime
t	t statistic
TBARS	thiobarbituric acid-reactive substances
TC	total carbon
TDLAS	tunable-diode laser absorption spectroscopy
Tg	teragram
TIA	transient ischemic attack
TOC	potassium channel transient outward currents
TOR	thermal-optical reflectance
TP	total particulate
TPLIF	two-photon laser-induced fluorescence
TRS	total reduced sulfur
TSDS	treatment, storage, or disposal facilities
TSP	total suspended particles
TSPM	total suspended particulate matter
TTFMS	two-tone frequency-modulated spectroscopy
TTX	tetrodotoxin
TTX-R	tetrodotoxin-resistant
TTX-S	tetrodotoxin-sensitive
UBRE	unbiased risk estimator
U-EPX	urinary eosinophil protein
UMD-CTM	University of Maryland Chemical Transport Model
URD	upper respiratory disease
URI	upper respiratory illness
URS	upper respiratory symptoms
UV	ultraviolet
V	vanadium
V_d	deposition velocity
$\dot{V}_E$	total ventilation rate
VEPs	visual-evoked potentials
VOC	volatile organic compound
W	tungsten
WHO	World Health Organization

XRF	X-ray fluorescence
Zn	zinc

AX1. CHAPTER 1 ANNEX–INTRODUCTION

The draft Annexes are prepared in support of the draft Integrated Science Assessment for Sulfur Oxides – Health Criteria (EPA/600/R-07/108). The Integrated Science Assessment (ISA) presents a concise synthesis of the most policy-relevant science to form the scientific foundation for the review of the primary (health-based) national ambient air quality standards (NAAQS) for sulfur dioxide (SO_2). This series of Annexes provide more extensive and detailed summaries of the most pertinent scientific literature. The Annexes identify, evaluate, and summarize scientific research in the areas of atmospheric sciences, air quality analyses, exposure assessment, dosimetry, controlled human exposure studies, toxicology, and epidemiology, focusing on studies relevant to the review of the primary NAAQS.

These draft Annexes are organized by scientific study areas and include research that is relevant to the key policy questions discussed previously to provide an evidence base supporting the development of the ISA, risk, and exposure assessments. In this Annex 1, we provide legislative background and history of previous reviews of the NAAQS for sulfur oxides. In Annex 2, we present evidence related to the physical and chemical processes controlling the production, destruction, and levels of sulfur oxides in the atmosphere, including both oxidized and reduced species. Annex 3 presents information on environmental concentrations, patterns, and human exposure to ambient sulfur oxides; however, most information relates to SO_2. Annex 4 presents results from toxicological studies as well as information on dosimetry of sulfur oxides. Annex 5 discusses evidence from epidemiologic studies. These Annexes include more detailed information on health or exposure studies that is summarized in tabular form, as well as more extensive discussion of atmospheric chemistry, source, exposure, and dosimetry information. Annex tables for health studies are generally organized to include information about (1) concentrations of sulfur oxides levels or doses and exposure times, (2) description of study methods employed, (3) results and comments, and (4) quantitative outcomes for sulfur oxides measures.

AX1.1 LEGISLATIVE REQUIREMENTS

Two sections of the Clean Air Act (CAA) govern the establishment and revision of the NAAQS. Section 108 (42 U.S.C. 7408) directs the Administrator to identify and list "air pollutants" that "in his judgment, may reasonably be anticipated to endanger public health and welfare" and whose "presence . . . in the ambient air results from numerous or diverse mobile or stationary sources" and to issue air quality criteria for those that are listed. Air quality criteria are intended to "accurately reflect the latest scientific knowledge useful in indicating the kind and extent of identifiable effects on public health or welfare which may be expected from the presence of [a] pollutant in ambient air . . . ."

Section 109 (42 U.S.C. 7409) directs the Administrator to propose and promulgate "primary" and "secondary" NAAQS for pollutants listed under section 108. 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 required to protect the public welfare from any known or anticipated adverse effects associated with the presence of [the] pollutant in the ambient air."[2]

The requirement that primary standards include 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 reasonable degree of protection against hazards that research has not yet identified. See Lead Industries Association v. EPA, 647 F.2d 1130, 1154 (D.C. Cir 1980), cert. denied, 449 U.S. 1042 (1980); American Petroleum Institute v. Costle, 665 F.2d 1176, 1186 (D.C. Cir. 1981), cert. denied, 455 U.S. 1034 (1982). Both kinds of uncertainties are components of the risk associated with

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

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

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 include 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.

In selecting a margin of safety, the EPA considers such factors as the nature and severity of the health effects involved, the size of sensitive population(s) at risk, and the kind and degree of the uncertainties that must be addressed. The selection of any particular approach to providing an adequate margin of safety is a policy choice left specifically to the Administrator's judgment. See Lead Industries Association v. EPA, supra, 647 F.2d at 1161-62.

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. See generally Whitman v. American Trucking Associations, 531 U.S. 457, 465-472, 475-76 (2001).

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 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) of EPA's Science Advisory Board.

AX1.2 HISTORY OF REVIEWS OF THE PRIMARY NAAQS FOR SO_2

On April 30, 1971, the EPA promulgated primary NAAQS for SO_2. These primary standards, which were based on the findings outlined in the original 1969 Air Quality Criteria for Sulfur Oxides, were set at 0.14 parts per million (ppm) averaged over a 24-hour period, not to be exceeded more than once per year, and 0.030 ppm annual arithmetic mean. In 1982, EPA

published the Air Quality Criteria for Particulate Matter and Sulfur Oxides along with an addendum of newly published controlled human exposure studies, which updated the scientific criteria upon which the initial standards were based (EPA, 1982). In 1986, a second addendum was published presenting newly available evidence from epidemiologic and controlled human exposure studies (EPA, 1986). In 1988, EPA reviewed and revised the health criteria upon which the SO_2 standards were based. As a result of that review, EPA published a proposed decision not to revise the existing standards (53 FR 14926). However, 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.

As a result of public comments on the 1988 proposal and other post-proposal developments, EPA published a second proposal on November 15, 1994 (59 FR 58958). The 1994 re-proposal was based in part on a supplement to the second addendum of the criteria document, which evaluated new findings on short-term SO_2 exposures in asthmatics (EPA, 1994a). As in the 1988 proposal, EPA proposed to retain the existing 24-hour and annual standards. The EPA also solicited comment on three regulatory alternatives to further reduce the health risk posed by exposure to high 5-minute peaks of SO_2 if additional protection were judged to be necessary. The three alternatives included: 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. On May 22, 1996, EPA's final decision, that revisions of the NAAQS for sulfur oxides were not appropriate at that time, was announced in the Federal Register. In that decision, EPA announced an intention to propose guidance, under section 303 of the Act, to assist states in responding to short-term peak levels of SO_2. The basis for the decision, and subsequent litigation, is discussed below in Chapter 3.

AX2. CHAPTER 2 ANNEX – ATMOSPHERIC CHEMISTRY OF NITROGEN AND SULFUR OXIDES

AX2.1 INTRODUCTION

Nitrogen oxides (NO_x) along with volatile organic compounds (VOCs) including anthropogenic and biogenic hydrocarbons, aldehydes, etc. and carbon monoxide (CO) serve as precursors in the formation of ozone (O_3) and other elements of photochemical smog. Nitrogen oxides are defined here as nitric oxide (NO) and nitrogen dioxide (NO_2), the latter of which is a U.S. Environmental Protection Agency (EPA) Criteria Air Pollutant; similarly, oxides of sulfur (SO_x) are defined here to be sulfur monoxide (SO), sulfur dioxide (SO_2), the largest component of SO_x and also a EPA Criteria Air Pollutant, and sulfur trioxide (SO_3). SO_3 rapidly reacts with water vapor to form H_2SO_4, and only SO_2 is present in the atmosphere at detectable levels.

Nitrogen dioxide is an oxidant and can further react to form other photochemical oxidants, in particular the organic nitrates, including peroxy acetyl nitrates (PAN) and higher PAN analogues. It can also react with toxic compounds such as polycyclic aromatic hydrocarbons (PAHs) to form nitro-PAHs, which may be even more toxic than the precursors. Nitrogen dioxide together with sulfur dioxide (SO_2), another EPA criteria air pollutant, can be oxidized to the strong mineral acids, nitric acid (HNO_3) and sulfuric acid (H_2SO_4), which contribute to the acidity of cloud, fog, and rainwater, and can form ambient particles.

The role of NO_x in O_3 formation was reviewed in Chapter 2 (Section 2.2) of the latest AQCD for Ozone and Other Photochemical Oxidants (U.S. Environmental Protection Agency, 2006 CD06), and in numerous texts (e.g., Seinfeld and Pandis, 1998; Jacob, 2000; Jacobson, 2002). Mechanisms for transporting O_3 precursors, the factors controlling the efficiency of O_3 production from NO_x, methods for calculating O_3 from its precursors, and methods for measuring NO_x were all reviewed in Section 2.6 of CD06. The main points from those discussions in CD06 and updates, based on new materials will be presented here. Ammonia (NH_3) is included here because its oxidation can be a source of NO_x, and it is a precursor for ammonium ions (NH_4^+), which play a key role in neutralizing acidity in ambient particles and in cloud, fog, and rain water. Ammonia is also involved in the ternary nucleation of new particles, and it reacts with gaseous HNO_3 to form ammonium nitrate (NH_4NO_3), which is a major

constituent of ambient Particulate Matter (PM) in many areas. Ammonia is also involved in over nitrification of aqueous and terrestrial ecosystems and participates in the N cascade (Galloway et al., 2003)

The atmospheric chemistry of NO_x is discussed in Section AX2.2, and of SO_2 in Section AX2.3. Mechanisms for the formation of aqueous-phase sulfate (SO_4^{2-}) and nitrate (NO_3^-) are reviewed in Section AX2.4. Sources and emissions of NO_x, NH_3, and SO_2 are discussed in Section AX2.5. Modeling methods used to calculate the atmospheric chemistry, transport, and fate of NO_x and SO_2 and their oxidation products are presented in Section AX2.6. Measurement techniques for the nitrogen-containing compounds and for SO_2, nitrates, sulfates, and ammonium ion are discussed in Section AX2.8. Estimates of policy-relevant background concentrations of NO_x and SO_x are given in Section AX2.9. An overall review of key points in this chapter is given in Section AX2.11.

The overall chemistry of reactive nitrogen compounds in the atmosphere is summarized in Figure AX2.1-1 and is described in greater detail in the following sections. Nitrogen oxides are emitted primarily as NO with smaller quantities of NO_2. Emissions of NO_x are spatially distributed vertically with some occurring at or near ground level and others aloft as indicated in Figure AX2.1-1. Because of atmospheric chemical reactions, the relative abundance of different compounds contributed by different sources varies with location. Both anthropogenic and natural (biogenic) processes emit NO_x. In addition to gas phase reactions, multiphase processes are important for forming aerosol-phase pollutants, including aerosol NO_3^-.

AX2.2 CHEMISTRY OF NITROGEN OXIDES IN THE TROPOSPHERE

AX2.2.1 Basic Chemistry

There is a rapid photochemical cycle in the troposphere that involves photolysis of NO_2 by solar UV-A radiation to yield NO and a ground-state oxygen atom, $O(^3P)$:

$$NO_2 + h\nu \rightarrow NO + O(^3P), \qquad \text{(AX2-1)}$$

This ground-state oxygen atom can then combine with molecular oxygen (O_2) to form O_3; and, colliding with any molecule from the surrounding air (M = N_2, O_2, etc), the newly formed O_3 molecule, transfers excess energy and is stabilized:

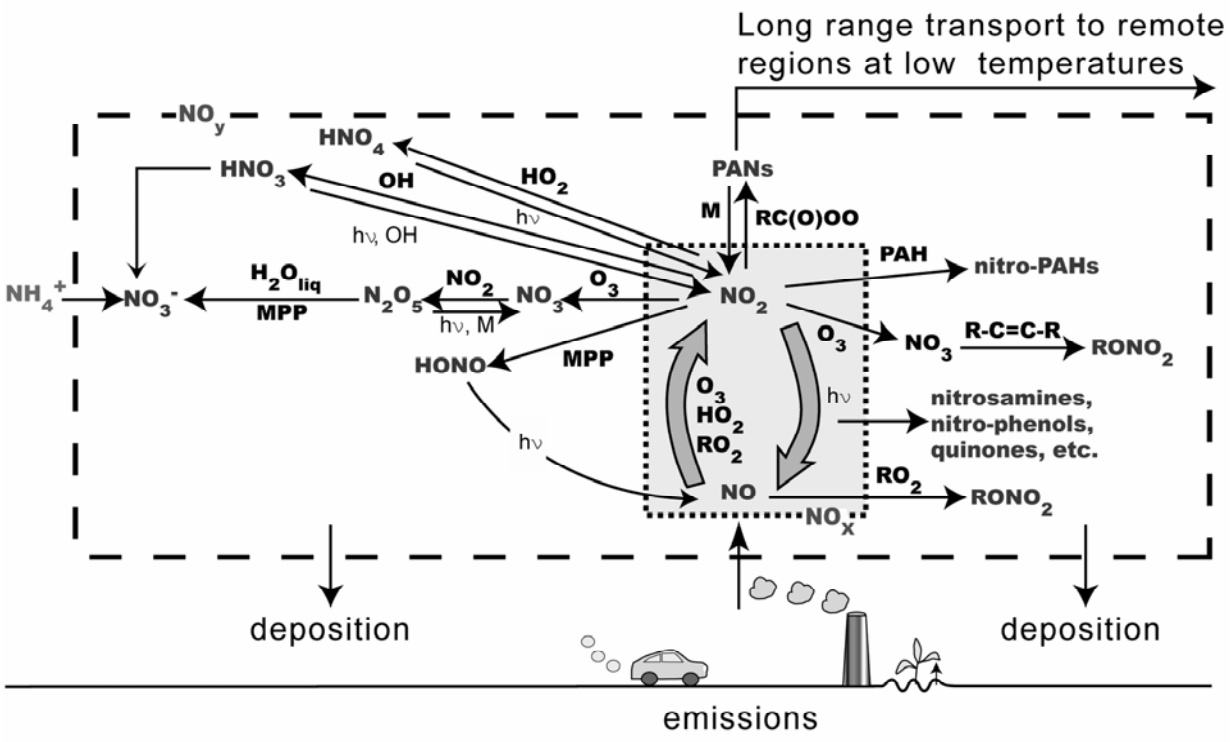


Figure AX2.1-1. Schematic diagram of the cycle of reactive nitrogen species in the atmosphere. MPP refers to multi-phase process; hν to a photon of solar energy.

$$O(^3P) + O_2 + M \rightarrow O_3 + M, \qquad \text{(AX2-2)}$$

where M = N_2, O_2. Reaction AX2-2 is the only significant reaction forming O_3 in the troposphere.

NO and O_3 react to reform NO_2:

$$NO + O_3 \rightarrow NO_2 + O_2. \qquad \text{(AX2-3)}$$

Reaction AX2-3 is responsible for O_3 decreases and NO_2 increases found near sources of NO (e.g., highways), especially at night when the actinic flux is 0. Oxidation of reactive VOCs leads to the formation of reactive radical species that allow the conversion of NO to NO_2 without the participation of O_3 (as in Reaction AX2-3):

$$NO \xrightarrow{HO_2,\ RO_2} NO_2. \qquad \text{(AX2-4)}$$

Ozone, therefore, can accumulate as NO_2 photolyzes as in Reaction AX2-1, followed by Reaction AX2-2. Specific mechanisms for the oxidation of a number of VOCs were discussed in the O_3 AQCD (U.S. Environmental Protection Agency, 2006).

It is often convenient to speak about families of chemical species defined in terms of members that interconvert rapidly among themselves on time scales that are shorter than those for formation or destruction of the family as a whole. For example, an "odd oxygen" (O_x) family can be defined as

$$O_x = \sum(O(^3P) + O(^1D) + O_3 + NO_2)$$

In much the same way, NO_x is sometimes referred to as "odd nitrogen". Hence, we see that production of O_x occurs by the schematic Reaction AX2-4, and that the sequence of reactions given by reactions AX2-1 through AX2-3 represents no net production of O_x. Definitions of species families and methods for constructing families are discussed in Jacobson (1999) and references therein. Other families that include nitrogen-containing species (and which will be referred to later in this chapter) include:

$$NO_x = (NO + NO_2),$$

One can then see that production of O_x occurs by the schematic Reaction AX2-4, and that the sequence of reactions given by reactions AX2-1 through AX2-3 represents no net production of O_x. Definitions of species families and methods for constructing families are discussed in Jacobson (1999) and references therein. Other families that include nitrogen-containing species, and which will be referred to later in this chapter, are: (which is the sum of the products of the oxidation of NO_x)

$$NO_Z = \sum (HNO_3 + HNO_4 + NO_3 + 2NO_2O_5 + PAN(CH_3CHO\text{ - }OO\text{ - }NO_2) + other\ organic\ nitraties + halogen\ nitrates + particulate\ nitrate);$$

$$NO_y = NO_x + NO_z + HONO;$$
$$and\ NH_x = NH_3 + NH_4^+$$

The reaction of NO_2 with O_3 leads to the formation of NO_3^- radical,

$$NO_2 + O_3 \rightarrow NO_3 + O_2, \quad \text{(AX2-5)}$$

However, because the NO_3 radical photolyzes rapidly (lifetime of ≈5 s during the photochemically most active period of the day around local solar noon (Atkinson et al., 1992a),

$$NO_3 + h\nu \rightarrow NO + O_{2(10\%)} \quad \text{(AX2-6a)}$$

$$NO_2 + O(^3P)_{(90\%)} \quad \text{(AX2-6b)}$$

its concentration remains low during daylight hours, but can increase after sunset to nighttime concentrations of $<5 \times 10^7$ to 1×10^{10} molecules cm^{-3} (<2 to 430 parts per trillion (ppt)) over continental areas influenced by anthropogenic emissions of NO_x (Atkinson et al., 1986). At night, NO_3, rather than the hydroxyl radical (OH), is the primary oxidant in the system.

Nitrate radicals can combine with NO_2 to form dinitrogen pentoxide (N_2O_5):

$$NO_3 + NO_2 \xleftrightarrow{M} N_2O_5 \quad \text{(AX2-7)}$$

and N_2O_5 both photolyzes and thermally decomposes back to NO_2 and NO_3 during the day; however, N_2O_5 concentrations ($[N_2O_5]$) can accumulate during the night to parts per billion (ppb) levels in polluted urban atmospheres.

The tropospheric chemical removal processes for NO_x include reaction of NO_2 with the OH radical and hydrolysis of N_2O_5 in aqueous aerosol solutions if there is no organic coating. Both of these reactions produce HNO_3.

$$OH + NO_2 \xrightarrow{M} HNO_3 \quad \text{(AX2-8)}$$

$$N_2O_5 \xrightarrow{H_20(1)} HNO_3 \quad \text{(AX2-9)}$$

The gas-phase reaction of the OH radical with NO_2 (Reaction AX2-8) initiates one of the major and ultimate removal processes for NO_x in the troposphere. This reaction removes OH and NO_2 radicals and competes with hydrocarbons for OH radicals in areas characterized by high NO_x concentrations, such as urban centers (see Section AX2.2.2). The timescale (τ) for

conversion of NO_x to HNO_3 in the planetary boundary layer at 40 N latitude ranges from about 4 hours in July to about 16 hours in January. The corresponding range in τ at 25 N latitude is between 4 and 5 hours, while at 50 N latitude, HNO_3 τ ranges from about 4 to 20 hours (Martin et al., 2003). In addition to gas-phase HNO_3, Golden and Smith (2000) have shown on the basis of theoretical studies that pernitrous acid (HOONO) is also produced by the reaction of NO_2 and OH radicals. However, this channel of production most likely represents a minor yield (approximately 15% at the surface) (Jet Propulsion Laboratory, 2003). Pernitrous acid will also thermally decompose and can photolyze. Gas-phase HNO_3 formed from Reaction AX2-8 undergoes wet and dry deposition to the surface, and uptake by ambient aerosol particles. Reaction AX2-8 limits NO_x τ to a range of hours to days.

In addition to the uptake of HNO_3 on particles and in cloud drops, it photolyzes and reacts with OH radicals via

$$HNO_3 + h\nu \rightarrow OH + NO_2 \qquad \text{(AX2-10)}$$

and

$$HNO_3 + OH \rightarrow NO_3 + H_2O. \qquad \text{(AX2-11)}$$

The lifetime of HNO_3 with respect to these two reactions is long enough for HNO_3 to act as a reservoir species for NO_x during long-range transport, contributing in this way to NO_2 levels and to O_3 formation in areas remote from the source region of the NO_x that formed this HNO_3.

Geyer and Platt (2002) concluded that Reaction AX2-9 constituted about 10% of the removal of NO_x at a site near Berlin, Germany during spring and summer. However, other studies found a larger contribution to HNO_3 production from Reaction AX2-9. Dentener and Crutzen (1993) estimated 20% in summer and 80% of HNO_3 production in winter is from Reaction AX2-9. Tonnesen and Dennis (2000) found between 16 to 31% of summer HNO_3 production was from Reaction AX2-9. The contribution of Reaction AX2-9 to HNO_3 formation is highly uncertain during both winter and summer. The importance of Reaction AX2-9 could be much higher during winter than during summer because of the much lower concentration of OH radicals and the enhanced stability of N_2O_5 due to lower temperatures and less sunlight. Note that Reaction AX2-9 proceeds as a heterogeneous reaction. Recent work in the northeastern

United States indicates that this reaction is proceeds at a faster rate in power plant plumes than in urban plumes (Brown et al., 2006a,b; Frost et al., 2006).

OH radicals also can react with NO to produce nitrous acid (HONO or HNO_2):

$$OH + NO \xrightarrow{M} HNO_2. \quad \text{(AX2-12)}$$

In the daytime, HNO_2 is rapidly photolyzed back to the original reactants:

$$HNO_2 + h\nu \rightarrow OH + NO. \quad \text{(AX2-13)}$$

Reaction AX2-12 is, however, a negligible source of HONO, which is formed mainly by multiphase processes (see Section AX2.2.3). At night, heterogeneous reactions of NO_2 in aerosols or at the earth's surface result in accumulation of HONO (Lammel and Cape, 1996; Jacob, 2000; Sakamaki et al., 1983; Pitts et al., 1984; Svensson et al., 1987; Jenkin et al., 1988; Lammel and Perner, 1988; Notholt et al., 1992a,b). Harris et al. (1982) and Zhang et al. (2006) (e.g.) suggested that photolysis of this HNO_2 at sunrise could provide an important early-morning source of OH radicals to drive O_3 formation

Hydroperoxy (HO_2) radicals can react with NO_2 to produce pernitric acid (HNO_4):

$$HO_2 + NO_2 + M \rightarrow HNO_4 + M \quad \text{(AX2-14)}$$

which then can thermally decompose and photolyze back to its original reactants. The acids formed in these gas-phase reactions are all water soluble. Hence, they can be incorporated into cloud drops and in the aqueous phase of particles.

Although the lifetimes of HNO_4 and N_2O_5 are short (minutes to hours) during typical summer conditions, they can be much longer at the lower temperatures and darkness found during the polar night. Under these conditions, species such as PAN, HNO_3, HNO_4, and N_2O_5 serve as NO_x reservoirs that can liberate NO_2 upon the return of sunlight during the polar spring. A broad range of organic nitrogen compounds can be directly emitted by combustion sources or formed in the atmosphere from NO_x emissions. Organic nitrogen compounds include the PANs, nitrosamines, nitro-PAHs, and the more recently identified nitrated organics in the quinone family. Oxidation of VOCs produces organic peroxy radicals (RO_2), as discussed in the latest AQCD for Ozone and Other Photochemical Oxidants (U.S. Environmental Protection Agency,

2006). Reaction of RO_2 radicals with NO and NO_2 produces organic nitrates ($RONO_2$) and peroxynitrates (RO_2NO_2):

$$RO_2 + NO \xrightarrow{M} RONO_2 \quad \text{(AX2-15)}$$

$$RO_2 + NO_2 \xrightarrow{M} RO_2NO_2 \quad \text{(AX2-16)}$$

Reaction (AX2-15) is a minor branch for the reaction of RO_2 with NO. The major branch produces RO and NO_2, as discussed in the next section; however, the organic nitrate yield increases with carbon number (Atkinson, 2000).

The most important of these organic nitrates is PAN, the dominant member of the broader family of peroxyacylnitrates which includes peroxypropionyl nitrate (PPN) of anthropogenic origin and peroxymethacrylic nitrate (MPAN) produced from isoprene oxidation. The PANs are formed by the combination reaction of acetyl peroxy radicals with NO_2:

$$CH_3C(O)\text{–}OO + NO_2 \rightarrow CH_3C(O)OONO_2 \quad \text{(AX2-17)}$$

where the acetyl peroxy radicals are formed mainly during the oxidation of ethane (C_2H_6). Acetaldehyde (CH_3CHO) is formed as an intermediate species during the oxidation of ethane. Acetaldehyde can be photolyzed or react with OH radicals to yield acetyl radicals:

$$CH_3\text{–}C(O)H + h\nu \rightarrow CH_3\text{–}C(O) + H \quad \text{(AX2-18)}$$

$$CH_3\text{–}C(O)H + OH \rightarrow CH_3\text{–}C(O) + H_2O \quad \text{(AX2-19)}$$

Acetyl radicals then react with O_2 to yield acetyl peroxy radicals

$$CH_3\text{–}C(O) + O_2 + M \rightarrow CH_3C(O)\text{–}OO + M \quad \text{(AX2-20)}$$

However, acetyl peroxy radicals will react with NO in areas of high NO concentrations

$$CH_3(CO)\text{–}OO + NO \rightarrow CH_3(CO)\text{–}O + NO_2 \quad \text{(AX2-21)}$$

and the acetyl-oxy radicals will then decompose

$$CH_3(CO)\text{–}O \rightarrow CH_3 + CO_2 \quad \text{(AX2-22)}$$

Thus, the formation of PAN is favored at conditions of high ratios of NO_2 to NO, which are most typically found under low NO_x conditions. The PANs both thermally decompose and photolyze back to their reactants on timescales of a few hours during warm sunlit conditions, with lifetimes with respect to thermal decomposition ranging from ~1 hour at 298 K to ~2.5 days at 273 K, up to several weeks at 250 K. Thus, they can provide an effective sink of NO_x at cold temperatures and high solar zenith angles, allowing release of NO_2 as air masses warm, in particular by subsidence. The PANs are also removed by uptake to vegetation (Sparks et al., 2003; Teklemariam and Sparks, 2004).

The organic nitrates may react further, depending on the functionality of the R group, but they will typically not return NO_x and can therefore be viewed mainly as a permanent sink for NO_x, as alkyl nitrates are sparingly soluble and will photolyze. This sink is usually small compared to HNO_3 formation, but the formation of isoprene nitrates may be a significant sink for NO_x in the United States in summer (Liang et al., 1998).

The peroxynitrates produced by (1-16) are thermally unstable and most have very short lifetimes (less than a few minutes) owing to thermal decomposition back to the original reactants. They are thus not effective sinks of NO_x.

AX2.2.2 Nonlinear Relations between Nitrogen Oxide Concentrations and Ozone Formation

Ozone is unlike some other species whose rates of formation vary directly with the emissions of their precursors in that O_3 production ($P(O_3)$) changes nonlinearly with the concentrations of its precursors. At the low NO_x concentrations found in most environments, ranging from remote continental areas to rural and suburban areas downwind of urban centers, the net production of O_3 increases with increasing NO_x. At the high NO_x concentrations found in downtown metropolitan areas, especially near busy streets and roadways, and in power plant plumes, there is net destruction of O_3 by (titration) reaction with NO. Between these two regimes is a transition stage in which O_3 shows only a weak dependence on NO_x concentrations. In the high NO_x regime, NO_2 scavenges OH radicals which would otherwise oxidize VOCs to produce peroxy radicals, which in turn would oxidize NO to NO_2. In the low NO_x regime, VOV (VOC) oxidation generates, or at least does not consume, free radicals, and O_3 production varies directly with NO_x. Sometimes the terms 'VOC-limited' and 'NO_x-limited' are used to describe these two regimes. However, there are difficulties with this usage because: (1) VOC

measurements are not as abundant as they are for NO_x, (2) rate coefficients for reaction of individual VOCs with free radicals vary over an extremely wide range, and (3) consideration is not given to CO nor to reactions that can produce free radicals without invoking VOCs. The terms NO_x-limited and NO_x-saturated (used by, e.g., Jaeglé et al., 2001) will be used wherever possible to describe these two regimes more adequately. However, the terminology used in original articles will also be kept. The chemistry of OH radicals, which are responsible for initiating the oxidation of hydrocarbons, shows behavior similar to that for O_3 with respect to NO_x concentrations (Hameed et al., 1979; Pinto et al., 1993; Poppe et al., 1993; Zimmerman and Poppe, 1993). These considerations introduce a high degree of uncertainty into attempts to relate changes in O_3 concentrations to emissions of precursors. It should also be noted at the outset that in a NO_x-limited (or NO_x-sensitive) regime, O_3 formation is not insensitive to radical production or the flux of solar UV photons, just that O_3 formation is more sensitive to NO_x. For example, global tropospheric O_3 is sensitive to the concentration of CH_4 even though the troposphere is predominantly NO_x-limited.

Various analytical techniques have been proposed that use ambient NO_x and VOC measurements to derive information about O_3 production and O_3-NO_x-VOC sensitivity. Previously (e.g., National Research Council, 1991), it was suggested that O_3 formation in individual urban areas could be understood in terms of measurements of ambient NO_x and VOC concentrations during the early morning. In this approach, the ratio of summed (unweighted by chemical reactivity) VOC to NO_x concentrations is used to determine whether conditions are NO_x-sensitive or VOC sensitive. This technique is inadequate to characterize O_3 formation because it omits many factors recognized as important for $P(O_3)$, including: the effect of biogenic VOCs (which are not present in urban centers during early morning); important individual differences in the ability of VOCs to generate free radicals, rather than just from total VOC concentration and other differences in O_3-forming potential for individual VOCs (Carter, 1995); the effect of multiday transport; and general changes in photochemistry as air moves downwind from urban areas (Milford et al., 1994).

Jacob et al. (1995) used a combination of field measurements and a chemical transport model (CTM) to show that the formation of O_3 changed from NO_x-limited to NO_x-saturated as the season changed from summer to fall at a monitoring site in Shenandoah National Park, VA. Photochemical production of O_3 generally occurs together with production of various other

species including HNO_3, organic nitrates, and hydrogen peroxide (H_2O_2). The relative rates of $P(O_3)$ and the production of other species varies depending on photochemical conditions, and can be used to provide information about O_3-precursor sensitivity.

There are no hard and fast rules governing the levels of NO_x at which the transition from NO_x-limited to NO_x-saturated conditions occurs. The transition between these two regimes is highly spatially and temporally dependent. In the upper troposphere, responses to NO_x additions from commercial aircraft have been found which are very similar to these in the lower troposphere (Bruhl et al., 2000). Bruhl et al. (2000) found that the NO_x levels for O_3 production versus loss are highly sensitive to the radical sources included in model calculations. They found that inclusion of only CH_4 and CO oxidation leads to a decrease in net O_3 production in the North Atlantic flight corridor due to NO emissions from aircraft. However, the additional inclusion of acetone photolysis was found to shift the maximum in O_3 production to higher NO_x mixing ratios, thereby reducing or eliminating areas in which O_3 production rates decreased due to aircraft emissions.

Trainer et al. (1993) suggested that the slope of the regression line between O_3 and summed NO_x oxidation products (NO_z, equal to the difference between measured total reactive nitrogen, NO_y, and NO_x) can be used to estimate the rate of $P(O_3)$ per NO_x (also known as the O_3 production efficiency, or OPE). Ryerson et al. (1998, 2001) used measured correlations between O_3 and NO_z to identify different rates of O_3 production in plumes from large point sources.

Sillman (1995) and Sillman and He (2002) identified several secondary reaction products that show different correlation patterns for NO_x-limited conditions and NO_x-saturated conditions. The most important correlations are for O_3 versus NO_y, O_3 versus NO_z, O_3 versus HNO_3, and H_2O_2 versus HNO_3. The correlations between O_3 and NO_y, and O_3 and NO_z are especially important because measurements of NO_y and NO_x are widely available. Measured O_3 versus NO_z (Figure AX2.2-1) shows distinctly different patterns in different locations. In rural areas and in urban areas such as Nashville, TN, O_3 shows a strong correlation with NO_z and a relatively steep slope to the regression line. By contrast, in Los Angeles O_3 also increases with NO_z, but the rate of increase of O_3 with NO_z is lower and the O_3 concentrations for a given NO_z value are generally lower.

The difference between NO_x-limited and NO_x-saturated regimes is also reflected in measurements of H_2O_2. Formation of H_2O_2 takes place by self-reaction of photochemically-generated HO_2 radicals, so that there is large seasonal variation of H_2O_2 concentrations, and

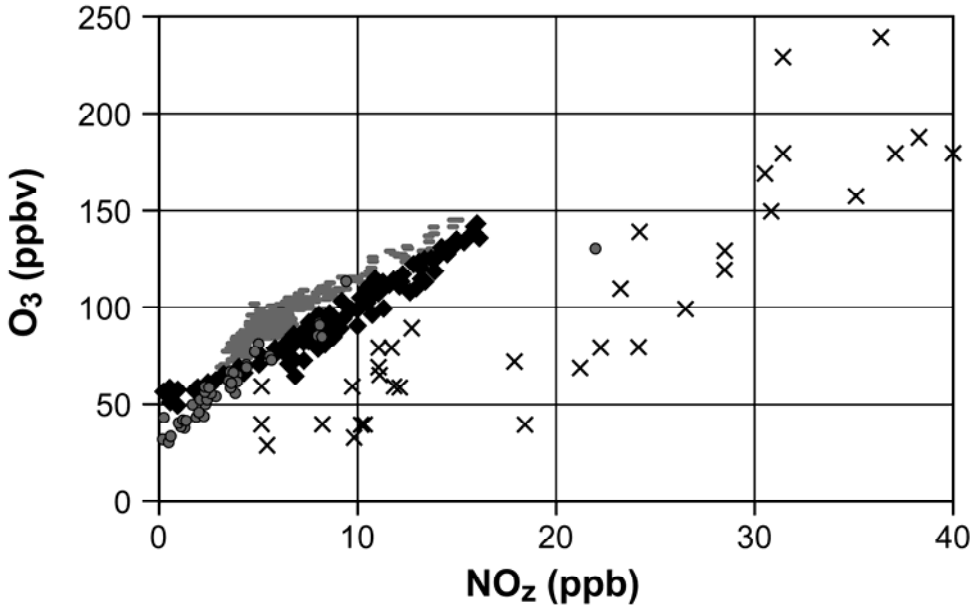


Figure AX2.2-1. Measured values of O_3 and NO_z (NO_y–NO_x) during the afternoon at rural sites in the eastern United States (gray circles) and in urban areas and urban plumes associated with Nashville, TN (gray dashes), Paris, FR (black diamonds) and Los Angeles, CA (X's)

values in excess of 1 ppb are mainly limited to the summer months when photochemistry is more active (Kleinman, 1991). Hydrogen peroxide is produced in abundance only when O_3 is produced under NO_x-limited conditions. When the photochemistry is NO_x-saturated, much less H_2O_2 is produced. In addition, increasing NO_x tends to slow the formation of H_2O_2 under NO_x-limited conditions. Differences between these two regimes are also related to the preferential formation of sulfate during summer and to the inhibition of sulfate and hydrogen peroxide during winter (Stein and Lamb, 2003). Measurements in the rural eastern United States (Jacob et al., 1995), at Nashville (Sillman et al., 1998), and at Los Angeles (Sakugawa and Kaplan, 1989) show large differences in H_2O_2 concentrations likely due to differences in NO_x availability at these locations.

AX2.2.3 Multiphase Chemistry Involving NO_x

Recent laboratory studies on sulfate and organic aerosols indicate that the reaction probability γ_{N2O5} is in the range of 0.01 to 0.05 (Kane et al., 2001; Hallquist et al., 2003; Thornton et al., 2003). Tie et al. (2003) found that a value of 0.04 in their global model gave the best simulation of observed NO_x concentrations over the Arctic in winter.

Using aircraft measurements over the northeastern United States., Brown et al. (2006b) found that the uptake coefficient for N_2O_5, γN_2O_5, on the surfaces of particles depends strongly on their sulfate content. They found that γN_2O_5 was highest (0.017) in regions where the aerosol sulfate concentration was highest and lower elsewhere (<0.0016). This result contrasts with that of Dentener and Crutzen (1993) who concluded that γN_2O_5 would be independent of aerosol composition, based on a value for γN_2O_5 of 0.1, implying that the heterogeneous hydrolysis of N_2O_5 would be saturated for typical ambient aerosol surface areas. The importance of this reaction to tropospheric chemistry depends on the value of γN_2O_5. If it is 0.01 or lower, there may be difficulty in explaining the loss of NO_y and the formation of aerosol nitrate, especially during winter. A decrease in N_2O_5 slows down the removal of NO_x by leaving more NO_2 available for reaction and thus increases O_3 production. Based on the consistency between measurements of NO_y partitioning and gas-phase models, Jacob (2000) considers it unlikely that HNO_3 is recycled to NO_x in the lower troposphere in significant concentrations. However, only one of the reviewed studies (Schultz et al., 2000) was conducted in the marine troposphere and none was conducted in the MBL. An investigation over the equatorial Pacific reported discrepancies between observations and theory (Singh et al., 1996) which might be explained by HNO_3 recycling. It is important to recognize that both Schultz et al. (2000) and Singh et al. (1996) involved aircraft sampling at altitude which, in the MBL, can significantly under-represent sea salt aerosols and thus most total NO_3 (defined to be $HNO_3 + NO_3^-$) and large fractions of NO_y in marine air (e.g., Huebert et al., 1996). Consequently, some caution is warranted when interpreting constituent ratios and NO_y budgets based on such data.

Recent work in the Arctic has quantified significant photochemical recycling of NO_3^- to NO_x and attendant perturbations of OH chemistry in snow (Honrath et al., 2000; Dibb et al., 2002; Domine and Shepson, 2002) which suggest the possibility that similar multiphase pathways could occur in aerosols. As mentioned above, NO_3^- is photolytically reduced to NO_2^- (Zafiriou and True, 1979) in acidic sea salt solutions (Anastasio et al., 1999). Further photolytic

reduction of NO_2^- to NO (Zafariou and True, 1979) could provide a possible mechanism for HNO_3 recycling. Early experiments reported production of NO_x during the irradiation of artificial seawater concentrates containing NO_3^- (Petriconi and Papee, 1972). Based on the above, HNO_3 recycling in sea salt aerosols is potentially important and warrants further investigation. Other possible recycling pathways involving highly acidic aerosol solutions and soot are reviewed by Jacob (2000).

Stemmler et al. (2006) studied the photosensitized reduction of NO_2 to HONO on humic acid films using radiation in the UV-A through the visible spectral regions. They also found evidence for reduction occurring in the dark, reactions which may occur involving surfaces containing partly oxidized aromatic structures. For example, Simpson et al. (2006) found that aromatic compounds constituted ~20% of organic films coating windows in downtown Toronto. They calculated production rates of HONO that are compatible with observations of high HONO levels in a variety of environments. The photolysis of HONO formed this way could account for up to 60% of the integrated source of OH radicals in the inner planetary boundary layer. A combination of high NO_2 levels and surfaces of soil and buildings and other man-made structures exposed to diesel exhaust would then be conducive to HONO formation and, hence, to high [OH] (Xu et al., 2006).

Ammann et al. (1998) reported the efficient conversion of NO_2 to HONO on fresh soot particles in the presence of water. They suggest that interaction between NO_2 and soot particles may account for high mixing ratios of HONO observed in urban environments. Conversion of NO_2 to HONO and subsequent photolysis and HONO to NO + OH would constitute a NO_x-catalyzed O_3 sink involving snow. High concentrations of HONO can lead to the rapid growth in OH concentrations shortly after sunrise, giving a "jump start" to photochemical smog formation. Prolonged exposure to ambient oxidizing agents appears to deactivate this process. Broske et al. (2003) studied the interaction of NO_2 on secondary organic aerosols and concluded that the uptake coefficients were too low for this reaction to be an important source of HONO in the troposphere.

Choi and Leu (1998) evaluated the interactions of HNO_3 on model black carbon soot (FW2), graphite, hexane, and kerosene soot. They found that HNO_3 decomposed to NO_2 and H_2O at higher HNO_3 surface coverages, i.e., $P(HNO_3) >= 10^{-4}$ Torr. None of the soot models used were reactive at low HNO_3 coverages, at $P(HNO_3) = 5 \times 10^{-7}$ Torr or at temperatures below

220 K. They conclude that it is unlikely that aircraft soot in the upper troposphere/lower stratosphere reduces HNO_3.

Heterogeneous production on soot at night is believed to be the mechanism by which HONO accumulates to provide an early morning source of HO_x in high NO_x environments (Harrison et al., 1996; Jacob, 2000). HONO has been frequently observed to accumulate to levels of several ppb overnight, and this has been attributed to soot chemistry (Harris et al., 1982; Calvert et al., 1994; Jacob, 2000).

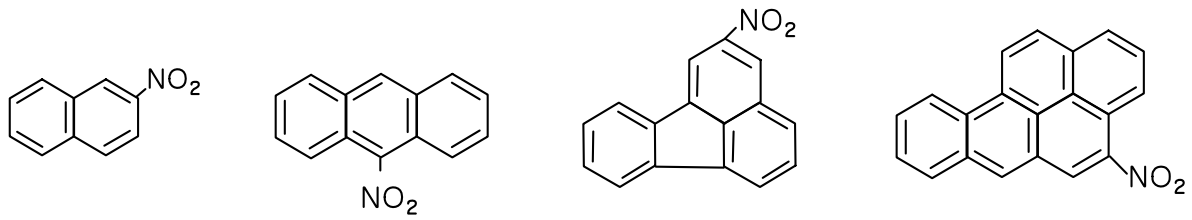
Longfellow et al. (1999) observed the formation of HONO when methane, propane, hexane, and kerosene soots were exposed to NO_2. They suggested that this reaction may account for some part of the unexplained high levels of HONO observed in urban areas. They comment that without details about the surface area, porosity, and amount of soot available for this reaction, reactive uptake values cannot be estimated reliably. They comment that soot and NO_2 are produced in close proximity during combustion, and that large quantities of HONO have been observed in aircraft plumes.

Saathoff et al. (2001) studied the heterogeneous loss of NO_2, HNO_3, NO_3/N_2O_5, HO_2/HO_2NO_2 on soot aerosol using a large aerosol chamber. Reaction periods of up to several days were monitored and results used to fit a detailed model. Saathoff et al. derived reaction probabilities at 294 K and 50% RH for NO_2, NO_3, HO_2, and HO_2NO_2 deposition to soot; HNO_3 reduction to NO_2; and N_2O_5 hydrolysis. When these probabilities were included in photochemical box model calculations of a 4-day smog event, the only noteworthy influence of soot was a 10% reduction in the second day O_3 maximum, for a soot loading of 20 $\mu g\ m^{-3}$, i.e., roughly a factor of 10 times observed black carbon loadings seen in United States urban areas, even during air pollution episodes.

Muñoz and Rossi (2002) conducted Knudsen cell studies of HNO_3 uptake on black and grey decane soot produced in lean and rich flames, respectively. They observed HONO as the main species released following HNO_3 uptake on grey soot, and NO and traces of NO_2 from black soot. They conclude that these reactions would only have relevance in special situations in urban settings where soot and HNO_3 are present in high concentrations simultaneously.

Formation of Nitro PAHs

Nitro-polycyclic aromatic hydrocarbons (nitro-PAHs) (see Figure AX2.2-2 for some example nitro-PAHs) are generated from incomplete combustion processes through electrophilic



2-nitronaphthalene 9-nitroanthracene 2-nitrofluoranthene 6-nitrobenzo(a)pyrene

Figure AX2.2-2. Structures of nitro-polycyclic aromatic hydrocarbons.

reactions of polycyclic aromatic hydrocarbons (PAHs) in the presence of NO_2 (International Agency for Research on Cancer [IARC], 1989; World Health Organization [WHO], 2003). Among combustion sources, diesel emissions have been identified as the major source of nitro-PAHs in ambient air (Bezabeh et al., 2003; Gibson, 1983; Schuetzle, 1983; Tokiwa and Ohnishi, 1986). Direct emissions of NPAHs in PM vary with type of fuel, vehicle maintenance, and ambient conditions (Zielinska et al., 2004).

In addition to being directly emitted, nitro-PAHs can also be formed from both gaseous and heterogeneous reactions of PAHs with gaseous nitrogenous pollutants in the atmosphere (Arey et al., 1986; Arey et al., 1989, Arey, 1998; Perrini, 2005; Pitts, 1987; Sasaki et al., 1997; Zielinska et al., 1989). Different isomers of nitro-PAHs are formed through different formation processes. For example, the most abundant nitro-PAH in diesel particles is 1-nitropyene (1NP), followed by 3-nitrofluoranthene (3NF) and 8-nitrofluoranthene (8NF) (Bezabeh et al., 2003; Gibson, 1983; Schuetzle, 1983; Tokiwa and Ohnishi, 1986). However, in ambient particulate organic matter (POM), 2-nitrofluoranthene (2NF) is the dominant compound, followed by 1NP and 2-nitropyrene (2NP) (Arey et al., 1989; Bamford et al., 2003; Reisen and Arey, 2005; Zielinska et al., 1989), although 2NF and 2NP are not directly emitted from primary combustion emissions. The reaction mechanisms for the different nitro-PAH formation processes have been well documented and are presented in Figure AX2.2-2.

The dominant process for the formation of nitro-PAHs in the atmosphere is gas-phase reaction of PAHs with OH radicals in the presence of NO_x (Arey et al., 1986, Arey, 1998; Atkinson and Arey, 1994; Ramdahl et al., 1986; Sasaki et al., 1997). Hydroxyl radicals can be generated photochemically or at night through ozone-alkene reactions, (Finlayson-Pitts and Pitts,

2000). The postulated reaction mechanism of OH with PAHs involves the addition of OH at the site of highest electron density of the aromatic ring, for example, the 1-position for pyrene (PY) and the 3-position for fluoranthene (FL). This reaction is followed by the addition of NO_2 to the OH-PAH adduct and elimination of water to form the nitroarenes (Figure AX2.2-3, Arey et al., 1986; Aktinson et al., 1990; Pitts, 1987). After formation, nitro-PAHs with low vapor pressures (such as 2NF and 2NP) immediately migrate to particles under ambient conditions (Fan et al., 1995; Feilberg et al., 1999). The second order rate-constants for the reactions of OH with most PAHs range from 10^{-10} to 10^{-12} $cm^3molecule^{-1}s^{-1}$ at 298 K with the yields ranging from ~0.06 to ~5% (Atkinson and Arey, 1994). 2NF and 2NP have been found as the most abundant nitro-PAHs formed via reactions of OH with gaseous PY and FL, respectively in ambient air.

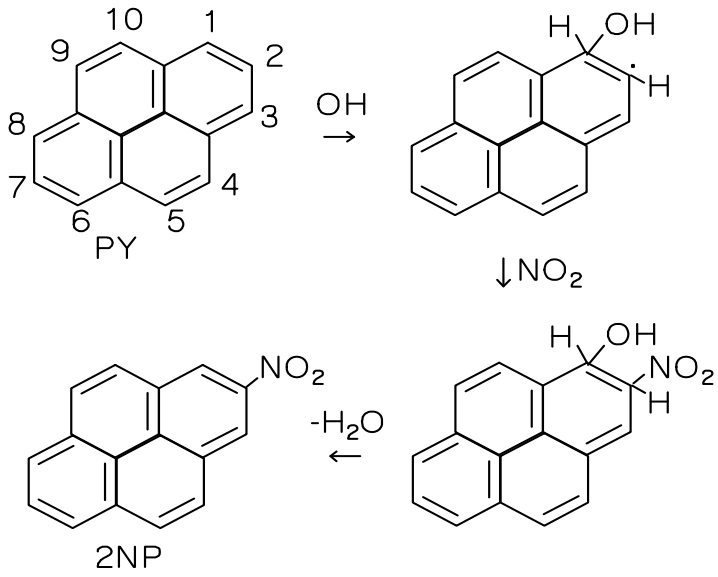


Figure AX2.2-3. Formation of 2-nitropyrene (2NP) from the reaction of OH with gaseous pyrene (PY).

The second important process for the formation of nitro-PAHs in the atmosphere is the nitration of PAHs by NO_3^- in the presence of NO_x at night (Atkinson et al., 1990; Atkinson and Arey, 1994; Sasaki et al., 1997). Nitrate radicals can be generated by reaction of ozone (O_3) with NO_2 in the atmosphere by Reaction AX2-5:

$$O_3 + NO_2 \rightarrow NO_3 + O_2 \quad \text{(AX2-5)}$$

Similar to the mechanism of OH reactions with PAHs, NO_3 initially adds to the PAH ring to form an NO_3-PAH adduct, followed by loss of HNO_3 to form nitro-PAHs (Atkinson et al., 1990; Atkinson and Arey, 1994; Sasaki et al., 1997). For example, in the mixture of naphthalene and N_2O_5-NO_3-NO_2, the major products formed through the NO_3 reaction are 1- and 2-nitro-naphthalene (1NN and 2NN) (Atkinson et al., 1990; Feilberg et al., 1999; Sasaki et al., 1997). 2NF and 4NP were reported as the primary products of the gas-phase reactions of FL and PY with NO_3 radical, respectively (Atkinson et al., 1990; Atkinson and Arey, 1994).

The reaction with NO_3 is of minor importance in the daytime because NO_3 radical is not stable in sunlight. In addition, given the rapid reactions of NO with NO_3 and with O_3 in the atmosphere (Finlayson-Pitts and Pitts 2000), concentrations of NO_3 at ground level are low during daytime. However, at night, concentrations of NO_3 radicals formed in polluted ambient air are expected to increase. According to Atkinson et al. (1991), the average NO_3 concentration is about 20 ppt in the lower troposphere at night and can be as high as 430 ppt. It is also worth noting that significant NO_3 radical concentrations are found at elevated altitudes where O_3 is high but NO is low (Reissell and Arey, 2001; Stutz et al., 2004). When NO_3 reaches high concentrations, the formation of nitro-PAHs by the reaction of gaseous PAHs with NO_3 may be of environmental significance. At $10^{-17} – 10^{-18}$ cm^3 $molecule^{-1}s^{-1}$, the rate constants of NO_3 with most PAHs are several orders of magnitude lower than those of OH with the same PAHs; however, the yields of nitro-PAHs from NO_3 reactions are generally much higher than those of OH reactions. For example, the yields of 1-NN and 2NF are 0.3% and 3%, respectively from OH reactions, but the yields are 17% and 24% for these two compounds generated from the NO_3 radical reactions (Atkinson and Arey, 1994). Therefore, formation of nitro-PAHs via reactions of NO_3 at nighttime under certain circumstances can be significant.

The third process of nitro-PAH formation in the atmosphere is nitration of PAHs by NO_2/N_2O_5 in the presence of trace amounts of HNO_3 (HNO_3) in both gas and particle phases. This mechanism could be operative throughout the day and night (Pitts et al., 1983, 1985a,b; Grosjean et al., 1983; Ramdahl et al., 1984; Kamens et al., 1990). The formation of nitro-fluoranthenes was observed when adsorbed FL was exposed to gaseous N_2O_5, and the distribution of product NF isomers was 3- > 8- > 7- > 1- NF (Pitts et al., 1985a,b). The proposed

mechanism for this reaction was an ionic electrophilic nitration by nitronium ion (NO_2^+). It was speculated that N_2O_5 became ionized prior to the reaction with FL (Zielinska et al., 1986). Only 1NP was observed for the reaction of PY with N_2O_5 on filters (Pitts et al., 1985b). Compared to the reactions of OH and NO_3, nitration of PAHs by NO_2/N_2O_5 is less important.

Measurements of nitro-PAHs in ambient air provide evidence for the proposed reaction mechanism, i.e. the reactions of OH and NO_3 radicals with PAHs are the major sources of nitro-PAHs (Bamford and Baker, 2003; Reisen and Arey, 2005; and references therein). 2NF is a ubiquitous component of ambient POM, much higher than 1NP, itself a marker of combustion sources. Nitro-PAH isomer ratios show strong seasonality. For instance, the mean ratios of 2NF/1NP were higher in summer than in winter (Bamford et al., 2003; Reisen and Arey, 2005), indicating that reactions of OH and NO_3 with FL are the major sources of nitro-PAHs in ambient air in summer. The ratio of 2NF/1NP was lower in winter than in summer because of lower OH concentrations and, therefore, less production of 2NF via atmospheric reactions. A ratio of 1NP/2NF greater than 1 was observed in locations with major contributions from vehicle emissions (Dimashki et al., 2000; Feilberg et al., 2001). In addition, the ratio of 2NF/2NP was also used to evaluate the contribution of OH and NO_3 initiated reactions to the ambient nitro-PAHs (Bamford et al., 2003; Reisen and Arey, 2005).

The concentrations for most nitro-PAHs found in ambient air are much lower than 1 pg/m^3, except NNs, 1NP, and 2NF, which can be present at several pg/m^3. These levels are much lower (~2 to ~1000 times lower) than their parent PAHs. However, nitro-PAHs are much more toxic than PAHs (Durant et al., 1996; Grosovsky et al., 1999; Salmeen et al., 1982; Tokiwa et al., 1998; Tokiwa and Ohnishi, 1986). Moreover, most nitro-PAHs are present in particles with a mass median diameter <0.1 μm.

Esteve et al. (2006) examined the reaction of gas-phase NO_2 and OH radicals with various PAHs adsorbed onto model diesel particulate matter (SRM 1650a, NIST). Using pseudo second order rate coefficients, they derived lifetimes for conversion of the particle-bound PAHs to nitro-PAHs of a few days (for typical urban NO_2 levels of 20 ppb). They also found that the rates of reaction of OH with the PAHs were about four orders of magnitude larger than for the reactions involving NO_2. However, since the concentrations of NO_2 used above are more than four orders of magnitude larger than those for OH (10^6-$10^7/cm^3$), they concluded that the pathway involving NO_2 is expected to be favored over that involving OH radicals. Consistent

with the importance of the gas-phase formation of NPAHS, both the mutagenic potency of PM and the content of NPAHs in PM vary by particle size, and are higher in the submicron size range (Xu and Lee, 2000; Kawanaka et al., 2004).

The major loss process of nitro-PAHs is photodecomposition (Fan et al., 1996; Feilberg et al., 1999; Feilberg and Nielsen, 2001), with lifetimes on the order of hours. However, lacking direct UV light sources indoors, nitro-PAHs are expected have a longer lifetimes (days) indoors than outdoors; and may therefore pose increased health risks. Many nitro-PAHs are semi- or nonvolatile organic compounds. As stated above, indoor environments have much greater surface areas than outdoors. Thus, it is expected that gas/particle distribution of nitro-PAHs indoors will be different from those in ambient air. A significant portion of nitro-PAHs will probably be adsorbed by indoor surfaces, such as carpets, leading to different potential exposure pathways to nitro-PAHs in indoor environments. The special characteristics of indoor environments, which can affect the indoor chemistry and potential exposure pathways significantly, should be taken into consideration when conducting exposure studies of nitro-PAHs.

Reaction with OH and NO_3 radicals is a major mechanism for removing gas-phase PAHs, with OH radical initiated reactions predominating depending on season (Vione et al., 2004; Bamford et al., 2003). Particle-bound PAH reactions occur but tend to be slower. Nitronaphthalenes tend to remain in the vapor phase, but because phase partitioning depends on ambient temperature, in very cold regions these species can condense (Castells et al., 2003) while the higher molecular weight PAHs such as the nitroanthracenes, nitrophenantrenes and nitrofluoranthenes condense in and on PM (Ciganek et al., 2004; Cecinato, 2003).

Multiphase Chemical Processes Involving Nitrogen Oxides and Halogens

Four decades of observational data on O_3 in the troposphere have revealed numerous anomalies not easily explained by gas-phase HO_x-NO_x photochemistry. The best-known example is the dramatic depletion of ground-level O_3 during polar sunrise due to multiphase catalytic cycles involving inorganic Br and Cl radicals (Barrie et al., 1988; Martinez et al., 1999; Foster et al., 2001). Other examples of anomalies in tropospheric O_3 at lower latitudes include low levels of O_3 (<10 ppbv) in the marine boundary layer (MBL) and overlying free troposphere (FT) at times over large portions of the tropical Pacific (Kley et al., 1996), as well as post-sunrise O_3 depletions over the western subtropical Pacific Ocean (Nagao et al., 1999), the temperate

Southern Ocean (Galbally et al., 2000), and the tropical Indian Ocean (Dickerson et al., 1999). The observed O_3 depletions in near-surface marine air are generally consistent with the model-predicted volatilization of Br_2, BrCl, and Cl_2 from sea salt aerosols through autocatalytic halogen "activation" mechanisms (e.g., Vogt et al., 1996; von Glasow et al., 2002a) involving these aqueous phase reactions.

$$HOBr + Br^- + H^+ \rightarrow Br_2 + H_2O \quad \text{(AX2-23)}$$

$$HOCL + Br^- + H^+ \rightarrow BrC1 + H_2O \quad \text{(AX2-24)}$$

$$HOC1 + C1^- + H^+ \rightarrow C1_2 + H_2O \quad \text{(AX2-25)}$$

In polluted marine regions at night, the heterogeneous reaction

$$N_2O_5 + C1^- \rightarrow C1NO_2 + NO_3^- \quad \text{(AX2-26)}$$

may also be important (Finlayson-Pitts et al., 1989; Behnke et al., 1997; Erickson et al., 1999). Diatomic bromine, BrCl, Cl_2, and $ClNO_2$ volatilize and photolyze in sunlight to produce atomic Br and Cl. The acidification of sea salt aerosol via incorporation of HNO_3 (and other acids) leads to the volatilization of HCl (Erickson et al., 1999), e.g.

$$HNO_3 + C1^- \rightarrow HC1 + NO_3^- \quad \text{(AX2-27)}$$

and the corresponding shift in phase partitioning can accelerate the deposition flux to the surface of total NO_3 (Russell et al., 2003; Fischer et al., 2006). However, Pryor and Sorensen (2000) have shown that the dominant form of nitrate deposition is a complex function of wind speed. In polluted coastal regions where HCl from Reaction 35 often exceeds 1 ppbv, significant additional atomic Cl^- is produced via:

$$HC1 + OH \rightarrow C1 + H_2O \quad \text{(AX2-28)}$$

(Singh and Kasting, 1988; Keene et al., 2007). Following production, Br and Cl atoms catalytically destroy O_3 via:

$$X + O_3 \rightarrow XO + O_2 \quad \text{(AX2-29)}$$

$$XO + HO_2 \rightarrow HOX + O_2 \quad \text{(AX2-30)}$$

$$HOX + h\nu \rightarrow OH + X \quad \text{(AX2-31)}$$

where (X = Br and Cl).

Formation of Br and Cl nitrates via

$$XO + NO_2 \rightarrow XNO_3 \quad \text{(AX2-32)}$$

and the subsequent reaction of XNO_3 with sea salt and sulfate aerosols via

$$XNO_3 + H_2O \rightarrow HOX + H^+ + NO_3^- \quad \text{(AX2-33)}$$

and:

$$XNO_3 + Y^- \rightarrow XY + NO_3^- \quad \text{(AX2-34)}$$

(where Y = Cl, Br, or I) accelerates the conversion of NO_x to particulate NO_3^- and thereby contributes indirectly to net O_3 destruction (Sander et al., 1999; Vogt et al., 1999, Pszenny et al., 2004). Most XNO_3 reacts via reaction 34 on sea salt whereas reaction 33 is more important on sulfate aerosols. Partitioning of HCl on sulfate aerosols following Henry's Law provides Cl^- for reaction 34 to form BrCl. Product NO_3^- from both reactions AX2-33 and AX2-34 partitions with the gas-phase HNO_3 following Henry's Law. Because most aerosol size fractions in the MBL are near equilibrium with respect to HNO_3 (Erickson et al., 1999; Keene et al., 2004), both sulfate and sea salt aerosol can sustain the catalytic removal of NO_x and re-activation of Cl and Br with no detectable change in composition. The photolytic reduction of NO_3^- in sea salt aerosol solutions recycles NO_x to the gas phase (Pszenny et al., 2004). Halogen chemistry also impacts O_3 indirectly by altering OH/HO_2 ratios ($XO + HO_2 \rightarrow HOX + O_2 \rightarrow OH + X$) (e.g., Stutz et al., 1999; Bloss et al., 2005).

In addition to O_3 destruction via reaction AX2-37, atomic Cl oxidizes hydrocarbons (HCs) primarily via hydrogen abstraction to form HCl vapor and organz products (Jobson et al., 1994; Pszenny et al., 2006). The enhanced supply of odd-H radicals from HC oxidation leads to net O_3 production in the presence of sufficient NO_x (Pszenny et al., 1993). Available evidence

suggests that Cl^- radical chemistry may be a significant net source for O_3 in polluted coastal/urban air (e.g., Tanaka et al., 2003; Finley and Saltzman, 2006).

An analogous autocatalyic O_3 destruction cycle involving multiphase iodine chemistry also operates in the marine atmosphere (Alicke et al., 1999, Vogt et al., 1999; McFiggans et al., 2000; Ashworth et al., 2002). In this case, the primary source of I is believed to be either photolysis of CH_2I_2, other I-containing gases (Carpenter et al., 1999; Carpenter, 2003), and/or perhaps I_2 (McFiggans et al., 2004; Saiz-Lopez and Plane, 2004; McFiggans, 2005) emitted by micro-and macro flora. Sea salt and sulfate aerosols provide substrates for multiphase reactions that sustain the catalytic I-IO cycle. The IO radical has been measured by long-path (LP) and/or multi axis (MAX) differential optical absorption spectroscopy (DOAS) at Mace Head, Ireland; Tenerife, Canary Islands; Cape Grim, Tasmania; and coastal New England, USA; having average daytime levels of about 1 ppt with maxima up to 7 ppt (e.g., Allan et al., 2000; Pikelnaya et al., 2006). Modeling suggests that up to 13% per day of O_3 in marine air may be destroyed via multiphase iodine chemistry (McFiggans et al., 2000). The reaction of IO with NO_2 followed by uptake of INO_3 into aerosols (analogous to Reactions AX2-9 through AX2-11) accelerates the conversion of NO_x to particulate NO_3^- and thereby contributes to net O_3 destruction. The reaction $IO + NO \rightarrow I + NO_2$ also influences NO_x cycling.

Most of the above studies have focused on halogen-radical chemistry and related influences on NO_x cycling in coastal and urban air. However, available evidence suggests that similar chemical transformations proceed in other halogen-rich tropospheric regimes. For example, Cl, Br, and/or I oxides have been measured at significant concentrations in near-surface air over the Dead Sea, Israel, the Great Salt Lake, Utah (e.g., Hebestreit et al., 1999; Stutz et al., 1999, 2002; Zingler and Platt, 2005), and the Salar de Uyuni salt pan in the Andes mountains (U. Platt, unpublished data, 2006); high column densities of halogenated compounds have also been observed from satellites over the northern Caspian Sea (Wagner et al., 2001; Hollwedel et al., 2004). The primary source of reactive halogens in these regions is thought to be from activation along the lives of that in reactions in AX2-23 through AX2-25 involving concentrated salt deposits on surface evaporite pans. High concentrations of BrO have also been measured in volcanic plumes (Bobrowski et al., 2003, Gerlach, 2004). Although virtually unexplored, the substantial emissions of inorganic halogens during biomass burning (Lobert et al., 1999; Keene et al., 2006) and in association with crustal dust (Keene et al., 1999; Sander et al., 2003) may

also support active halogen-radical chemistry and related transformations involving NO_x downwind of sources. Finally, observations from satellites, balloons, and aircraft indicate that BrO is present in the free troposphere at levels sufficient to significantly influence photochemistry (e.g., von Glasow et al., 2004).

AX2.3 CHEMISTRY OF SULFUR OXIDES IN THE TROPOSPHERE

The four known monomeric sulfur oxides are sulfur monoxide (SO), sulfur dioxide (SO_2), sulfur trioxide (SO_3), and disulfur monoxide (S_2O). SO can be formed by photolysis of SO_2 at wavelengths less than 220 nm, and so could only be found in the middle and upper stratosphere (Pinto et al., 1989). SO_3 can be emitted from the stacks of power plants and factories however, it reacts extremely rapidly with 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 atmospheric chemistry and human exposures.

Sulfur dioxide can be oxidized either in the gas phase, or, because it is soluble, in the aqueous phase in cloud drops. The gas-phase oxidation of SO_2 proceeds through the reaction

$$SO_2 + OH + M \rightarrow HSO_3 + M \quad \text{(AX2-35)}$$

followed by

$$HSO_3 + O_2 \rightarrow SO_3 + HO_2 \quad \text{(AX2-36)}$$

$$SO_3 + H_2O \rightarrow H_2SO_4 \quad \text{(AX2-37)}$$

Since H_2SO_4 is extremely soluble, it will be removed rapidly by transfer to the aqueous phase of aerosol particles and cloud drops. Rate coefficients for reaction of SO_2 with HO_2 or NO_3 are too low to be significant (JPL, 2003).

SO_2 is chiefly but not exclusively primary in origin; it is also produced by the photochemical oxidation of reduced sulfur compounds such as dimethyl sulfide (CH_3-S-CH_3), hydrogen sulfide (H_2S), carbon disulfide (CS_2), carbonyl sulfide (OCS), methyl mercaptan (CH_3-S-H), and dimethyl disulfide (CH_3-S-S-CH_3) which are all mainly biogenic in origin. Their sources are discussed in Section AX2.5. Table AX2.3-1 lists the atmospheric lifetimes of reduced sulfur species with respect to reaction with various oxidants. Except for OCS, which is

lost mainly by photolysis (τ~6 months), all of these species are lost mainly by reaction with OH and NO_3 radicals. Because OCS is relatively long-lived in the troposphere, it can be transported upwards into the stratosphere. Crutzen (1976) proposed that its oxidation serves as the major source of sulfate in the stratospheric aerosol layer sometimes referred to the "Junge layer," (Junge et al., 1961) during periods when volcanic plumes do not reach the stratosphere. However, the flux of OCS into the stratosphere is probably not sufficient to maintain this stratospheric aerosol layer. Myhre et al. (2004) propose instead that SO_2 transported upwards from the troposphere is the most likely source, have become the upward flux of OCS is too small to sustain observed sulfate loadings in the Junge layer. In addition, insitu measurements of the isotopic composition of sulfur do not match those of OCS (Leung et al., 2002). Reaction with NO_3 radicals at night most likely represents the major loss process for dimethyl sulfide and methyl mercaptan. The mechanisms for the oxidation of DMS are still 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 OH addition branch increases in importance as temperatures decrease and becoming the major pathway below temperatures of 285 K (Ravishankara, 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., 1991). Following H atom abstraction from DMS, the main reaction products include MSA and SO_2. The ratio of MSA to SO_2 is strongly temperature dependent, varying from about 0.1 in tropical waters to about 0.4 in Antarctic waters (Seinfeld and Pandis, 1998). Excess sulfate (over that expected from the sulfate in seawater) in marine aerosol is related mainly to the production of SO_2 from the oxidation of DMS. Transformations among atmospheric sulfur compounds are summarized in Figure AX2.3-1.

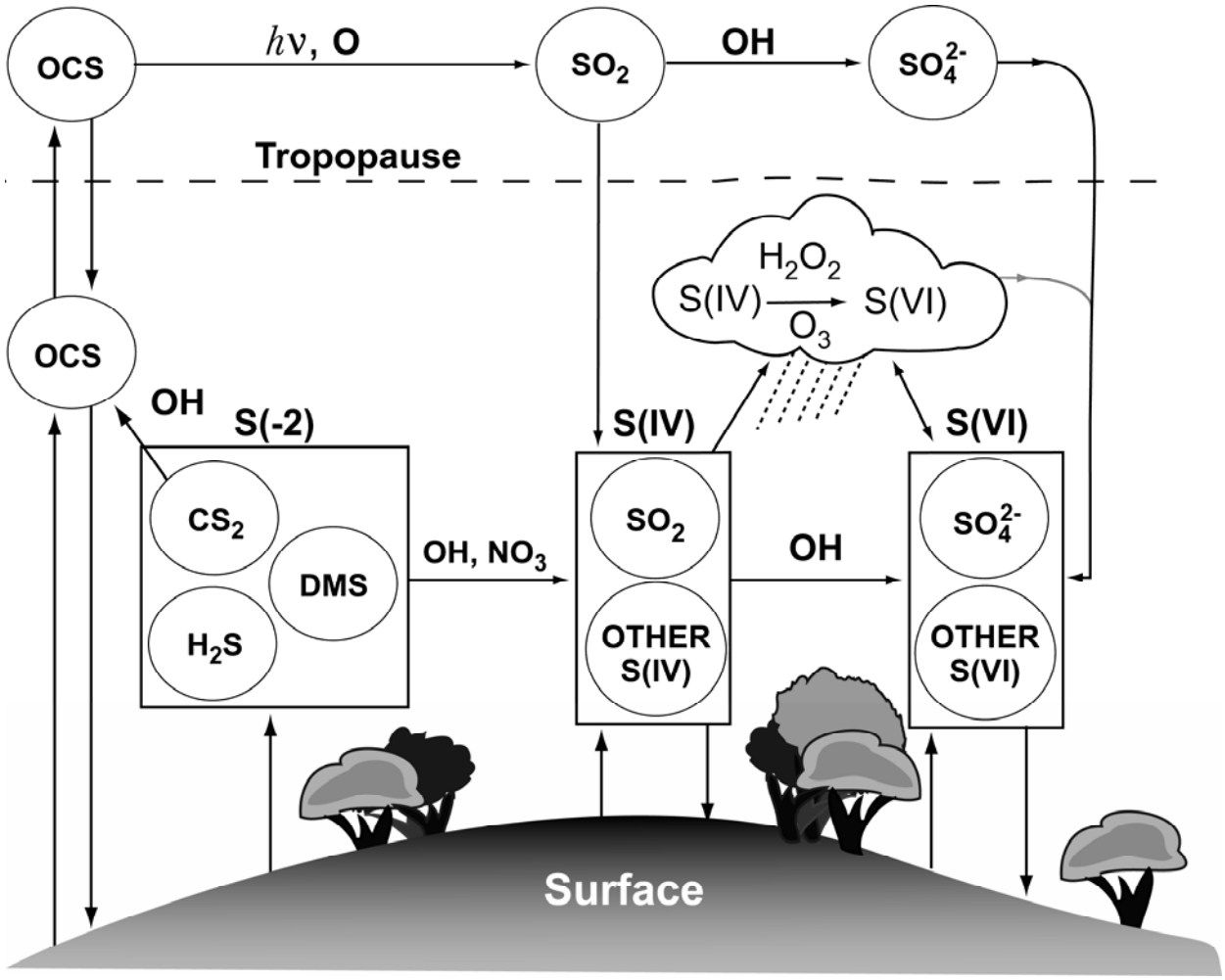


Figure AX2.3-1. Transformations of sulfur compounds in the atmosphere.

Source: Adapted from Berresheim et al. (1995).

Multiphase Chemical Processes Involving Sulfur Oxides and Halogens

Chemical transformations involving inorganic halogenated compounds effect changes in the multiphase cycling of sulfur oxides in ways analogous to their effects on NO_x. Oxidation of dimethylsulfide $(CH_3)_2S$ by BrO produces dimethylsulfoxide $(CH_3)_2SO$ (Barnes et al., 1991; Toumi, 1994), and oxidation by atomic chloride leads to formation of SO_2 (Keene et al., 1996). $(CH_3)_2SO$ and SO_2 are precursors for methanesulfonic acid (CH_3SO_3H) and H_2SO_4. In the MBL, virtually all H_2SO_4 and CH_3SO_3H vapor condenses onto existing aerosols or cloud droplet, which subsequently evaporate, thereby contributing to aerosol growth and acidification. Unlike CH_3SO_3H, H_2SO_4 also has the potential to produce new particles (Korhonen et al., 1999; Kumala

et al., 2000), which in marine regions is thought to occur primarily in the free troposphere. Saiz-Lopez et al. (2004) estimated that observed levels of BrO at Mace Head would oxidize $(CH_3)_2S$ about six times faster than OH and thereby substantially increase production rates of H_2SO_4 and other condensible S species in the MBL. Sulfur dioxide is also scavenged by deliquesced aerosols and oxidized to H_2SO_4 in the aqueous phase by several strongly pH-dependent pathways (Chameides and Stelson, 1992; Vogt et al., 1996; Keene et al., 1998). Model calculations indicate that oxidation of S(IV) by O_3 dominates in fresh, alkaline sea salt aerosols, whereas oxidation by hypohalous acids (primarily HOCl) dominates in moderately acidic solutions. Additional particulate non-sea salt (nss) SO_4^{2-} is generated by SO_2 oxidation in cloud droplets (Clegg and Toumi, 1998). Ion-balance calculations indicate that most nss SO_4^{2-} in short-lived (two to 48 hours) sea salt size fractions accumulates in acidic aerosol solutions and/or in acidic aerosols processed through clouds (e.g., Keene et al., 2004). The production, cycling, and associated radiative effects of S-containing aerosols in marine and coastal air are regulated in part by chemical transformations involving inorganic halogens (von Glasow et al., 2002b). These transformations include: dry-deposition fluxes of nss SO_4^{2-} in marine air dominated, naturally, by the sea salt size fractions (Huebert et al., 1996; Turekian et al., 2001); HCl phase partitioning that regulates sea salt pH and associated pH-dependent pathways for S(IV) oxidation (Keene et al., 2002; Pszenny et al., 2004); and potentially important oxidative reactions with reactive halogens for $(CH_3)_2S$ and S(IV). However, both the absolute magnitudes and relative importance of these processes in MBL S cycling are poorly understood.

Iodine chemistry has been linked to ultrafine particle bursts at Mace Head (O'Dowd et al., 1999, 2002). Observed bursts coincide with the elevated concentrations of IO and are characterized by particle concentrations increasing from background levels to up to 300,000 cm^{-3} on a time scale of seconds to minutes. This newly identified source of marine aerosol would provide additional aerosol surface area for condensation of sulfur oxides and thereby presumably diminish the potential for nucleation pathways involving H_2SO_4. However, a subsequent investigation in polluted air along the New England, USA coast found no correlation between periods of nanoparticle growth and corresponding concentrations of I oxides (Russell et al., 2006). The potential importance of I chemistry in aerosol nucleation and its associated influence on sulfur cycling remain highly uncertain.

AX2.4 MECHANISMS FOR THE AQUEOUS PHASE FORMATION OF SULFATE AND NITRATE

The major species containing sulfur in clouds are HSO_3^- and SO_3^{2-}, which are derived from the dissolution of SO_2 in water and are referred to as S(IV); and HSO_4^- and SO_4^{2-}, which are referred to as S(VI). The major species capable of oxidizing S(IV) to S(VI) in cloud water are O_3, peroxides (either H_2O_2 or organic peroxides), OH radicals, and ions of transition metals such as Fe and Cu that can catalyze the oxidation of S(IV) to S(VI) by O_2.

The basic mechanism of the aqueous phase oxidation of SO_2 has long been studied and can be found in numerous texts on atmospheric chemistry, e.g., Seinfeld and Pandis (1998), Jacob (2000), and Jacobson (2002). The steps involved in the aqueous phase oxidation of SO_2 can be summarized as follows (Jacobson, 2002):

Dissolution of SO_2

$$SO_2(g) \Leftrightarrow SO_2(aq) \qquad \text{(AX2-38)}$$

The formation and dissociation of H_2SO_3

$$SO_2(aq) + H_2O(aq) \Leftrightarrow H_2SO_3 \Leftrightarrow H^+ + HSO_3^- \Leftrightarrow 2H^+ + SO_3^{2-} \qquad \text{(AX2-39)}$$

In the pH range commonly found in rainwater (2 to 6), the most important reaction converting S(IV) to S(VI) is

$$HSO_3^- + H_2O_2 + H^+ \Leftrightarrow SO_4^{2-} + H_2O + 2H^+ \qquad \text{(AX2-40)}$$

as SO_3^{2-} is much less abundant than HSO_3^-.

Major pathways for the aqueous phase oxidation of S(IV) to S(VI) as a function of pH are shown in Figure AX2.4-1. For pH up to about 5.3, H_2O_2 is seen to be the dominant oxidant; above 5.3, O_3, followed by Fe(III) becomes dominant. Higher pHs are expected to be found mainly in marine aerosols. However, in marine aerosols, the chloride-catalyzed oxidation of S(IV) may be more important (Zhang and Millero, 1991; Hoppel and Caffrey, 2005). Because NH_4^+ is so effective in controlling acidity, it affects the rate of oxidation of S(IV) to S(VI) and the rate of dissolution of SO_2 in particles and cloud drops.

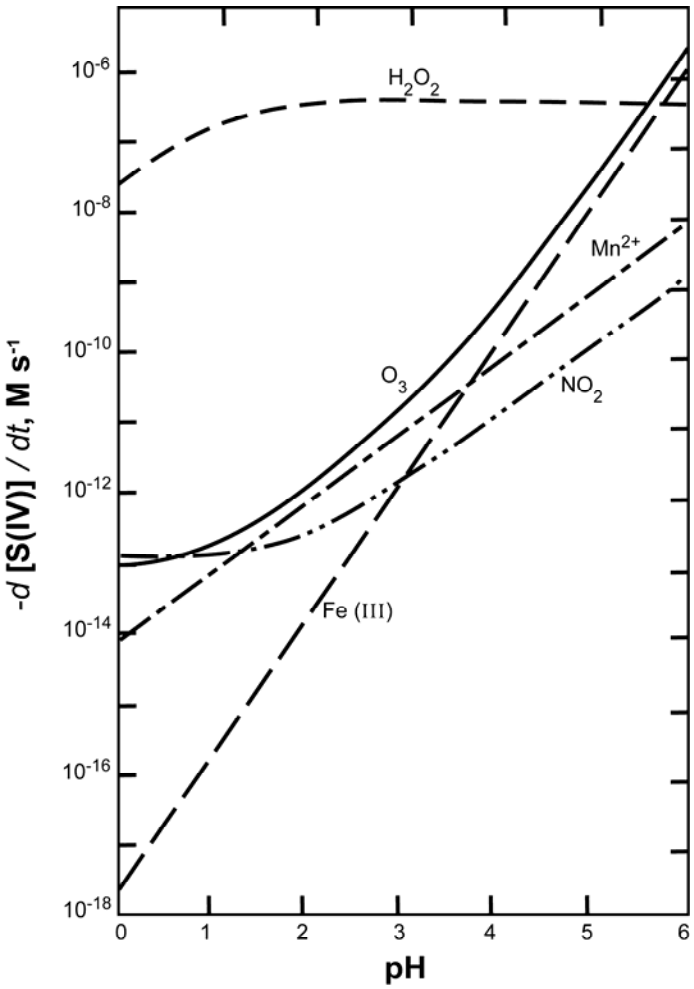


Figure AX2.4-1. Comparison of aqueous-phase oxidation paths. The rate of conversion of S(IV) to S(VI) is shown as a function of pH. Conditions assumed are: $[SO_2(g)]$ = 5 ppb; $[NO_2(g)]$ = 1 ppb; $[H_2O_2(g)]$ = 1 ppb; $[O_3(g)]$ = 50 ppb; [Fe(III)(aq)] = 0.3 µM; [Mn(II)(aq)] = 0.3 µM.

Source: Seinfeld and Pandis (1998).

Nitrogen dioxide is also taken up in cloud drops and can be oxidized to NO_3^-, although it is much less soluble than SO_2 and this pathway is of minor importance. Instead, the uptake of more highly soluble nitrogen-containing acids initiates aqueous-phase chemistry of NO_3 formation.

Warneck (1999) constructed a box model describing the chemistry of the oxidation of SO_2 and NO_2 including the interactions of N and S species and minor processes in sunlit cumulus clouds. The relative contributions of different reactions to the oxidation of S(IV) species to

S(VI) and NO_2 to NO_3^- 10 minutes after cloud formation are given in Tables AX2.4-1a and AX2.4-1b. The two columns show the relative contributions with and without transition metal ions. As can be seen from Table AX2.4-1a, SO_2 within a cloud (gas + cloud drops) is oxidized mainly by H_2O_2 in the aqueous phase, while and the gas-phase oxidation by OH radicals is small by comparison. A much smaller contribution in the aqueous phase is made by methyl hydroperoxide (CH_3OOH) because it is formed mainly in the gas phase and its Henry's Law constant is several orders of magnitude smaller that of H_2O_2. After H_2O_2, HNO_4 is the major contributor to S(IV) oxidation. The contribution from the gas phase oxidation of SO_2 to be small by comparison to the aqueous -phase reactions given above.

In contrast to the oxidation of SO_2, Table AX2.4-1b shows that the oxidation of NO_2 occurs mainly in the gas phase within clouds, implying that the gas phase oxidation of NO_2 by OH radicals predominates. Clouds occupy about 15%, on average, of the volume of the troposphere.

The values shown in Tables AX2.4-1a and AX2.4-1b indicate that only about 20% of SO_2 is oxidized in the gas phase, but about 90% of NO_2 is oxidized in the gas phase. Thus, SO_2 is oxidized mainly by aqueous-phase reactions, but NO_2 is oxidized mainly by gas phase reactions.

Multiphase Chemical Processes Involving Sulfur Oxides and Ammonia

The phase partitioning of NH_3 with deliquesced aerosol solutions is controlled primarily by the thermodynamic properties of the system expressed as follows:

$$NH_{3g} \overset{K_H}{\leftrightarrow} [NH_{3aq}] \overset{K_b}{\leftrightarrow} [NH_4^+] + K_W/[H^+] \qquad \text{(AX2-41)}$$

where K_H and K_b are the temperature-dependent Henry's Law and dissociation constants (62 M atm^{-1}) (1.8×10^{-5} M), respectively, for NH_3, and K_w is the ion product of water (1.0×10^{-14} M) (Chameides, 1984). It is evident that for a given amount of NH_x (NH_3 + particulate NH_4^+) in the system, increasing aqueous concentrations of particulate H^+ will shift the partitioning of NH_3 towards the condensed phase. Consequently, under the more polluted conditions characterized by higher concentrations of acidic sulfate aerosol, ratios of gaseous NH_3 to particulate NH_4^+ decrease (Smith et al., 2007). It also follows that in marine air, where

aerosol acidity varies substantially as a function of particle size, NH_3 partitions preferentially to the more acidic sub-µm size fractions (e.g., Keene et al., 2004; Smith et al., 2007).

Because the dry-deposition velocity of gaseous NH_3 to the surface is substantially greater than that for the sub-µm, sulfate aerosol size factions with which most particulate NH_4^+ is associated, dry-deposition fluxes of total NH_3 are dominated by the gas phase fraction (Russell et al., 2003; Smith et al., 2007). Consequently, partitioning with highly acidic sulfate aerosols effectively increases the atmospheric lifetime of total NH_3 against dry deposition. This shift has important consequences for NH_3 cycling and potential ecological effects. In coastal New England during summer, air transported from rural eastern Canada contains relatively low concentrations of particulate non-sea salt (nss) SO_4^{2-} and total NH_3 (Smith et al., 2007). Under these conditions, the roughly equal partitioning of total NH_3 between the gas and particulate phases sustains substantial dry-deposition fluxes of total NH_3 to the coastal ocean (median of 10.7 µmol m^{-2} day^{-1}). In contrast, heavily polluted air transported from the industrialized midwestern United States contains concentrations of nss SO_4^{2-} and total NH_3 that are, about a factory of 3 greater, based on median values. Under these conditions, most total NH_3 (>85%) partitions to the highly acidic sulfate aerosol size fractions and, consequently, the median dry-deposition flux of total NH_3 is 30% lower than that under the cleaner northerly flow regime. The relatively longer atmospheric lifetime of total NH_3 against dry deposition under more polluted conditions implies that, on average, total NH_3 would accumulate to higher atmospheric concentrations under these conditions and also be subject to atmospheric transport over longer distances. Consequently, the importance NH_x of removal via wet deposition would also increase. Because of the inherently sporadic character of precipitation, we might expect by greater heterogeneity in NH_3 deposition fields and any potential responses by sensitive ecosystems downwind of major S-emission regions.

AX2.5 TRANSPORT OF NITROGEN AND SULFUR OXIDES IN THE ATMOSPHERE

Major episodes of high O_3 concentrations in the eastern United Sates and in Europe are associated with slow moving high-pressure systems. High-pressure systems during the warmer seasons are associated with subsidence, resulting in warm, generally cloudless conditions with light winds. The subsidence results in stable conditions near the surface, which inhibit or reduce

the vertical mixing of O_3 precursors (NO_x, VOCs, and CO). Photochemical activity is enhanced because of higher temperatures and the availability of sunlight. However, it is becoming increasingly apparent that transport of O_3 and NO_x and VOC from distant sources can provide significant contributions to local [O_3] even in areas where there is substantial photochemical production. There are a number of transport phenomena occurring either in the upper boundary layer or in the free troposphere which can contribute to high O_3 values at the surface. These phenomena include stratospheric-tropospheric exchange (STE), deep and shallow convection, low-level jets, and the so-called "conveyor belts" that serve to characterize flows around frontal systems.

Convective Transport

Crutzen and Gidel (1983), Gidel (1983), and Chatfield and Crutzen (1984) hypothesized that convective clouds played an important role in rapid atmospheric vertical transport of trace species and first tested simple parameterizations of convective transport in atmospheric chemical models. At nearly the same time, evidence was shown of venting the boundary layer by shallow, fair weather cumulus clouds (e.g., Greenhut et al., 1984; Greenhut, 1986). Field experiments were conducted in 1985 which resulted in verification of the hypothesis that deep convective clouds are instrumental in atmospheric transport of trace constituents (Dickerson et al., 1987). Once pollutants are lofted to the middle and upper troposphere, they typically have a much longer chemical lifetime and with the generally stronger winds at these altitudes, they can be transported large distances from their source regions. Transport of NO_x from the boundary layer to the upper troposphere by convection tends to dilute the higher in the boundary layer concentrations and extend the NO_x lifetime from less than 24 hours to several days. Photochemical reactions occur during this long-range transport. Pickering et al. (1990) demonstrated that venting of boundary layer NO_x by convective clouds (both shallow and deep) causes enhanced O_3 production in the free troposphere. The dilution of NO_x at the surface can often increase O_3 production efficiency. Therefore, convection aids in the transformation of local pollution into a contribution to global atmospheric pollution. Downdrafts within thunderstorms tend to bring air with less NO_x from the middle troposphere into the boundary layer. Lightning produces NO which is directly injected chiefly into the middle and upper troposphere. The total global production of NO by lightning remains uncertain, but is on the order of 10% of the total.

Observations of the Effects of Convective Transport

The first unequivocal observations of deep convective transport of boundary layer pollutants to the upper troposphere were documented by Dickerson et al. (1987). Instrumentation aboard three research aircraft measured CO, O_3, NO, NO_x, NO_y, and hydrocarbons in the vicinity of an active mesoscale convective system near the Oklahoma/Arkansas border during the 1985 PRE-STORM experiment. Anvil penetrations about two hours after maturity found greatly enhanced mixing ratios inside the cloud of all of the aforementioned species compared with outside it. Nitric oxide mixing ratios in the anvil averaged 3 to 4 ppbv, with individual 3-min observations reaching 6 ppbv; boundary layer NO_x was typically 1.5 ppbv or less outside the cloud. Therefore, the anvil observations represent a mixture of boundary layer NO_x and NO_x contributed by lightning. Luke et al. (1992) summarized the air chemistry data from all 18 flights during PRE-STORM by categorizing each case according to synoptic flow patterns. Storms in the maritime tropical flow regime transported large amounts of CO, O_3, and NO_y into the upper troposphere with the midtroposphere remaining relatively clean. During frontal passages a combination of stratiform and convective clouds mixed pollutants more uniformly into the middle and upper levels.

Prather and Jacob (1997) and Jaegle et al. (1997) noted that precursors of HO_x are also transported to the upper troposphere by deep convection, in addition to primary pollutants (e.g., NO_x, CO, VOCs). The HO_x precursors of most importance are water vapor, HCHO, H_2O_2, CH_3OOH, and acetone. The hydroperoxyl radical is critical for oxidizing NO to NO_2 in the O_3 production process as described above.

Over remote marine areas, the effects of deep convection on trace gas distributions differ from those over moderately polluted continental regions. Chemical measurements taken by the NASA ER-2 aircraft during the Stratosphere-Troposphere Exchange Project (STEP) off the northern coast of Australia show the influence of very deep convective events. Between 14.5 and 16.5 km on the February 2-3, 1987 flight, chemical profiles that included pronounced maxima in CO, water vapor, and CCN, and minima of NO_y, and O_3 (Pickering et al., 1993). Trajectory analysis showed that these air parcels likely were transported from convective cells 800-900 km upstream. Very low marine boundary layer mixing ratios of NO_y and O_3 in this remote region were apparently transported upward in the convection. A similar result was noted in CEPEX (Central Equatorial Pacific Experiment; Kley et al., 1996) and in INDOEX (Indian

Ocean Experiment) (deLaat et al., 1999) where a series of ozonesonde ascents showed very low upper tropospheric O_3 following deep convection. It is likely that similar transport of low-ozone tropical marine boundary layer air to the upper troposphere occurs in thunderstorms along the east coast of Florida. Deep convection occurs frequently over the tropical Pacific. Low-ozone and low-NO_x convective outflow likely will descend in the subsidence region of the subtropical eastern Pacific, leading to some of the cleanest air that arrives at the west coast of the United States.

The discussion above relates to the effects of specific convective events. Observations have also been conducted by NASA aircraft in survey mode, in which the regional effects of many convective events can be measured. The SONEX (Subsonic Assessment Ozone and Nitrogen Oxides Experiment) field program in 1997 conducted primarily upper tropospheric measurements over the North Atlantic. The regional effects of convection over North America and the Western Atlantic on upper tropospheric NO_x were pronounced (Crawford et al., 2000; Allen et al., 2000). A discussion of the results of model calculations of convection and its effects can be found in Section AX2.7.

Effects on Photolysis Rates and Wet Scavenging

Thunderstorm clouds are optically very thick, and, therefore, have major effects on radiative fluxes and photolysis rates. Madronich (1987) provided modeling estimates of the effects of clouds of various optical depths on photolysis rates. In the upper portion of a thunderstorm anvil, photolysis is likely to be enhanced by a factor of 2 or more due to multiple reflections off the ice crystals. In the lower portion and beneath the cloud, photolysis is substantially decreased. With enhanced photolysis rates, the NO/NO_2 ratio in the upper troposphere is driven to larger values than under clear-sky conditions. Existing experimental evidence seems to confirm, at least qualitatively these model results (Kelley et al., 1994).

Thunderstorm updraft regions, which contain copious amounts of water, are regions where efficient scavenging of soluble species can occur (Balkanski et al., 1993). Nitrogen dioxide itself is not very soluble and therefore wet scavenging is not a major removal process for it. However, a major NO_x reservoir species, HNO_3 is extremely soluble. Very few direct field measurements of the amounts of specific trace gases that are scavenged in storms are available. Pickering et al. (2001) used a combination of model estimates of soluble species that did not include wet scavenging and observations of these species from the upper tropospheric outflow

region of a major line of convection observed near Fiji. Over 90% of the and in the outflow air appeared to have been removed by the storm. About 50% of CH_3OOH and about 80% of HCHO had been lost.

Convective processes and small-scale turbulence transport pollutants both upward and downward throughout the planetary boundary layer and the free troposphere. Ozone and its precursors (NO_x, CO, and VOCs) can be transported vertically by convection into upper part of the mixed layer on one day, then transported overnight as a layer of elevated mixing ratios, perhaps by a nocturnal low-level jet, and then entrained into a growing convective boundary layer downwind and brought back to the surface.

Because NO and NO_2 are only slightly soluble, they can be transported over longer distances in the gas phase than can more soluble species which can be depleted by deposition to moist surfaces, or taken up more readily on aqueous surfaces of particles. During transport, they can be transformed into reservoir species such as HNO_3, PANs, and N_2O_5. These species can then contribute to local NO_x concentrations in remote areas. For example, it is now well established that PAN decomposition provides a major source of NO_x in the remote troposphere (Staudt et al., 2003). PAN decomposition in subsiding air masses from Asia over the eastern Pacific could make an important contribution to O_3 and NO_x enhancement in the United States (Kotchenruther et al., 2001; Hudman et al., 2004). Further details about mechanisms for transporting ozone and its precursors were described at length in CD06.

AX2.6 SOURCES AND EMISSIONS OF NITROGEN OXIDES, AMMONIA, AND SULFUR DIOXIDE

All three of the species listed in the title to this section have both natural and anthropogenic sources. In Section AX2.6.1, interactions of NO_x with the terrestrial biosphere are discussed. Because of the tight coupling between processes linking emissions and deposition, they are discussed together. In Section AX2.6.2, emissions of NO_x, NH_3, and SO_2 are discussed. Field studies evaluating emissions inventories are discussed in Section AX2.6.3.

AX2.6.1 Interactions of Nitrogen Oxides with the Biosphere

Nitrogen oxides affect vegetated ecosystems, and in turn the atmospheric chemistry of NO_x is influenced by vegetation. Extensive research on nitrogen inputs from the atmosphere to

forests was conducted in the 1980s as part of the Integrated Forest Study, and is summarized by Johnson and Lindberg (1992). The following sections discuss sources of NO_x from soil, deposition of NO_x to foliage, reactions with biogenic hydrocarbons, and ecological effects of nitrogen deposition.

NO_x Sources

Soil NO

Nitric oxide NO from soil metabolism is the dominant, but not exclusive, source of nitrogen oxides from the biosphere to the atmosphere. As noted below, our understanding of NO_2 exchange with vegetation suggests that there should be emission of NO_2 from foliage when ambient concentrations are less than about 1 ppb. However, Lerdau et al. (2000) have pointed out that present understanding of the global distribution of NO_x is not consistent with a large source that would be expected in remote forests if NO_2 emission was important when atmospheric concentrations were below the compensation point.

The pathways for nitrification and denitrification include two gas-phase intermediates, NO and N_2O, some of which can escape. While N_2O is of interest for its greenhouse gas potential and role in stratospheric chemistry it is not considered among the reactive nitrogen oxides important for urban and regional air quality and will not be discussed further. Temperature and soil moisture are critical factors that control the rates of reaction and importantly the partitioning between NO and N_2O which depend on oxygen levels: in flooded soils where oxygen levels are low, N_2O is the dominant soil nitrogen gas; as soil dries, allowing more O_2 to diffuse, NO emissions increase. In very dry soils microbial activity is inhibited and emissions of both N_2O and NO decrease. Nitrogen metabolism in soil is strongly dependent on the substrate concentrations. Where nitrogen is limiting, nitrogen is efficiently retained and little gaseous nitrogen is released. Where nitrogen is in excess of demand, gaseous nitrogen emissions increase; consequently, soil NO emissions are highest in fertilized agriculture and tropical soils (Davidson and Kingerlee, 1997; Williams et al., 1992).

Sinks

Several reactive nitrogen are species are deposited to vegetation, among them, HNO_3, NO_2, PAN, and organic nitrates.

HNO_3

Deposition of HNO_3 appears to be relatively simple. Field observations based on concentration gradients and recently using eddy covariance demonstrate rapid deposition that approaches the aerodynamic limit (as constrained by atmospheric turbulence) in the Wesely (1989) formulation based on analogy to resistance. Surface resistance for HNO_3 uptake by vegetation is negligible. Deposition rates are independent of leaf area or stomatal conductance, implying that deposition occurs to branches, soil, and leaf cuticle as well as internal leaf surfaces.

Deposition velocities (V_d) typically exceed 1 cm $s^{-1}$and exhibit a daily pattern controlled by turbulence characteristics: midday maximum and lower values at night when there is stable boundary layer.

Deposition of NO_2

Nitrogen dioxide interaction with vegetation is more complex. Application of ^{15}N-labeled Nitrogen Dioxide demonstrates that Nitrogen Dioxide is absorbed and metabolized by foliage (Siegwolf et al., 2001; Mocker et al., 1998; Segschneider et al., 1995; Weber et al., 1995). Exposure to NO_2 induces nitrate reductase (Weber et al., 1995, 1998), a necessary enzyme for assimilating oxidized nitrogen. Understanding of NO_2 interactions with foliage is largely based on leaf cuvette and growth chamber studies, which expose foliage or whole plants to controlled levels of NO_2 and measure the fraction of NO_2 removed from the chamber air. A key finding is that the fit of NO_2 flux to NO_2 concentration, has a non-zero intercept, implying a compensation point or internal concentration. In studies at very low NO_2 concentrations emission from foliage is observed (Teklemariam and Sparks, 2006). Evidence for a compensation point is not solely based on the fitted intercept. Nitrogen dioxide uptake rate to foliage is clearly related to stomatal conductance. Internal resistance is variable, and may be associated with concentrations of reactive species such as ascorbate in the plant tissue that react with NO_2 (Teklemariam and Sparks, 2006). Foliar NO_2 emissions show some dependence on nitrogen content (Teklemariam and Sparks, 2006). Internal NO_2 appears to derive from plant nitrogen metabolism.

Two approaches to modeling NO_2 uptake by vegetation are the resistance-in-series analogy which considers flux (F) as the product of concentration (C) and V_d, where is related to the sum of aerodynamic, boundary layer, and internal resistances (R_a, R_b, and R_c ; positive fluxes are from atmosphere to foliage)

$$F = CV_d \quad \text{(AX2-42)}$$

$$V_d = (R_a + R_b + R_c)^{-1} \quad \text{(AX2-43)}$$

R_a and R_b and controlled by turbulence in the mixed layer; R_c is dependent on characteristics of the foliage and other elements of the soil, and may be viewed as 2 combination of resistance internal to the foliage and external on the cuticle, soils, and bark. This approach is amenable to predicting deposition in regional air quality models (Wesely, 1989). Typically, the NO_2, V_d is less than that for O_3, due to the surface's generally higher resistance to NO_2 uptake, consistent with NO_2's lower reactivity.

Alternatively, NO_2 exchange with foliage can be modeled from a physiological viewpoint where the flux from the leaf is related to the stomatal conductance and a concentration gradient between the ambient air and interstitial air in the leaf. This approach best describes results for exchange with individual foliage elements, and is expressed per unit leaf (needle) area. While this approach provides linkage to leaf physiology, it is not straightforward to scale up from the leaf to ecosystem scale:

$$J = g_s(C_a - C_i) \quad \text{(AX2-44)}$$

This model implicitly associates the compensation point with a finite internal concentration. Typically observed compensation points are around 1 ppb. Finite values of internal NO_2 concentration are consistent with metabolic pathways that include oxides of nitrogen. In this formulation, the uptake will be linear with NO_2 concentration, which is typically observed with foliar chamber studies.

Several studies have shown the UV dependence of NO_2 emission, which implies some photo-induced surface reactions that release NO_2. Rather than model this as a UV-dependent internal concentration, it would be more realistic to add an additional term to account for emission that is dependent on light levels and other surface characteristics:

$$J = g_s(C_a - C_i) = J_s(UV) \quad \text{(AX2-45)}$$

The mechanisms for surface emission are discussed below. Measurement of NO_2 flux is confounded by the rapid interconversion of NO, NO_2, and O_3 (Gao et al., 1991).

PAN Deposition

Peroxyacetyl nitrate is phytotoxic, so clearly it is absorbed at the leaf. Observations based on inference from concentration gradients and rates of decline at night (Shepson et al., 1992; Schrmipf et al., 1996) and leaf chamber studies (Teklemariam and Sparks, 2004) have indicated that PAN uptake is slower than that of O_3; however, recent work in coniferous canopy with direct eddy covariance PAN flux measurements indicated a V_d more similar to that of O_3. Uptake of PAN is under stomatal control, has a non-zero deposition at night, and is influenced by leaf wetness (Turnipseed et al., 2006). On the other hand, flux measurements determined by gradient methods over a grass surface showed a V_d closer to 0.1 cm s^{-1}, with large uncertainty (Doskey et al., 2004). A factor of 10 uncertainty remains in V_d 0.1-1 cm s^{-1} giving a range. Whether the discrepancies are methodological or indicate intrinsic differences between different vegetation is unknown. Uptake of PAN is smaller than its thermal decomposition in all cases.

Organic Nitrates

The biosphere also interacts with NO_x through hydrocarbon emissions and their subsequent reactions to form multi-functional organic nitrates. Isoprene nitrates are an important class of these. Isoprene reacts with OH to form a radical that adds NO_2 to form a hydroxyalkyl nitrate. The combination of hydroxyl and nitrate functional group makes these compounds especially soluble with low vapor pressures; they likely deposit rapidly (Shepson et al., 1996; Treves et al., 2000). Many other unsaturated hydrocarbons react by analogous routes. Observations at Harvard Forest show a substantial fraction of total NO_y not accounted for by NO, NO_2 and PAN, which is attributed to the organic nitrates (Horii et al., 2006, Munger et al., 1998). Furthermore, the total NO_y flux exceeds the sum of HNO_3, NO_x, and PAN, which implies that the organic nitrates are a substantial fraction of nitrogen deposition. Other observations that show evidence of hydoxyalkyl nitrates include those of Grossenbacher et al. (2001) and Day et al. (2003).

Formation of the hydroxyalkyl nitrates occurs after VOC + OH reaction. In some sense, this mechanism is just an alternate pathway for OH to react with NO_x to form a rapidly depositing species. If VOC were not present, OH would be available to react with NO_2 when it is present instead to form HNO_3.

HONO

Nitrous acid formation on vegetative surfaces at night has long been observed based on measurements of positive gradients (Harrison and Kitto, 1994). Surface reactions of NO_2 enhanced by moisture were proposed to explain these results. Production was evident at sites with high ambient NO_2; at low concentration, uptake of HONO exceeded the source. Daytime observations of HONO when rapid photolysis is expected to deplete ambient concentrations to very low levels implies a substantial source of photo-induced HONO formation at a variety of forested sites where measurements have been made. Estimated source strengths are 200-1800 pptv hr^{-1} in the surface layer (Zhou et al., 2002a, 2003), which is about 20 times faster than all nighttime sources. Nitrous acid sources could be important to OH/HO_2 budgets as HONO is rapidly photolyzed by sunlight to OH and NO. Additional evidence of light-dependent reactions to produce HONO comes from discovery of a HONO artifact in pyrex sample inlet lines exposed to ambient light. Either covering the inlet or washing it eliminated the HONO formation (Zhou et al., 2002b). Similar reactions might serve to explain observations of UV-dependent production of NO_x in empty foliar cuvettes that had been exposed to ambient air (Hari et al., 2003; Raivonen et al., 2003).

Production of HONO in the dark is currently believed to occur via a heterogeneous reaction involving NO_2 on wet surfaces (Jenkin et al., 1988; Pitts et al., 1984; He et al., 2006; Sakamaki et al., 1983), and it is proposed that the mechanism has first-order dependence in both NO_2 and H_2O (Kleffmann et al., 1998; Svensson et al., 1987) despite the stoichiometry. However, the molecular pathway of the mechanism is still under debate. Jenkin et al. (1988) postulated a $H_2O{\cdot}NO_2$ water complex reacting with gas phase NO_2 to produce HONO, which is inconsistent with the formation of an N_2O_4 intermediate leading to HONO as proposed by Finlayson-Pitts et al. (2003). Another uncertainty is whether the reaction forming HONO is dependent on water vapor (Svensson et al., 1987; Stutz et al., 2004) or water adsorbed on surfaces (Kleffmann et al., 1998). Furthermore, the composition of the surface and the available amount of surface or surface-to-volume ratio can significantly influence the HONO production rates (Kaiser and Wu, 1977; Kleffmann et al., 1998; Svensson et al., 1987), which may explain the difference in the rates observed between laboratory and atmospheric measurements.

There is no consensus on a chemical mechanism for photo-induced HONO production. Photolysis of HNO_3 or NO_3^- absorbed on ice or in surface water films has been proposed

(Honrath et al., 2002; Ramazan et al., 2004; Zhou et al., 2001, 2003). Alternative pathways include NO_2 interaction with organic surfaces such as humic substances (George et al., 2005; Stemmler et al., 2006). Note that either NO_3^- photolysis or heterogeneous reaction of NO_2 are routes for recycling deposited nitrogen oxides back to the atmosphere in an active form. Nitrate photolysis would return nitrogen that heretofore was considered irreversibly deposited, surface reactions between NO_2 and water films or organic molecules would decrease the effectiveness of observed NO_2 deposition if the HONO were re-emitted.

Fast Homogeneous Reactions

Inferences from observations at Blodgett Forest (Cohen et al. in prep) suggest that radicals from O_3 + VOC react with NO_x in the canopy to produce HNO_3 and organic nitrates among other species. This mechanism would contribute to canopy retention of soil NO emission in forests with high VOC possibly more effectively than the NO to NO_2 conversion and foliar uptake of NO_2 that has been proposed to reduce the amount of soil NO that escapes to the supra-canopy atmosphere (Jacob and Bakwin, 1991).

Some NO_2 and HNO_3 Flux Data from Harvard Forest

Observations from TDL Measurements of NO_2

Harvard Forest is a rural site in central Massachusetts, where ambient NO_x, NO_y, and other pollutant concentrations and fluxes of total NO_y have been measured since 1990 (Munger et al., 1996). An intensive study in 2000 utilized a Tunable Diode Laser Absorption Spectrometer (TDLAS) to measure NO_2 and HNO_3. TDLAS has an inherently fast response, and for species such as NO_2 and HNO_3 with well-characterized spectra it provides an absolute and specific measurement. Absolute concentrations of HNO_3 were measured, and the flux inferred based on the dry deposition inferential method that uses momentum flux measurements to compute a deposition velocity and derives an inferred flux (Wesely and Hicks, 1977; Hicks et al., 1987). Direct eddy covariance calculations for HNO_3 were not possible because the atmospheric variations were attenuated by interaction with the inlet walls despite very short residence time and use of fluorinated silane coatings to make the inlet walls more hydrophobic. Nitrogen Oxide response was adequate to allow both concentration and eddy covariance flux determination. Simultaneously, NO and NO_y eddy covariance fluxes were determined with two separate O_3

chemiluminescence detectors, one equipped with a H_2-gold catalyst at the inlet to convert all reactive nitrogen compounds to NO. Additionally, the measurements include concentration gradients for NO, NO_2, and O_3 over several annual cycles to examine their vertical profiles in the forest canopy.

Overall, the results show typical NO_2 concentrations of 1 ppb under clean-air conditions and mean concentrations up to 3 ppb at night and 1 ppb during daytime for polluted conditions. Net positive fluxes (emission) of NO_2 were evident in the daytime and negative fluxes (deposition) were observed at night (Figure AX2.6-1). Nitric oxide fluxes were negative during the daytime and near zero at night.

In part the opposite NO and NO_2 fluxes are simply consequences of variable NO/NO_2 distributions responding to vertical gradients in light intensity and O_3 concentration, which resulted in no net flux of NO_x (Gao et al., 1993). In the Harvard Forest situation, the NO and NO_2 measurements were not at the same height above the canopy, and the resulting differences derive at least in part from the gradient in flux magnitude between the two inlets (Figure AX2.6-2).

At night, when NO concentrations are near 0 due to titration by ambient O_3 there is not a flux of NO to offset NO_2 fluxes. Nighttime data consistently show NO_2 deposition (Figure AX2.6-3), which increases with increasing NO_2 concentrations. Concentrations above 10 ppb were rare at this site, but the few high NO_2 observations suggest a nonlinear dependence on concentration. The data fit a model with V_d of −0.08 plus an enhancement term that was second order in NO_2 concentration. The second order term implies that NO_2 deposition rates to vegetation in polluted urban sites would be considerably larger than what was observed at this rural site.

After accounting for the NO-NO_2 null cycle the net NO_x flux could be derived. Overall, there was a net deposition of NO_x during the night and essentially zero flux in the day, with large variability in the magnitude and sign of individual flux observations (Figure AX2.6-3). For the periods with [NO_2] > 2 ppb, deposition was always observed. These canopy-scale field observations are consistent with a finite compensation point for NO_2 in the canopy that offsets foliar uptake or even reverses it when concentrations are especially low. At concentrations above the compensation point, NO_x is absorbed by the canopy. Examination of concentration profiles corroborates the flux measurements (Figure AX2.6-4). During daytime for low-NO_x

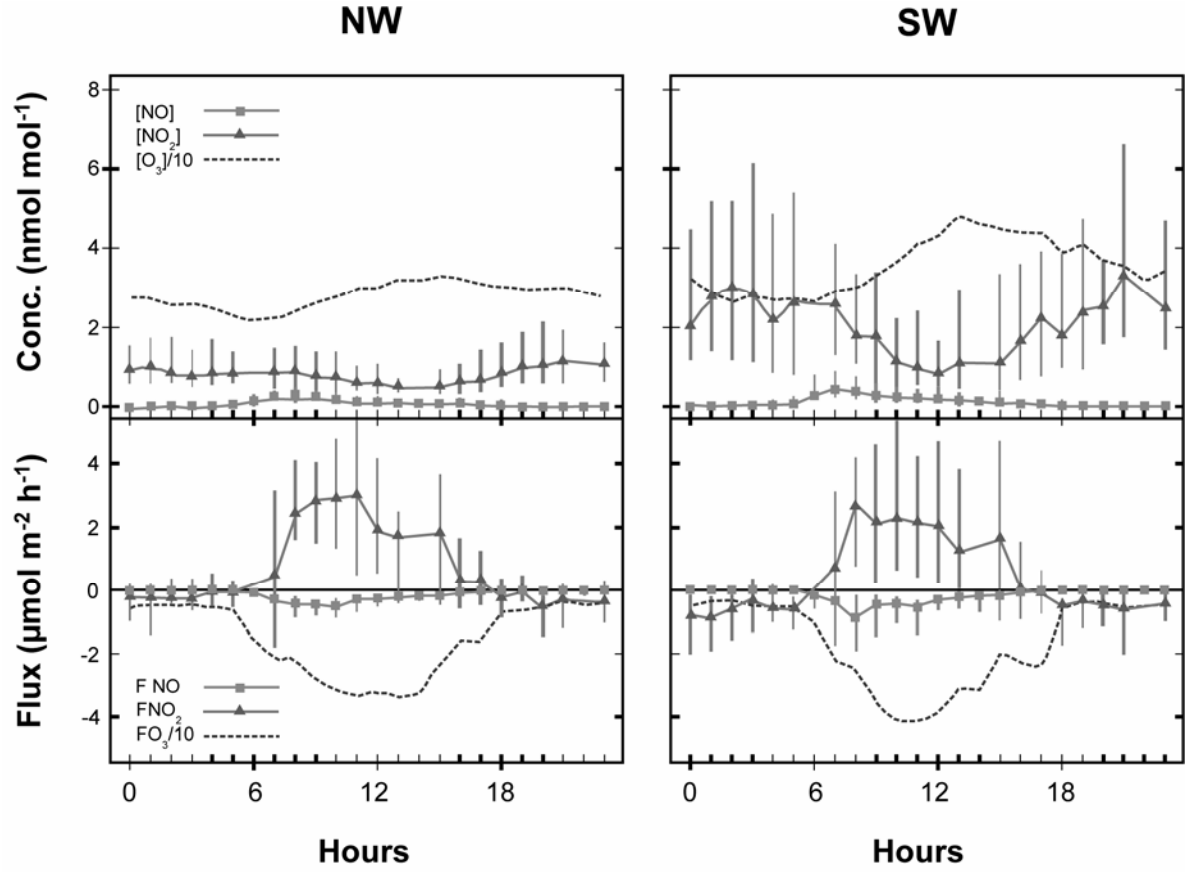


Figure AX2.6-1. **Diel cycles of median concentrations (upper panels) and fluxes (lower panels) for the Northwest clean sector, left panels) and Southwest (polluted sector, right panels) wind sectors at Harvard Forest, April-November, 2000, for NO, NO_2, and O_3/10. NO and O_3 were sampled at a height of 29 m, and NO_2 at 22 m. Vertical bars indicate 25th and 27th quartiles for NO and NO_2 measurements. NO_2 concentration and nighttime deposition are enhanced under southwesterly conditions, as are O_3 and the morning NO maximum.**

Source: Horii et al. (2004).

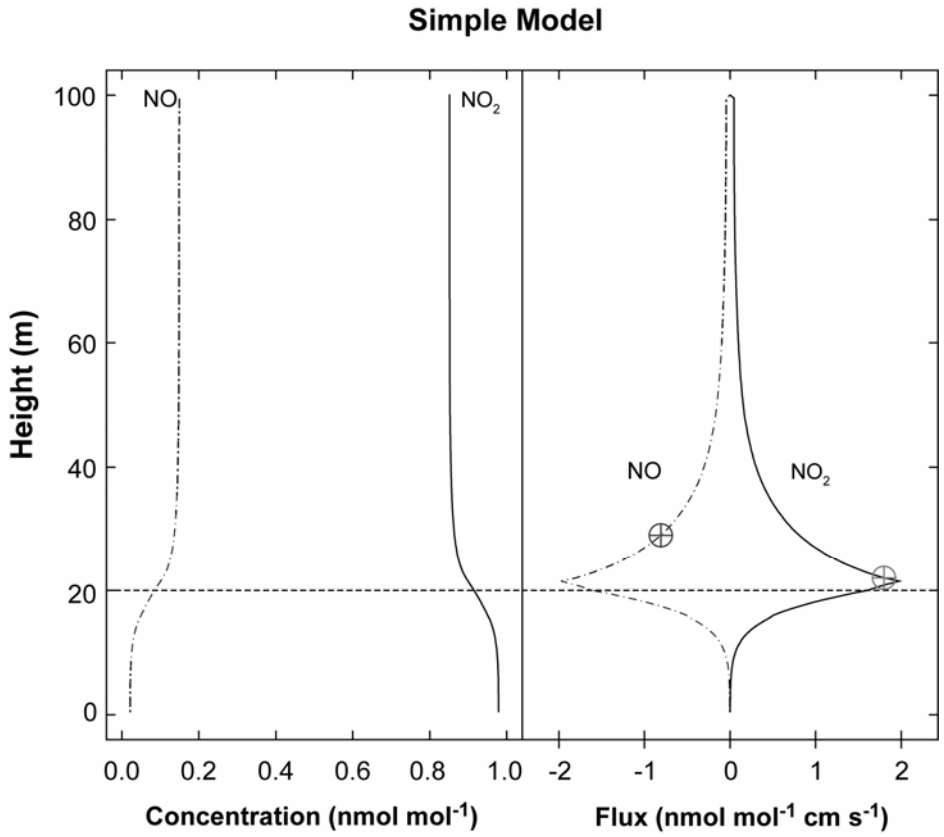


Figure AX2.6-2. **Simple NO_x photochemical canopy model outputs. Left panel, concentrations of NO (dashed) and NO_2 (solid); right, fluxes of NO (dashed) and NO_2 (solid). Symbols indicate measurement heights for NO (29m) and NO_2 (22m) at Harvard Forest. The model solves the continuity equation for NO concentration at 200 levels, d/dz(-Kc(dNO/dz)) = PNO − LNO, where PNO = [NO]/t1, LNO = [NO]/t2, and zero net deposition or emission of NO_x is allowed. NO_x (NO + NO_2) is normalized to 1ppb. t1 = 70s in this example. Due to the measurement height difference, observed upward NO_2 flux due to photochemical cycling alone should be substantially larger than observed downward NO flux attributable to the same process.**

Source: Horii (2002).

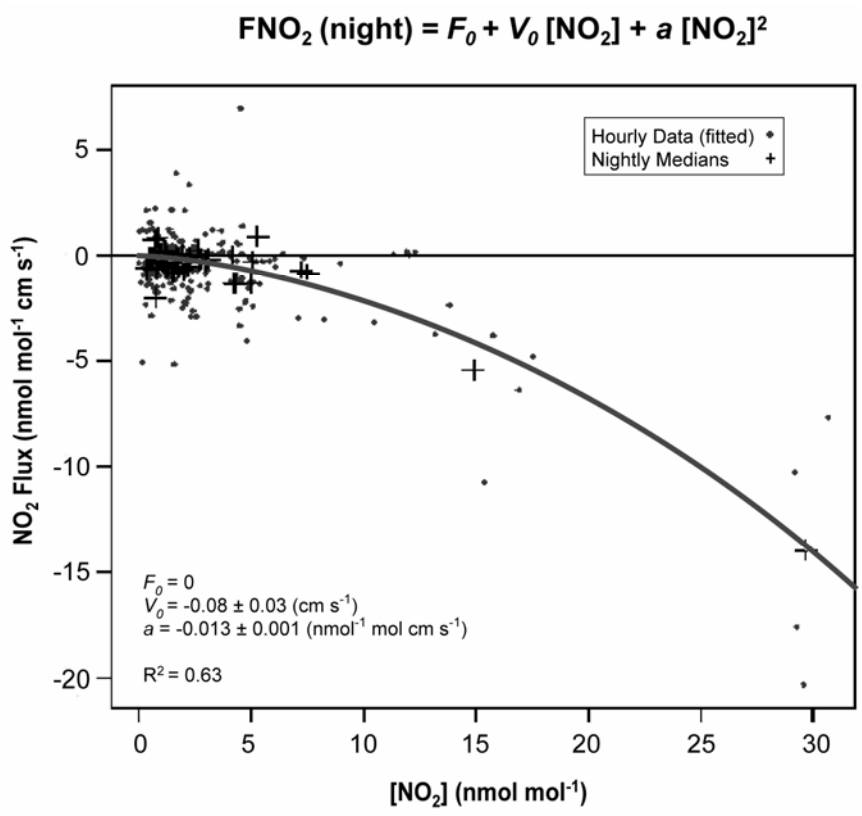


Figure AX2.6-3. Hourly (dots) and median nightly (pluses) NO_2 flux vs. concentration, with results of least-squares fit on the hourly data (curve). The flux is expressed in units of concentration times velocity (nmol mol^{-1} cm s^{-1}) in order to simplify the interpretation of the coefficients in the least-squares fit. Pressure and temperature corrections have been taken into account in the conversion from density to mixing ratio.

Source: Horii et al. (2004).

conditions, there is a local maximum in the concentration profile near the top of the canopy where O_3 has a local minimum, which is consistent with foliar emission or light-dependent production of NO_x in the upper canopy. Depletion is evident for both NO_x and O_3 near the forest floor. Air reaching the ground has passed through the canopy where uptake is efficient and the vertical exchange rates near the ground are slow. At night, the profiles generally decrease with decreasing height above the ground, showing only uptake. At higher concentrations, the daytime NO_x concentrations are nearly constant through the canopy; no emission is evident from the sunlit leaves.

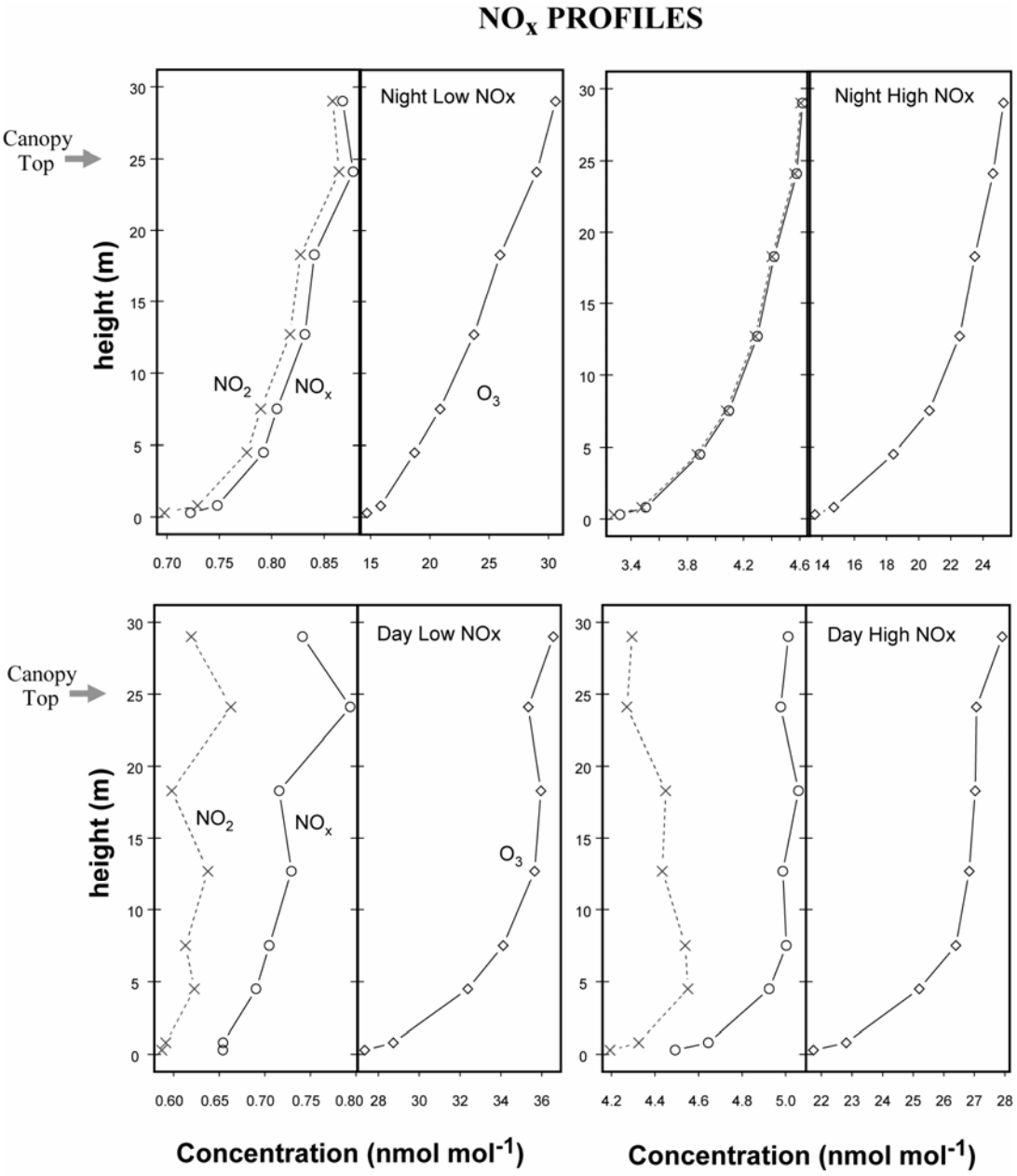


Figure AX2.6-4. Averaged profiles at Harvard Forest give some evidence of some NO_2 input near the canopy top from light-mediated ambient reactions, or emission from open stomates.

Source: Horii et al. (2004).

Figure AX2.6-5 compares observed fluxes of all the observed species. The measured NO_x and estimated PAN fluxes are small relative to the observed total NO_y flux. In clean air, HNO_3 accounts for nearly all the NO_y flux and the sum of all measured species is about equal to

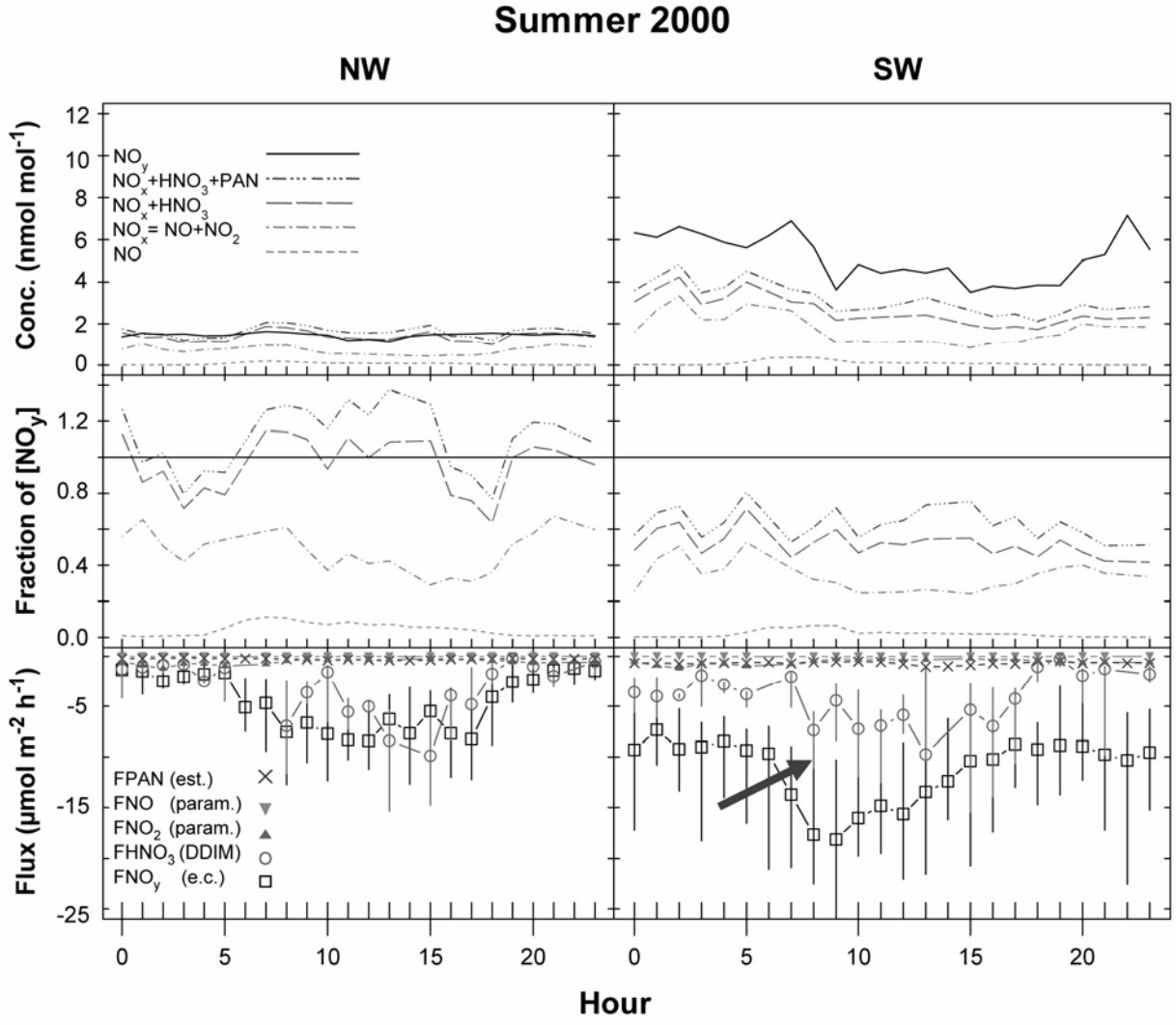


Figure AX2.6-5. Summer (June-August) 2000 median concentrations (upper panels), fractions of NO_y (middle panels), and fluxes (lower panels) of NO_y and component species separated by wind direction (Northwest on the left and Southwest on the right). Vertical lines in the flux panels show 25th and 75th quartiles of $F(NO_y)$ and $F(HNO_3)$; negative fluxes represent deposition; $F(NO_x)$ is derived from eddy covariance F(NO) and $F(NO_2)$ measurements (corrected for photochemical cycling), $F(HNO_3)$ is inferred, and $F(NO_y)$ was measured by eddy covariance. The sum of NO_x, HNO_3, and PAN accounts for all of the NO_y concentration and flux for Northwesterly (unpolluted background) flows, whereas up to 50% of NO_y and $F(NO_y)$ under Southwesterly flows are in the form of reactive nitrogen species whose fluxes are not measured or estimated here.

Source: Horii et al. (2006).

the NO_y concentration. However, in polluted conditions, unmeasured species are up to 25% of the NO_y, and HNO_3 fluxes cannot account for all the total NO_y flux observed. Likely these unmeasured NO_y species are hydroxyalkyl nitrates and similar compounds and are rapidly deposited. Although NO_2 uptake may be important to the plant, because it is an input directly to the interior of foliage that can be used immediately in plant metabolism, it is evidently not a significant part of overall nitrogen deposition to rural sites. The deposition of HNO_3 and multifunctional organic nitrates are the largest elements of the nitrogen dry deposition budget. Two key areas of remaining uncertainty are the production of HONO over vegetation and the role of very reactive biogenic VOCs. HONO is important because its photolysis is a source of OH radicals, and its formation may represent an unrecognized mechanism to regenerate photochemically active NO_x from nitrate that had been considered terminally removed from the atmosphere.

Ecosystem Effects

In addition to the contribution to precipitation acidity, atmospheric nitrogen oxides have ecological effects. Total loading by both and wet and dry deposition is the relevant metric for considering ecosystem impacts. At low inputs, nitrogen deposition adds essential nutrients to terrestrial ecosystems. Most temperate forests are nitrogen limited; thus the inputs stimulate growth. Anthropogenic nitrogen may influence some plant species different and alter the distribution of plant species (cf. Wedin and Tilman, 1996). At high nitrogen loading, where nitrogen inputs exceed nutrient requirements, deleterious effects including forest decline associated with 'nitrogen saturation' are seen (Aber at al., 1998; Driscoll et al., 2003). In aquatic ecosystems, however, nitrogen is may or may not be limiting, but in brackish waters atmospheric deposition of anthropogenic nitrogen is suspected of contributing to eutrophication of some coastal waters and lakes (see Bergstrom and Jansson, 2006; Castro and Driscoll, 2002).

AX2.6.2 Emissions of NO_x, NH_3, and SO_2

Emissions of NO_x

Estimated annual emissions of NO_x, NH_3, and SO_2 for 2002 (U.S. Environmental Protection Agency, 2006) are shown in Table AX2.6-1. Methods for estimating emissions of criteria pollutants, quality assurance procedures, and examples of emissions calculated by using

data are given in U.S. Environmental Protection Agency (1999). Discussions of uncertainties in current emissions inventories and strategies for improving them can be found in NARSTO (2005).

As can be seen from the table, combustion by stationary sources, such as electrical utilities and various industries, accounts for roughly half of total anthropogenic emissions of NO_x. Mobile sources account for the other half, with highway vehicles representing the major mobile source component. Approximately half the mobile source emissions are contributed by diesel engines, the remainder are emitted by gasoline-fueled vehicles and other sources.

Emissions of NO_x associated with combustion arise from contributions from both fuel nitrogen and atmospheric nitrogen. Combustion zone temperatures greater than about 1300 K are required to fix atmospheric N_2:

$$N_2 + O_2 \rightarrow 2NO \qquad \text{(AX2-46)}$$

Otherwise, NO can be formed from fuel N according to this reaction:

$$C_aH_bO_cN_d + O_2 \rightarrow xCO_2 + yH_2O + zNO \qquad \text{(AX2-47)}$$

In addition to NO formation by the schematic reactions given above, some NO_2 and CO are also formed depending on temperatures, concentrations of OH and HO_2 radicals and O_2 levels. Fuel nitrogen is highly variable in fossil fuels, ranging from 0.5 to 2.0 percent by weight (wt %) in coal to 0.05% in light distillates (e.g., diesel fuel), to 1.5 wt % in heavy fuel oils (UK AQEG, 2004). The ratio of NO_2 to NO_x in primary emissions ranges from 3 to 5 % from gasoline engines, 5 to 12% from heavy-duty diesel trucks, 5 to 10% from vehicles fueled by compressed natural gas and from 5 to 10% from stationary sources. In addition to NO_x, motor vehicles also emit HONO, with ratios of HONO to NO_x ranging from 0.3% in the Caldecott Tunnel, San Francisco Bay (Kirchstetter and Harley, 1996) to 0.5 to 1.0% in studies in the United Kingdom (UK AQEG, 2004). The NO_2 to NO_x ratios in emissions from turbine jet engines are as high as 32 to 35 % during taxi and takeoff (CD93). Sawyer et al. (2000) have reviewed the factors associated with NO_x emissions by mobile sources. Marine transport represents a minor source of NO_x, but it constitutes a larger source in the EU where it is expected to represent about two-thirds of land-based sources (UK AQEG, 2004).

NO_x Emissions from Natural Sources (Soil, Wild Fires, and Lightning)

Soil

Emission rates of NO from cultivated soil depend mainly on fertilization levels and soil temperature. About 60% of the total NO_x emitted by soils occurs in the central corn belt of the United States. The oxidation of NH_3, emitted mainly by livestock and soils, leads to the formation of NO, **also** NH_4^+ and NO_3^- fertilizers lead to NO emissions from soils. Estimates of emissions from natural sources are less certain than those from anthropogenic sources. On a global scale, the contribution of soil emissions to the oxidized nitrogen budget is on the order of 10% (van Aardenne et al., 2001; Finlayson-Pitts and Pitts, 2000; Seinfeld and Pandis, 1998), but NO_x emissions from fertilized fields are highly variable. Soil NO emissions can be estimated from the fraction of the applied fertilizer nitrogen emitted as NO_x, but the flux varies strongly with land use and temperature. Estimated globally averaged fractional applied nitrogen loss as NO varies from 0.3% (Skiba et al., 1997) to 2.5% (Yienger and Levy, 1995). Variability within biomes to which fertilizer is applied, such as shortgrass versus tallgrass prairie, accounts for a factor of three in uncertainty (Williams et al., 1992; Yienger and Levy, 1995; Davidson and Kingerlee, 1997).

The local contribution can be much greater than the global average, particularly in summer and especially where corn is grown extensively. Williams et al. (1992) estimated that contributions to NO budgets from soils in Illinois are about 26% of the emissions from industrial and commercial processes in that State. In Iowa, Kansas, Minnesota, Nebraska, and South Dakota, all states with smaller human populations, soil emissions may dominate the NO budget. Conversion of NH_3 to NO_3 (nitrification) in aerobic soils appears to be the dominant pathway to NO. The mass and chemical form of nitrogen (reduced or oxidized) applied to soils, the vegetative cover, temperature, soil moisture, and agricultural practices such as tillage all influence the amount of fertilizer nitrogen released as NO.

Emissions of NO from soils peak in summer when O_3 formation is also at a maximum. An NRC panel report (NRC, 2002) outlined the role of agriculture in emissions of air pollutants including NO and NH_3. That report recommends immediate implementation of best management practices to control these emissions, and further research to quantify the magnitude of emissions and the impact of agriculture on air quality. Civerolo and Dickerson (1998) report

that use of the no-till cultivation technique on a fertilized cornfield in Maryland reduced NO emissions by a factor of seven.

NO_x from Biomass Burning

During biomass burning, nitrogen is derived mainly from fuel nitrogen and not from atmospheric N_2, since temperatures required to fix atmospheric N_2 are likely to be found only in the flaming crowns of the most intense boreal forest fires. Nitrogen is present mainly in plants as amino (NH_2) groups in amino acids. During combustion, nitrogen is released mainly in unidentified forms, presumably as N_2, with very little remaining in fuel ash. Apart from N_2, the most abundant species in biomass burning plumes is NO. Emissions of NO account for only about 10 to 20% relative to fuel N (Lobert et al., 1991). Other species such as NO_2, nitriles, ammonia, and other nitrogen compounds account for a similar amount. Emissions of NO_x are about 0.2 to 0.3% relative to total biomass burned (e.g., Andreae, 1991; Radke et al., 1991). Westerling et al. (2006) have noted that the frequency and intensity of wildfires in the western United States have increased substantially since 1970.

Lightning Production of NO

Annual global production of NO by lightning is the most uncertain source of reactive nitrogen. In the last decade, literature values of the global average production rate range from 2 to 20 Tg N per year. However, the most likely range is from 3 to 8 Tg N per year, because the majority of the recent estimates fall in this range. The large uncertainty stems from several factors: (1) a large range of NO production rates per meter of flash length (as much as two orders of magnitude); (2) the open question of whether cloud-to-ground (CG) flashes and intracloud flashes (IC) produce substantially different amounts of NO; (3) the global flash rate; and (4) the ratio of the number of IC flashes to the number of CG flashes. Estimates of the amount of NO produced per flash have been made based on theoretical considerations (e.g., Price et al., 1997), laboratory experiments (e.g., Wang et al., 1998); field experiments (e.g., Stith et al., 1999; Huntrieser et al., 2002, 2007) and through a combination of cloud-resolving model simulations, observed lightning flash rates, and anvil measurements of NO (e.g., DeCaria et al., 2000, 2005; Ott et al., 2007). The latter method was also used by Pickering et al. (1998), who showed that only ~5 to 20% of the total NO produced by lightning in a given storms exists in the boundary layer at the end of a thunderstorm. Therefore, the direct contribution to boundary layer O_3

production by lightning NO is thought to be small. However, lightning NO production can contribute substantially to O_3 production in the middle and upper troposphere. DeCaria et al. (2005) estimated that up to 10 ppbv of ozone was produced in the upper troposphere in the first 24 hours following a Colorado thunderstorm due to the injection of lightning NO. A series of midlatitude and subtropical thunderstorm events have been simulated with the model of DeCaria et al. (2005), and the derived NO production per CG flash averaged 500 moles/flash while average production per IC flash was 425 moles/flash (Ott et al., 2006).

A major uncertainty in mesoscale and global chemical transport models is the parameterization of lightning flash rates. Model variables such as cloud top height, convective precipitation rate, and upward cloud mass flux have been used to estimate flash rates. Allen and Pickering (2002) have evaluated these methods against observed flash rates from satellite, and examined the effects on ozone production using each method.

Uses of Satellite Data to Derive Emissions

Satellite data have been shown to be useful for optimizing estimates of emissions of NO_2. (Leue et al., 2001; Martin et al., 2003; Jaegle et al., 2005). Satellite-borne instruments such as GOME (Global Ozone Monitoring Experiment; Martin et al., 2003; and references therein) and SCIAMACHY (Scanning Imaging Absorption Spectrometer for Atmospheric Chartography; Bovensmann et al., 1999) retrieve tropospheric columns of NO_2, which can then be combined with model-derived chemical lifetimes of NO_x to yield emissions of NO_x.

Top-down inference of NO_x emission inventory from the satellite observations of NO_2 columns by mass balance requires at minimum three pieces of information: the retrieved tropospheric NO_2 column, the ratio of tropospheric NO_x to NO_2 columns, and the NO_x lifetime against loss to stable reservoirs. A photochemical model has been used to provide information on the latter two pieces of information. The method is generally applied exclusively to land surface emissions, excluding lightning. Tropospheric NO_2 columns are insensitive to lightning NO_x emissions since most of the lightning NO_x in the upper troposphere is present as NO at the local time of the satellite measurements (Ridley et al., 1996), owing to the slower reactions of NO with O_3 there.

Jaeglé et al. (2005) applied additional information on the spatial distribution of emissions and on fire activity to partition NO_x emissions into sources from fossil fuel combustion, soils, and biomass burning. Global a posteriori estimates of soil NO_x emissions are 68% larger than

the a priori estimates. Large increases are found for the agricultural region of the western United States during summer, increasing total U.S. soil NO_x emissions by a factor of 2 to 0.9 Tg N yr^{-1}. Bertram et al. (2005) found clear signals in the SCIAMACHY observations of short intense NO_x pulses following springtime fertilizer application and subsequent precipitation over agricultural regions of the western United States. For the agricultural region in North-Central Montana, they calculate a yearly SCIAMACHY top-down estimate that is 60% higher than a commonly used model of soil NO_x emissions by Yienger and Levy (1995).

Martin et al. (2006) retrieved tropospheric nitrogen dioxide (NO_2) columns for May 2004 to April 2005 from the SCIAMACHY satellite instrument to derive top-down NO_x emissions estimates via inverse modeling with a global chemical transport model (GEOS-Chem). The top-down emissions were combined with a priori information from a bottom-up emission inventory with error weighting to achieve an improved a posteriori estimate of the global distribution of surface NO_x emissions. Their a posteriori inventory improves the GEOS-Chem simulation of NO_x, PAN, and HNO_3 with respect to airborne in situ measurements over and downwind of New York City. Their a posteriori inventory shows lower NO_x emissions from the Ohio River valley during summer than during winter, reflecting recent controls on NO_x emissions from electric utilities. Their a posteriori inventory is highly consistent ($R^2 = 0.82$, bias = 3%) with the NEI99 inventory for the United States. In contrast, their a posteriori inventory is 68% larger than a recent inventory by Streets et al. (2003) for East Asia for the year 2000.

Emissions of NH_3

Emissions of NH_3 show a strikingly different pattern from those of NO_x. Three-way catalysts used in motor vehicles emit small amounts of NH_3 as a byproduct during the reduction of NO_x. Stationary combustion sources make only a small contribution to emissions of NH_3 because efficient combustion favors formation of NO_x and, NH_3 from combustion is produced mainly by inefficient, low temperature fuel combustion. For these reasons, most emissions of NH_3 arise from fertilized soils and from livestock.

The initial step in the oxidation of atmospheric NH_3 to NO is by reaction with OH radicals. However, the lifetime of NH_3 from this pathway is sufficiently long (~1-2 months using typical OH values 1-2 × 10^6/cm^3) that it is a small sink compared to uptake of NH_3 by cloud drops, dry deposition, and aerosol particles. Thus, the gas-phase oxidation of NH_3 makes a

very small contribution as a source of NO. Holland et al. (2005) estimated wet and dry deposition of NH_x, based on measurements over the continental United States, and found that emissions of NH_3 in the National Emissions Inventory are perhaps underestimated by about a factor of two to three. Reasons for this imbalance include under-representation of deposition monitoring sites in populated areas and the neglect of off-shore transport in their estimate. The use of fixed deposition velocities that do not reflect local conditions at the time of measurement introduces additional uncertainty into their estimates of dry deposition.

Emissions of SO_2

As can be seen from Table AX2.6-1, emissions of SO_2 are due mainly to the combustion of fossil fuels by electrical utilities and industry. Transportation related sources make only a minor contribution. As a result, most SO_2 emissions originate from point sources. Since sulfur is a volatile component of fuels, it is almost quantitatively released during combustion and emissions can be calculated on the basis of the sulfur content of fuels to greater accuracy than for other pollutants such as NO_x or primary PM.

The major natural sources of SO_2 are volcanoes and biomass burning and DMS oxidation over the oceans. SO_2 constitutes a relatively minor fraction (0.005% by volume) of volcanic emissions (Holland, 1978). The ratio of H_2S to SO_2 is highly variable in volcanic gases. It is typically much less than one, as in the Mt. Saint Helen's eruption (Turco et al., 1983). However, in addition to being degassed from magma, H_2S can be produced if ground waters, especially those containing organic matter, come into contact with volcanic gases. In this case, the ratio of H_2S to SO_2 can be greater than one. H_2S produced this way would more likely be emitted through side vents than through eruption columns (Pinto et al., 1989). Primary particulate sulfate is a component of marine aerosol and is also produced by wind erosion of surface soils.

Volcanic sources of SO_2 are limited to the Pacific Northwest, Alaska, and Hawaii. Since 1980, the Mount St. Helens volcano in the Washington Cascade Range (46.20 N, 122.18 W, summit 2549 m asl) has been a variable source of SO_2. Its major effects came in the explosive eruptions of 1980, which primarily affected the northern part of the mountainous western half of the United States. The Augustine volcano near the mouth of the Cook Inlet in southwestern Alaska (59.363 N, 153.43 W, summit 1252 m asl) has had variable SO_2 emission since its last major eruptions in 1986. Volcanoes in the Kamchatka peninsula of eastern region of Siberian Russia do not significantly effect surface SO_2 concentrations in northwestern North America.

The most serious effects in the United States from volcanic SO_2 occurs on the island of Hawaii. Nearly continuous venting of SO_2 from Mauna Loa and Kilauea produces SO_2 in such large amounts that >100 km downwind of the island SO_2 concentrations can exceed 30 ppbv (Thornton and Bandy, 1993). Depending on wind direction, the west coast of Hawaii (Kona region) has had significant deleterious effects from SO_2 and acidic sulfate aerosols for the past decade.

Emissions of SO_2 from burning vegetation are generally in the range of 1 to 2% of the biomass burned (see e.g., Levine et al., 1999). Sulfur is bound in amino acids in vegetation. This organically bound sulfur is released during combustion. However, unlike nitrogen, about half of the sulfur initially present in vegetation is found in the ash (Delmas, 1982). Gaseous emissions are mainly in the form of SO_2 with much smaller amounts of H_2S and OCS. The ratio of gaseous nitrogen to sulfur emissions is about 14, very close to their ratio in plant tissue (Andreae, 1991). The ratio of reduced nitrogen and sulfur species such as NH_3 and H_2S to their more oxidized forms, such as NO and SO_2, increases from flaming to smoldering phases of combustion, as emissions of reduced species are favored by lower temperatures and O_2 reduced availability.

Emissions of reduced sulfur species are associated typically with marine organisms living either in pelagic or coastal zones and with anaerobic bacteria in marshes and estuaries. Mechanisms for their oxidation were discussed in Section AX2.2. Emissions of dimethyl sulfide (DMS) from marine plankton represent the largest single source of reduced sulfur species to the atmosphere (e.g., Berresheim et al., 1995). Other sources such as wetlands and terrestrial plants and soils probably account for less than 5% of the DMS global flux, with most of this coming from wetlands.

The coastal and wetland sources of DMS have a dormant period in the fall/winter from senescence of plant growth. Marshes die back in fall and winter, so dimethyl sulfide emissions from them are lower, reduced light levels in winter at mid to high latitudes reduce cut phytoplankton growth which also tends to reduce DMS emissions. Western coasts at mid to high latitudes have reduced levels of the light that drive photochemical production and oxidation of DMS. Freezing at mid and high latitudes affects the release of biogenic sulfur gases, particularly in the nutrient-rich regions around Alaska. Transport of SO_2 from regions of biomass burning

seems to be limited by heterogeneous losses that accompany convective processes that ventilate the surface layer and the lower boundary layer (Thornton et al., 1996, TRACE-P data archive).

However, it should be noted that reduced sulfur species are also produced by industry. For example, DMS is used in petroleum refining and in petrochemical production processes to control the formation of coke and carbon monoxide. In addition, it is used to control dusting in steel mills. It is also used in a range of organic syntheses. It also has a use as a food flavoring component. It can also be oxidized by natural or artificial means to dimethyl sulfoxide (DMSO), which has several important solvent properties.

AX2.6.3 Field Studies Evaluating Emissions Inventories

Comparisons of emissions model predictions with observations have been performed in a number of environments. A number of studies of ratios of concentrations of CO to NO_x and NMOC to NO_x during the early 1990s in tunnels and ambient air (summarized in Air Quality Criteria for Carbon Monoxide (U.S. Environmental Protection Agency, 2000)) indicated that emissions of CO and NMOC were systematically underestimated in emissions inventories. However, the results of more recent studies have been mixed in this regard, with many studies showing agreement to within ±50% (U.S. Environmental Protection Agency, 2000). Improvements in many areas have resulted from the process of emissions model development, evaluation, and further refinement. It should be remembered that the conclusions from these reconciliation studies depend on the assumption that NO_x emissions are predicted correctly by emissions factor models. Roadside remote sensing data indicate that over 50% of NMHC and CO emissions are produced by less than about 10% of the vehicles (Stedman et al., 1991). These "super-emitters" are typically poorly maintained vehicles. Vehicles of any age engaged in off-cycle operations (e.g., rapid accelerations) emit much more than if operated in normal driving modes. Bishop and Stedman (1996) found that the most important variables governing CO emissions are fleet age and owner maintenance.

Emissions inventories for North America can be evaluated by comparison to measured long-term trends and or ratios of pollutants in ambient air. A decadal field study of ambient CO at a rural site in the Eastern United States (Hallock-Waters et al., 1999) indicates a downward trend consistent with the downward trend in estimated emissions over the period 1988 to 1999 (U.S. Environmental Protection Agency, 1997), even when a global downward trend is

accounted for. Measurements at two urban areas in the United States confirmed the decrease in CO emissions (Parrish et al., 2002). That study also indicated that the ratio of CO to NO_x emissions decreased by almost a factor of three over 12 years (such a downward trend was noted in AQCD 96). Emissions estimates (U.S. Environmental Protection Agency, 1997) indicate a much smaller decrease in this ratio, suggesting that NO_x emissions from mobile sources may be underestimated and/or increasing. Parrish et al. (2002) conclude that O_3 photochemistry in U.S. urban areas may have become more NO_x-limited over the past decade.

Pokharel et al. (2002) employed remotely sensed emissions from on-road vehicles and fuel use data to estimate emissions in Denver. Their calculations indicate a continual decrease in CO, HC, and NO emissions from mobile sources over the 6-year study period. Inventories based on the ambient data were 30 to 70% lower for CO, 40% higher for HC, and 40 to 80% lower for NO than those predicted by the MOBILE6 model.

Stehr et al. (2000) reported simultaneous measurements of CO, SO_2, and NO_y at an East Coast site. By taking advantage of the nature of mobile sources (they emit NO_x and CO but little SO_2) and power plants (they emit NO_x and SO_2 but little CO), the authors evaluated emissions estimates for the eastern United States. Results indicated that coal combustion contributes 25 to 35% of the total NO_x emissions in rough agreement with emissions inventories (U.S. Environmental Protection Agency, 1997).

Parrish et al. (1998) and Parrish and Fehsenfeld (2000) proposed methods to derive emission rates by examining measured ambient ratios among individual VOC, NO_x and NO_y. There is typically a strong correlation among measured values for these species because emission sources are geographically collocated, even when individual sources are different. Correlations can be used to derive emissions ratios between species, including adjustments for the impact of photochemical aging. Investigations of this type include correlations between CO and NO_y (e.g., Parrish et al., 1991), between individual VOC species and NO_y (Goldan et al., 1995, 1997, 2000) and between various individual VOC (Goldan et al., 1995, 1997; McKeen and Liu, 1993; McKeen et al., 1996). Buhr et al. (1992) derived emission estimates from principal component analysis (PCA) and other statistical methods. Many of these studies are summarized in Trainer et al. (2000), Parrish et al. (1998), and Parrish and Fehsenfeld (2000). Goldstein and Schade (2000) also used species correlations to identify the relative impacts of anthropogenic and biogenic emissions. Chang et al. (1996, 1997) and Mendoza-Dominguez and Russell (2000,

2001) used the more quantative technique of inverse modeling to derive emission rates, in conjunction with results from chemistry-transport models.

AX2.7 METHODS USED TO CALCULATE CONCENTRATIONS OF NITROGEN OXIDES AND THEIR CHEMICAL INTERACTIONS IN THE ATMOSPHERE

Atmospheric chemistry and transport models are the major tools used to calculate the relations among O_3, other oxidants, and their precursors, the transport and transformation of air toxics, the production of secondary organic aerosol, the evolution of the particle size distribution, and the production and deposition of pollutants affecting ecosystems. Chemical transport models are driven by emissions inventories for primary species such as the precursors for O_3 and PM and by meterological fields produced by other numerical models. Emissions of precursor compounds can be divided into anthropogenic and natural source categories. Natural sources can be further divided into biotic (vegetation, microbes, animals) and abiotic (biomass burning, lightning) categories. However, the distinction between natural sources and anthropogenic sources is often difficult to make as human activities affect directly, or indirectly, emissions from what would have been considered natural sources during the preindustrial era. Emissions from plants and animals used in agriculture have been referred to as anthropogenic or natural in different applications. Wildfire emissions may be considered to be natural, except that forest management practices may have led to the buildup of fuels on the forest floor, thereby altering the frequency and severity of forest fires. Needed meteorological quantities such as winds and temperatures are taken from operational analyses, reanalyses, or circulation models. In most cases, these are off-line analyses, i.e., they are not modified by radiatively active species such as O_3 and particles generated by the model.

A brief overview of atmospheric chemistry-transport models is given in Section AX2.7.1. A discussion of emissions inventories of precursors used by these models is given in Section AX2.7.2. Uncertainties in emissions estimates have also been discussed in Air Quality Criteria for Particulate Matter (U.S. Environmental Protection Agency, 2004). Chemistry-transport model evaluation and an evaluation of the reliability of emissions inventories are presented in Section AX2.7.4.

AX2.7.1 Chemistry-Transport Models

Atmospheric CTMs have been developed for application over a wide range of spatial scales ranging from neighborhood to global. Regional scale CTMs are used: 1) to obtain better understanding of the processes controlling the formation, transport, and destruction of gas-and particle-phase criteria and hazardous air pollutants; 2) to understand the relations between O_3 concentrations and concentrations of its precursors such as NO_x and VOCs, the factors leading to acid deposition, and hence to possible damage to ecosystems; and 3) to understand relations among the concentration patterns of various pollutants that may exert adverse health effects. Chemistry Transport Models are also used for determining control strategies for O_3 precursors. However, this application has met with varying degrees of success because of the highly nonlinear relations between O_3 and emissions of its precursors, and uncertainties in emissions, parameterizations of transport, and chemical production and loss terms. Uncertainties in meteorological variables and emissions can be large enough to lead to significant errors in developing control strategies (e.g., Russell and Dennis, 2000; Sillman et al., 1995).

Global scale CTMs are used to address issues associated with climate change, stratospheric ozone depletion, and to provide boundary conditions for regional scale models. CTMs include mathematical (and often simplified) descriptions of atmospheric transport, the transfer of solar radiation through the atmosphere, chemical reactions, and removal to the surface by turbulent motions and precipitation for pollutants emitted into the model domain. Their upper boundaries extend anywhere from the top of the mixing layer to the mesopause (about 80 km in height), to obtain more realistic boundary conditions for problems involving stratospheric dynamics. There is a trade-off between the size of the modeling domain and the grid resolution used in the CTM that is imposed by computational resources.

There are two major formulations of CTMs in current use. In the first approach, grid-based, or Eulerian, air quality models, the region to be modeled (the modeling domain) is subdivided into a three-dimensional array of grid cells. Spatial derivatives in the species continuity equations are cast in finite-difference there are also some finite-element models, but not many applications form over this grid, and a system of equations for the concentrations of all the chemical species in the model are solved numerically at each grid point. Time dependent continuity (mass conservation) equations are solved for each species including terms for transport, chemical production and destruction, and emissions and deposition (if relevant), in

each cell. Chemical processes are simulated with ordinary differential equations, and transport processes are simulated with partial differential equations. Because of a number of factors such as the different time scales inherent in different processes, the coupled, nonlinear nature of the chemical process terms, and computer storage limitations, all of the terms in the equations are not solved simultaneously in three dimensions. Instead, operator splitting, in which terms in the continuity equation involving individual processes are solved sequentially, is used. In the second CTM formulation, trajectory or Lagrangian models, a large number of hypothetical air parcels are specified as following wind trajectories. In these models, the original system of partial differential equations is transformed into a system of ordinary differential equations.

A less common approach is to use a hybrid Lagrangian/Eulerian model, in which certain aspects of atmospheric chemistry and transport are treated with a Lagrangian approach and others are treaded in a**n** Eulerian manner (e.g., Stein et al., 2000). Each approach has **its** their advantages and disadvantages. The Eulerian approach is more general in that it includes processes that mix air parcels and allows integrations to be carried out for long periods during which individual air parcels lose their identity. There are, however, techniques for including the effects of mixing in Lagrangian models such as FLEXPART (e.g., Zanis et al., 2003), ATTILA (Reithmeier and Sausen, 2002), and CLaMS (McKenna et al., 2002).

Regional Scale Chemistry Transport Models

Major modeling efforts within the U.S. Environmental Protection Agency center on the Community Multiscale Air Quality modeling system (CMAQ, Byun and Ching, 1999; Byun and Schere, 2006). A number of other modeling platforms using Lagrangian and Eulerian frameworks have been reviewed in the 96 AQCD for O_3 (U.S. Environmental Protection Agency, 1997), and in Russell and Dennis (2000). The capabilities of a number of CTMs designed to study local- and regional-scale air pollution problems are summarized by Russell and Dennis (2000). Evaluations of the performance of CMAQ are given in Arnold et al. (2003), Eder and Y (2005), Appel et al. (2005), and Fuentes and Raftery (2005). The domain of CMAQ can extend from several hundred km to the hemispherical scale. In addition, both of these classes of models allow the resolution of the calculations over specified areas to vary. CMAQ is most often driven by the MM5 mesoscale meteorological model (Seaman, 2000), though it may be driven by other meteorological models (e.g., RAMS). Simulations of O_3 episodes over regional domains have been performed with a horizontal resolution as low as 1 km, and smaller

calculations over limited domains have been accomplished at even finer scales. However, simulations at such high resolutions require better parameterizations of meteorological processes such as boundary layer fluxes, deep convection and clouds (Seaman, 2000), and finer-scale emissions. Finer spatial resolution is necessary to resolve features such as urban heat island circulations; sea, bay, and land breezes; mountain and valley breezes, and the nocturnal low-level jet.

The most common approach to setting up the horizontal domain is to nest a finer grid within a larger domain of coarser resolution. However, there are other strategies such as the stretched grid (e.g., Fox-Rabinovitz et al., 2002) and the adaptive grid. In a stretched grid, the grid's resolution continuously varies throughout the domain, thereby eliminating any potential problems with the sudden change from one resolution to another at the boundary. Caution should be exercised in using such a formulation, because certain parameterizations that are valid on a relatively coarse grid scale (such as convection) may not be valid on finer scales. Adaptive grids are not fixed at the start of the simulation, but instead adapt to the needs of the simulation as it evolves (e.g., Hansen et al., 1994). They have the advantage that they can resolve processes at relevant spatial scales. However, they can be very slow if the situation to be modeled is complex. Additionally, if adaptive grids are used for separate meteorological, emissions, and photochemical models, there is no reason a priori why the resolution of each grid should match, and the gains realized from increased resolution in one model will be wasted in the transition to another model. The use of finer horizontal resolution in CTMs will necessitate finer-scale inventories of land use and better knowledge of the exact paths of roads, locations of factories, and, in general, better methods for locating sources and estimating their emissions.

The vertical resolution of these CTMs is variable, and usually configured to have higher resolution near the surface and decreasing aloft. Because the height of the boundary layer is of critical importance in simulations of air quality, improved resolution of the boundary layer height would likely improve air quality simulations. Additionally, current CTMs do not adequately resolve fine scale features such as the nocturnal low-level jet in part because little is known about the nighttime boundary layer.

CTMs require time-dependent, three-dimensional wind fields for the period of simulation. The winds may be either generated by a model using initial fields alone or with four-dimensional data assimilation to improve the model's performance, fields (i.e., model equations

can be updated periodically or "nudged", to bring results into agreement with observations. Modeling efforts typically focus on simulations of several days' duration, the typical time scale for individual O_3 episodes, but there have been several attempts at modeling longer periods. For example, Kasibhatla and Chameides (2000) simulated a four-month period from May to September of 1995 using MAQSIP. The current trend in modeling applications is towards annual simulations. This trend is driven in part by the need to better understand observations of periods of high wintertime PM (e.g., Blanchard et al., 2002) and the need to simulate O_3 episodes occurring outside of summer.

Chemical kinetics mechanisms (a set of chemical reactions) representing the important reactions occurring in the atmosphere are used in CTMs to estimate the rates of chemical formation and destruction of each pollutant simulated as a function of time. Unfortunately, chemical mechanisms that explicitly treat the reactions of each individual reactive species are too computationally demanding to be incorporated into CTMs. For example, a master chemical mechanism includes approximately 10,500 reactions involving 3603 chemical species (Derwent et al., 2001). Instead, "lumped" mechanisms, that group compounds of similar chemistry together, are used. The chemical mechanisms used in existing photochemical O_3 models contain significant uncertainties that may limit the accuracy of their predictions; the accuracy of each of these mechanisms is also limited by missing chemistry. Because of different approaches to the lumping of organic compounds into surrogate groups, chemical mechanisms can produce somewhat different results under similar conditions. The CB-IV chemical mechanism (Gery et al., 1989), the RADM II mechanism (Stockwell et al., 1990), the SAPRC (e.g., Wang et al., 2000a,b; Carter, 1990) and the RACM mechanisms can be used in CMAQ. Jimenez et al. (2003) provide brief descriptions of the features of the main mechanisms in use and they compared concentrations of several key species predicted by seven chemical mechanisms in a box model simulation over 24 h. The average deviation from the average of all mechanism predictions for O_3 and NO over the daylight period was less than 20%, and was 10% for NO_2 for all mechanisms. However, much larger deviations were found for HNO_3, PAN, HO_2, H_2O_2, C_2H_4, and C_5H_8 (isoprene). An analysis for OH radicals was not presented. The large deviations shown for most species imply differences between the calculated lifetimes of atmospheric species and the assignment of model simulations to either NO_x-limited or radical quantity limited regimes between mechanisms. Gross and Stockwell (2003) found small differences between

mechanisms for clean conditions, with differences becoming more significant for polluted conditions, especially for NO_2 and organic peroxy radicals. They caution modelers to consider carefully the mechanisms they are using. Faraji et al. (2006) found differences of 40% in peak 1h O_3 in the Houston-Galveston-Brazoria area between simulations using SAPRAC and CB4. They attributed differences in predicted O_3 concentrations to differences in the mechanisms of oxidation of aromatic hydrocarbons.

CMAQ and other CTMs (e.g., PM-CAMx) incorporate processes and interactions of aerosol-phase chemistry (Mebust et al., 2003). There have also been several attempts to study the feedbacks of chemistry on atmospheric dynamics using meteorological models, like MM5 (e.g., Grell et al., 2000; Liu et al., 2001a; Lu et al., 1997; Park et al., 2001). This coupling is necessary to simulate accurately feedbacks such as may be caused by the heavy aerosol loading found in forest fire plumes (Lu et al., 1997; Park et al., 2001), or in heavily polluted areas. Photolysis rates in CMAQ can now be calculated interactively with model produced O_3, NO_2, and aerosol fields (Binkowski et al., 2007).

Spatial and temporal characterizations of anthropogenic and biogenic precursor emissions must be specified as inputs to a CTM. Emissions inventories have been compiled on grids of varying resolution for many hydrocarbons, aldehydes, ketones, CO, NH_3, and NO_x. Emissions inventories for many species require the application of some algorithm for calculating the dependence of emissions on physical variables such as temperature and to convert the inventories into formatted emission files required by a CTM. For example, preprocessing of emissions data for CMAQ is done by the SMOKE (Spare-Matrix Operator Kernel Emissions) system. For many species, information concerning the temporal variability of emissions is lacking, so long-term (e.g., annual or O_3-season) averages are used in short-term, episodic simulations. Annual emissions estimates are often modified by the emissions model to produce emissions more characteristic of the time of day and season. Significant errors in emissions can occur if an inappropriate time dependence or a default profile is used. Additional complexity arises in model calculations because different chemical mechanisms are based on different species, and inventories constructed for use with another mechanism must be adjusted to reflect these differences. This problem also complicates comparisons of the outputs of these models because one chemical mechanism may produce some species not present in another mechanism yet neither may agree with the measurements.

In addition to wet deposition, dry deposition (the removal of chemical species from the atmosphere by interaction with ground-level surfaces) is an important removal process for pollutants on both urban and regional scales and must be included in CTMs. The general approach used in most models is the resistance in series method, in which where dry deposition is parameterized with a V_d, which is represented as $v_d = (r_a + r_b + r_c)^{-1}$ where r_a, r_b, and r_c represent the resistance due to atmospheric turbulence, transport in the fluid sublayer very near the elements of surface such as leaves or soil, and the resistance to uptake of the surface itself. This approach works for a range of substances, although it is inappropriate for species with substantial emissions from the surface or for species whose deposition to the surface depends on its concentration at the surface itself. The approach is also modified somewhat for aerosols: the terms r_b and r_c are replaced with a surface V_d to account for gravitational settling. In their review, Wesley and Hicks (2000) point out several shortcomings of current knowledge of dry deposition. Among those shortcomings are difficulties in representing dry deposition over varying terrain where horizontal advection plays a significant role in determining the magnitude of r_a and difficulties in adequately determining a V_d for extremely stable conditions such as those occurring at night (e.g., Mahrt, 1998). Under the best of conditions, when a model is exercised over a relatively small area where dry deposition measurements have been made, models still commonly show uncertainties at least as large as ±30% (e.g., Massman et al., 1994; Brook et al., 1996; Padro, 1996). Wesely and Hicks (2000) state that an important result of these comparisons is that the current level of sophistication of most dry deposition models is relatively low, and that deposition estimates therefore must rely heavily on empirical data. Still larger uncertainties exist when the surface features in the built environment are not well known or when the surface comprises a patchwork of different surface types, as is common in the eastern United States.

The initial conditions, i.e., the concentration fields of all species computed by a model, and the boundary conditions, i.e., the concentrations of species along the horizontal and upper boundaries of the model domain throughout the simulation must be specified at the beginning of the simulation. It would be best to specify initial and boundary conditions according to observations. However, data for vertical profiles of most species of interest are sparse. The results of model simulations over larger, preferably global, domains can also be used. As may be expected, the influence of boundary conditions depends on the lifetime of the species under

consideration and the time scales for transport from the boundaries to the interior of the model domain (Liu et al., 2001b).

Each of the model components described above has an associated uncertainty, and the relative importance of these uncertainties varies with the modeling application. The largest errors in photochemical modeling are still thought to arise from the meteorological and emissions inputs to the model (Russell and Dennis, 2000). Within the model itself, horizontal advection algorithms are still thought to be significant source of uncertainty (e.g., Chock and Winkler, 1994), though more recently, those errors are thought to have been reduced (e.g., Odman et al., 1996). There are also indications that problems with mass conservation continue to be present in photochemical and meteorological models (e.g., Odman and Russell, 1999); these can result in significant simulation errors. The effects of errors in initial conditions can be minimized by including several days "spin-up" time in a simulation to allow the model to be driven by emitted species before the simulation of the period of interest begins.

While the effects of poorly specified boundary conditions propagate through the model's domain, the effects of these errors remain undetermined. Because many meteorological processes occur on spatial scales which are smaller than the model grid spacing (either horizontally or vertically) and thus are not calculated explicitly, parameterizations of these processes must be used and these introduce additional uncertainty.

Uncertainty also arises in modeling the chemistry of O_3 formation because it is highly nonlinear with respect to NO_x concentrations. Thus, the volume of the grid cell into which emissions are injected is important because the nature of O_3 chemistry (i.e., O_3 production or titration) depends in a complicated way on the concentrations of the precursors and the OH radical as noted earlier. The use of ever-finer grid spacing allows regions of O_3 titration to be more clearly separated from regions of O_3 production. The use of grid spacing fine enough to resolve the chemistry in individual power-plant plumes is too demanding of computer resources for this to be attempted in most simulations. Instead, parameterizations of the effects of sub-grid-scale processes such as these must be developed; otherwise serious errors can result if emissions are allowed to mix through an excessively large grid volume before the chemistry step in a model calculation is performed. In light of the significant differences between atmospheric chemistry taking place inside and outside of a power plant plume (e.g., Ryerson et al., 1998 and Sillman, 2000), inclusion of a separate, meteorological module for treating large, tight plumes is

necessary. Because the photochemistry of O_3 and many other atmospheric species is nonlinear, emissions correctly modeled in a tight plume may be incorrectly modeled in a more dilute plume. Fortunately, it appears that the chemical mechanism used to follow a plume's development need not be as detailed as that used to simulate the rest of the domain, as the inorganic reactions are the most important in the plume see (e.g., Kumar and Russell, 1996). The need to include explicitly plume-in-grid chemistry only down to the level of the smallest grid disappears if one uses the adaptive grid approach mentioned previously, though such grids are more computationally intensive. The differences in simulations are significant because they can lead to significant differences in the calculated sensitivity of O_3 to its precursors (e.g., Sillman et al., 1995).

Because the chemical production and loss terms in the continuity equations for individual species are coupled, the chemical calculations must be performed iteratively until calculated concentrations converge to within some preset criterion. The number of iterations and the convergence criteria chosen also can introduce error.

Global Scale CTMs

The importance of global transport of O_3 and O_3 precursors and their contribution to regional O_3 levels in the United States is slowly becoming apparent. There are presently on the order of 20 three-dimensional global models that have been developed by various groups to address problems in tropospheric chemistry. These models resolve synoptic meteorology, O_3-NO_x-CO-hydrocarbon photochemistry, have parameterizations for wet and dry deposition, and parameterize sub-grid scale vertical mixing processes such as convection. Global models have proven useful for testing and advancing scientific understanding beyond what is possible with observations alone. For example, they can calculate quantities of interest that cannot be measured directly, such as the export of pollution from one continent to the global atmosphere or the response of the atmosphere to future perturbations to anthropogenic emissions.

Global simulations are typically conducted at a horizontal resolution of about 200 km^2. Simulations of the effects of transport from long-range transport link multiple horizontal resolutions from the global to the local scale. Finer resolution will only improve scientific understanding to the extent that the governing processes are more accurately described at that scale. Consequently, there is a critical need for observations at the appropriate scales to evaluate the scientific understanding represented by the models.

During the recent IPCC-AR4 tropospheric chemistry study coordinated by the European Union project Atmospheric Composition Change: the European Network of excellence (ACCENT), 26 atmospheric CTMs were used to estimate the impacts of three emissions scenarios on global atmospheric composition, climate, and air quality in 2030 (Dentener et al., 2006a). All models were required to use anthropogenic emissions developed at IIASA (Dentener et al., 2005) and GFED version 1 biomass burning emissions (van der Werf et al., 2003) as described in Stevenson et al. (2006). The base simulations from these models were evaluated against a suite of present-day observations. Most relevant to this assessment report are the evaluations with ozone and NO_2, and for nitrogen and sulfur deposition (Stevenson et al., 2006; van Noije et al., 2006; Dentener et al., 2006a), which are summarized briefly below.

An analysis of the standard deviation of zonal mean and tropospheric column O_3 reveals large inter-model variability in the tropopause region and throughout the polar troposphere, likely reflecting differences in model tropopause levels and the associated stratospheric injection of O_3 to the troposphere (Stevenson et al., 2006). Ozone distributions in the tropics also exhibit large standard deviations (~30%), particularly as compared to the mid-latitudes (~20%), indicating larger uncertainties in the processes that influence ozone in the tropics: deep tropical convection, lightning NO_x, isoprene emissions and chemistry, and biomass burning emissions (Stevenson et al., 2006).

Stevenson et al., (2006) found that the model ensemble mean (MEM) typically captures the observed seasonal cycles to within one standard deviation. The largest discrepancies between the MEM and observations include: (1) an underestimate of the amplitude of the seasonal cycle at 30°-90°N with a 10 ppbv overestimate of winter ozone, possibly due to the lack of a seasonal cycle in anthropogenic emissions or to shortcomings in the stratospheric influx of O_3, and (2) an overestimate of O_3 throughout the northern tropics. However, the MEM was found to capture the observed seasonal cycles in the Southern Hemisphere, suggesting that the models adequately represent biomass burning and natural emissions.

The mean present-day global ozone budget across the current generation of CTMs differs substantially from that reported in the IPCC TAR, with a 50% increase in the mean chemical production (to 5100 Tg O_3 yr^{-1}), a 30% increase in the chemical and deposition loss terms (to 4650 and 1000 Tg O_3 yr^{-1}, respectively) and a 30% decrease in the mean stratospheric input flux (to 550 Tg O_3 yr^{-1}) (Stevenson et al., 2006). The larger chemical terms as compared to the IPCC

TAR are attributed mainly to higher NO_x (as well as an equatorward shift in distribution) and isoprene emissions, although more detailed NMHC schemes and/or improved representations of photolysis, convection, and stratospheric-tropospheric exchange may also contribute (Stevenson et al., 2006).

A subset of 17 of the 26 models used in the Stevenson et al. (2006) study was used to compare with three retrievals of NO_2 columns from the GOME instrument (van Noije et al., 2006) for the year 2000. The higher resolution models reproduce the observed patterns better, and the correlation among simulated and retrieved columns improved for all models when simulated values are smoothed to a $5° \times 5°$ grid, implying that the models do not accurately reproduce the small-scale features of NO_2 (van Noije et al., 2006). Van Noije et al. (2006) suggest that variability in simulated NO_2 columns may reflect a model differences in OH distributions and the resulting NO_x lifetimes, as well as differences in vertical mixing which strongly affect partitioning between NO and NO_2. Overall, the models tend to underestimate concentrations in the retrievals in industrial regions (including the eastern United States) and overestimate them in biomass burning regions (van Noije et al., 2006).

Over the eastern United States, and industrial regions more generally, the spread in absolute column abundances is generally larger among the retrievals than among the models, with the discrepancy among the retrievals particularly pronounced in winter (van Noije et al., 2006), suggesting that the models are biased low, or that the European retrievals may be biased high as the Dalhousie/SAO retrieval is closer to the model estimates. The lack of seasonal variability in fossil fuel combustion emissions may contribute to a wintertime model underestimate (van Noije et al., 2006) that is manifested most strongly over Asia. In biomass burning regions, the models generally reproduce the timing of the seasonal cycle of the retrievals, but tend to overestimate the seasonal cycle amplitude, partly due to lower values in the wet season, which may reflect an underestimate in wet season soil NO emissions (van Noije et al., 2006; Jaegle et al., 2004, 2005).

Deposition in Global CTMs

Both wet and dry deposition are highly parameterized in global CTMs. While all current models implement resistance schemes for dry deposition, the generated V_d generated from different models can vary highly across terrains (Stevenson et al., 2006). The accuracy of wet

deposition in global CTMs is tied to spatial and temporal distribution of model precipitation and the treatment of chemical scavenging. Dentener et al. (2006b) compared wet deposition across 23 models with available measurements around the globe. Figures AX2.7-1 and AX2.7-2 below extract the results of a comparison of the 23-model mean versus observations from Dentener et al. (2006b) over the eastern United States for nitrate and sulfate deposition, respectively. The mean model results are strongly correlated with the observations ($r > 0.8$), and usually capture the magnitude of wet deposition to within a factor of 2 over the eastern United States (Dentener et al., 2006b). Dentener et al. (2006b) conclude that 60-70% of the participating models capture the measurements to within 50% in regions with quality controlled observations. This study then identified world regions receiving >1000 mg (N) m^{-2} yr^{-1} (the "critical load") and found that 20% of the natural vegetation (non-agricultural) in the United States is exposed to nitrogen deposition in excess of the critical load threshold (Dentener et al., 2006b).

Modeling the Effects of Convection

The effects of deep convection can be simulated using cloud-resolving models, or in regional or global models in which the convection is parameterized. The Goddard Cumulus Ensemble (GCE) model (Tao and Simpson, 1993) has been used by Pickering et al. (1991; 1992a,b; 1993; 1996), Scala et al. (1990) and Stenchikov et al. (1996) in the analysis of convective transport of trace gases. The cloud model is nonhydrostatic and contains a detailed representation of cloud microphysical processes. Two- and three-dimensional versions of the model have been applied in transport analyses. The initial conditions for the model are usually from a sounding of temperature, water vapor and winds representative of the region of storm development. Model-generated wind fields can be used to perform air parcel trajectory analyses and tracer advection calculations.

Such methods were used by Pickering et al. (1992b) to examine transport of urban plumes by deep convection. Transport of an Oklahoma City plume by the 10-11 June 1985 PRE-STORM squall line was simulated with the 2-D GCE model. This major squall line passed over the Oklahoma City metropolitan area, as well as more rural areas to the north. Chemical observations ahead of the squall line were conducted by the PRE-STORM aircraft. In this event, forward trajectories from the boundary layer at the leading edge of the storm showed that almost 75% of the low-level inflow was transported to altitudes exceeding 8 km. Over 35% of

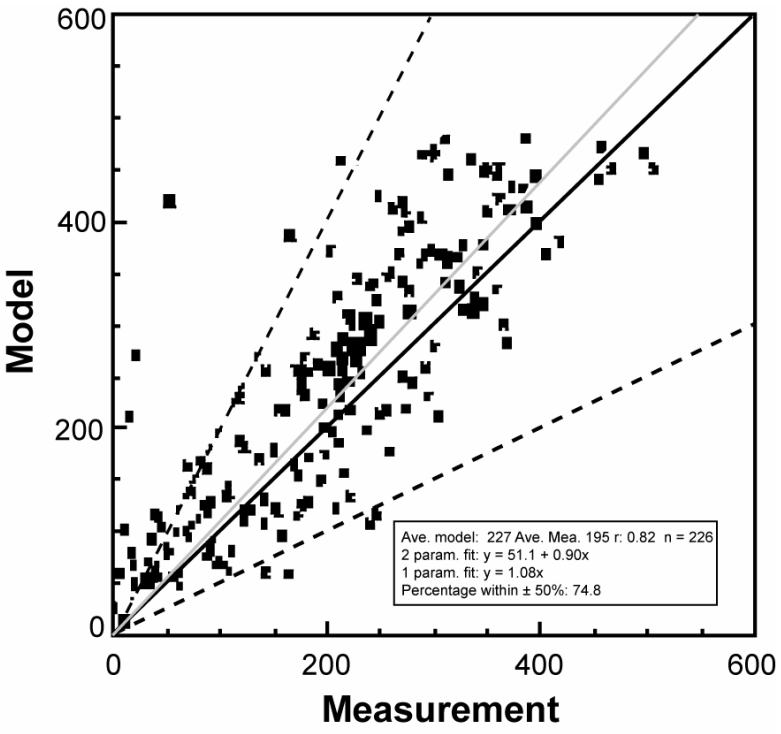


Figure AX2.7-1. Scatter plot of total nitrate (HNO_3 plus aerosol nitrate) wet deposition (mg(N)m $2yr^{-1}$) of the mean model versus measurements for the North American Deposition Program (NADP) network. Dashed lines indicate factor of 2. The gray line is the result of a linear regression fitting through 0.

Source: Dentener et al. (2006b).

the air parcels reached altitudes over 12 km. Tracer transport calculations were performed for CO, NO_x, O_3, and hydrocarbons. Rural boundary layer NO_x was only 0.9 ppbv, whereas the urban plume contained about 3 ppbv. In the rural case, mixing ratios of 0.6 ppbv were transported up to 11 km. Cleaner air descended at the rear of the storm lowering NO_x at the surface from 0.9 to 0.5 ppbv. In the urban plume, mixing ratios in the updraft core reached 1 ppbv between 14 and 15 km. At the surface, the main downdraft lowered the NO_x mixing ratios from 3 to 0.7 ppbv.

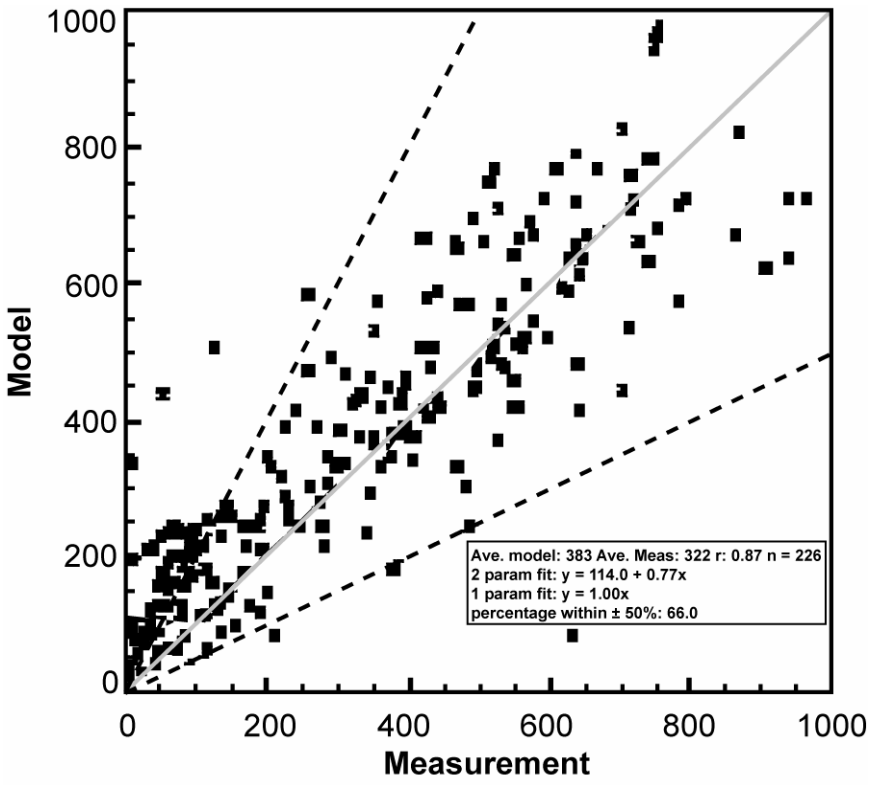


Figure AX2.7-2. Same as Figure AX2.7-1 but for sulfate wet deposition ($mg(S)m^{-2}yr^{-1}$).

Source: Dentener et al. (2006b).

Regional chemical transport models have been used for applications such as simulations of photochemical O_3 production, acid deposition, and fine PM. Walcek et al. (1990) included a parameterization of cloud-scale aqueous chemistry, scavenging, and vertical mixing in the chemistry model of Chang et al. (1987). The vertical distribution of cloud microphysical properties and the amount of sub-cloud-layer air lifted to each cloud layer are determined using a simple entrainment hypothesis (Walcek and Taylor, 1986). Vertically integrated O_3 formation rates over the northeast U. S. were enhanced by ~50% when the in-cloud vertical motions were included in the model.

Wang et al. (1996) simulated the 10-11 June 1985 PRE-STORM squall line with the NCAR/Penn State Mesoscale Model (MM5; Grell et al., 1994; Dudhia, 1993). Convection was parameterized as a sub-grid-scale process in MM5 using the Kain Fritsch (1993) scheme. Mass

fluxes and detrainment profiles from the convective parameterization were used along with the 3-D wind fields in CO tracer transport calculations for this convective event.

Convective transport in global chemistry and transport models is treated as a sub-grid-scale process that is parameterized typically using cloud mass flux information from a general circulation model or global data assimilation system. While GCMs can provide data only for a "typical" year, data assimilation systems can provide "real" day-by-day meteorological conditions, such that CTM output can be compared directly with observations of trace gases. The NASA Goddard Earth Observing System Data Assimilation System (GEOS-1 DAS and successor systems; Schubert et al., 1993; Bloom et al., 1996; Bloom et al., 2005) provides archived global data sets for the period 1980 to present, at $2^o \times 2.5^o$ or better resolution with 20 layers or more in the vertical. Deep convection is parameterized with the Relaxed Arakawa-Schubert scheme (Moorthi and Suarez, 1992) in GEOS-1 and GEOS-3 and with the Zhang and McFarlane (1995) scheme in GEOS-4. Pickering et al. (1995) showed that the cloud mass fluxes from GEOS-1 DAS are reasonable for the 10-11 June 1985 PRE-STORM squall line based on comparisons with the GCE model (cloud-resolving model) simulations of the same storm. In addition, the GEOS-1 DAS cloud mass fluxes compared favorably with the regional estimates of convective transport for the central U. S. presented by Thompson et al. (1994). However, Allen et al. (1997) have shown that the GEOS-1 DAS overestimates the amount and frequency of convection in the tropics and underestimates the convective activity over midlatitude marine storm tracks.

Global models with parameterized convection and lightning have been run to examine the roles of these processes over North America. Lightning contributed 23% of upper tropospheric NO_y over the SONEX region according to the UMD-CTM modeling analysis of Allen et al. (2000). During the summer of 2004 the NASA Intercontinental Chemical Transport Experiment - North America (INTEX-NA) was conducted primarily over the eastern two-thirds of the United States, as a part of the International Consortium for Atmospheric Research on Transport and Transformation (ICARTT). Deep convection was prevalent over this region during the experimental period. Cooper et al. (2006) used a particle dispersion model simulation for NO_x to show that 69-84% of the upper tropospheric O_3 enhancement over the region in Summer 2004 was due to lightning NO_x. The remainder of the enhancement was due to convective transport of O_3 from the boundary layer or other sources of NO_x. Hudman et al.

(2007) used a GEOS-Chem model simulation to show that lightning was the dominant source of upper tropospheric NO_x over this region during this period. Approximately 15% of North American boundary layer NO_x emissions were shown to have been vented to the free troposphere over this region based on both the observations and the model.

AX2.7.2 CTM Evaluation

The comparison of model predictions with ambient measurements represents a critical task for establishing the accuracy of photochemical models and evaluating their ability to serve as the basis for making effective control strategy decisions. The evaluation of a model's performance, or its adequacy to perform the tasks for which it was designed can only be conducted within the context of measurement errors and artifacts. Not only are there analytical problems, but there are also problems in assessing the representativeness of monitors at ground level for comparison with model values which represent typically an average over the volume of a grid box.

Evaluations of CMAQ are given in Arnold et al. (2003) and Fuentes and Raftery (2005). Discrepancies between model predictions and observations can be used to point out gaps in current understanding of atmospheric chemistry and to spur improvements in parameterizations of atmospheric chemical and physical processes. Model evaluation does not merely involve a straightforward comparison between model predictions and the concentration field of the pollutant of interest. Such comparisons may not be meaningful because it is difficult to determine if agreement between model predictions and observations truly represents an accurate treatment of physical and chemical processes in the CTM or the effects of compensating errors in complex model routines. Ideally, each of the model components (emissions inventories, chemical mechanism, meteorological driver) should be evaluated individually. However, this is rarely done in practice.

Chemical transport models for O_3 formation at the urban/regional scale have traditionally been evaluated based on their ability to simulate correctly O_3. A series of performance statistics that measure the success of individual model simulations to represent the observed distribution of ambient O_3, as represented by a network of surface measurements at the urban scale were recommended by the EPA (U.S. Environmental Protection Agency, 1991; see also Russell and Dennis, 2000). These statistics consist of the following:

- Unpaired peak O_3 concentration within a metropolitan region (typically for a single day).
- Normalized bias equal to the summed difference between model and measured hourly concentrations divided by the sum of measured hourly concentrations.
- Normalized gross error, equal to the summed unsigned (absolute value) difference between model and measured hourly concentrations divided by the sum of measured hourly concentrations.

Unpaired peak prediction accuracy, A_u;

$$A_u = \frac{C_p(x,t)_{max} - C_o(x',t')_{max}}{C_o(x',t')_{max}} * 100\%, \quad \text{(AX2-48)}$$

Normalized bias, D;

$$D = \frac{1}{N} \sum_{i=1}^{N} \frac{\{C_p(x_i,t) - C_o(x_i,t)\}}{C_o(x_i,t)}, t = 1,24. \quad \text{(AX2-49)}$$

Gross error, E_d (for hourly observed values of O_3 >60ppb)

$$E_d = \frac{1}{N} \sum_{i=1}^{N} \frac{\left| C_p(x_i,t) - C_o(x_i,t) \right|}{C_o(x_i,t)}, t = 1,24. \quad \text{(AX2-50)}$$

The following performance criteria for regulatory models were recommended in U.S. Environmental Protection Agency (1991): unpaired peak O_3 to within ±15% or ±20%; normalized bias within ± 5% to ± 15%; and normalized gross error less than 30% to 35%, but only when O_3 the concentration >60 ppb. This can lead to difficulties in evaluating model performance since nighttime and diurnal cycles are ignored. A major problem with this method of model evaluation is that it does not provide any information about the accuracy of O_3-precursor relations predicted by the model. The process of O_3 formation is sufficiently complex that models can predict O_3 correctly without necessarily representing the O_3 formation process properly. If the O_3 formation process is incorrect, then the modeled source-receptor relations will also be incorrect.

Studies by Sillman et al. (1995, 2003), Reynolds et al. (1996), and Pierce et al. (1998) have identified instances in which different model scenarios can be created with very different O_3-precursor sensitivity, but without significant differences in the predicted O_3 fields. Figures AX2.7-3a,b provides an example. Referring to the O_3-NO_x-VOC isopleth plot (Figure AX2.7-4), it can be seen that similar O_3 concentrations can be found for photochemical conditions that have very different sensitivity to NO_x and VOCs.

Global-scale CTMs have generally been evaluated by comparison with measurements for a wide array of species, rather than just for O_3 (e.g., Wang et al., 1998; Emmons et al., 2000; Bey et al., 2001; Hess, 2001; Fiore et al., 2002). These have included evaluation of major primary species (NO_x, CO, and selected VOCs) and an array of secondary species (HNO_3, PAN, H_2O_2) that are often formed concurrently with O_3. Models for urban and regional O_3 have also been evaluated against a broader ensemble of measurements in a few cases, often associated with measurement intensives (e.g., Jacobson et al., 1996; Lu et al., 1997; Sillman et al., 1998). The results of a comparison between observed and computed concentrations from Jacobson et al. (1996) for the Los Angeles Basin are shown in Figures AX2.7-5a,b.

The highest concentrations of primary species usually occur in close proximity to emission sources (typically in urban centers) and at times when dispersion rates are low. The diurnal cycle includes high concentrations at night, with maxima during the morning rush hour, and low concentrations during the afternoon (Figure AX2.7-5a). The afternoon minima are driven by the much greater rate of vertical mixing at that time. Primary species also show a seasonal maximum during winter, and are often high during fog episodes in winter when vertical mixing, is suppressed. By contrast, secondary species such as O_3 are typically highest during the afternoon (the time of greatest photochemical activity), on sunny days and during summer.

During these conditions, concentrations of primary species may be relatively low. Strong correlations between primary and secondary species are generally observed only in downwind rural areas where all anthropogenic species are simultaneously elevated. The difference in the diurnal cycles of primary species (CO, NO_x, and ethane) and secondary species (O_3, PAN, and HCHO) is evident in Figure AX2.7-5b.

Models for urban and regional chemistry have been evaluated less extensively than global-scale models in part because the urban/regional context presents a number of difficult

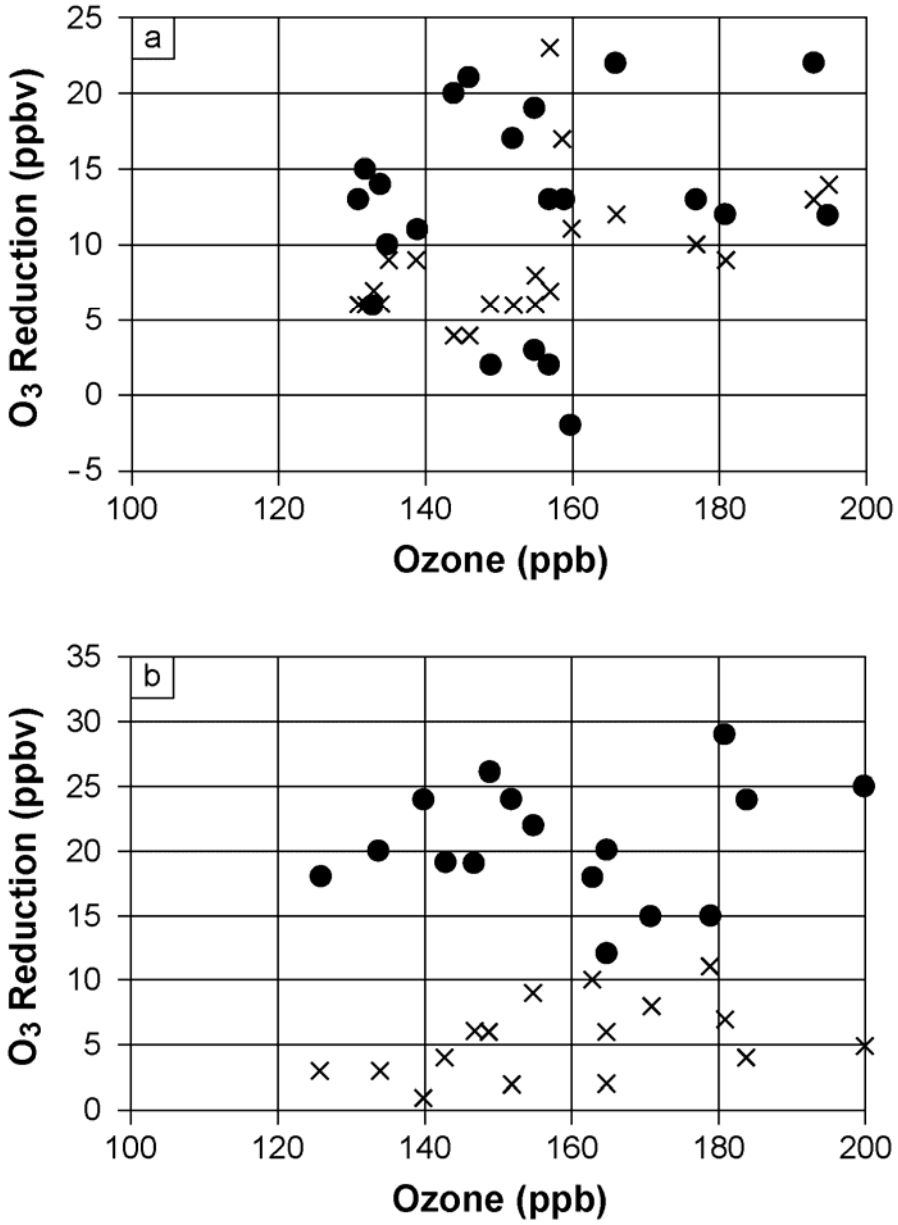


Figure AX2.7-3a,b. Impact of model uncertainty on control strategy predictions for O_3 for two days (August 10a and 11b, 1992) in Atlanta, GA. The figures show the predicted reduction in peak O_3 resulting from 35% reductions in anthropogenic VOC emissions (crosses) and from 35% reductions in NO_x (solid circles) in a series of model scenarios with varying base case emissions, wind fields, and mixed layer heights.

Source: Results are plotted from tabulated values published in Sillman et al. (1995, 1997).

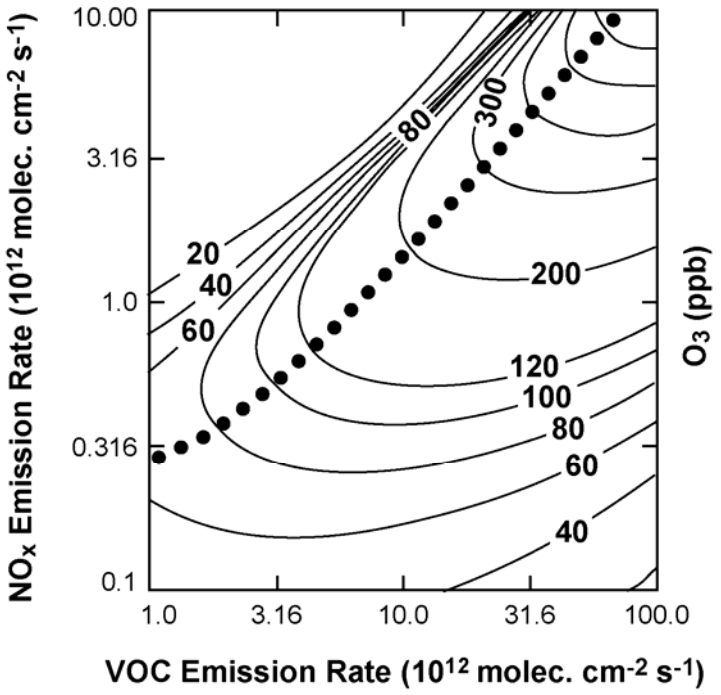


Figure AX2.7-4. **Ozone isopleths (ppb) as a function of the average emission rate for NO_x and VOC (10^{12} molec. cm^{-2} s^{-1}) in zero dimensional box model calculations. The isopleths (solid lines) represent conditions during the afternoon following 3-day calculations with a constant emission rate, at the hour corresponding to maximum O_3. The ridge line (shown by solid circles) lies in the transition from NO_x-saturated to NO_x-limited conditions.**

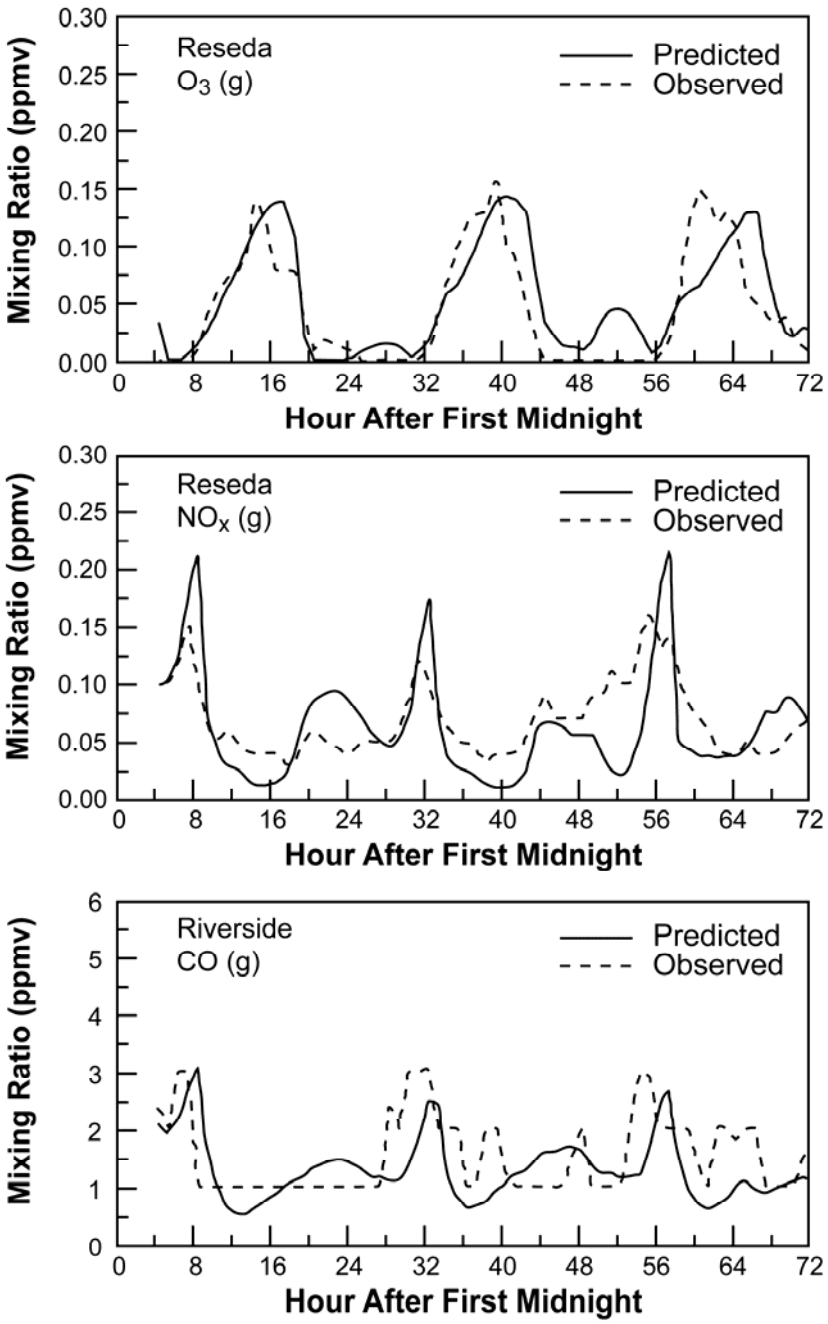


Figure AX2.7-5a. Time series for measured gas-phase species in comparison with results from a photochemical model. The dashed lines represent measurements, and solid lines represent model predictions (in parts per million, ppmv) for August 26–28, 1988 at sites in southern California. The horizontal axis represents hours past midnight, August 25. Results represent O_3 and NO_x at Reseda and CO at Riverside.

Source: Jacobson et al. (1996).

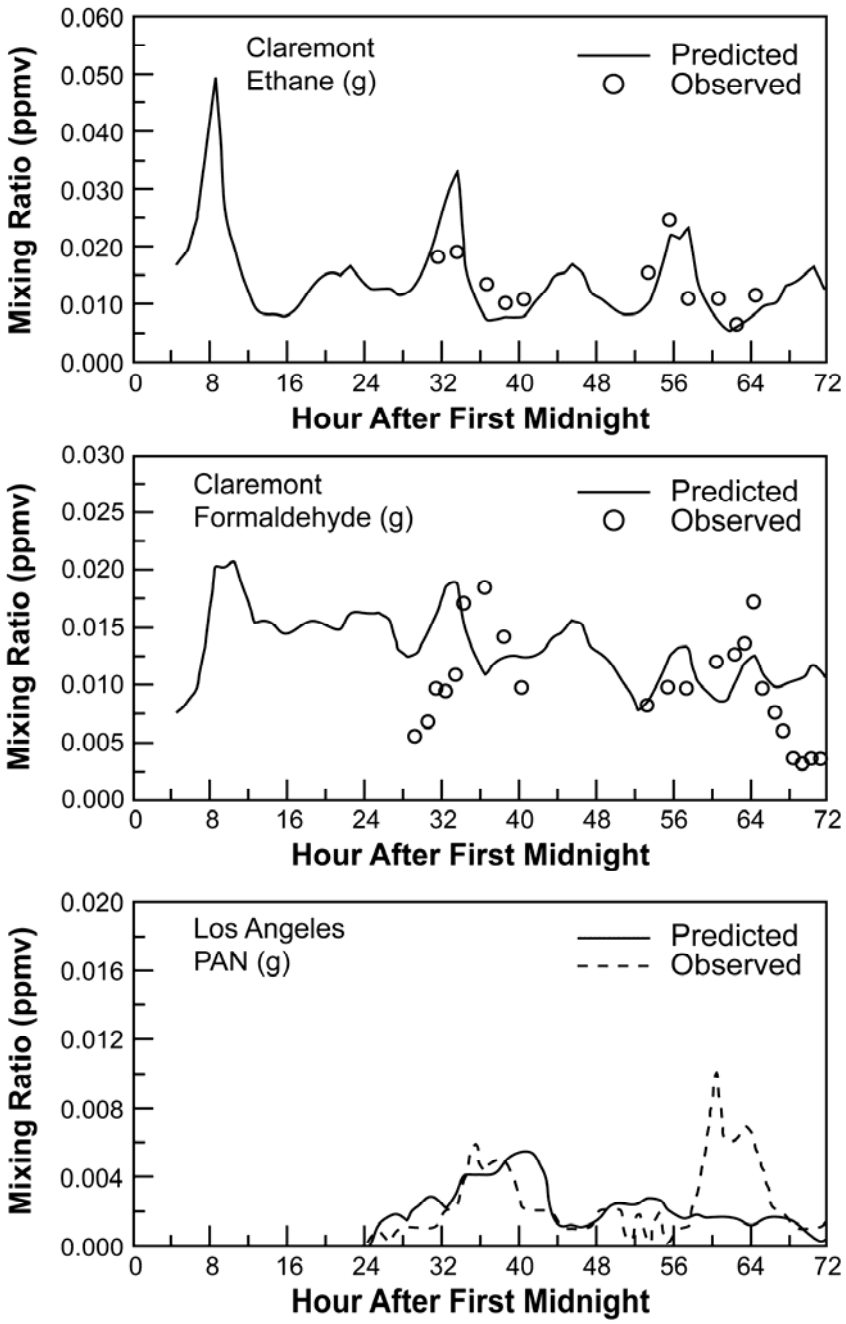


Figure AX2.7-5b. Time series for measured gas-phase species in comparison with results from a photochemical model. The circles represent measurements, and solid lines represent model predictions (in parts per million, ppmv) for August 26–28, 1988 at sites in southern California. The horizontal axis represents hours past midnight, August 25. Results represent ethane and formaldehyde at Claremont and PAN at Los Angeles.

Source: Jacobson et al. (1996).

challenges. Global-scale models typically represent continental-scale events and can be evaluated effectively against a sparse network of measurements. By contrast, urban/regional models are critically dependent on the accuracy of local emission inventories and event-specific meteorology, and must be evaluated separately for each urban area that is represented.

The evaluation of urban/regional models is also limited by the availability of data. Measured NO_x and speciated VOC concentrations are widely available through the EPA PAMs network, but questions have been raised about the accuracy of those measurements and the data have not yet been analyzed thoroughly. Evaluation of urban/regional models versus measurements has generally relied on results from a limited number of field studies in the United States. Short-term, research-grade measurements for species relevant to O_3 formation, including VOCs, NO_x, PAN, HNO_3, and H_2O_2 are also available at selected rural and remote sites (e.g., Daum et al., 1990, 1996; Martin et al., 1997; Young et al., 1997; Thompson et al., 2000; Hoell et al., 1997, 1999; Fehsenfeld et al., 1996a; Emmons et al., 2000; Hess, 2001; Carroll et al., 2001). The equivalent measurements are available for some polluted rural sites in the eastern United States, but only at a few urban locations (Meagher et al., 1998; Hübler et al., 1998; Kleinman et al., 2000, 2001; Fast et al., 2002; new SCAQS-need reference). Extensive measurements have also been made in Vancouver (Steyn et al., 1997) and in several European cities (Staffelbach et al., 1997; Prévôt et al., 1997, Dommen et al., 1999; Geyer et al., 2001; Thielman et al., 2001; Martilli et al., 2002; Vautard et al., 2002).

The results of straightforward comparisons between observed and predicted concentrations of O_3 can be misleading because of compensating errors, although this possibility is diminished when a number of species are compared. Ideally, each of the main modules of a CTM system (for example, the meteorological model and the chemistry and radiative transfer routines) should be evaluated separately. However, this is rarely done in practice. To better indicate how well physical and chemical processes are being represented in the model, comparisons of relations between concentrations measured in the field and concentrations predicted by the model can be made. These comparisons could involve ratios and correlations between species. For example, correlation coefficients could be calculated between primary species as a means of evaluating the accuracy of emission inventories or between secondary species as a means of evaluating the treatment of photochemistry in the model. In addition, spatial relations involving individual species (correlations, gradients) can also be used as a means

of evaluating the accuracy of transport parameterizations. Sillman and He (2002) examined differences in correlation patterns between O_3 and NO_z in Los Angeles, CA, Nashville, TN, and various sites in the rural United States. Model calculations (Figure AX2.7-6) show differences in correlation patterns associated with differences in the sensitivity of O_3 to NO_x and VOCs. Primarily NO_x-sensitive (NO_x-limited) areas in models show a strong correlation between O_3 and NO_z with a relatively steep slope, while primarily VOC-sensitive (NO_x-saturated) areas in models show lower O_3 for a given NO_z and a lower O_3-NO_z slope. They found that differences found in measured data ensembles were matched by predictions from chemical transport models.

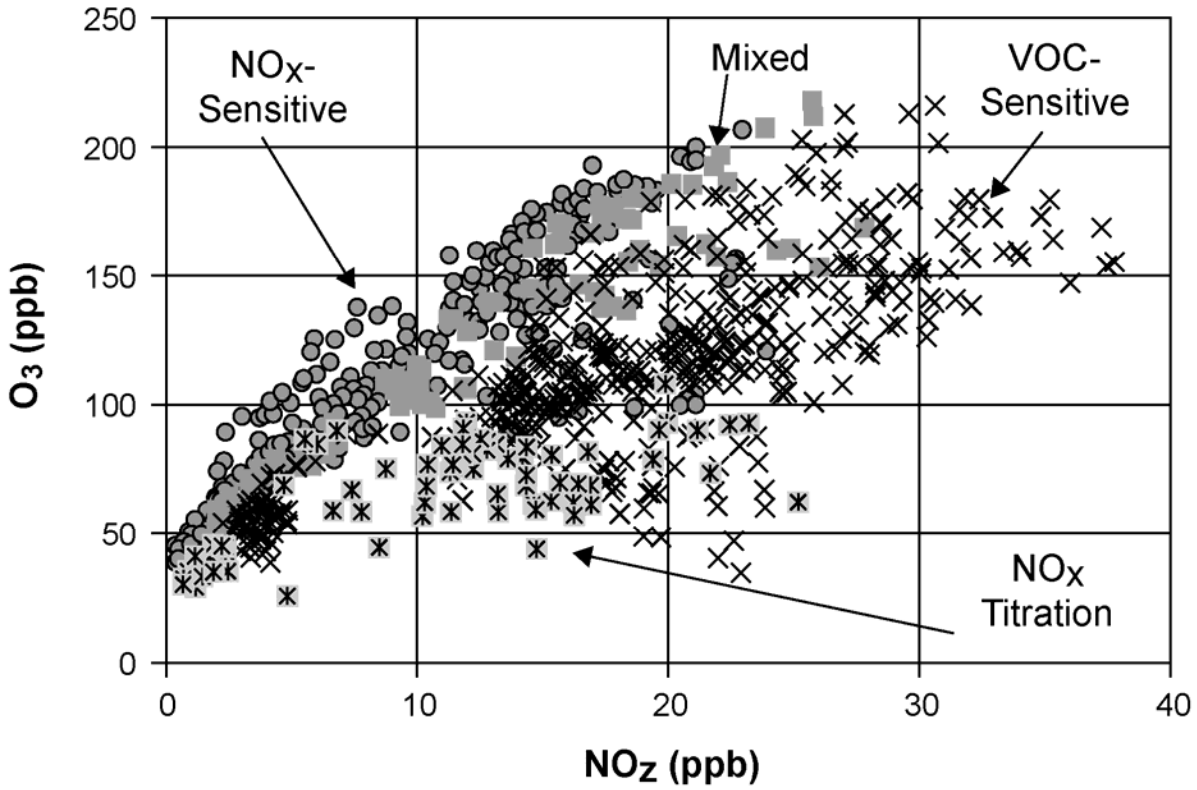


Figure AX2.7-6. Correlations for O_3 versus NO_z (NO_y–NO_x) in ppb from chemical transport models for the northeast corridor, Lake Michigan, Nashville, the San Joaquin Valley, and Los Angeles. Each location is classified as NO_x-limited or NO_x-sensitive (circles), NO_x-saturated or VOC-sensitive (crosses), mixed or with near-zero sensitivity (squares), and dominated by NO_x titration (asterisks) based on the model response to reduced NO_x and VOC.

Source: Sillman and He (2002).

Measurements in rural areas in the eastern United States show differences in the pattern of correlations for O_3 versus NO_z between summer and autumn (Jacob et al., 1995; Hirsch et al., 1996), corresponding to the transition from NO_x-limited to NO_x-saturated patterns, a feature which is also matched by CTMs.

The difference in correlations between secondary species in NO_x-limited to NO_x-saturated environments can also be used to evaluate the accuracy of model predictions in individual applications. Figures AX2.7-7a and AX2.7-7b show results for two different model scenarios for Atlanta. As shown in the figures, the first model scenario predicts an urban plume with high NO_y and O_3 formation apparently suppressed by high NO_y. Measurements show much lower NO_y in the Atlanta plume. This error was especially significant because the model locations sensitive to NO_x. The second model scenario (with primarily NO_x-sensitive conditions) shows much better agreement with measured values. Figure AX2.7-8a,b shows model-measurement comparisons for secondary species in Nashville, showing better agreement with measured with conditions. Greater confidence in the predictions made by CTMs will be gained by the application of techniques such as these on a more routine basis.

The ability of chemical mechanisms to calculate the concentrations of free radicals under atmospheric conditions was tested in the Berlin Ozone Experiment, BERLIOZ (Volz-Thomas et al., 2003) during July and early August at a site located about 50 km NW of Berlin. (This location was chosen because O_3 episodes in central Europe are often associated with SE winds.)

Concentrations of major compounds such as O_3, hydrocarbons, etc., were fixed at observed values. In this regard, the protocol used in this evaluation is an example of an observationally high NO_y were not sensitive to NO_x, while locations with lower NO_y were primarily based method. Figure AX2.7-9 compares the concentrations of RO_2, HO_2, and OH radicals predicted by RACM and MCM with observations made by the laser-induced fluorescence (LIF) technique and by matrix isolation ESR spectroscopy (MIESR). Also shown are the production rates of O_3 calculated using radical concentrations predicted by the mechanisms and those obtained by measurements, and measurements of NO_x concentrations. As can be seen, there is good agreement between measurements of RO_2, HO_2, OH, radicals with values predicted by both mechanisms at high concentrations of NO_x (>10 ppb). However, at lower NO_x concentrations, both mechanisms substantially overestimate OH concentrations and

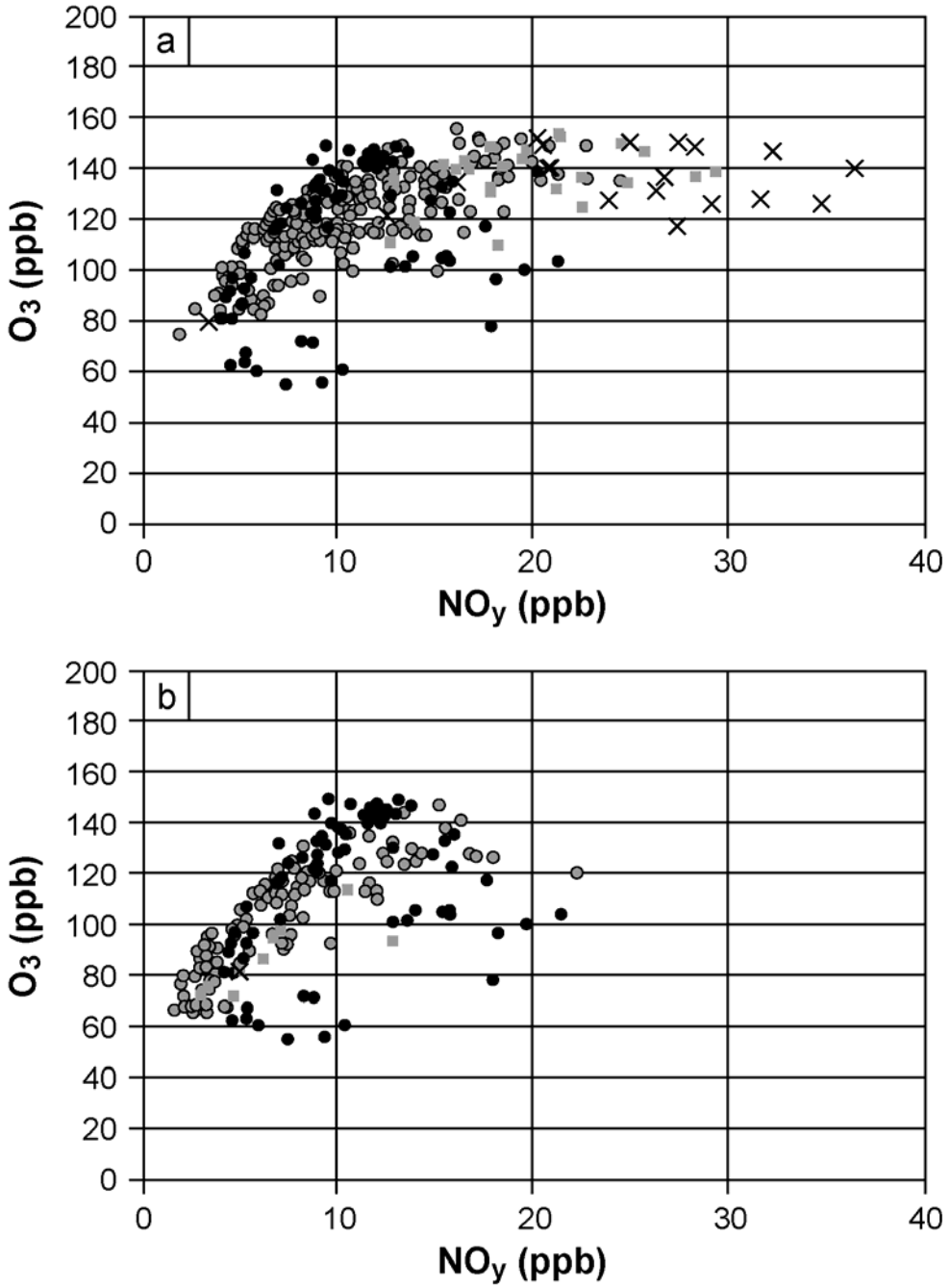


Figure AX2.7-7a,b. Evaluation of model versus measured O_3 versus NO_y for two model scenarios for Atlanta. The model values are classified as NO_x- limited (circles), NO_x-saturated (crosses), or mixed or with low sensitivity to NO_x (squares). Diamonds represent aircraft measurements.

Source: Sillman et al. (1997).

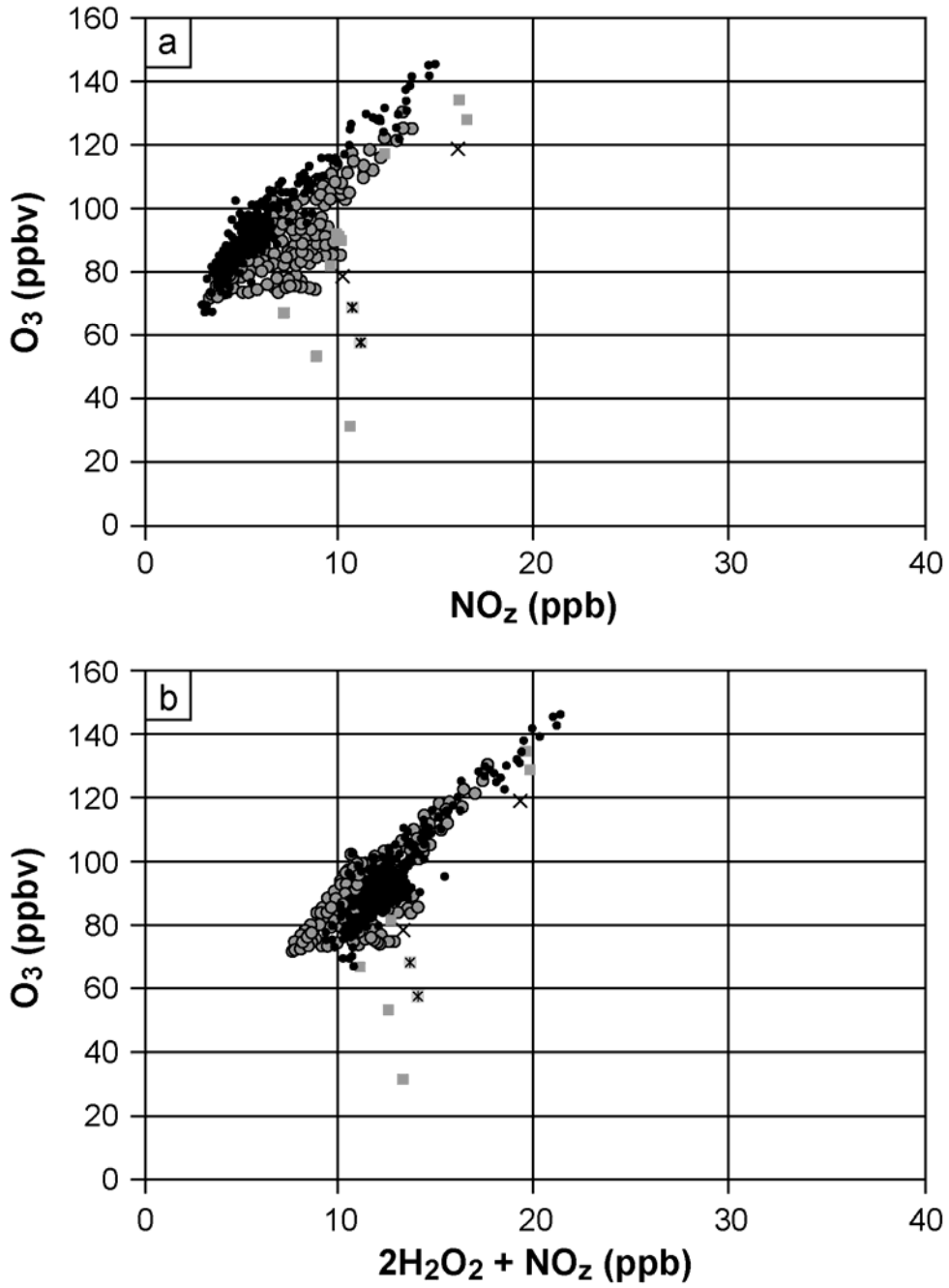


Figure AX2.7-8a,b. Evaluation of model versus: (a) measured O_3 versus NO_z and (b) O_3 versus the sum $2H_2O_2 + NO_z$ for Nashville, TN. The model values are classified as NO_x-limited (gray circles), NO_x-saturated (X's), mixed or near-zero sensitivity (squares), or dominated by NO_x titration (filled circles). Diamonds represent aircraft measurements.

Source: Sillman et al. (1998).

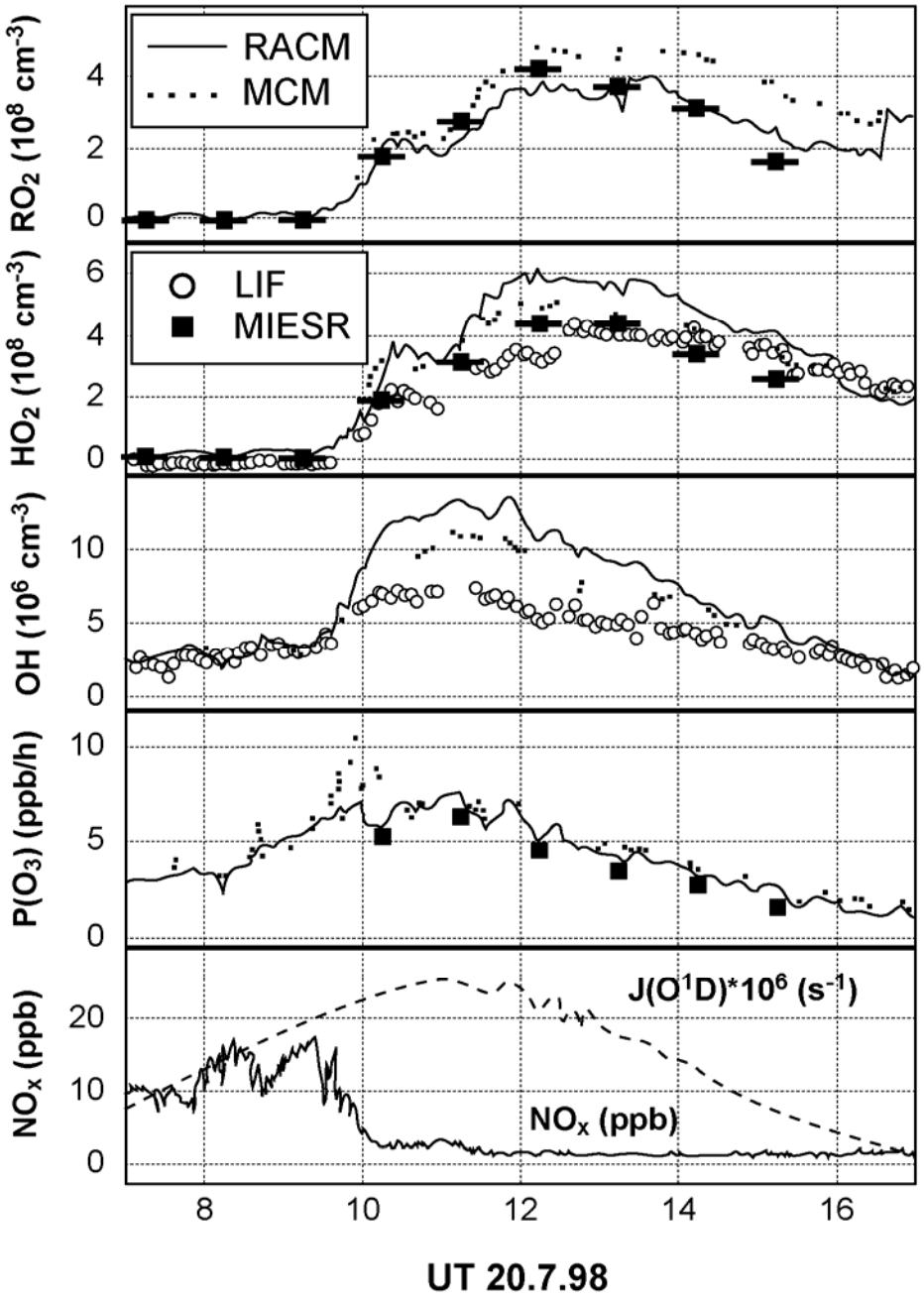


Figure AX2.7-9. Time series of concentrations of RO_2, HO_2, and OH radicals, local O_3 photochemical production rate and concentrations of NO_x from measurements made during BERLIOZ. Also shown are comparisons with results of photochemical box model calculations using the RACM and MCM chemical mechanisms.

Source: Volz-Thomas et al. (2003).

moderately overestimate HO_2 concentrations. Agreement between models and measurements is generally better for organic peroxy radicals, although the MCM appears to overestimate their concentrations somewhat. In general, the mechanisms reproduced the HO_2 to OH and RO_2 to OH ratios better than the individual measurements. The production of O_3 was found to increase linearly with NO (for NO < 0.3 ppb) and to decrease with NO (for NO > 0.5 ppb).

OH and HO_2 concentrations measured during the $PM_{2.5}$ Technology Assessment and Characterization Study conducted at Queens College in New York City in the summer of 2001 were also compared with those predicted by RACM (Ren et al., 2003). The ratio of observed to predicted HO_2 concentrations over a diurnal cycle was 1.24 and the ratio of observed to predicted OH concentrations was about 1.10 during the day, but the mechanism significantly underestimated OH concentrations during the night.

AX2.8 SAMPLING AND ANALYSIS OF NITROGEN AND SULFUR OXIDES

AX2.8.1 Availability and Accuracy of Ambient Measurements for NO_y

Section AX2.8.1-AX2.8.4 focus on current methods and on promising new technologies, but no attempt is made here to cover the extensive development of these methods or of methods such as wet chemical techniques, no longer in widespread use. More detailed discussions of these methods may be found elsewhere (U.S. Environmental Protection Agency, 1993, 1996). McClenny (2000), Parrish and Fehsenfeld (2000), and Clemitshaw (2004) reviewed methods for measuring NO_x and NO_y compounds. Discussions in Sections 2.8.1-2.8.4 center on chemiluminescence and optical Federal Reference and Equivalent Methods (FRM and FEM, respectively).

The use of methods such as observationally based methods or source apportionment models, either as stand-alone methods or as a basis for evaluating chemical transport models, is often limited by the availability and accuracy of measurements. Measured NO_x and speciated VOC concentrations are widely available in the United States through the PAMS network. However, challenges have been raised about both the accuracy of the measurements and their applicability.

The PAMs network currently includes measured NO and NO_x. However, Cardelino and Chameides (2000) reported that measured NO during the afternoon was frequently at or below the detection limit of the instruments (1 ppb), even in large metropolitan regions (Washington, DC; Houston, TX; New York, NY). Nitric **di**oxide measurements are made with commercial chemilluminescent detectors with hot molybdenum converters. However, these measurements typically include a wide variety of other reactive N species, such as organic nitrates in addition to NO_x, and cannot be interpreted as a "pure" NO_x measurement (see summary in Parrish and Fehsenfeld, 2000). Detection of these species can be considered an interference or a cross sensitivity useful for understanding the chemistry of the air.

Total reactive nitrogen (NO_y) is included in the PAMS network only at a few sites. The possible expansion of PAMS to include more widespread NO_y measurements has been suggested (McClenny, 2000). NO_y measurements are also planned for inclusion in the NCore network (U.S. Environmental Protection Agency, 2005). A major issue to be considered when measuring NO_x and NO_y is the possibility that HNO_3, a major component of NO_y, is sometimes lost in inlet tubes and not measured (Luke et al., 1998; Parrish and Fehsenfeld, 2000). This problem is especially critical if measured NO_y is used to identify NO_x-limited versus NO_x-saturated conditions. The problem is substantially alleviated although not necessarily completely solved by using much shorter inlets on NO_y monitors than on NO_x monitors and by the use of surfaces less likely to take up HNO_3. The correlation between O_3 and NO_y differs for NO_x-limited versus NO_x-saturated locations, but this difference is driven primarily by differences in the ratio of O_3 to HNO_3. If HNO_3 were omitted from the NO_y measurements, then the measurements would represent a biased estimate and their use would be problematic.

AX2.8.1.1 Calibration Standards

Calibration gas standards of NO, in N_2 (certified at concentrations of approximately 5 to 40 ppm) are obtainable from the Standard Reference Material (SRM) Program of the National Institute of Standards and Technology (NIST), formerly the National Bureau of Standards (NBS), in Gaithersburg, MD. These SRMs are supplied as compressed gas mixtures at about 135 bar (1900 psi) in high-pressure aluminum cylinders containing 800 L of gas at standard temperature and pressure, dry (STPD) National Bureau of Standards, 1975; Guenther et al., 1996). Each cylinder is supplied with a certificate stating concentration and uncertainty. The concentrations are certified to be accurate to ±1 percent relative to the stated values. Because of

the resources required for their certification, SRMs are not intended for use as daily working standards, but rather as primary standards against which transfer standards can be calibrated.

Transfer stand-alone calibration gas standards of NO in N_2 (at the concentrations indicated above) are obtainable from specialty gas companies. Information as to whether a company supplies such mixtures is obtainable from the company, or from the SRM Program of NIST. These NIST Traceable Reference Materials (NTRMs) are purchased directly from industry and are supplied as compressed gas mixtures at approximately 135 bar (1900 psi) in high-pressure aluminum cylinders containing 4,000 L of gas at STPD. Each cylinder is supplied with a certificate stating concentration and uncertainty. The concentrations are certified to be accurate to within ±1 percent of the stated values (Guenther et al., 1996). Additional details can be found in the previous AQCD for O_3 (U.S. Environmental Protection Agency, 1996).

AX2.8.1.2 Measurement of Nitric Oxide

Gas-phase Chemiluminescence (CL) Methods

Nitric oxide can be measured reliably using the principle of gas-phase chemiluminescence induced by the reaction of NO with O_3 at low pressure. Modern commercial NO_x analyzers have sufficient sensitivity and specificity for adequate measurement in urban and many rural locations (U.S. Environmental Protection Agency, 1993, 1996, 2006). Research grade CL instruments have been compared under realistic field conditions to spectroscopic instruments, and the results indicate that both methods are reliable (at concentrations relevant to smog studies) to better than 15 percent with 95 percent confidence. Response times are on the order of 1 minute. For measurements meaningful for understanding O_3 formation, emissions modeling, and N deposition, special care must be taken to zero and calibrate the instrument frequently. A chemical zero, obtained by reacting the NO up-stream and out of view of the photomultiplier tube, is preferred because it accounts for interferences such as light emitting reactions with unsaturated hydrocarbons. Calibration should be performed with NTRM-of compressed NO in N_2. Standard additions of NO at the inlet will account for NO loss or conversion to NO_2 in the lines. In summary, CL methods, when operated carefully in an appropriate manner, can be suitable for measuring or monitoring NO (e.g., Crosley, 1996).

Spectroscopic Methods for Nitric Oxide

Nitric oxide has also been successfully measured in ambient air with direct spectroscopic methods; these include two-photon laser-induced fluorescence (TPLIF), tunable diode laser absorption spectroscopy (TDLAS), and two-tone frequency-modulated spectroscopy (TTFMS). These were reviewed thoroughly in the previous AQCD and will be only briefly summarized here. The spectroscopic methods demonstrate excellent sensitivity and selectivity for NO with detection limits on the order of 10 ppt for integration times of 1 min. Spectroscopic methods compare well with the CL method for NO in controlled laboratory air, ambient air, and heavily polluted air (e.g., Walega et al., 1984; Gregory et al., 1990; Kireev et al., 1999). These spectroscopic methods remain in the research arena due to their complexity, size, and cost, but are essential for demonstrating that CL methods are reliable for monitoring NO concentrations involved in O_3 formation—from around 20 ppt to several hundred of ppb.

Atmospheric pressure laser ionization followed by mass spectroscopy has also been deployed for detection of NO and NO_2. Garnica et al. (2000) describe a technique involving selective excitation at one wavelength followed by ionization at a second wavelength. They report good selectivity and detection limits well below 1 ppb. The practicality of the instrument for ambient monitoring, however, has yet to be demonstrated.

AX2.8.1.3 Measurements of Nitrogen Dioxide

Gas-Phase Chemiluminescence Methods

Reduction of NO_2 to NO, on the surface of a heated (to 300 to 400 °C) molybdenum oxide substrate followed by detection of the chemiluminescence produced during the reaction of NO with O_3 at low pressure as described earlier for measurement of NO serves as the basis of the FRM for measurement of ambient NO_2. However, the substrate used in the reduction of NO_2 to NO is not specific to NO_2; hence the chemiluminescence analyzers are subject to interference nitrogen oxides other than NO_2 produced by oxidized NO_y compounds, or NO_z. Thus, this technique will overestimate NO_2 concentrations particularly in areas downwind of sources of NO and NO_2 as NO_x is oxidized to NO_z in the form of PANs and other organic nitrates, and HNO_3 and HNO_4. Many of these compounds are reduced at the catalyst with nearly the same efficiency as NO_2. Interferences have also been found from a wide range of other compounds as described in the latest AQCD for NO_2.

Other Methods

Nitrogen dioxide can be selectively converted to NO by photolysis. For example, (Ryerson et al., 2000) developed a gas-phase chemiluminescence method using a photolytic converter based on a Hg lamp with increased radiant intensity in the region of peak NO_2 photolysis (350 to 400 nm) and producing conversion efficiencies of 70% or more in less than 1 s. Metal halide lamps with conversion efficiency of about 50% and accuracy on the order of 20% (Nakamura, et al., 2003) have been used. Because the converter produces little radiation at wavelengths less than 350 nm, interferences from HNO_3 and PAN are minimal. Alternative methods to photolytic reduction followed by CL are desirable to test the reliability of this widely used technique. Any method based on a conversion to measured species presents potential for interference a problem. Several atmospheric species, PAN and HO_2NO_2 for example, dissociate to NO_2 at higher temperatures.

Laser induced fluorescence for NO_2 detection involves excitation of atmospheric NO_2 with laser light emitted at wavelengths too long to induce photolysis. The resulting excited molecules relax in a photoemissive mode and the fluorescing photons are counted. Because collisions would rapidly quench the electronically excited NO_2, the reactions are conducted at low pressure. Matsumi et al. (2001) describe a comparison of LIF with a photofragmentation chemiluminescence instrument. The LIF system involves excitation at 440 nm with a multiple laser system. They report sensitivity of 30 ppt in 10 s and good agreement between the two methods under laboratory conditions at mixing ratios up to 1.0 ppb. This high-sensitivity LIF system has yet to undergo long-term field tests. Cleary et al. (2002) describe field tests of a system that uses continuous, supersonic expansion followed by excitation at 640 nm with a commercial cw external-cavity tunable diode laser. More recently, LIF has been successfully used to detect NO_2 with accuracy of about 15% and detections limits well below 1 ppb. When coupled with thermal dissociation, the technique also measures peroxy nitrates such as PAN, alkyl nitrates, HNO_4 and HNO_3 (Cohen, 1999; Day et al., 2002; Farmer et al., 2006; Perez et al., 2007; Thornton et al., 2003). This instrument can have very fast sampling rates be fast (>1 Hz) and shows good correlation with chemiluminescent techniques, but remains a research-grade device.

Nitrogen Dioxide can be detected by differential optical absorption spectroscopy (DOAS) in an open, long-path system by measuring narrow band absorption features over a background

of broad band extinction (e.g., Stutz et al., 2000; Kim and Kim, 2001). A DOAS system manufactured by OPSIS is designated as a Federal Equivalent Method for measuring NO_2. DOAS systems can also be configured to measure NO, HONO, and NO_3 radicals. Typical detection limits are 0.2 to 0.3 ppbv for NO, 0.05 to 0.1 ppbv for NO_2, 0.05 to 0.1 ppbv for HONO, and 0.001 to 0.002 ppbv for NO_3, at path lengths of 0.2, 5, 5, and 10 km, respectively. The obvious advantage compared to fixed point measurements is that concentrations relevant to a much larger area are obtained, especially if multiple targets are used. At the same time, any microenvironmental artifacts are minimized over the long path integration. A major limitation in this technique had involved inadequate knowledge of absorption cross sections. Harder et al. (1997) conducted an experiment in rural Colorado involving simultaneous measurements of NO_2 by DOAS and by photolysis followed by chemiluminescence. They found differences of as much as 110% in clean air from the west, but for NO_2 mixing ratios in excess of 300 ppt, the two methods agreed to better than 10%. Stutz (2000) cites two intercomparisons of note. Nitric oxide was measured by DOAS, by photolysis of NO_2 followed by chemiluminescence, and by LIF during July 1999 as part of the SOS in Nashville, TN. On average, the three methods agreed to within 2%, with some larger differences likely caused by spatial variability over the DOAS path. In another study in Europe, and a multi-reflection set-up over a 15 km path, negated the problem of spatial averaging here agreement with the chemiluminescence detector following photolytic conversion was excellent (slope = 1.006 ± 0.005; intercept = 0.036 ± 0.019; r = 0.99) over a concentration range from about 0.2 to 20 ppbv.

Nitric oxide can also be detected from space with DOAS-like UV spectroscopy techniques (Kim et al., 2006; Ma et al., 2006). These measurements appear to track well with emissions estimates and can be a useful indicator of column content as well as for identifying hot spots in sources. **See also** Richter et al., 2005. Leigh (2006) report on a DOAS method that uses the sun as a light source and compares well with an in situ chemiluminescence detector in an urban environment.

Chemiluminescence on the surface of liquid Luminol has also been used for measurement of NO_2 (Gaffney et al., 1998; Kelly et al., 1990; Marley et al., 2004; Nikitas et al., 1997; Wendel et al., 1983). This technique is sensitive and linear, and more specific than hot MoOx. Luminol does not emit light when exposed to NHO_3 or alkyl nitrates, but does react with PAN. This interference can be removed by chromatographic separation prior to detection and the resulting

measurement compares well with more specific techniques for moderate to high (≥1 ppb) mixing ratios of NO_2.

Several tunable diode laser spectroscopy techniques have been used successfully for NO_2 detection (Eisele et al., 2003; Osthoff et al., 2006). These devices remain research grade instruments, not yet practical for urban monitoring.

Measurements of Total Oxidized Nitrogen Species, NO_y

Gold catalyzed CO, or H_2 reduction or as conversion on hot molybdenum oxide catalyst have been used to reduce NO_y to NO before then detection by chemiluminescence (Fehsenfeld et al., 1987; Crosley, 1996). Both techniques offer generally reliable measurements, with response times on the order of 60 s and a linear dynamic range demonstrated in field intercomparisons from about 10 ppt to 10's of ppb. Under certain conditions, HCN, NH_3, RNO_2, and CH_3CN can be converted to NO, but at normal concentrations and humidity these are minor interferences. Thermal decomposition followed by LIF has also been used for NO_y detection, as described above. In field comparisons, instruments based on these two principles generally showed good agreement (Day et al., 2002). The experimental uncertainty is estimated to be of 15-30%.

AX2.8.1.4 Monitoring for NO_2 Compliance Versus Monitoring for Ozone Formation

Regulatory measurements of NO_2 have been focused on demonstrating compliance with the NAAQS for NO_2. Today, few locations violate that standard, but NO_2 and related NO_y compounds remain among the most important atmospheric trace gases to measure and understand. Commercial instruments for NO/NO_x detection are generally constructed with an internal converter for reduction of NO_2 to NO, and generate a signal referred to as NO_x. These converters, generally constructed of molybdenum oxides (MoOx), reduce not only NO_2 but also most other NO_y species. Unfortunately, with an internal converter, the instruments may not give a faithful indication of NO_y either—reactive species such as HNO_3 will adhere to the walls of the inlet system. Most recently, commercial vendors such as Thermo Environmental (Franklin, MA) have offered NO/NO_y detectors with external Mo converters. If such instruments are calibrated through the inlet with a reactive nitrogen species such as propyl nitrate, they give accurate measurements of total NO_y, suitable for evaluation of photochemical models. (Crosley, 1996; Fehsenfeld et al., 1987; Nunnermacker et al., 1998; Rodgers and Davis, 1989). Under conditions

of fresh emissions, such as in urban areas during the rush hour, $NO_y \approx NO_x$ and these monitors can be used for testing emissions inventories (Dickerson, et al., 1995; Parrish, 2006). The State of Maryland for example is making these true NO_y measurements at the Piney Run site in the western part of the state. These data produced at this site can be more reliably compared to the output of CMAQ and other chemical transport models.

Summary of Methods for Measuring NO_2

A variety of techniques exist for reliable monitoring of atmospheric NO_2 and related reactive nitrogen species. For demonstration of compliance with the NAAQS for NO_2, commercial chemiluminescence instruments are adequate. For certain conditions, luminol chemiluminescence is adequate. Precise measurements of NO_2 can be made with research grade instruments such as LIF and TDLS. For path-integrated concentration determinations UV spectroscopic methods provide useful information. Commercial NO_x instruments are sensitive to other NO_y species, but do not measure NO_y quantitatatively. NO_y instruments with external converters offer measurements more useful for comparison to chemical transport model calculations.

AX2.8.2 Measurements of HNO_3

Accurate measurement of HNO_3, has presented a long-standing analytical challenge to the atmospheric chemistry community. In this context, it is useful to consider the major factors that control HNO_3 partitioning between the gas and deliquesced-particulate phases in ambient air. In equation form,

$$HNO_{3g} \overset{K_H}{\longleftrightarrow} [HNO_{3aq}] \overset{K_a}{\longleftrightarrow} [H^+] + [NO_3^-] \qquad \text{(AX2-51)}$$

where K_H is the Henry's Law constant in M atm^{-1} and K_a is the acid dissociation constant in M.

Thus, the primary controls on HNO_3 phase partitioning are its thermodynamic properties (K_H, K_a, and associated temperature corrections), aerosol liquid water content (LWC), solution pH, and kinetics. Aerosol LWC and pH are controlled by the relative mix of different acids and bases in the system, hygroscopic properties of condensed compounds, and meteorological conditions (RH, temperature, and pressure). It is evident from relationship AX2-51 that, in the presence of chemically distinct aerosols of varying acidities (e.g., super-µm predominantly sea

salt and sub-µm predominantly S aerosol), HNO_3 will partition preferentially with the less-acidic particles; and this is consistent with observations (e.g., Huebert et al., 1996; Keene and Savoie, 1998; Keene et al., 2002). Kinetics are controlled by atmospheric concentrations of HNO_3 vapor and particulate NO_3^- and the size distribution and corresponding atmospheric lifetimes of particles against deposition. Sub-µm diameter aerosols typically equilibrate with the gas phase in seconds to minutes while super-um aerosols require hours to a day or more (e.g., Meng and Seinfeld, 1996; Erickson et al., 1999). Consequently, smaller aerosol size fractions are typically close to thermodynamic equilibrium with respect to HNO_3 whereas larger size fractions (for which atmospheric lifetimes against deposition range from hours to a few days) are often undersaturated (e.g., Erickson et al., 1999; Keene and Savioe, 1998).

Many sampling techniques for HNO_3 (e.g., annular denuder, standard filterpack and mist-chamber samplers) employ upstream prefilters to remove particulate species from sample air. However, when chemically distinct aerosols with different pHs (e.g., sea salt and S aerosols) mix together on a bulk filter, the acidity of the bulk mixture will be greater than that of the less acidic aerosols with which most NO_3^- is associated. This change in pH may cause the bulk mix to be supersaturated with respect to HNO_3 leading to volatilization and, thus, positive measurement bias in HNO_3 sampled downstream. Alternatively, when undersaturated super-µm size fractions (e.g., sea salt) accumulate on a bulk filter and chemically interact over time with HNO_3 in the sample air stream, scavenging may lead to negative bias in HNO_3 sampled downstream. Because the magnitude of both effects will vary as functions of the overall composition and thermodynamic state of the multiphase system, the combined influence can cause net positive or net negative measurement bias in resulting data. Pressure drops across particle filters can also lead to artifact volatilization and associated positive bias in HNO_3 measured downstream.

Widely used methods for measuring HNO_3 include standard filterpacks configured with nylon or alkaline-impregnated filters (e.g., Goldan et al., 1983; Bardwell et al., 1990), annular denuders (EPA Method IP-9), and standard mist chambers (Talbot et al., 1990). Samples from these instruments are typically analyzed by ion chromatography. Intercomparisons of these measurement techniques (e.g., Hering et al., 1988; Tanner et al., 1989; Talbot et al., 1990) report differences on the order of a factor of two or more.

More recently, sensitive HNO_3 measurements based on the principle of Chemical Ionization Mass Spectroscopy (CIMS) have been reported (e.g., Huey et al., 1998; Mauldin

et al., 1998; Furutani and Akimoto, 2002; Neuman et al., 2002). CIMS relies on selective formation of ions such as $SiF_5^- \cdot HNO_3$ or $HSO_4^- \cdot HNO_3$ followed by detection via mass spectroscopy. Two CIMS techniques and a filter pack technique were intercompared in Boulder, CO (Fehsenfeld et al., 1998). Results indicated agreement to within 15% between the two CIMS instruments and between the CIMS and filterpack methods under relatively clean conditions with HNO_3 mixing ratios between 50 and 400 pptv. In more polluted air, the filterpack technique generally yielded higher values than the CIMS suggesting that interactions between chemically distinct particles on bulk filters is a more important source of bias in polluted continental air. Differences were also greater at lower temperature when particulate NO_3^- corresponded to relatively greater fractions of total NO_3^-.

AX2.8.3 Techniques for Measuring Other NO_y Species

Methods for sampling and analysis of alkyl nitrates in the atmosphere have been reviewed by Parrish and Fehsenfeld (2000). Peroxyacetylnitrate, PPN, and MPAN are typically measured using a chromatograph followed by electron capture detectors or GC/ECD (e.g., Gaffney et al., 1998), although other techniques such as FTIR could also be used. Field measurements are made using GC/ECD with a total uncertainty of ± 5 pptv + 15% (Roberts et al., 1998).

In the IMPROVE network and in the EPA's speciation network, particulate nitrate in the $PM_{2.5}$ size range is typically collected on nylon filters downstream of annular denuders coated with a basic solution capable of removing acidic gases such as HNO_3, HNO_2, and SO_2. Filter extracts are then analyzed by ion chromatography (IC) for nitrate, sulfate, and chloride. Nitrite ions are also measured by this technique but their concentrations are almost always beneath detection limits. However, both of these networks measure nitrate only in the $PM_{2.5}$ fraction. Because of interactions with more highly acidic components on filter surfaces, there could be volatilization of nitrate in PM_{10} samples. These effects are minimized if separate aerosol size fractions are collected, i.e., the more acidic $PM_{2.5}$ and the more alkaline $PM_{10-2.5}$ as in a dichotomous sampler or multistage impactor.

AX2.8.4 Remote Sensing of Tropospheric NO_2 Columns for Surface NO_x Emissions and Surface NO_2 Concentrations

Table AX2.8-1 contains an overview of the three satellite instruments that are used retrieve tropospheric NO_2 columns from measurements of solar backscatter. All three instruments are in polar sun-synchronous orbits with global measurements in the late morning and early afternoon. The spatial resolution of the measurement from SCIAMACHY is 7 times better than that from GOME (Ozone Monitoring Instrument), and that from OMI (Ozone Monitoring Instrument) is 40 times better than that from GOME.

Figure AX2.8-1 shows tropospheric NO_2 columns retrieved from SCIAMACHY. Pronounced enhancements are evident over major urban and industrial emissions. The high degree of spatial heterogeneity over the southwestern United States provides empirical evidence that most of the tropospheric NO_2 column is concentrated in the lower troposphere. Tropospheric NO_2 columns are more sensitive to NO_x in the lower troposphere than in the upper troposphere (Martin et al., 2002). This sensitivity to NO_x in the lower troposphere is due to the factor of 25 decrease in the NO_2/NO ratio from the surface to the upper troposphere (Bradshaw et al., 1999) that is driven by the temperature dependence of the NO + O_3 reaction. Martin et al. (2004a) integrated in situ airborne measurements of NO_2 and found that during summer the lower mixed layer contains 75% of the tropospheric NO_2 column over Houston and Nashville. However, it should be noted that these measurements are also sensitive to surface albedo and aerosol loading.

The retrieval involves three steps: (1) determining total NO_2 line-of-sight (slant) columns by spectral fitting of solar backscatter measurements, (2) removing the stratospheric columns by using data from remote regions where the tropospheric contribution to the column is small, and (3) applying an air mass factor (AMF) for the scattering atmosphere to convert tropospheric slant columns into vertical columns. The retrieval uncertainty is determined by (1) and (2) over remote regions where there is little tropospheric NO_2, and by (3) over regions in regions of elevated tropospheric NO_2 (Martin et al., 2002; Boersma et al., 2004).

The paucity of in situ NO_2 measurements motivates the inference of surface NO_2 concentrations from satellite measurements of tropospheric NO_2 columns. This prospect would take advantage of the greater sensitivity of tropospheric NO_2 columns to NO_x in the lower

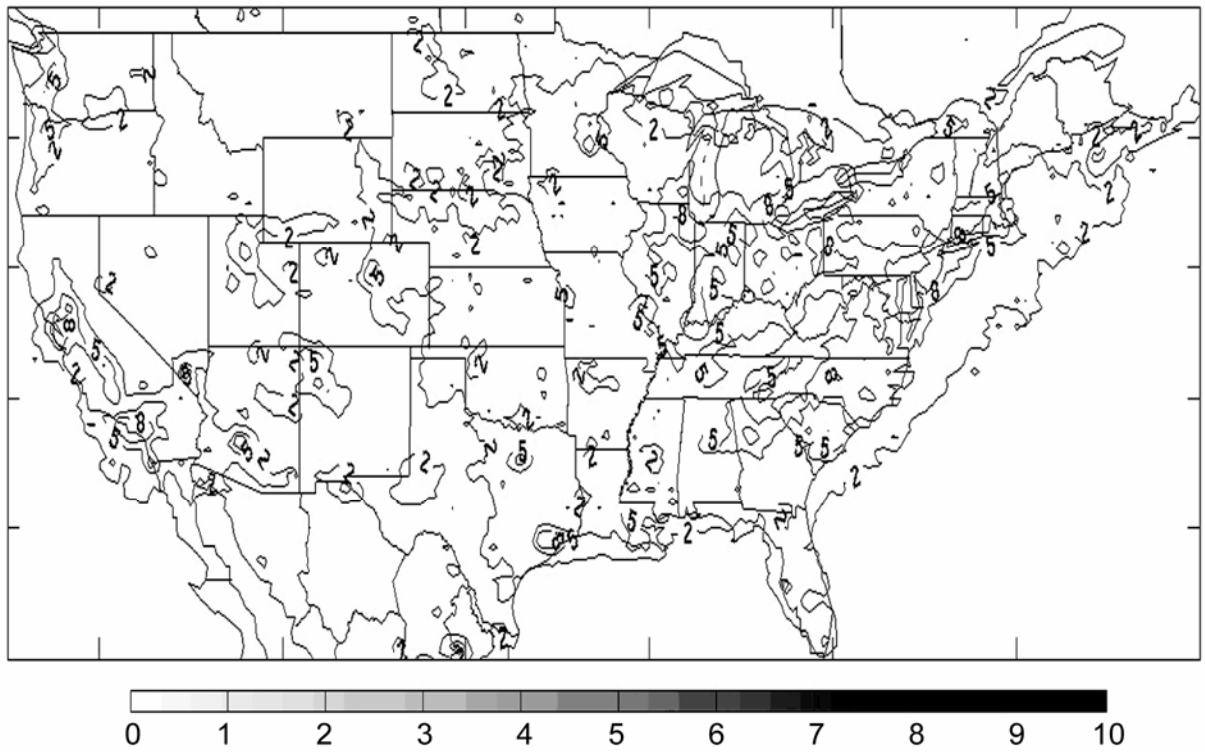


Figure AX2.8-1. Tropospheric NO_2 columns (molecules NO_2/ cm^2) retrieved from the SCIAMACHY satellite instrument for 2004-2005.

Source: Martin et al. (2006).

troposphere than in the upper troposphere as discussed earlier. Tropospheric NO_2 columns show a strong correlation with in situ NO_2 measurements in northern Italy (Ordonez et al., 2006).

Quantitative calculation of surface NO_2 concentrations from a tropospheric NO_2 column would require information on the relative vertical profile. Comparison of vertical profiles of NO_2 in a chemical transport model (GEOS-Chem) versus in situ measurements over and downwind of North America shows a high degree of consistency (Martin et al., 2004b; Martin et al., 2006), suggesting that chemical transport models could be used to infer the relationship between surface NO_2 concentrations and satellite observations of the tropospheric NO_2 column.

However, the satellites carrying the spectrometer (GOME/SCIAMACHY/OMI) are in near polar, sun-synchronous orbits. As a result, these measurements are made only once per day, typically between about 10:00 to 11:00 a.m. or **1 p.m.** local time, during a brief overflight. Thus the utility of these measurements is limited as they would likely miss short-term features.

AX2.8.5 SAMPLING AND ANALYSIS FOR SO_2

Currently, ambient SO_2 is measured using instruments based on pulsed fluorescence. The UV fluorescence monitoring method for atmospheric SO_2 was developed to improve upon the flame photometric detection (FPD) method for SO_2, which in turn had displaced the pararosaniline wet chemical method for SO_2 measurement. The pararosaniline method is still the FRM for atmospheric SO_2, but is rarely used because of its complexity and slow response, even in its automated forms. Both the UV fluorescence and FPD methods are designated as FEMs by the EPA, but UV fluorescence has largely supplanted the FPD approach because of the UV method's inherent linearity, sensitivity, and the absence of consumables, such as the hydrogen gas needed for the FPD method.

Basically, SO_2 molecules absorb ultraviolet (UV) light at one wavelength and emit UV light at longer wavelengths. This process is known as fluorescence, and involves the excitation of the SO_2 molecule to a higher energy (singlet) electronic state. Once excited, the molecule decays non-radiatively to a lower energy electronic state from which it then decays to the original, or ground, electronic state by emitting a photon of light at a longer wavelength (i.e., lower energy) than the original, incident photon. The process can be summarized by the following equations:

$$SO_2 + h\nu_1 \rightarrow SO_2^* \qquad \text{(AX2-52)}$$

$$SO_2^* \rightarrow SO_2 + h\nu_2 \qquad \text{(AX2-53)}$$

where SO_2^* represents the excited state of SO_2, $h\nu_1$, and $h\nu_2$ represent the energy of the excitation and fluorescence photons, respectively, and $h\nu_2 < h\nu_1$. The intensity of the emitted light is 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, allowing only photons with wavelengths around the SO_2 absorption peak (near 214 nm) to enter the optical chamber. The light passing through the source bandwidth filter is collimated using a UV lens and passes through the optical chamber, where it is detected on the opposite side of the chamber by the reference detector. A photomultiplier tube (PMT) is offset from and placed perpendicular to the light path to detect the SO_2 fluorescence. Since the SO_2 fluorescence (330 nm) is at a wavelength that is different from the 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. The Detection Limit (DL) for a non-trace level SO_2 analyzer is 10 parts per billion (ppb) (Code of Federal Regulations, Volume 40, Part 53.23c). The SO_2 measurement method is subject to both positive and negative interference.

Sources of Positive Interference

The most common source of interference is from other gases that fluoresce in a similar fashion to SO_2 when exposed to far UV radiation. The most significant of these are polycyclic aromatic hydrocarbons (PAHs); of which naphthalene is a prominent example. Xylene is another hydrocarbon that can cause interference.

Such compounds absorb UV photons and fluoresce in the region of the SO_2 fluorescence. Consequently, any such aromatic hydrocarbons that are in the optical chamber can act as a positive interference. To remove this source of interference, the high sensitivity SO_2 analyzers, such as those to be used in the NCore network (U.S. Environmental Protection Agency, 2005), have hydrocarbon scrubbers to remove these compounds from the sample stream before the sample air enters the optical chamber.

Another potential source of positive interference is nitric oxide (NO). NO fluoresces in a spectral region that is close to the SO_2 fluorescence. However, in high sensitivity SO_2 analyzers, the bandpass filter in front of the PMT is designed to prevent NO fluorescence from reaching the PMT and being detected. Care must be exercised when using multicomponent calibration gases containing both NO and SO_2 that the NO rejection ratio of the SO_2 analyzer is sufficient to prevent NO interference. The most common source of positive bias (as constrasted with positive spectral interference) in high-sensitivity SO_2 monitoring is stray light reaching the optical chamber. Since SO_2 can be electronically excited by a broad range of UV wavelengths, any stray light with an appropriate wavelength that enters the optical chamber can excite SO_2 in the sample and increase the fluorescence signal.

Furthermore, stray light at the wavelength of the SO_2 fluorescence that enters the optical chamber may impinge on the PMT and increase the fluorescence signal. Several design features are incorporated to minimize the stray light that enters the chamber. These features include the use of light filters, dark surfaces, and opaque tubing to prevent light from entering the chamber.

Luke (1997) reported the positive artifacts of a modified pulsed fluorescence detector generated by the co-existence of NO, CS_2, and a number of 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 reduced by using a hydrocarbon "kicker" membrane. At a flow rate of 300 standard cc min^{-1} and a pressure drop of 645 torr across the kicker, the interference from ppm levels of many aromatic hydrocarbons was eliminated entirely.

Nicks and Benner (2001) described a sensitive SO_2 chemiluminescence detector, which was based on a differential measurement where response from ambient SO_2 is determined by the difference between air containing SO_2 and air scrubbed of SO_2 where both air samples contain other detectable sulfur species, and the positive artifact could also be reduced through this way.

Sources of Negative Interference

Nonradiative deactivation (quenching) of excited SO_2 molecules can occur from collisions with common molecules in air, including nitrogen, oxygen, and water. During collisional quenching, the excited SO_2 molecule transfers energy, kinetically allowing the SO_2 molecule to return to the original lower energy state without emitting a photon. Collisional quenching results in a decrease in the SO_2 fluorescence and results in the underestimation of SO_2 concentration in the air sample. The concentrations of nitrogen and oxygen are constant in the ambient air, so quenching from those species at a surface site is also constant, but the water vapor content of air can vary. Luke (1997) reported that the response of the detector could be reduced by about 7% and 15% at water vapor mixing ratios of 1 and 1.5 mole percent (RH = 35 to 50% at 20-25 °C and 1 atm for a modified pulsed fluorescence detector (Thermo Environmental Instruments, Model 43s). Condensation of water vapor in sampling lines must be avoided, as it can absorb SO_2 from the sample air. The simplest approach to avoid condensation is to heat sampling lines to a temperature above the expected dew point, and within a few degrees of the controlled optical bench temperature. At very high SO_2 concentrations, reactions between electronically excited SO_2 and ground state SO_2 to form SO_3 and SO might occur (Calvert et al., 1978). However, this possibility has not been examined.

Other Techniques for Measuring SO_2

A more sensitive SO_2 measurement method than the UV-fluorescence method was reported by Thornton et al. (2002). Thornton et al (2002) reported an atmospheric pressure ionization mass spectrometer. The high measurement precision and instrument sensitivity were achieved by adding isotopically labeled SO_2 ($^{34}S^{16}O_2$) continuously to the manifold as an internal standard. Field studies showed that the method precision was better than 10% and the limit of detection was less than 1 pptv for a sampling interval of 1s.

Sulfur Dioxide can be measured by LIF at around 220 nm (Matsumi et al., (2005). Because the laser wavelength is alternately tuned to an SO_2 absorption peak at 220.6 and bottom at 220.2 nm, and the difference signal at the two wavelengths is used to extract the SO_2 concentration, the technique eliminates interference from either absorption or fluorescence by other species and has high sensitivity (5 pptv in 60 sec). Sulfur Dioxide can also be measured by the same DOAS instrument that can measure NO_2.

Photoacoutsic techniques have been employed for SO_2 detection, but they generally have detection limits suitable only for source monitoring (Gondal, 1997; Gondal and Mastromarino, 2001).

Chemical Ionization Mass Spectroscopy (CIMS) utilizes ionization via chemical reactions in the gas phase to determine an unknown sample's mass spectrum and identity. High sensitivity (10 ppt or better) has been achieved with uncertainty of ~15% when a charcoal scrubber is used for zeroing and the sensitivity is measured with isotopically labeled $^{34}SO_2$ (Hanke et al., 2003; Huey et al., 2004; Hennigan et al., 2006).

AX2.8.6 Sampling and Analysis for Sulfate, Nitrate, and Ammonium

Sampling Artifacts

Sulfate, nitrate, and ammonium are commonly present in $PM_{2.5}$. Most $PM_{2.5}$ samplers **have** a size-separation device to separate particles so that only those particles approximately 2.5 µm or less are collected on the sample filter. Air is drawn through the sample filter at a controlled flow rate by a pump located downstream of the sample filter. The systems have two critical flow rate components for the capture of fine particulate: (1) the flow of air through the sampler must be at a flow rate that ensures that the size cut at 2.5 µm occurs; and (2) the flow

rate must be optimized to capture the desired amount of particulate loading with respect to the analytical method detection limits.

When using the system described above to collect sulfate, nitrate and particulate ammonium, sampling artifacts can occur because of: (1) positive sampling artifact for sulfate, nitrate, and particulate ammonium due to chemical reaction; and (2) negative sampling artifact for nitrate and ammonium due to the decomposition and evaporation.

Sampling and Analysis Techniques

Denuder-Filter Based Sampling and Analysis Techniques for Sulfate, Nitrate, and Ammonium

There are two major PM speciation ambient air-monitoring networks in the United States: the Speciation Trend Network (STN), and the Interagency Monitoring of Protected Visual Environments (IMPROVE) network. The current STN samplers include three filters: (1) Teflon for equilibrated mass and elemental analysis including elemental sulfur; (2) a HNO_3 denuded nylon filter for ion analysis including NO_3 and SO_4, (3) a quartz-fiber filter for elemental and organic carbon. The IMPROVE sampler, which collects two 24-h samples per week, simultaneously collects one sample of PM_{10} on a Teflon filter, and three samples of $PM_{2.5}$ on Teflon, nylon, and quartz filters. $PM_{2.5}$ mass concentrations are determined gravimetrically from the $PM_{2.5}$ Teflon filter sample. The $PM_{2.5}$ Teflon filter sample is also used to determine concentrations of selected elements. The $PM_{2.5}$ nylon filter sample, which is preceded by a denuder to remove acidic gases, is analyzed to determine nitrate and sulfate aerosol concentrations. Finally, the $PM_{2.5}$ quartz filter sample is analyzed for OC and EC using the thermal-optical reflectance (TOR) method. The STN and the IMPROVE networks represent a major advance in the measurement of nitrate, because the combination of a denuder (coated with either Na_2CO_3 or MgO) to remove HNO_3 vapor and a Nylon filter to adsorb HNO_3 vapor volatilizing from the collected ammonium nitrate particles overcomes the loss of nitrate from Teflon filters.

The extent to which sampling artifacts for particulate NH_3^+ have been adequately addressed in the current networks is not clear. Recently, new denuder-filter sampling systems have been developed to measure sulfate, nitrate, and ammonium with an adequate correction of ammonium sampling artifacts. The denuder-filter system, Chembcomb Model 3500 speciation sampling cartridge developed by Rupprecht & Patashnick Co, Inc. could be used to collect

nitrate, sulfate, and ammonium simultaneously. The sampling system contains a single-nozzle size-selective inlet, two honeycomb denuders, the aerosol filter and two backup filters (Keck and Wittmaack, 2005). The first denuder in the system is coated with 0.5% sodium carbonate and 1% glycerol and collects acid gases such as HCL, SO_2, HONO, and HNO_3. The second denuder is coated with 0.5% phosphoric acid in methanol for collecting NH_3. Backup filters collect the gases behind denuded filters. The backup filters are coated with the same solutions as the denuders. A similar system based on the same principle was applied by Possanzini et al. (1999). The system contains two NaCl-coated annular denuders followed by other two denuders coated with $NaCO_3$/glycerol and citric acid, respectively. This configuration was adopted to remove HNO_3 quantitatively on the first NaCl denuder. The third and forth denuder remove SO_2 and NH_3, respectively. A polyethylene cyclone and a two-stage filter holder containing three filters is placed downstream of the denuders. Aerosol fine particles are collected on a Teflon membrane. A backup nylon filter and a subsequent citric acid impregnated filter paper collect dissociation products (HNO_3 and NH_3) of ammonium nitrate evaporated from the filtered particulate matter.

Several traditional and new methods could be used to quantify elemental S collected on filters: energy dispersive X-ray fluorescence, synchrotron induced X-ray fluorescence, proton induced X-ray emission (PIXE), total reflection X-ray fluorescence, and scanning electron microscopy. Energy dispersive X-ray fluorescence (EDXRF) (Method IO-3.3, U.S. Environmental Protection Agency, 1997; see 2004 PM CD for details) and PIXE are the most commonly used methods. Since sample filters often contain very small amounts of particle deposits, preference is given to methods that can accommodate small sample sizes and require little or no sample preparation or operator time after the samples are placed into the analyzer. X-ray fluorescence (XRF) meets these needs and leaves the sample intact after analysis so it can be submitted for additional examinations by other methods as needed. To obtain the greatest efficiency and sensitivity, XRF typically places the filters in a vacuum which may cause volatile compounds (nitrates and organics) to evaporate. As a result, species that can volatilize such as ammonium nitrate and certain organic compounds can be lost during the analysis. The effects of this volatilization are important if the PTFE filter is to be subjected to subsequent analyses of volatile species.

Polyatomic ions such as sulfate, nitrate, and ammonium are quantified by methods such as ion chromatography (IC) (an alternative method commonly used for ammonium analysis is automated colorimetry). All ion analysis methods require a fraction of the filter to be extracted in deionized distilled water for sulfate and $NaCO_3$/$NaHCO_3$ solution for nitrate and then filtered to remove insoluble residues prior to analysis. The extraction volume should be as small as possible to avoid over-diluting the solution and inhibiting the detection of the desired constituents at levels typical of those found in ambient $PM_{2.5}$ samples. During analysis, the sample extract passes through an ion-exchange column which separates the ions in time for individual quantification, usually by an electroconductivity detector. The ions are identified by their elution/retention times and are quantified by the conductivity peak area or peak height.

In a side-by-side comparison of two of the major aerosol monitoring techniques (Hains et al., 2007), $PM_{2.5}$ mass and major contributing species were well correlated among the different methods with r-values in excess of 0.8. Agreement for mass, sulfate, OC, TC, and ammonium was good while that for nitrate and BC was weaker. Based on reported uncertainties, however, even daily concentrations of $PM_{2.5}$ mass and major contributing species were often significantly different at the 95% confidence level. Greater values of $PM_{2.5}$ mass and individual species were generally reported from Speciation Trends Network methods than from the Desert Research Institute Sequential Filter Samplers. These differences can only be partially accounted for by known random errors. The authors concluded that the current uncertainty estimates used in the STN network may underestimate the actual uncertainty.

Positive Sampling Artifacts

The reaction of SO_2 (and other acid gases) with basic sites on glass fiber filters or with basic coarse particles on the filter leads to the formation of sulfate (or other nonvolatile salts, e.g., nitrate, chloride). These positive artifacts lead to the overestimation of total mass, and sulfate, and probably also nitrate concentrations. These problems were largely overcome by changing to quartz fiber or Teflon filters and by the separate collection of $PM_{2.5}$. However, the possible reaction of acidic gases with basic coarse particles remains a possibility, especially with PM_{10} and $PM_{10-2.5}$ measurements. These positive artifacts could be effectively eliminated by removing acidic gases in the sampling line with denuders coated with NaCl or Na_2CO_3.

Positive sampling artifacts also occur during measurement of particulate NH_4. The reaction of NH_3 with acidic particles (e.g. $2NH_3 + H_2SO_4 \rightarrow (NH_4)2SO_4$), either during sampling or during transportation, storage, and equilibration could lead to an overestimation of particulate NH_4 concentrations. Techniques have been developed to overcome this problem: using a denuder to remove NH_3 during sampling and to protect the collected PM from NH_3 (Suh et al., 1992, 1994; Brauer et al., 1991; Koutrakis et al., 1988a,b; Keck and Wittmaack, 2006; Possanzini et al., 1999; Winberry et al., 1999). Hydrogen fluoride, citric acid, and phosphorous acids have been used as coating materials for the NH_3 denuder. Positive artifacts for particulate NH_4 can also be observed during sample handling due to contamination. No chemical analysis method, no matter how accurate or precise, can adequately represent atmospheric concentrations if the filters to which these methods are applied are improperly handled. Ammonia is emitted directly from human sweat, breath and smoking. It can then react with acidic aerosols on the filter to form ammonium sulfate, ammonium bisulfate and ammonium nitrate if the filter was not properly handled (Sutton et al., 2000). Therefore, it is important to keep filters away from ammonia sources, such as human breath, to minimize neutralization of the acidic compounds. Also, when filters are handled, preferably in a glove box, the analyst should wear gloves that are antistatic and powder-free to act as an effective contamination barrier.

Negative Sampling Artifact

Although sulfate is relatively stable on a Teflon filter, it is now well known that volatilization losses of particulate nitrates occur during sampling.

For nitrate, the effect on the accuracy of atmospheric particulate measurements from these volatilization losses is more significant for $PM_{2.5}$ than for PM_{10}. The FRM for $PM_{2.5}$ will likely suffer a loss of nitrates similar to that experienced with other simple filter collection systems. Sampling artifacts resulting from the loss of particulate nitrates represents a significant problem in areas such as southern California that experience high loadings of nitrates. Hering and Cass (1999) discussed errors in $PM_{2.5}$ mass measurements due to the volatilization of particulate nitrate. They examined data from two field measurement campaigns that were conducted in southern California: (1) the Southern California Air Quality Study (SCAQS) (Lawson, 1990) and (2) the 1986 CalTech study (Solomon et al., 1992). In both these studies, side-by-side sampling of $PM_{2.5}$ was conducted. One sampler collected particles directly onto a

Teflon filter. The second sampler consisted of a denuder to remove gaseous HNO_3 followed by a nylon filter that absorbed the HNO_3 as it evaporated from $NITXNO_3$. In both studies, the denuder consisted of MgO-coated glass tubes (Appel et al., 1981). Fine particulate nitrate collected on the Teflon filter was compared to fine particulate nitrate collected on the denuded nylon filter. In both studies, the $PM_{2.5}$ mass lost because of ammonium nitrate volatilization represented a significant fraction of the total $PM_{2.5}$ mass. The fraction of mass lost was higher during summer than during fall (17% versus 9% during the SCAQS study, and 21% versus 13% during the CalTech study). In regard to percentage loss of nitrate, as opposed to percentage loss of mass discussed above, Hering and Cass (1999) found that the amount of nitrate remaining on the Teflon filter samples was on average 28% lower than that on the denuded nylon filters.

Hering and Cass (1999) also analyzed these data by extending the evaporative model developed by Zhang and McMurry (1987). The extended model used by Hering and Cass (1999) takes into account the dissociation of collected particulate ammonium nitrate on Teflon filters into HNO_3 and NH_3 via three mechanisms: (1) the scrubbing of HNO_3 and NH_3 in the sampler inlet (John et al. (1988) showed that clean PM_{10} inlet surfaces serve as an effective denuder for HNO_3); (2) the heating of the filter substrate above ambient temperature by sampling; and (3) the pressure drop across the Teflon filter. For the sampling systems modeled, the flow-induced pressure drop was measured to be less than 0.02 atm, and the corresponding change in vapor pressure was 2%, so losses driven by pressure drop were not considered to be significant in this work. Losses from Teflon filters were found to be higher during the summer than during the winter, higher during the day compared to night, and reasonably consistent with modeled predictions.

Finally, during the SCAQS (Lawson, 1990) study, particulate samples also were collected using a Berner impactor and greased Tedlar substrates in size ranges from 0.05 to 10 μm in aerodynamic diameter. The Berner impactor $PM_{2.5}$ nitrate values were much closer to those from the denuded nylon filter than those from the Teflon filter, the impactor nitrate values being ~2% lower than the nylon filter nitrate for the fall measurements and ~7% lower for the summer measurements. When the impactor collection was compared to the Teflon filter collection for a nonvolatile species (sulfate), the results were in agreement. Chang et al. (2000) discuss reasons for reduced loss of nitrate from impactors.

Brook and Dann (1999) observed much higher nitrate losses during a study in which they measured particulate nitrate in Windsor and Hamilton, Ontario, Canada, by three techniques: (1) a single Teflon filter in a dichotomous sampler, (2) the Teflon filter in an annular denuder system (ADS), and (3) total nitrate including both the Teflon filter and the nylon back-up filter from the ADS. The Teflon filter from the dichotomous sampler averaged only 13% of the total nitrate, whereas the Teflon filter from the ADS averaged 46% of the total nitrate. The authors concluded that considerable nitrate was lost from the dichotomous sampler filters during handling, which included weighing and X-ray fluorescence (XRF) measurement in a vacuum.

Kim et al. (1999) also examined nitrate-sampling artifacts by comparing denuded and non-denuded quartz and nylon filters during the PM_{10} Technical Enhancement Program (PTEP) in the South Coast Air Basin of California. They observed negative nitrate artifacts (losses) for most measurements; however, for a significant number of measurements, they observed positive nitrate artifacts. Kim et al. (1999) pointed out that random measurement errors make it difficult to measure true amounts of nitrate loss.

Diffusion denuder samplers, developed primarily to measure particle strong acidity (Koutrakis et al., 1988b, 1992), also can be used to study nitrate volatilization. Such techniques were used to measure loss of particulate nitrate from Teflon filters in seven U.S. cities (Babich et al., 2000). Measurements were made with two versions of the Harvard-EPA Annular Denuder System (HEADS). HNO_3 vapor was removed by a Na_2CO_3-coated denuder. Particulate nitrate was the sum of nonvolatile nitrate collected on a Teflon filter and volatized nitrate collected on a Na_2CO_3-coated filter downstream of the Teflon filter (full HEADS) or on a Nylon filter downstream of the Teflon filter (Nylon HEADS). It was found that the full HEADS (using a Na2CO3 filter) consistently underestimated the total particulate nitrate by approximately 20% compared to the nylon HEADS. Babich et al. (2000) found significant nitrate losses in Riverside, CA; Philadelphia, PA; and Boston, MA, but not in Bakersfield, CA; Chicago, IL; Dallas, TX; or Phoenix, AZ, where measurements were made only during the winter. Tsai and Huang (1995) used a diffusion denuder to study the positive and negative artifacts on glass and quartz filters. They found positive artifacts attributed to SO_2 and HNO_3 reaction with basic sites on glass fibers and basic particles and negative artifacts attributed to loss of HNO_3 and HCl due to volatilization of NH_4NO_3 and NH_4Cl and reaction of these species with acid sulfates.

Volatile compounds can also leave the filter after sampling and prior to filter weighing or chemical analysis. Losses of NO_3, NH_4, and Cl from glass and quartz-fiber filters that were stored in unsealed containers at ambient air temperatures for 2 to 4 weeks prior to analysis exceeded 50 percent (Witz et al., 1990). Storing filters in sealed containers and under refrigeration will minimize these losses.

Negative sampling artifacts due to decomposition and volatilization are also significant for particulate ammonium. Ammonium particulates, especially NH_4 N_3 nitrate NH_4 Cl are very sensitive to some environmental factors, such as temperature, relative humidity, acidity of aerosols, as well as to filter type (Spurny, 1999; Keck and Wittmaack, 2005). Any change in these parameters during the sampling period influences the position of the equilibrium between the particle phase and the gas phase. Keck and Wittmaack (2005) observed that at temperatures below 0C, acetate-nitrate, quartz fiber, and Teflon filters could properly collect particulate NH_4 NH_3 and Cl. At temperature above 0C, the salts were lost from quartz fiber and Teflon filters, more so the higher the temperature and with no significant difference between quartz fiber and Teflon filters. The salts were lost completely from denuded quartz fiber filters above about 20C, and from non-undenuded quartz fiber and Teflon filters above about 25C. It is anticipated that current sampling techniques underestimate NH_4 concentrations due to the volatilization of NH_4, but fine particle mass contains many acidic compounds and consequently, a fraction of volatilized NH_4 (in the form of NH_3) can be retained on a PTFE filter by reaction with the acid compounds. Therefore, it is reasonable to assume that NH_4 loss will be less than the nitrate loss. Techniques have been applied to particulate ammonium sampling to correct particulate ammonium concentrations due to evaporation: a backup filter coated with hydrofluoric acids, citric acid, or phosphorous acids, is usually introduced to absorb the evaporated ammonium (as ammonia); the total ammonium concentration is the sum of the particle phase ammonium collected on the Teflon filter and the ammonia concentration collected on the backup filter.

Other Measurement Techniques

Nitrate

An integrated collection and vaporization cell was developed by Stolzenburg and Hering (2000) that provides automated, 10-min resolution monitoring of fine-particulate nitrate. In this system, particles are collected by a humidified impaction process and analyzed in place by flash

vaporization and chemiluminescent detection of the evolved NO_x. In field tests in which the system was collocated with two FRM samplers, the automated nitrate sampler results followed the results from the FRM, but were offset lower. The system also was collocated with a HEADS and a SASS speciation sampler (MetOne Instruments). In all these tests, the automated sampler was well correlated to other samplers with slopes near 1 (ranging from 0.95 for the FRM to 1.06 for the HEADS) and correlation coefficients ranging from 0.94 to 0.996. During the Northern Front Range Air Quality Study in Colorado (Watson et al., 1998), the automated nitrate monitor captured the 12-min variability in fine-particle nitrate concentrations with a precision of approximately ± 0.5 $\mu g/m^3$ (Chow et al., 1998). A comparison with denuded filter measurements followed by ion chromatographic (IC) analysis (Chow and Watson, 1999) showed agreement within ± 0.6 $\mu g/m^3$ for most of the measurements, but exhibited a discrepancy of a factor of two for the elevated nitrate periods. More recent intercomparisons took place during the 1997 Southern California Ozone Study (SCOS97) in Riverside, CA. Comparisons with 14 days of 24-h denuder-filter sampling gave a correlation coefficient of $R^2 = 0.87$ and showed no significant bias (i.e., the regression slope is not significantly different from 1). As currently configured, the system has a detection limit of 0.7 $\mu g/m^3$ and a precision of 0.2 $\mu g/m^3$.

Sulfate

Continuous methods for the quantification of aerosol sulfur compounds first remove gaseous sulfur (e.g., SO_2, H_2S) from the sample stream by a diffusion tube denuder followed by the analysis of particulate sulfur (Cobourn et al., 1978; Durham et al., 1978; Huntzicker et al., 1978; Mueller and Collins, 1980; Tanner et al., 1980). Another approach is to measure total sulfur and gaseous sulfur separately by alternately removing particles from the sample stream. Particulate sulfur is obtained as the difference between the total and gaseous sulfur (Kittelson et al., 1978). The total sulfur content is measured by a flame photometric detector (FPD) by introducing the sampling stream into a fuel-rich, hydrogen-air flame (e.g., Stevens et al., 1969; Farwell and Rasmussen, 1976) that reduces sulfur compounds and measures the intensity of the chemiluminescence from electronically excited sulfur molecules (S2*). Because the formation of S2* requires two sulfur atoms, the intensity of the chemiluminescence is theoretically proportional to the square of the concentration of molecules that contain a single sulfur atom. In practice, the exponent is between 1 and 2 and depends on the sulfur compound being analyzed (Dagnall et al., 1967; Stevens et al., 1971). Calibrations are performed using both particles and

gases as standards. The FPD can also be replaced by a chemiluminescent reaction with ozone that minimizes the potential for interference and provides a faster response time (Benner and Stedman, 1989, 1990). Capabilities added to the basic system include in situ thermal analysis and sulfuric acid speciation (Cobourn et al., 1978; Huntzicker et al., 1978; Tanner et al., 1980; Cobourn and Husar, 1982). Sensitivities for particulate sulfur as low as 0.1 $\mu g/m^3$, with time resolution ranging from 1 to 30 min, have been reported. Continuous measurements of particulate sulfur content have also been obtained by on-line XRF analysis with resolution of 30 min or less (Jaklevic et al., 1981). During a field-intercomparison study of five different sulfur instruments, Camp et al. (1982) reported four out of five FPD systems agreed to within ± 5% during a 1-week sampling period.

AX2.9 POLICY RELEVANT BACKGROUND CONCENTRATIONS OF NITROGEN AND SULFUR OXIDES

Background concentrations of nitrogen and sulfur oxides used for purposes of informing decisions about NAAQS are referred to as Policy Relevant Background (PRB) concentrations. Policy Relevant Background concentrations are those concentrations that would occur in the United States in the absence of anthropogenic emissions in continental North America (defined here as the United States, Canada, and Mexico). Policy Relevant Background concentrations include contributions from natural sources everywhere in the world and from anthropogenic sources outside these three countries. Background levels so defined facilitate separation of pollution levels that can be controlled by U.S. regulations (or through international agreements with neighboring countries) from levels that are generally uncontrollable by the United States. EPA assesses risks to human health and environmental effects from NO_2 and SO_2 levels in excess of PRB concentrations.

Contributions to PRB concentrations include natural emissions of NO_2, SO_2, and photochemical reactions involving natural emissions of reduced nitrogen and sulfur compounds, as well as their long-range transport from outside North America. Natural sources of NO_2 and its precursors include biogenic emissions, wildfires, lightning, and the stratosphere. Natural sources of reduced nitrogen compounds, mainly NH_3, include biogenic emissions and wildfires. Natural sources of reduced sulfur species include anaerobic microbial activity in wetlands and volcanic activity. Volcanos and biomass burning are the major natural source of SO_2. Biogenic

emissions from agricultural activities are not considered in the formation of PRB concentrations. Discussions of the sources and estimates of emissions are given in Section AX2.6.2.

Analysis of PRB Contribution to Nitrogen and Sulfur oxide Concentrations and Deposition over the United States

The MOZART-2 global model of tropospheric chemistry (Horowitz et al., 2003) is used to diagnose the PRB contribution to nitrogen and sulfur oxide concentrations, as well as to total (wet plus dry) deposition. The model setup for the present-day simulation has been published in a series of papers from a recent model intercomparison (Dentener et al., 2006a,b; Shindell et al., 2006; Stevenson et al., 2006; van Noije et al., 2006). MOZART-2 is driven by National Center for Environmental Prediction meteorological fields and IIASA 2000 emissions at a resolution of $1.9° \times 1.9°$ with 28 sigma levels in the vertical, and it includes gas- and aerosol phase chemistry. Results shown in Figures AX2.9-1 to AX2.9-5 are for the meteorological year 2001. Note that color images are available on the web. An additional "policy relevant background" simulation was conducted in which continental North American anthropogenic emissions were set to zero.

We first examine the role of PRB in contributing to NO_2 and SO_2 concentrations in surface air. Figure AX2.9-1 shows the annual mean NO_2 concentrations in surface air in the base case simulation (top panel) and the PRB simulation (middle panel), along with the percentage contribution of the background to the total base case NO_2 (bottom panel). Maximum concentrations in the base case simulation occur along the Ohio River Valley and in the Los Angeles basin. While present-day concentrations are often above 5 ppbv, PRB is less than 300 pptv over most of the continental United States, and less than 100 pptv in the eastern United States. The distribution of PRB (middle panel of Figure AX2.9-1) largely reflects the distribution of soil NO emissions, with some local enhancements due to biomass burning such as is seen in western Montana. In the northeastern United States, where present-day NO_2 concentrations are highest, PRB contributes <1% to the total.

The spatial pattern of present-day SO_2 concentrations over the United States is similar to that of NO_2, with highest concentrations (>5 ppbv) along the Ohio River valley (upper panel Figure AX2.9-2). Background SO_2 concentrations are orders of magnitude smaller, below 10 pptv over much of the United States (middle panel of Figure AX2.9-2). Maximum PRB concentrations of SO_2 are 30 ppt. In the Northwest where there are geothermal sources of SO_2, the contribution of PRB to total SO_2 is 70 to 80%. However, with the exception of the West

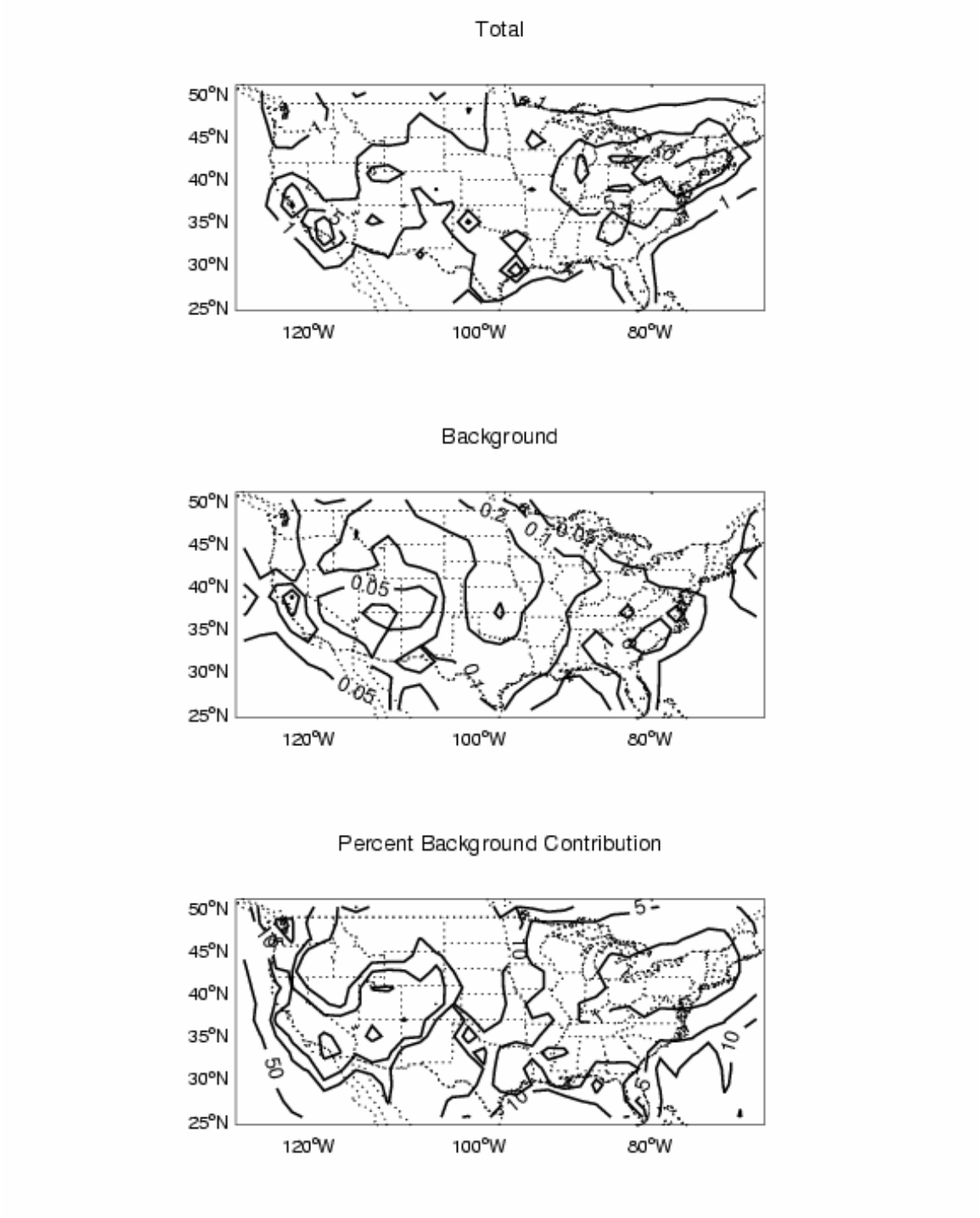


Figure AX2.9-1. Annual mean concentrations of NO_2 (ppbv) in surface air over the United States in the present-day (upper panel) and policy relevant background (middle panel) MOZART-2 simulations. The bottom panel shows the percentage contribution of the background to the present-day concentrations. Please see text for details.

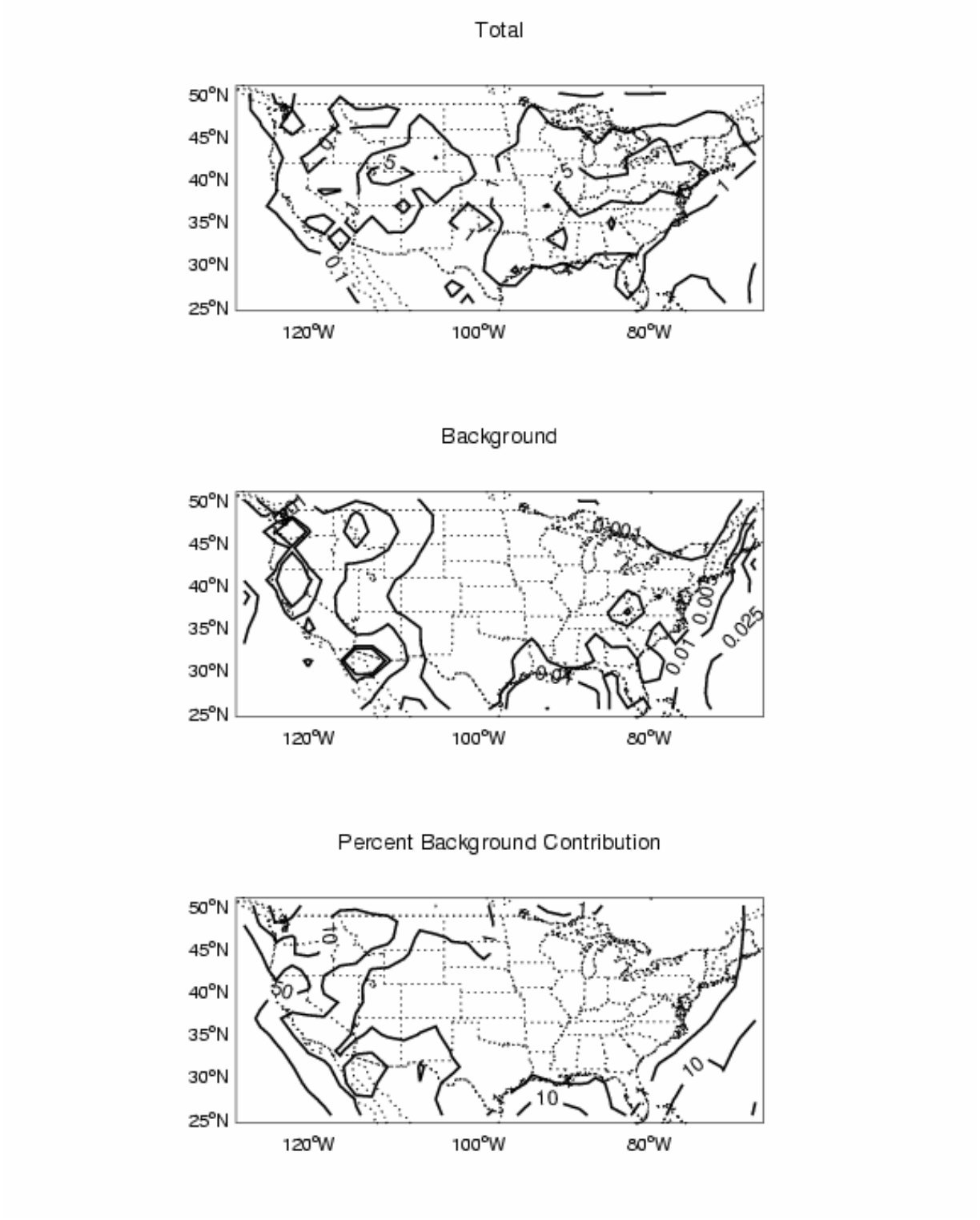


Figure AX2.9-2. Same as Figure AX2.9-1 but for SO_2 concentrations.

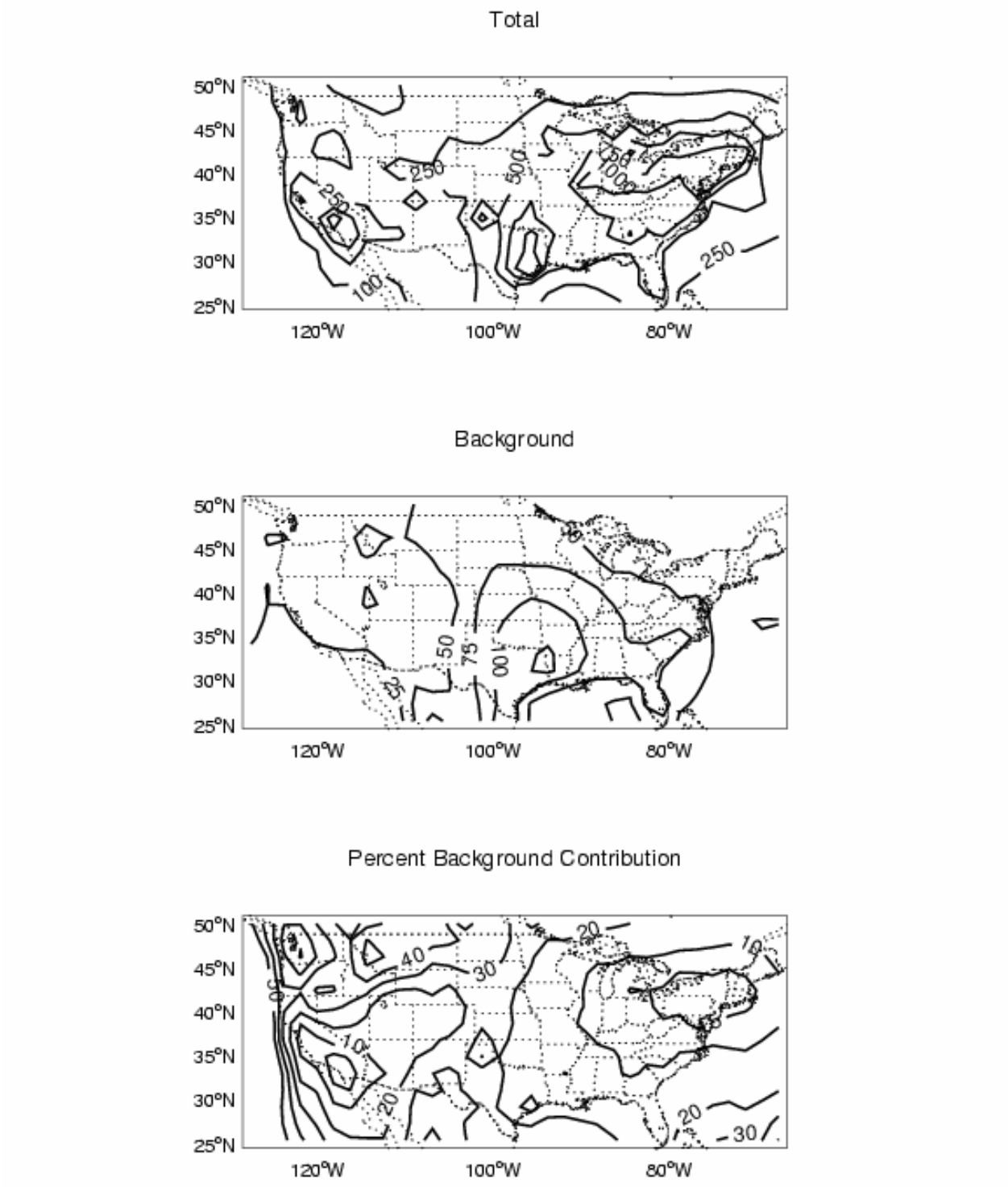


Figure AX2.9-3. Same as for Figure AX2.9-1 but for wet and dry deposition of HNO_3, NH_4NO_3, NO_x, HO_2NO_2, and organic nitrates (mg N $m^{-2}y^{-1}$).

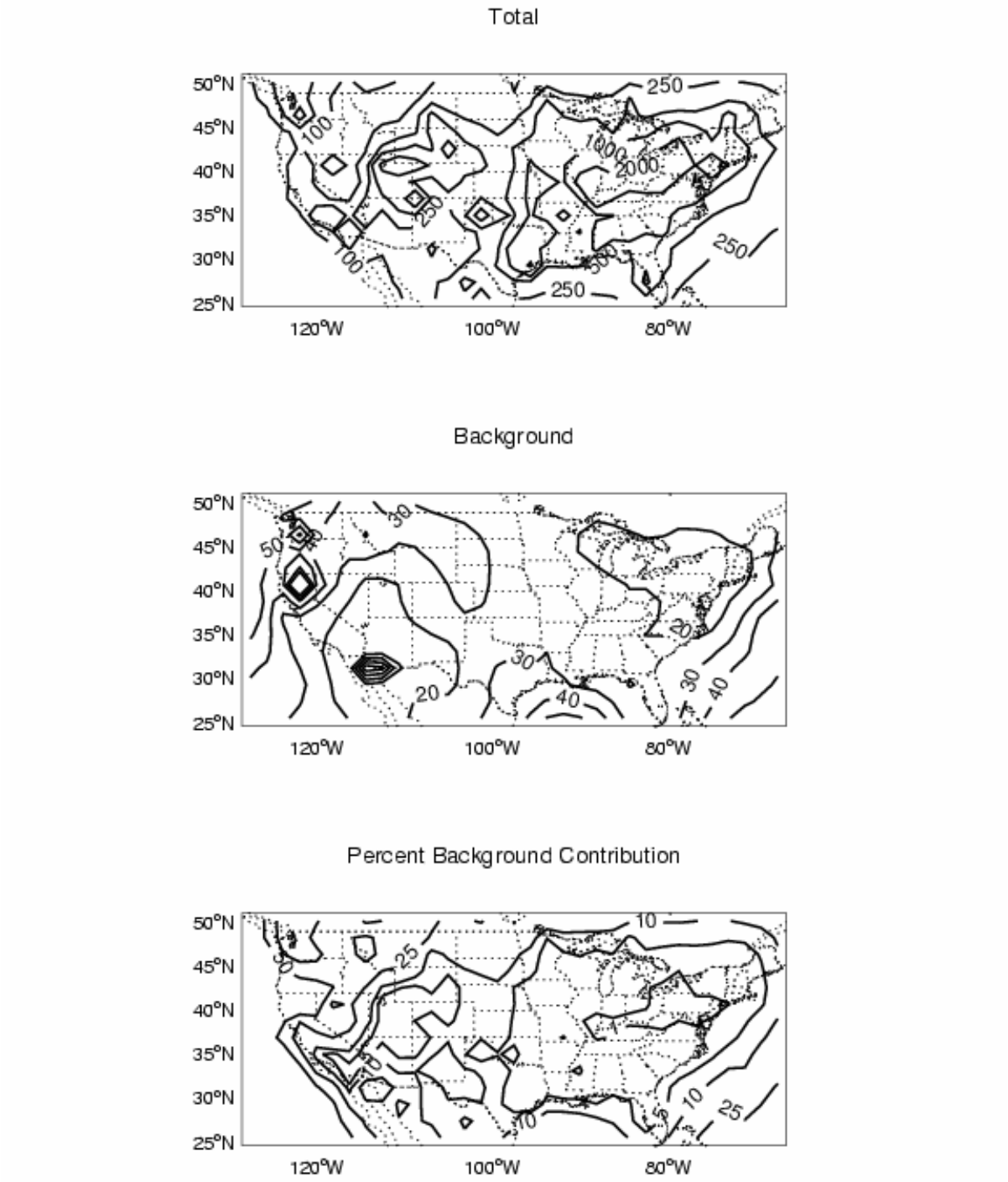


Figure AX2.9-4. Same as Figure AX2.9-1 but for SO_x deposition (SO_2 + SO_4) (mg S $m^{-2}y^{-1}$).

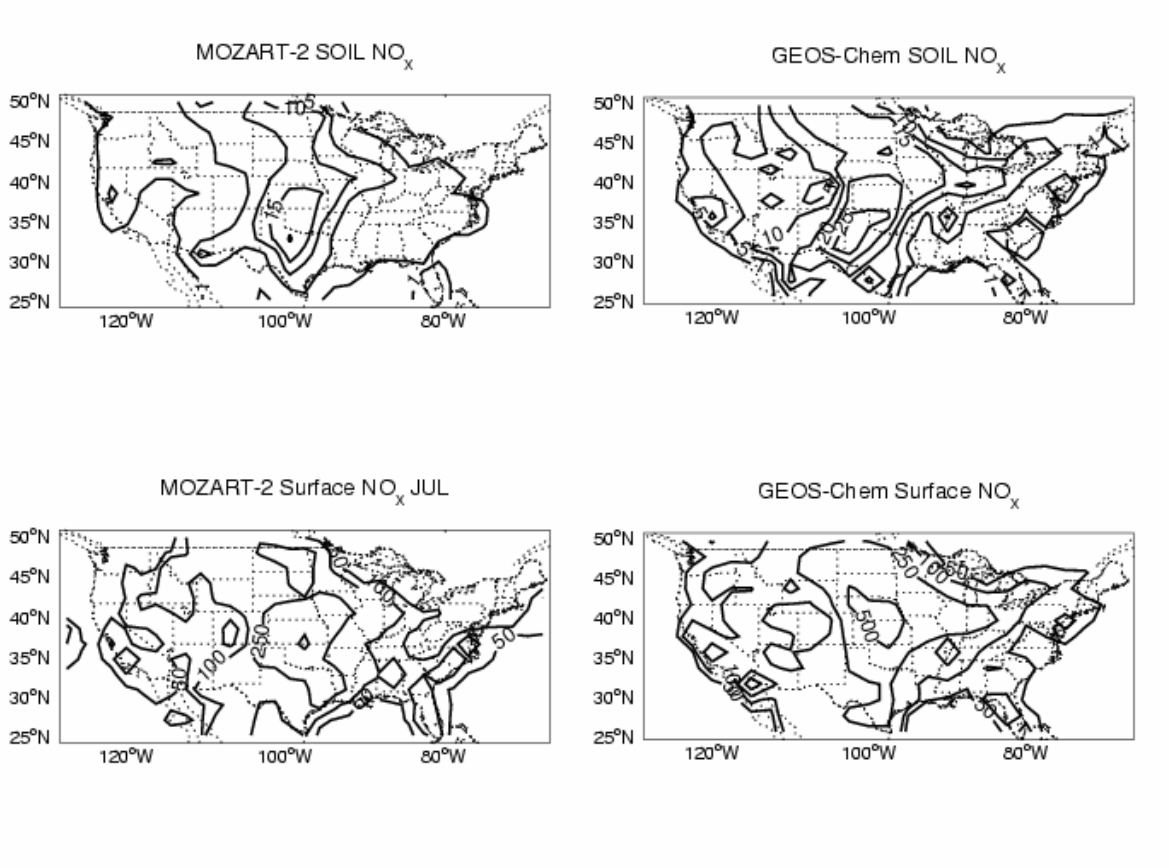


Figure AX2.9-5. July mean soil NO emissions (upper panels; 1×10^{9} molecules cm^{-2} s^{1}) and surface PRB NO_x concentrations (lower panels; pptv) over the United States from MOZART-2 (left) and GEOS-Chem (right) model simulations in which anthropogenic O_3 precursor emissions were set to zero in North America.

Coast where volcanic SO_2 emissions enhance PRB concentrations, the PRB contributes <1% to present-day SO_2 concentrations in surface air (bottom panel Figure AX2.9-2).

The spatial pattern of NO_y (defined here as HNO_3, NH_4NO_3, NO_x, HO_2NO_2, and organic nitrates) wet and dry deposition is shown in Figure AX2.9-3. Figure AX2.9-3 (upper panel) shows that highest values are found in the eastern United States in and downwind of the Ohio River Valley. The pattern of nitrogen deposition in the PRB simulation (Figure AX2.9-3, middle panel), however, shows maximum deposition centered over Texas and in the Gulf Coast region, reflecting a combination of nitrogen emissions from lightning in the Gulf region, biomass burning in the Southeast, and from microbial activity in soils (maximum in central Texas and

Oklahoma). The bottom panel of Figure AX2.9-3 shows that the PRB contribution to nitrogen deposition is less than 20% over the eastern United States, and typically less than 50% in the western United States where NO_y deposition is low (25-50 mg N m^{-2} yr^{-1}).

Present-day SO_x (SO_2 + $SO_4^{=}$) deposition is largest in the Ohio River Valley, likely due to coal-burning power plants in that region, while background deposition is typically at least an order of magnitude smaller (Figure AX2.9-4). Over the eastern United States, the background contribution to SO_x deposition is <10%, and it is even smaller (<1%) where present-day SO_x deposition is highest. The contribution of PRB to sulfate deposition is highest in the western United States (>20%) because of geothermal sources of SO_2 and oxidation of dimethyl sulfide in the surface of the eastern Pacific.

Thus far, the discussion has focused on results from the MOZART-2 tropospheric chemistry model. In Figure AX2.9-5, results from MOZART-2 are compared with those from another tropospheric chemistry model, GEOS-Chem (Bey et al., 2001), which was previously used to diagnose PRB O_3 (Fiore et al., 2003; U.S. Environmental Protection Agency, 2006). In both models, the surface PRB NO_x concentrations tend to mirror the distribution of soil NO emissions, which are highest in the Midwest. The higher soil NO emissions in GEOS-Chem (by nearly a factor of 2) as compared to MOZART-2 reflect different assumptions regarding the contribution to soil NO emissions largely through fertilizer, since GEOS-Chem total soil NO emissions are actually higher than MOZART-2 (0.07 versus 0.11 Tg N) over the United States in July. Even with the larger PRB soil NO emissions, surface NO_x concentrations in GEOS-Chem are typically below 500 pptv.

It is instructive to also consider measurements of SO_2 at relatively remote monitoring sites, i.e., site located in sparsely populate areas not subject to obvious local sources of pollution. Berresheim et al. (1993) used a type of atmospheric pressure ionization mass spectrometer (APIMS) at Cheeka Peak, WA (48.30N 124.62W, 480 m asl), in April 1991 during a field study for DMS oxidation products. Sulfur Dioxide concentrations ranged between 20 and 40 pptv. 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 pptv were observed in northwestern Nebraska in October 1999 at 150m above ground using the NCAR C-130 (Thornton, unpublished data). These data are comparable to remote central south Pacific convective boundary layer SO_2 (Thornton et al., 1999).

Volcanic sources of SO_2 in the UNITED STATES are limited to the Pacific Northwest, Alaska, and Hawaii. Since 1980 the Mt. St. Helens volcano in Washington Cascade Range (46.20 N, 122.18 W, summit 2549 m asl) has been a variable source of SO_2. Its major impact came in the explosive eruptions of 1980, which primarily affected the northern part of the mountain west of the UNITED STATES. The Augustine volcano near the mouth of the Cook Inlet in southwestern Alaska (59.363 N, 153.43 W, summit 1252 m asl) has had SO_2 emissions of varying extents since its last major eruptions in 1986. Volcanoes in the Kamchatka peninsula of eastern region of Siberian Russia do not particularly impact the surface concentrations in the northwestern NA. The most serious impact in the United States from volcanic SO_2 occurs on the island of Hawaii. Nearly continuous venting of SO_2 from Mauna Loa and Kilauea produce SO_2 in such large amounts so that >100 km downwind of the island SO_2 concentrations can exceed 30 ppbv (Thornton and Bandy, 1993). Depending on the wind direction the west coast of Hawaii (Kona region) has had significant impacts from SO_2 and acidic sulfate aerosols for the past decade. Indeed, SO_2 levels in Volcanoes National Park, HI exceeded the 3-h and the 24-h NAAQS in 2004 -2005. The area's design value is 0.6 ppm for the 3-h, and 0.19 ppm for the 24-h NAAQS (U.S. Environmental Protection Agency, 2006).

Overall, the background contribution to nitrogen and sulfur oxides over the United States is relatively small, except for SO_2 in areas where there is volcanic activity.

TABLE AX2.3-1. ATMOSPHERIC LIFETIMES OF SULFUR DIOXIDE AND REDUCED SULFUR SPECIES WITH RESPECT TO REACTION WITH OH, NO_3, AND CL RADICALS

	OH		NO_3		Cl	
Compound	**$k \times 10^{12}$**	**τ**	**$k \times 10^{12}$**	**τ**	**$k \times 10^{12}$**	**τ**
SO_2	1.6	7.2d	NA		NA	
CH_3-S-CH_3	5.0	2.3 d	1.0	1.1 h	400	29 d
H_2S	4.7	2.2 d	NA		74	157 d
CS_2	1.2	9.6 d	<0.0004	> 116 d	<0.004	NR
OCS	0.0019	17 y	<0.0001	> 1.3 y	<0.0001	NR
CH_3-S-H	33	8.4 h	0.89	1.2 h	200	58 d
CH_3-S-S-CH_3	230	1.2 h	0.53	2.1 h	NA	

Notes:

NA = Reaction rate coefficient not available. NR = Rate coefficient too low to be relevant as an atmospheric loss mechanism. Rate coefficients were calculated at 298 K and 1 atmosphere.

y = year. d = day. h = hour. OH = $1 \times 10^6/cm^3$; $NO_3 = 2.5 \times 10^8/cm^3$; Cl = $1 \times 10^3/cm^3$.

[1] Rate coefficients were taken from JPL Chemical Kinetics Evaluation No. 14 (JPL, 2003).

TABLE AX2.4-1a. RELATIVE CONTRIBUTIONS OF VARIOUS REACTIONS TO THE TOTAL S(IV) OXIDATION RATE WITHIN A SUNLIT CLOUD, 10 MINUTES AFTER CLOUD FORMATION

Reaction	% of Total [a]	% of Total [b]
Gas Phase		
$OH + SO_2$	3.5	3.1
Aqueous Phase		
$O_3 + HSO_3^-$	0.6	0.7
$O_3 + SO_3^{2-}$	7.0	8.2
$H_2O_2 + SO_3^-$	78.4	82.1
$CH_3OOH + HSO_3^-$	0.1	0.1
$HNO_4 + HSO_3^-$	9.0	4.4
$HOONO + HSO_3^-$	<0.1	<0.1
$HSO_5^- + HSO_3^-$	1.2	<0.1
$SO_5^- + SO_3^{2-}$	<0.1	<0.1
$HSO_5^- + Fe^{2+}$		0.6

[a] In the absence of transition metals.

[b] In the presence of iron and copper ions.

Source: Adapted from Warneck (1999).

TABLE AX2.4-1b. RELATIVE CONTRIBUTIONS OF VARIOUS GAS AND AQUEOUS PHASE REACTIONS TO AQUEOUS NITRATE FORMATION WITHIN A SUNLIT CLOUD, 10 MINUTES AFTER CLOUD FORMATION

Reaction	% of Total [a]	% of Total [b]
Gas Phase		
$OH + NO_2 + M$	57.7	67.4
Aqueous Phase		
$N_2O_{5g} + H_2O$	8.1	11.2
$NO_3 + Cl^-$	<0.1	0.1
$NO_3 + HSO_3^-$	0.7	1.0
$NO_3 + HCOO^-$	0.6	0.8
$HNO_4 + HSO_3^-$	31.9	20.5
$HOONO + NO_3^-$	0.8	<0.1
$O_3 + NO_2^-$	<0.1	<0.1

[a] In the absence of transition metals.

[b] In the presence of iron and copper ions.

Source: Adapted from Warneck (1999).

TABLE AX2.6-1. EMISSIONS OF NITROGEN OXIDES, AMMONIA, AND SULFUR DIOXIDE IN THE UNITED STATES IN 2002

2002 Emissions (Tg/year)	NO_x [1]	NH_3	SO_2
Source Category			
TOTAL ALL SOURCES	23.19	4.08	16.87
FUEL COMBUSTION TOTAL	9.11	0.02	14.47
FUEL COMB. ELEC. UTIL.	5.16	<0.01	11.31
Coal	4.50	<0.01	10.70
Bituminous	2.90		8.04
Subbituminous	1.42		2.14
anthracite & lignite	0.18		0.51
Other	<0.01		
Oil	0.14	<0.01	0.38
Residual	0.13		0.36
Distillate	0.01		0.01
Gas	0.30	<0.01	0.01
Natural	0.29		
Process	0.01		
Other	0.05	<0.01	0.21
Internal Combustion	0.17	<0.01	0.01
FUEL COMBUSTION INDUSTRIAL	3.15	<0.01	2.53
Coal	0.49	<0.01	1.26
Bituminous	0.25		0.70
Subbituminous	0.07		0.10
anthracite & lignite	0.04		0.13
Other	0.13		0.33
Oil	0.19	<0.01	0.59
Residual	0.09		0.40
Distillate	0.09		0.16
Other	0.01		0.02
Gas	1.16	<0.01	0.52
Natural	0.92		
Process	0.24		
Other	<0.01		
Other	0.16	<0.01	0.15
wood/bark waste	0.11		
liquid waste	0.01		
Other	0.04		
Internal Combustion	1.15	<0.01	0.01

TABLE AX2.6-1 (cont'd). EMISSIONS OF NITROGEN OXIDES, AMMONIA, AND SULFUR DIOXIDE IN THE UNITED STATES IN 2002

2002 Emissions (Tg/year)	NO_x [1]	NH_3	SO_2
FUEL COMB. OTHER	0.80	<0.01	0.63
Commercial/Institutional Coal	0.04	<0.01	0.16
Commercial/Institutional Oil	0.08	<0.01	0.28
Commercial/Institutional Gas	0.25	<0.01	0.02
Misc. Fuel Comb. (Except Residential)	0.03	<0.01	0.01
Residential Wood	0.03		<0.01
Residential Other	0.36		0.16
distillate oil	0.06		0.15
bituminous/subbituminous coal	0.26		<0.01
Other	0.04		<0.01
INDUSTRIAL PROCESSES TOTAL	1.10	0.21	1.54
CHEMICAL & ALLIED PRODUCT MFG	0.12	0.02	0.36
Organic Chemical Mfg	0.02	<0.01	0.01
Inorganic Chemical Mfg	0.01	<0.01	0.18
sulfur compounds			0.17
Other			0.02
Polymer & Resin Mfg	<0.01	<0.01	<0.01
Agricultural Chemical Mfg	0.05	0.02	0.05
ammonium nitrate/urea mfg.		<0.01	
Other		0.02	
Paint, Varnish, Lacquer, Enamel Mfg	0.00		0.00
Pharmaceutical Mfg	0.00		0.00
Other Chemical Mfg	0.03	<0.01	0.12
METALS PROCESSING	0.09	<0.01	0.30
Non-Ferrous Metals Processing	0.01	<0.01	0.17
Copper			0.04
Lead			0.07
Zinc			0.01
Other			<0.01
Ferrous Metals Processing	0.07	<0.01	0.11
Metals Processing NEC	0.01	<0.01	0.02

TABLE AX2.6-1 (cont'd). EMISSIONS OF NITROGEN OXIDES, AMMONIA, AND SULFUR DIOXIDE IN THE UNITED STATES IN 2002

2002 Emissions (Tg/year)	NO_x [1]	NH_3	SO_2
PETROLEUM & RELATED INDUSTRIES	0.16	<0.01	0.38
Oil & Gas Production	0.07	<0.01	0.11
natural gas			0.11
Other			0.01
Petroleum Refineries & Related Industries	0.05	<0.01	0.26
fluid catalytic cracking units		<0.01	0.16
Other		<0.01	0.07
Asphalt Manufacturing	0.04		0.01
OTHER INDUSTRIAL PROCESSES	0.54	0.05	0.46
Agriculture, Food, & Kindred Products	0.01	<0.01	0.01
Textiles, Leather, & Apparel Products	<0.01	<0.01	<0.01
Wood, Pulp & Paper, & Publishing Products	0.09	<0.01	0.10
Rubber & Miscellaneous Plastic Products	<0.01	<0.01	<0.01
Mineral Products	0.42	<0.01	0.33
cement mfg	0.24		0.19
glass mfg	0.01		
Other	0.10		0.09
Machinery Products	<0.01	<0.01	<0.01
Electronic Equipment	<0.01	<0.01	<0.01
Transportation Equipment	<0.01		<0.01
Miscellaneous Industrial Processes	0.01	0.05	0.02
SOLVENT UTILIZATION	0.01	<0.01	<0.01
Degreasing	<0.01	<0.01	<0.01
Graphic Arts	<0.01	<0.01	<0.01
Dry Cleaning	<0.01	<0.01	<0.01
Surface Coating	<0.01	<0.01	<0.01
Other Industrial	<0.01	<0.01	<0.01
Nonindustrial	<0.01		
Solvent Utilization NEC	<0.01		

TABLE AX2.6-1 (cont'd). EMISSIONS OF NITROGEN OXIDES, AMMONIA, AND SULFUR DIOXIDE IN THE UNITED STATES IN 2002

2002 Emissions (Tg/year)	NO_x [1]	NH_3	SO_2
STORAGE & TRANSPORT	<0.01	<0.01	0.01
Bulk Terminals & Plants	<0.01	<0.01	<0.01
Petroleum & Petroleum Product Storage	<0.01	<0.01	<0.01
Petroleum & Petroleum Product Transport	<0.01	<0.01	<0.01
Service Stations: Stage II	<0.01		<0.01
Organic Chemical Storage	<0.01	<0.01	<0.01
Organic Chemical Transport	0.01		<0.01
Inorganic Chemical Storage	<0.01	<0.01	<0.01
Inorganic Chemical Transport	<0.01		<0.01
Bulk Materials Storage	0.01	<0.01	<0.01
WASTE DISPOSAL & RECYCLING	0.17	0.14	0.03
Incineration	0.06	<0.01	0.02
Industrial			
Other			<0.01
Open Burning	0.10	<0.01	<0.01
Industrial			<0.01
land clearing debris			
Other			<0.01
POTW	<0.01	0.14	<0.01
Industrial Waste Water	<0.01	<0.01	<0.01
TSDF	<0.01	<0.01	<0.01
Landfills	<0.01	<0.01	<0.01
Industrial			<0.01
Other			<0.01
Other	<0.01	<0.01	<0.01

TABLE AX2.6-1 (cont'd). EMISSIONS OF NITROGEN OXIDES, AMMONIA, AND SULFUR DIOXIDE IN THE UNITED STATES IN 2002

2002 Emissions (Tg/year)	NO_x [1]	NH_3	SO_2
TRANSPORTATION TOTAL	12.58	0.32	0.76
HIGHWAY VEHICLES	8.09	0.32	0.30
Light-Duty Gas Vehicles & Motorcycles	2.38	0.20	0.10
light-duty gas vehicles	2.36		0.10
Motorcycles	0.02		0.00
Light-Duty Gas Trucks	1.54	0.10	0.07
light-duty gas trucks 1	1.07		0.05
light-duty gas trucks 2	0.47		0.02
Heavy-Duty Gas Vehicles	0.44	<0.01	0.01
Diesels	3.73	<0.01	0.12
heavy-duty diesel vehicles	3.71		
light-duty diesel trucks	0.01		
light-duty diesel vehicles	0.01		
OFF-HIGHWAY	4.49	<0.01	0.46
Non-Road Gasoline	0.23	<0.01	0.01
Recreational	0.01		
Construction	0.01		
Industrial	0.01		
lawn & garden	0.10		
Farm	0.01		
light commercial	0.04		
Logging	<0.01		
airport service	<0.01		
railway maintenance	<0.01		
recreational marine vessels	0.05		
Non-Road Diesel	1.76	<0.01	0.22
Recreational	0.00		
Construction	0.84		
Industrial	0.15		
lawn & garden	0.05		
Farm	0.57		
light commercial	0.08		
Logging	0.02		
airport service	0.01		
railway maintenance	<0.01		
recreational marine vessels	0.03		

TABLE AX2.6-1 (cont'd). EMISSIONS OF NITROGEN OXIDES, AMMONIA, AND SULFUR DIOXIDE IN THE UNITED STATES IN 2002

2002 Emissions (Tg/year)	NO_x [1]	NH_3	SO_2
Aircraft	0.09		0.01
Marine Vessels	1.11		0.18
Diesel	1.11		
residual oil			
Other			
Railroads	0.98		0.05
Other	0.32	<0.01	0.00
liquefied petroleum gas	0.29		
compressed natural gas	0.04		
MISCELLANEOUS	0.39	3.53	0.10
Agriculture & Forestry	<0.01	3.45	<0.01
agricultural crops		<0.01	
agricultural livestock		2.66	
Other Combustion		0.08	0.10
Health Services			
Cooling Towers			
Fugitive Dust			
Other			
Natural Sources	3.10	0.03	

[1] Emissions are expressed in terms of NO_2.

[2] Estimate based on Guenther et al. (2000).

Source: U.S. Environmental Protection Agency (2006).

TABLE AX2.8-1. SATELLITE INSTRUMENTS USED TO RETRIEVE TROPOSPHERIC NO_2 COLUMNS.

Instrument	Coverage	Typical U.S. Measurement Time	Typical Resolution (km)	Return Time (days)[1]	Instrument Overview
GOME	1995-2002	10:30-11:30 AM	320×40	3	Burrows et al. (1999)
SCIAMACHY	2002-	10:00-11:00 AM	30×60	6	Bovensmann et al. (1999)
OMI	2004-	12:45-1:45 PM	13×24	1	Levelt et al. (2006)

[1] Return time is reported here for cloud free conditions. Note that due to precession of the satellite's orbit, return measurements are close to but not made over the same location. In practice, clouds decrease observation frequency by a factor of 2.

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AX3. CHAPTER 3 ANNEX – A FRAMEWORK FOR MODELING HUMAN EXPOSURES TO SO_2 AND RELATED AIR POLLUTANTS

AX3.1 INTRODUCTION: CONCEPTS, TERMINOLOGY, AND OVERALL SUMMARY

Predictive (or prognostic) exposure modeling studies[1], specifically focusing on SO_2, could not be identified in the literature, though, often, statistical (diagnostic) analyses have been reported using data obtained in various field exposure studies. However, existing prognostic modeling systems for the assessment of inhalation exposures can in principle be directly applied to, or adapted for, SO_2 studies; specifically, such systems include APEX, SHEDS, and MENTOR-1A, to be discussed in the following sections. Nevertheless, it should be mentioned that such applications will be constrained by data limitations, such as the degree of ambient concentration characterization (e.g., concentrations at the local level) and quantitative information on indoor sources and sinks.

Predictive models of human exposure to ambient air pollutants such as SO_2 can be classified and differentiated based upon a variety of attributes. For example, exposure models can be classified as:

- models of potential (typically maximum) outdoor exposure versus models of actual exposures (the latter including locally modified microenvironmental exposures, both outdoor and indoor),
- Population Based Exposure Models (PBEM) versus Individual Based Exposure Models (IBEM),
- deterministic versus probabilistic (or statistical) exposure models,
- observation-driven versus mechanistic air quality models (see Section AX3.4 for discussions about the construction, uses and limitations of this class of mathematical models.

[1] i.e. assessments that start from emissions and demographic information and explicitly consider the physical and chemical processes of environmental and microenvironmental transport and fate, in conjunction with human activities, to estimate inhalation intake and uptake.

Some points should be made regarding terminology and essential concepts in exposure modeling, before proceeding to the overview of specific developments reported in the current research literature:

First, it must be understood that there is significant variation in the definitions of many of the terms used in the exposure modeling literature; indeed, the science of exposure modeling is a rapidly evolving field and the development of a standard and commonly accepted terminology is an ongoing process (see, e.g., WHO, 2004).

Second, it should also be mentioned that, very often, procedures that are called exposure modeling, exposure estimation, etc. in the scientific literature, may in fact refer to only a sub-set of the complete set of steps or components required for a comprehensive exposure assessment. For example, certain self-identified exposure modeling studies focus solely on refining the sub-regional or local spatio-temporal dynamics of pollutant concentrations (starting from raw data representing monitor observations or regional grid-based model estimates). Though not exposure studies per se, such efforts have value and are included in the discussion of the next sub-section, as they provide potentially useful tools that can be used in a complete exposure assessment. On the other hand, formulations that are self-identified as exposure models but actually focus only on ambient air quality predictions, such as chemistry-transport models, are not included in the discussion that follows.

Third, the process of modeling human exposures to ambient pollutants (traditionally focused on ozone) is very often identified explicitly with population-based modeling, while models describing the specific mechanisms affecting the exposure of an actual individual (at specific locations) to an air contaminant (or to a group of co-occurring gas and/or aerosol phase pollutants) are usually associated with studies focusing specifically on indoor air chemistry modeling.

Finally, fourth, the concept of microenvironments, introduced in earlier sections of this document, should be clarified further, as it is critical in developing procedures for exposure modeling. In the past, microenvironments have typically been defined as individual or aggregate locations (and sometimes even as activities taking place within a location) where a homogeneous concentration of the pollutant is encountered. Thus a microenvironment has often been identified with an ideal (i.e. perfectly mixed) compartment of classical compartmental modeling. More recent and general definitions view the microenvironment as a control volume, either

indoors or outdoors, that can be fully characterized by a set of either mechanistic or phenomenological governing equations, when appropriate parameters are available, given necessary initial and boundary conditions. The boundary conditions typically would reflect interactions with ambient air and with other microenvironments. The parameterizations of the governing equations generally include the information on attributes of sources and sinks within each microenvironment. This type of general definition allows for the concentration within a microenvironment to be non-homogeneous (non-uniform), provided its spatial profile and mixing properties can be fully predicted or characterized. By adopting this definition, the number of microenvironments used in a study is kept manageable, but variability in concentrations in each of the microenvironments can still be taken into account. Microenvironments typically used to determine exposure include indoor residential microenvironments, other indoor locations (typically occupational microenvironments), outdoors near roadways, other outdoor locations, and in-vehicles. Outdoor locations near roadways are segregated from other outdoor locations (and can be further classified into street canyons, vicinities of intersections, etc.) because emissions from automobiles alter local concentrations significantly compared to background outdoor levels. Indoor residential microenvironments (kitchen, bedroom, living room, etc. or aggregate home microenvironment) are typically separated from other indoor locations because of the time spent there and potential differences between the residential environment and the work/public environment.

Once the actual individual and relevant activities and locations (for Individual Based Modeling), or the sample population and associated spatial (geographical) domain (for Population Based Modeling) have been defined along with the temporal framework of the analysis (time period and resolution), the comprehensive modeling of individual/population exposure to SO_2 (and related pollutants) will in general require seven steps (or components, as some of them do not have to be performed in sequence) that are listed below. This list represents a composite based on approaches and frameworks described in the literature over the last twenty-five years (Ott, 1982; Ott, 1985; Lioy, 1990; U.S. Environmental Protection Agency, 1992; Georgopoulos and Lioy, 1994; U.S. Environmental Protection Agency, 1997; Price et al., 2003; Georgopoulos et al., 2005; WHO, 2005; U.S. Environmental Protection Agency, 2006a; Georgopoulos and Lioy, 2006) as well on the structure of various inhalation exposure models (NEM/pNEM, HAPEM, SHEDS, REHEX, EDMAS, MENTOR, ORAMUS, APEX, AIRPEX,

AIRQUIS, etc., to be discussed in the following section) that have been used in the past or in current studies to specifically assess inhalation exposures. Figure AX3.1-1, adapted from Georgopoulos et al. (2005), schematically depicts the sequence of steps involved that are summarized here (and further discussed in the following sub-sections).

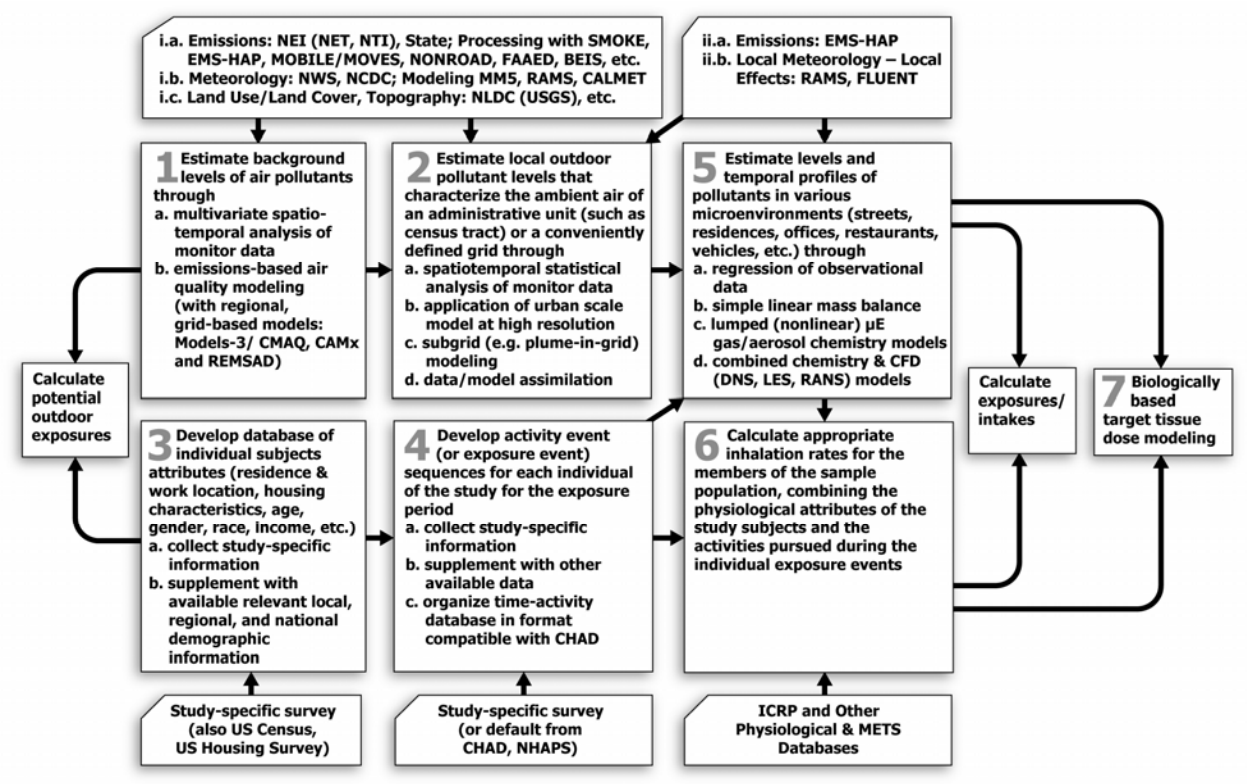

Figure AX3.1-1. Schematic description of a general framework identifying the processes (steps or components) involved in assessing inhalation exposures and doses for individuals and populations. In general terms, existing comprehensive exposure modeling systems such as SHEDS, APEX, and MENTOR-1A follow this framework.

Source: Figure adapted with modifications from Georgopoulos et al. (2005).

1. Estimation of the background or ambient levels of both SO_2 and related pollutants. This is done through either (or a combination of):
   a. multivariate spatio-temporal analysis of fixed monitor data, or
   b. emissions-based, photochemical, air quality modeling (typically with a regional, grid-based model such as Models-3/CMAQ or CAMx) applied in a coarse resolution mode.

2. Estimation of local outdoor pollutant levels of both SO_2 and related pollutants. These levels could typically characterize the ambient air of either an administrative unit (such as a census tract, a municipality, a county, etc.) or a conveniently defined grid cell of an urban scale air quality model. Again, this may involve either (or a combination of):

   a. spatio-temporal statistical analysis of monitor data, or

   b. application of an urban multi-scale, grid based model (such as CMAQ or CAMx) at its highest resolution (typically around 2-4 km), or

   c. correction of the estimates of the regional model using some scheme that adjusts for observations and/or for subgrid chemistry and mixing processes.

3. Characterization of relevant attributes of the individuals or populations under study (residence and work locations, occupation, housing data, income, education, age, gender, race, weight, and other physiological characteristics). For Population Based Exposure Modeling (PBEM) one can either:

   a. select a fixed-size sample population of virtual individuals in a way that statistically reproduces essential demographics (age, gender, race, occupation, income, education) of the administrative population unit used in the assessment (e.g., a sample of 500 people is typically used to represent the demographics of a given census tract, whereas a sample of about 10,000 may be needed to represent the demographics of a county), or

   b. divide the population-of interest into a set of cohorts representing selected subpopulations where the cohort is defined by characteristics known to influence exposure.

4. Development of activity event (or exposure event) sequences for each member of the sample population (actual or virtual) or for each cohort for the exposure period. This could utilize:

   a. study-specific information, if available

   b. existing databases based on composites of questionnaire information from past studies

   c. time-activity databases, typically in a format compatible with U.S. Environmental Protection Agency's Consolidated Human Activity Database (CHAD - McCurdy et al., 2000)

5. Estimation of levels and temporal profiles of both SO_2 and related pollutants in various outdoor and indoor microenvironments such as street canyons, roadway

intersections, parks, residences, offices, restaurants, vehicles, etc. This is done through either:

a. linear regression of available observational data sets,

b. simple mass balance models (with linear transformation and sinks) over the volume (or a portion of the volume) of the microenvironment,

c. lumped (nonlinear) gas or gas/aerosol chemistry models, or

d. detailed combined chemistry and Computational Fluid Dynamics modeling.

6. Calculation of appropriate inhalation rates for the members of the sample population, combining the physiological attributes of the (actual or virtual) study subjects and the activities pursued during the individual exposure events.

7. Calculation of target tissue dose through biologically based modeling estimation (specifically, respiratory dosimetry modeling in the case of SO_2 and related reactive pollutants) if sufficient information is available.

Implementation of the above framework for comprehensive exposure modeling has benefited significantly from recent advances and expanded availability of computational technologies such as Relational Database Management Systems (RDBMS) and Geographic Information Systems (GIS) (Purushothaman and Georgopoulos, 1997, 1999a,b; Georgopoulos et al., 2005).

In fact, only relatively recently comprehensive, predictive, inhalation exposure modeling studies for ozone, PM, and various air toxics, have attempted to address/incorporate all the components of the general framework described here. In practice, the majority of past exposure modeling studies have either incorporated only subsets of these components or treated some of them in a simplified manner, often focusing on the importance of specific factors affecting exposure. Of course, depending on the objective of a particular modeling study, implementation of only a limited number of steps may be necessary. For example, in a regulatory setting, when comparing the relative effectiveness of emission control strategies, the focus can be on expected changes in ambient levels (corresponding to those observed at NAAQS monitors) in relation to the density of nearby populations. The outdoor levels of pollutants, in conjunction with basic demographic information, can thus be used to calculate upper bounds of population exposures associated with ambient air (as opposed to total exposures that would include contributions from

indoor sources) useful in comparing alternative control strategies. Though the metrics derived would not be quantitative indicators of actual human exposures, they can serve as surrogates of population exposures associated with outdoor air, and thus aid in regulatory decision making concerning pollutant standards and in studying the efficacy of emission control strategies. This approach has been used in studies performing comparative evaluations of regional and local emissions reduction strategies in the eastern United States (e.g., Purushothaman and Georgopoulos, 1997; Georgopoulos et al., 1997a; Foley et al., 2003).

AX3.2 POPULATION EXPOSURE MODELS: THEIR EVOLUTION AND CURRENT STATUS

Existing comprehensive inhalation exposure models consider the trajectories of individual human subjects (actual or virtual), or of appropriately defined cohorts, in space and time as sequences of exposure events. In these sequences, each event is defined by time, a geographic location, a microenvironment, and the activity of the subject. U.S. Environmental Protection Agency offices (OAQPS and NERL) have supported the most comprehensive efforts in developing models implementing this general concept (see, e.g., Johnson, 2002), and these efforts have resulted in the NEM/pNEM (National Exposure Model and Probabilistic National Exposure Model - Whitfield et al., 1997), HAPEM (Hazardous Air Pollutant Exposure Model - Rosenbaum, 2005), SHEDS (Simulation of Human Exposure and Dose System - Burke et al., 2001), APEX (Air Pollutants Exposure model – U.S. Environmental Protection Agency, 2006b,c), and MENTOR (Modeling Environment for Total Risk studies - Georgopoulos et al., 2005; Georgopoulos and Lioy, 2006) families of models. European efforts have produced some formulations with similar general attributes as the above U.S. models but, generally, involving simplifications in some of their components. Examples of European models addressing exposures to photochemical oxidants (specifically ozone) include the AirPEx (Air Pollution Exposure) model (Freijer et al., 1998), which basically replicates the pNEM approach and has been applied to the Netherlands, and the AirQUIS (Air Quality Information System) model (Clench-Aas et al., 1999).

The NEM/pNEM, SHEDS, APEX, and MENTOR-1A (MENTOR for One-Atmosphere studies) families of models provide exposure estimates defined by concentration and breathing rate for each individual exposure event, and then average these estimates over periods typically

ranging from one h to one year. These models allow simulation of certain aspects of the variability and uncertainty in the principal factors affecting exposure. An alternative approach is taken by the HAPEM family of models that typically provide annual average exposure estimates based on the quantity of time spent per year in each combination of geographic locations and microenvironments. The NEM, SHEDS, APEX, and MENTOR-type models are therefore expected to be more appropriate for pollutants with complex chemistry such as SO_2, and could provide useful information for enhancing related health assessments.

More specifically, regarding the consideration of population demographics and activity patterns:

1. pNEM divides the population of interest into representative cohorts based on the combinations of demographic characteristics (age, gender, and employment), home/work district, residential cooking fuel and replicate number, and then assigns an activity diary record from CHAD (Consolidated Human Activities Database) to each cohort according to demographic characteristic, season, day-type (weekday/weekend) and temperature.
2. HAPEM6 divides the population of interest into demographic groups based on age, gender and race, and then for each demographic group/day-type (weekday/weekend) combination, selects multiple activity patterns randomly (with replacement) from CHAD and combines them to find the averaged annual time allocations for group members in each census tract for different day types.
3. SHEDS, APEX, and MENTOR-1A generate population demographic files, which contain a user-defined number of person records for each census tract of the population based on proportions of characteristic variables (age, gender, employment, and housing) obtained from the population of interest, and then assign a matching activity diary record from CHAD to each individual record of the population based on the characteristic variables. It should be mentioned that, in the formulations of these models, workers may commute from one census tract to another census tract for work. So, with the specification of commuting patterns, the variation of exposure concentrations due to commuting between different census tracts can be captured.

The essential attributes of the pNEM, HAPEM, APEX, SHEDS, and MENTOR-1A models are summarized in Table AX3.2-1.

The conceptual approach originated by the SHEDS models was modified and expanded for use in the development of MENTOR-1A (Modeling Environment for Total Risk – One Atmosphere). Flexibility was incorporated into this modeling system, such as the option of including detailed indoor chemistry and other relevant microenvironmental processes, and

providing interactive linking with CHAD for consistent definition of population characteristics and activity events (Georgopoulos et al., 2005).

NEM/pNEM implementations have been extensively applied to ozone studies in the 1980s and 1990s. The historical evolution of the pNEM family of models of OAQPS started with the introduction of the first NEM model in the 1980s (Biller et al., 1981). The first such implementations of pNEM/O_3 in the 1980s used a regression-based relationship to estimate indoor ozone concentrations from outdoor concentrations. The second generation of pNEM/O_3 was developed in 1992 and included a simple mass balance model to estimate indoor ozone concentrations. A report by Johnson et al. (2000) describes this version of pNEM/O_3 and summarizes the results of an initial application of the model to 10 cities. Subsequent enhancements to pNEM/O_3 and its input databases included revisions to the methods used to estimate equivalent ventilation rates, to determine commuting patterns, and to adjust ambient ozone levels to simulate attainment of proposed NAAQS. During the mid-1990s, the Environmental Protection Agency applied updated versions of pNEM/O_3 to three different population groups in selected cities: (1) the general population of urban residents, (2) outdoor workers, and (3) children who tend to spend more time outdoors than the average child. This version of pNEM/O_3 used a revised probabilistic mass balance model to determine ozone concentrations over one-h periods in indoor and in-vehicle microenvironments (Johnson, 2001).

In recent years, pNEM has been replaced by (or "evolved to") the Air Pollution Exposure Model (APEX). APEX differs from earlier pNEM models in that the probabilistic features of the model are incorporated into a Monte Carlo framework (Langstaff, 2007; U.S. Environmental Protection Agency, 2006b,c). Like SHEDS and MENTOR-1A, instead of dividing the population-of-interest into a set of cohorts, APEX generates individuals as if they were being randomly sampled from the population. APEX provides each generated individual with a demographic profile that specifies values for all parameters required by the model. The values are selected from distributions and databases that are specific to the age, gender, and other specifications stated in the demographic profile. The Environmental Protection Agency has applied APEX to the study of exposures to ozone and other criteria pollutants; APEX can be modified and used for the estimation of SO_2 exposures, if required.

Reconfiguration of APEX for use with SO_2 or other pollutants would require significant literature review, data analysis, and modeling efforts. Necessary steps include determining

spatial scope and resolution of the model; generating input files for activity data, air quality and temperature data; and developing definitions for microenvironments and pollutant-microenvironment modeling parameters (penetration and proximity factors, indoor source emissions rates, decay rates, etc.) (ICF Consulting, 2005). To take full advantage of the probabilistic capabilities of APEX, distributions of model input parameters should be used wherever possible.

AX3.3 CHARACTERIZATION OF AMBIENT CONCENTRATIONS OF SO_2 AND RELATED AIR POLLUTANTS

As mentioned earlier, background and regional outdoor concentrations of pollutants over a study domain may be estimated through emissions-based mechanistic modeling, through ambient data based modeling, or through a combination of both. Emissions-based models calculate the spatio-temporal fields of the pollutant concentrations using precursor emissions and meteorological conditions as inputs and using numerical representations of transformation reactions to drive outputs. The ambient data based models typically calculate spatial or spatio-temporal distributions of the pollutant through the use of interpolation schemes, based on either deterministic or stochastic models for allocating monitor station observations to the nodes of a virtual regular grid covering the region of interest. The geostatistical technique of kriging provides various standard procedures for generating an interpolated spatial distribution for a given time, from data at a set of discrete points. Kriging approaches were evaluated by Georgopoulos et al. (Georgopoulos et al., 1997b) in relation to the calculation of local ambient ozone concentrations for exposure assessment purposes, using either monitor observations or regional/urban photochemical model outputs. It was found that kriging is severely limited by the nonstationary character of the concentration patterns of reactive pollutants; so the advantages this method has in other fields of geophysics do not apply here. The above study showed that the appropriate semivariograms had to be hour-specific, complicating the automated reapplication of any purely spatial interpolation over an extended time period.

Spatio-temporal distributions of pollutant concentrations such as ozone, PM, and various air toxics have alternatively been obtained using methods of the Spatio-Temporal Random Field (STRF) theory (Christakos and Vyas, 1998a,b). The STRF approach interpolates monitor data in both space and time simultaneously. This method can thus analyze information on temporal

trends which cannot be incorporated directly in purely spatial interpolation methods such as standard kriging. Furthermore, the STRF method can optimize the use of data which are not uniformly sampled in either space or time. STRF was further extended within the Bayesian Maximum Entropy (BME) framework and applied to ozone interpolation studies (Christakos and Hristopulos, 1998; Christakos and Kolovos, 1999; Christakos, 2000). It should be noted that these studies formulate an over-arching scheme for linking air quality with population dose and health effects; however, they are limited by the fact that they do not include any microenvironmental effects. MENTOR has incorporated STRF/BME methods as one of the steps for performing a comprehensive analysis of exposure to ozone and PM (Georgopoulos et al., 2005).

The issue of subgrid variability (SGV) from the perspective of interpreting and evaluating the outcomes of grid-based, multiscale, photochemical air quality simulation models is discussed in Ching et al. (2006), who suggest a framework that can provide for qualitative judgments on model performance based on comparing observations to the grid predictions and its SGV distribution. From the perspective of Population Exposure Modeling, the most feasible/practical approach for treating subgrid variability of local concentrations is probably through 1) the identification and proper characterization of an adequate number of outdoor microenvironments (potentially related to different types of land use within the urban area as well as to proximity to different types of roadways) and 2) then, concentrations in these microenvironments will have to be adjusted from the corresponding local background ambient concentrations through either regression of empirical data or various types of local atmospheric dispersion/transformation models. This is discussed further in the next subsection.

AX3.4 CHARACTERIZATION OF MICROENVIRONMENTAL CONCENTRATIONS

Once the background and local ambient spatio-temporal concentration patterns have been derived, microenvironments that can represent either outdoor or indoor settings when individuals come in contact with the contaminant of concern (e.g., SO_2) must be characterized. This process can involve modeling of various local sources and sinks, and interrelationships between ambient and microenvironmental concentration levels. Three general approaches have been used in the past to model microenvironmental concentrations:

- Empirical (typically linear regression) fitting of data from studies relating ambient/local and microenvironmental concentration levels to develop analytical relationships.
- Parameterized mass balance modeling over, or within, the volume of the microenvironment. This type of modeling has ranged from very simple formulations, i.e. from models assuming ideal (homogeneous) mixing within the microenvironment (or specified portions of it) and only linear physicochemical transformations (including sources and sinks), to models incorporating analytical solutions of idealized dispersion formulations (such as Gaussian plumes), to models that take into account aspects of complex multiphase chemical and physical interactions and nonidealities in mixing.
- Detailed Computational Fluid Dynamics (CFD) modeling of the outdoor or indoor microenvironment, employing either a Direct Numerical Simulation (DNS) approach, a Reynolds Averaged Numerical Simulation (RANS) approach, or a Large Eddy Simulation (LES) approach, the latter typically for outdoor situations (see, e.g., Milner et al., 2005; Chang and Meroney, 2003; Chang, 2006).

Parameterized mass balance modeling is the approach currently preferred for exposure modeling for populations. As discussed earlier, the simplest microenvironmental setting corresponds to a homogeneously mixed compartment, in contact with possibly both outdoor/local environments as well as other microenvironments. The air quality of this idealized microenvironment is affected mainly by the following processes:

a. Transport processes: These can include advection/convection and dispersion that are affected by local processes and obstacles such as vehicle induced turbulence, street canyons, building structures, etc.

b. Sources and sinks: These can include local outdoor emissions, indoor emissions, surface deposition, etc.

c. Transformation processes: These can include local outdoor as well as indoor gas and aerosol phase chemistry, such as formation of secondary organic and inorganic aerosols.

Exposure modeling also requires information on activity patterns to determine time spent in various microenvironments and estimates of inhalation rates to characterize dose. The next two subsections describe recent work done in these areas.

AX3.4.1 Characterization of Activity Events

An important development in inhalation exposure modeling has been the consolidation of existing information on activity event sequences in the Consolidated Human Activity Database (CHAD) (McCurdy, 2000; McCurdy et al., 2000). Indeed, most recent exposure models are designed (or have been re-designed) to obtain such information from CHAD which incorporates 24-h time/activity data developed from numerous surveys. The surveys include probability-based recall studies conducted by Environmental Protection Agency 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 one or more days of sequential activities, in which each activity is defined by start time, duration, activity type (140 categories), and microenvironment classification (110 categories). Activities vary from one min to one h in duration, with longer activities being subdivided into clock-hour durations to facilitate exposure modeling. A distribution of values for the ratio of oxygen uptake rate to body mass (referred to as metabolic equivalents or METs) is provided for each activity type listed in CHAD. The forms and parameters of these distributions were determined through an extensive review of the exercise and nutrition literature. The primary source of distributional data was Ainsworth et al. (1993), a compendium developed specifically to facilitate the coding of physical activities and to promote comparability across studies.

AX3.4.2 Characterization of Inhalation Intake and Uptake

Use of the information in CHAD provides a rational way for incorporating realistic intakes into exposure models by linking inhalation rates to activity information. As mentioned earlier, each cohort of the pNEM-type models, or each (virtual or actual) individual of the SHEDS, MENTOR, APEX, and HAPEM4 models, is assigned an exposure event sequence derived from activity diary data. Each exposure event is typically defined by a start time, a duration, assignments to a geographic location and microenvironment, and an indication of activity level. The most recent versions of the above models have defined activity levels using the activity classification coding scheme incorporated into CHAD. A probabilistic module within these models converts the activity classification code of each exposure event to an energy expenditure rate, which in turn is converted into an estimate of oxygen uptake rate. The oxygen

uptake rate is then converted into an estimate of total ventilation rate ($\dot{V}_E$), expressed in liters min^{-1}. Johnson (2001) reviewed briefly the physiological principles incorporated into the algorithms used in pNEM to convert each activity classification code to an oxygen uptake rate and describes the additional steps required to convert oxygen uptake to $\dot{V}_E$.

McCurdy (1997a,b, 2000) has recommended that the ventilation rate should be estimated as a function of energy expenditure rate. The energy expended by an individual during a particular activity can be expressed as EE = (MET)(RMR) in which EE is the average energy expenditure rate (kcal min^{-1}) during the activity and RMR is the resting metabolic rate of the individual expressed in terms of number of energy units expended per unit of time (kcal min^{-1}). MET (the metabolic equivalent of tasks) is a ratio specific to the activity and is dimensionless. If RMR is specified for an individual, then the above equation requires only an activity-specific estimate of MET to produce an estimate of the energy expenditure rate for a given activity. McCurdy et al. (2000) developed distributions of MET for the activity classifications appearing in the CHAD database.

AX3.5 CONCLUDING COMMENTS

An issue that should be mentioned in closing is that of evaluating comprehensive prognostic exposure modeling studies, for either individuals or populations, with field data. Although databases that would be adequate for performing a comprehensive evaluation are not expected to be available any time soon, there have been a number of studies, reviewed in earlier sections of this Chapter, that can be used to start building the necessary information base. Some of these studies report field observations of personal, indoor, and outdoor levels and have also developed simple semi-empirical personal exposure models that were parameterized using the observational data and regression techniques.

In conclusion, though existing inhalation exposure modeling systems have evolved considerably in recent years, limitations of available modeling methods and data in relation to potential SO_2 studies should be taken into account. Existing prognostic modeling systems for inhalation exposure can in principle be directly applied to, or adapted for, SO_2 studies; APEX, SHEDS, and MENTOR-1A are candidates. However, such applications would be constrained by

data limitations such as ambient characterization at the local scale and by lack of quantitative information for indoor sources and sinks.

TABLE AX3.2-1. THE ESSENTIAL ATTRIBUTES OF THE PNEM, HAPEM, APEX, SHEDS, AND MENTOR-1A

	pNEM	HAPEM	APEX	SHEDS	MENTOR-1A
Exposure Estimate	Hourly averaged	Annual averaged	Hourly averaged	Activity event based	Activity event based
Characterization of the High-End Exposures	Yes	No	Yes	Yes	Yes
Typical Spatial Scale/Resolution	Urban areas/Census tract level	Ranging from urban to national/ Census tract level	Urban area/Census tract level	Urban areas/Census tract level	Multiscale/ Census tract level
Temporal Scale/Resolution	A yr/one h	A yr/one h	A yr/one h	A yr/event based	A yr/activity event based time step
Population Activity Patterns Assembly	Top-down approach	Top-down approach	Bottom-up "person-oriented" approach	Bottom-up "person-oriented" approach	Bottom-up "person-oriented" approach
Microenvironment Concentration Estimation	Non-steady-state and steady-state mass balance equations (hard-coded)	Linear relationship method (hard-coded)	Non-steady-state mass balance and linear regression (flexibility of selecting algorithms)	Steady-state mass balance equation (residential) and linear regression (non-residential) (hard-coded)	Non-steady-state mass balance equation with indoor air chemistry module or regression methods (flexibility of selecting algorithms)
Microenvironmental (ME) Factors	Random samples from probability distributions	Random samples from probability distributions	Random samples from probability distributions	Random samples from probability distributions	Random samples from probability distributions
Specification of Indoor Source Emissions	Yes (gas-stove, tobacco smoking)	Available; set to zero in HAPEM6	Yes (multiple sources defined by the user)	Yes (gas-stove, tobacco smoking, other sources)	Yes (multiple sources defined by the user)
Commuting Patterns	Yes	Yes	Yes	Yes	Yes
Exposure Routes	Inhalation	Inhalation	Inhalation	Inhalation	Multiple (optional)
Potential Dose Calculation	Yes	No	Yes	Yes	Yes
Physiologically Based Dose	No	No	No	Yes	Yes
Variability/ Uncertainty	Yes	No	Yes	Yes	Yes (Various "Tools")

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AX4. CHAPTER 4 ANNEX – TOXICOLOGICAL STUDIES OF THE HEALTH EFFECTS OF SULFUR OXIDES

TABLE AX4-1. PHYSIOLOGICAL EFFECTS OF SO_2 EXPOSURE

Concentration	Duration	Species	Effects	Reference
Acute and Subacute Exposures				
~1 ppm (2.62 mg/m^3); head only	1 h	Hartley guinea pig, male, age not reported, 200-300 g, n = 8-23/group	An 11% increase in pulmonary resistance and 12% decrease in dynamic compliance were observed. Neither effect persisted into the 1-h period following exposure. No effects were observed for breathing frequency, tidal volume, or min volume.	Amdur et al. (1983)
1 ppm (2.62 mg/m^3); nose only	3 h/day for 6 days; animals evaluated for up to 48 h following exposure; exposures occurred in a furnace	Hartley guinea pig, male, age not reported, 250-320 g, n = ≤18 group/time point	No effect was observed on residual volume, functional reserve capacity, vital capacity, total lung capacity, respiratory frequency, tidal volume, pulmonary resistance, or pulmonary compliance at 1 or 48 h after the last exposure.	Conner et al. (1985)
5 ppm (13.1 mg/m^3); apperantly intratracheal	45 min	Rabbit, sex not reported, adult, mean 2.0 kg, n = 5-9/group; rabbits were mechanically ventilated	Bivagotomy had no effect on SO_2-induced increases in lung resistance (54% increase before vagotomy and 56% increase after vagotomy). Reflex bronchoconstrictive response to phenyldiguanide (intravenously administered) was eliminated by exposure to SO_2 but SO_2 had no effect on lung resistance induced by intravenously-administered histamine. **The study authors concluded that (1) vagal reflex is not responsible for SO_2-induced increase in lung resistance and (2) transient alteration in tracheobronchial wall following SO_2 exposure may have reduced accessibility of airway nervous receptors to phenyldiguanide.**	Barthélemy et al. (1988)
5 ppm (13.1 mg/m^3); whole body	2 h/day for 13 wks	New Zealand White rabbit, male and female, 1-day-old, weight not reported, n = 3-4/group, immunized against *Alternaria tenuis*	No effects on lung resistance, dynamic compliance, transpulmonary pressure, tidal volume, respiration rate, or min volume.	Douglas et al. (1994)

TABLE AX4-1 (cont'd). PHYSIOLOGICAL EFFECTS OF SO_2 EXPOSURE

Concentration	Duration	Species	Effects	Reference
Subchronic and Chronic Exposure				
15 or 50 ppm (39.3 or 131 mg/m^3); intratracheal exposure	2 h/day, 4 or 5 days/wk, for 5 mos (low dose group) or 10-11 mos (high dose group); study authors stated that physiological changes were observed within 5 mos; there was a 7-9 mo recovery period	Mongrel dogs, adult, sex not reported, 10-20 kg; n = 3-4/group (3 hyperresponsive, 3 hyporesponsive, and 1 avg responsive)	At 15 ppm, there was no clinical evidence of bronchitis; pulmonary resistance increased by 35-38% in 2 of 3 dogs, and dynamic lung compliance decreased in 1 of 3 dogs, but the physiological changes were not significant for the group as a whole. At 50 ppm, cough and mucous hypersecretion were observed; the symptoms ceased during the recovery period. Pulmonary resistance increased by 56% during the treatment period and an additional 28% during the recovery period for a total increase of 99%; dynamic lung compliance decreased in 2 of 4 dogs and increased in 1 of 4 dogs during treatment but there were no significant changes in the group as a whole. **Study authors considered 15 ppm to be the lower limit of exposure that failed to produce physiological changes.**	Scanlon et al. (1987)
1 ppm (2.62 mg/m^3); whole body	5 h/day, 5 days/wk for 4 mos	Sprague-Dawley rat, male, young adult, initial weight not reported, n = 12-15/data point	Physiological tests were conducted in anesthetized animals; many of the tests were conducted while the rat was allowed to breathe spontaneously and during paralysis. SO_2 exposure resulted in an 11% decrease in residual volume (only during paralysis) and reduced quasistatic compliance (only examined in paralyzed animals). **Study authors noted that because residual volume was only decreased in paralyzed rats and the magnitude of effect was very small, it may have been due to chance. Quasistatic compliance values were observed to be very high in controls and may have accounted for the effect in the treatment group.**	Smith et al. (1989)

TABLE AX4-2. INFLAMMATORY RESPONSES FOLLOWING SO_2 EXPOSURE

Concentration	Duration	Species	Effects	Reference
Acute/Subacute/Subchronic				
10 ppm (26.2 mg/m^3); nose only	4 h	Outbred Swiss mouse, female, age and weight not reported, n = 10/ experimental value	No evidence was seen of inflammatory response in terms of total cell number, lymphocyte/polymorphonuclear leukocytes differentials, or total protein level taken from BAL fluid.	Clarke et al. (2000)
14, 28, or 56 mg/m^3; (5.35, 10.7, or 21.4 ppm); whole body	4 h/day for 7 days	Kunming albino mouse, male, age not reported, 18-22 g, n = 10/group	In lung tissue, in vivo SO_2 exposure (low, mid concentrations) significantly elevated levels of the pro-inflammatory cytokines interleukin-6 and tumor necrosis factor-α, but did not affect levels of the anti-inflammatory cytokine transforming growth factor-β1. In serum, the only effect observed was a low-dose elevation of tumor necrosis factor- α.	Meng et al. (2005a)
5, 50, or 100 ppm (13.1, 131, or 262 mg/m^3); whole body	5 h/day for 7-28 days	Wistar rat, male, 7 wks old, weight not reported, n = 4-5/treatment group, 8 controls	No lung injury was observed and evidence of inflammatory response was only observed in the 100 ppm group. A 4-fold increase in BAL fluid leukocyte numbers was observed in the 100 ppm group at day 14; the increase lessened at days 21 and 28 but remained higher than controls. The number of macrophages in BAL fluid was increased at day 28 in the 100 ppm group. Neutrophil numbers were 120 times higher than controls at day 14 in the 100 ppm group but returned to normal by day 21. Blood neutrophils were depleted in rats exposed to 50 ppm on days 7-21 but were increased in rats exposed to 5 ppm (significant) and 100 ppm (non-significant) at day 14. Lung epithelial permeability was not affected.	Langley-Evans et al. (1996)

BAL = bronchoalveolar lavage

TABLE AX4-3. EFFECTS OF SO_2 EXPOSURE ON HYPERSENSITIVITY/ALLERGIC REACTIONS

Concentration	Duration	Species	Effects	Reference
Antigen Sensitization/Allergic Reactions - Acute/Subacute				
5 ppm (13.1 mg/m^3); head only	4 h	Sheep, sex and age not reported, mean weight 38 ± 7 kg, n = 7/group	Acute exposure to 5 ppm SO_2 did not produce significant airway changes (pulmonary resistance, static compliance, dynamic compliance, tidal volume, breathing frequency) in either normal or allergic (sensitized to Ascaris suum antigen) sheep, nor increase airway reactivity (measured as pulmonary resistance increase after aerosolized carbachol provocation) in normal sheep. **However, 5 ppm SO_2 did significantly increase airway reactivity in allergic sheep, which have antigen-induced airway responses similar to humans with allergic airway disease, and thus may model airway responses to SO_2 in a sensitive human subpopulation**.	Abraham et al. (1981)
0.1 ppm (0.26 mg/m^3); whole body; with and without exposure to ovalbumin	5 h/day for 5 days.	Dunkin-Hartley guinea pig, male, age not reported, 250-350 g, n = 7-12/group	After bronchial challenge, the ovalbumin/SO_2-exposed group had significantly increased enhanced pause (indicator of airway obstruction) and eosinophil counts in BAL fluids than all other groups, including the SO_2 group. The bronchial and lung tissue of this group showed infiltration of inflammatory cells, bronchiolar epithelial damage, and mucus and cell plug in the lumen. **Study authors concluded that low level SO_2 may enhance the development of ovalbumin-induced asthmatic reactions in guinea pigs.**	Park et al. (2001)
0.1, 4.3, or 16.6 ppm (0, 0.26, 11.3, or 43.5 mg/m^3); whole body; animals were sensitized to ovalbumin on the last 3 days of exposure.	8 h/day for 5 days	Perlbright-White Guinea pig, female, age not reported, 300-350 g, n = 5 or 6/group (14 controls)	Bronchial provocation with ovalbumin was conducted every other day for 2 wks, starting at 1 wk after the last exposure. Numbers of animals displaying symptoms of bronchial obstruction after ovalbumin provocation was increased in all SO_2 groups compared to air-exposed groups. Anti-ovalbumin antibodies (IgG total and IgG1) were increased in BAL fluid and serum of SO_2-exposed compared to air-exposed controls, with statistical significance obtained for IgG total in BAL fluid at $\geq$4.3 ppm SO_2 and in serum at all SO_2 concentrations. **Results indicate that in this model, subacute exposure to even low concentrations of SO_2 can potentiate allergic sensitization of the airway.**	Riedel et al. (1988)

TABLE AX4-3 (cont'd). EFFECTS OF SO_2 EXPOSURE ON HYPERSENSITIVITY/ALLERGIC REACTIONS

Concentration	Duration	Species	Effects	Reference
Antigen Sensitization/Allergic Reactions - Subchronic				
5 ppm (13.1 mg/m3); whole body; sensitized with Candida albicans on day 1 and wk 4	4 h/day, 5 days/wk, 6 wks	Hartley guinea pig, male, age not reported, ~200 g, n = 12/group	Respiratory challenge with *Candida albicans* was conducted 2 wks after the last exposure. At 15 h after challenge increased number of SO_2-exposed animals displayed prolonged expiration, inspiration, or both. **Study authors concluded that exposure to SO_2 increased dyspneic symptoms**.	Kitabatake et al. (1992, 1995)
General Bronchial Reactivity Studies - Acute				
5 ppm (13.1 mg/m^3); whole body	2 h	New Zealand White rabbit, sex not reported, apparently 3 mos old, 2.2-3.1 kg, n = 6/group	No effect on airway responsiveness to inhaled histamine, as measured by provocation concentrations of histamine required to increase pulmonary resistance by 50% and decrease dynamic compliance by 35%.	Douglas et al. (1994)
10 or 30 ppm (26.2 or 78.6 mg/m^3); intratracheal	5 min; a second exposure was conducted 20 days later, after exposure to the antiallergic drug	Mongrel dogs, male and female, age and weight not reported; n = 5-15/group	No effect was observed at 10 ppm. At 30 ppm hyperresponsiveness and hypersensitivity to aerosolized methacholine and 5-hydroxytryptamine was observed for up to 24 h following exposure. Twenty days later, pretreatment with aerosolized 4% Wy-41,195 or disodium cromoglycate (antiallergic drugs) at high doses lessened the methacholine-induced hypersensitivity observed after exposure to 30 ppm SO_2. The calculations used to determine hyperresponsive and hyperreactivity were not clear.	Lewis and Kirchner (1984)
General Bronchial Reactivity Studies - Chronic				
15 or 50 ppm (39.3 or 131 mg/m^3); intratracheal	2 h/day, 4 or 5 days/wk for 5 mos (low dose group) or 10-11 mos (high dose group); study authors stated that physiological changes were observed within 5 mos; there was a 7-9 mo recovery period.	Mongrel dogs, adult, sex not reported, 10-20 kg; n = 3-4/group (3 hyperresponsive, 3 hyporesponsive, and 1 avg responsive)	Bronchial reactivity in response to inhaled histamine or methacholine was not affected in either treatment group, as determined by the concentration of histamine or methacholine required to double pulmonary resistance or the concentrations required to decrease dynamic compliance by 65% (ED65).	Scanlon et al. (1987)

BAL = bronchoalveolar lavage
IgG = immunoglobulin

TABLE AX4-4. EFFECTS OF SO_2 EXPOSURE ON HOST LUNG DEFENSES

Concentration	Duration	Species	Effects	Reference
Clearance - Subchronic				
5 ppm (13.1 mg/m^3); nose only	2 h/day, 5 days/wk for 4 wks	F344/Crl rat, male and female, 10-11 wks old, weight not reported, n = 6/sex/group	There was no effect on pulmonary clearance of radiolabeled aluminosilicate particles (MMAD 1.0 µM).	Wolff et al. (1989)
Immune Responses - Acute/Subacute				
10 ppm (26.2 mg/m^3); nose only	4 h	Specific pathogen-free white Swiss mice, female, 5 wks old, 20-23 g, n = 5/group	No effect was observed on in situ F_c-receptor-mediated phagocytosis of sheep red blood cells by AM, which was assessed 3 days after exposure to SO_2.	Jakab et al. (1996)
10 ppm (26.2 mg/m^3) SO_2; nose only	4 h	Outbred Swiss mouse, female, age and weight not specified, n = 10/experimental value	No effect on in situ AM phagocytosis (data not shown) or on intrapulmonary bactericidal activity toward *Staphylococcus aureus*.	Clarke et al. (2000)
10 ppm (26.2 mg/m^3); whole body	24 h, 1 wk, 2 wks, or 3 wks	OF_1 mice, female, age not reported, mean 20.6 g, n = 768 (32/group)	Respiratory challenge with *Klebsiella pneumoniae* resulted in increased mortality and decreased survival time in the 1, 2, and 3 wk SO_2 exposure groups compared to controls. Differences did not correlate with exposure length.	Azoulay-Dupuis et al. (1982)

AM = alveolar or pulmonary macrophages
MAD = median aerodynamic diameter
MMAD = mass median aerodynamic diameter

TABLE AX4-5. EFFECTS OF SO_2 EXPOSURE ON CARDIOVASCULAR ENDPOINTS

Concentration	Duration	Species	Effects	Reference
In Vitro Exposure				
Bisulfite/sulfite, 1:3 molar/molar, 10 µM	Not reported	Ventricular myocytes isolated from Wistar rats, adult, 200-300 g, n = 8	Effects of the 10 µM bisulfite/sulfite mixture on sodium current included a shift of steady state inactivation curve to a more positive potential, a shift of the time-dependent recovery from inactivation curve to the left, accelerated recovery, and shortened inactivation and activation time constants. It was concluded that the bisulfite/sulfite mixture stimulated cardiac sodium channels.	Nie and Meng (2005)
Bisulfite/sulfite, 1:3 molar/molar, 10 µM	Not reported	Ventricular myocytes isolated from Wistar rats, adult, 200-300 g, n = 8	Effects of the 10 µM bisulfite/sulfite mixture on voltage-dependent L-type calcium currents included a shift of steady-state activation and inactivation to more positive potentials, accelerated recovery from inactivation, and shortened fast and slow time inactivation constants. **Study authors stated that their results suggested the possibility cardiac injury following SO_2 inhalation.**	Nie and Meng (2006)
Acute/Subacute Exposure				
1.0, 2.5, or 5 ppm (2.62, 6.55, or 13.1 mg/m^3) in cold dry air; apparently intratracheal	In pre-exposure period: 15-min exposure to warm humid air, 10-min exposure to cold dry air, and 15-min exposure to warm humid air. In exposure period: 10-min exposures to each SO_2 concentration or cold dry air were preceded and followed by 15-min exposures to warm humid air.	Duncan-Hartley guinea pigs, male, age and weight not reported, n = 7-12/group, mechanically ventilated; animals were hyperventilated during cold air and SO_2 exposure to simulate exercise	Arterial blood pressure increased transiently during exposure to 5 ppm SO_2 in cold dry air. No analyses were done to determine the effects on blood pressure were caused by exposure to cold air or SO_2.	Hälinen et al. (2000a)

TABLE AX4-5 (cont'd). EFFECTS OF SO_2 EXPOSURE ON CARDIOVASCULAR ENDPOINTS

Concentration	Duration	Species	Effects	Reference
Acute/Subacute Exposure				
1 ppm (2.62 mg/m^3) in cold dry air; apparently intratracheal	60 min	Duncan-Hartley guinea pigs, male, age and weight not reported, n = 8-9/group, mechanically ventilated; animals were hyperventilated during cold air and SO_2 exposure to simulate exercise	Blood pressure and heart rate increased similarly with exposure to cold dry air or SO_2 in cold dry air. Blood pressure generally increased during the first 10-20 min of exposure and remained steady from that point forward. The increase in heart rate was gradual. No analyses were done to determine if the effects on blood pressure were caused by exposure to cold air or SO_2.	Hälinen et al. (2000b)
1 ppm (2.62 mg/m^3); nose only	4 h	F344 rat, male, 18 mos old, weight not reported, n = 20 (crossover design)	SO_2 exposure had no effect on spontaneous arrythmia frequency in aged rats. **Study authors urged caution in the interpretation of effects because occurrence of arrhythmias in aged rats was sporadic and variable from day to day.**	Nadziejko et al. (2004)
10, 20, or 40 ppm (26.2, 52.4, or 105 mg/m^3); whole body	6 h	Wistar rat, male, 7-8 wks old, 180-200 g; n = 10/group	A dose-related decrease in blood pressure was observed at ≥20 ppm.	Meng et al. (2003b)
10, 20, or 40 ppm (26.2, 52.4, or 104.8 mg/m^3); whole body	6 h/day for 7 days	Wistar rat, male, 7-8 wks old, 180-200 g; n = 10/group	Dose-related decreases in blood pressure were observed on exposure day 3 in the 10 ppm group, exposure days 2-6 in the 20 ppm group, and all exposure days in the 40 ppm group. **The study authors noted possible adaptive mechanism in the low but not the high dose group.**	Meng et al. (2003b)
5, 50, or 100 ppm (13.1, 131, or 262 mg/m^3); whole body	5 h/day for 7-28 days	Wistar rat, male, 7 wks old, weight not reported, n = 4-5/treatment group, 8 controls	GSH was depleted in the heart at 5 and 100 ppm. At 50 ppm, GSH level decreased in heart at 7 days and returned to normal by 14 days. No effects were observed for other GSH-related enzymes. Injury and inflammation were not assessed in heart, but assessment in lung revealed no effect.	Langley-Evans et al. (1996)
22, 56, or 112 mg/m^3 (8.4, 21, or 43 ppm); whole body	6 h/day for 7 days	Kunming albino mice, male and female, 5 wks old, 19 ± 2 g, n = 10/sex/group	Changes observed in heart (concentrations of effect) included: lower SOD activity in males and females (≥8.4 ppm), higher TBARS level in males and females (≥8.4 ppm), lower GPx activity in males (8.4 and 21 ppm; also 43 ppm according to text) and lower GSH level in males (43 ppm). **Study authors concluded that SO_2 induced oxidative damage in hearts of mice.**	Meng et al. (2003a)

TABLE AX4-5 (cont'd). EFFECTS OF SO_2 EXPOSURE ON CARDIOVASCULAR ENDPOINTS

Concentration	Duration	Species	Effects	Reference
Acute/Subacute Exposure				
22, 64, or 148 mg/m^3 (8.4, 24.4, or 56.5 ppm); whole body	6 h/day for 7 days	Kunming-strain mice, male, age not reported, 18-20 g, n = 10/group	GSH, GST, and glucose-6-phosphate dehydrogenase activities were decreased in the heart at 148 mg/m^3.	Wu and Meng (2003)

GPx = glutathione peroxidase
GSD = geometric standard deviation
GSH = glutathione
GST = glutathione-S-transferase
MMAD = mass median aerodynamic diameter
SOD = superoxide dismutase
TBARS = thiobarbituric acid-reactive substances

TABLE AX4-6. NERVOUS SYSTEM—NEUROPHYSIOLOGY AND BIOCHEMISTRY EFFECTS OF SO_2 AND DERIVATIVES

Concentration	Duration	Species	Effects	Reference
In Vitro/Ex Vivo				
1, 10, 50, or 100 µM SO_2 derivatives (1:3, $NaHSO_3$ to Na_2SO_3)	Not specified	Wistar rat, sex not reported, 6-12 days old, weight and number not reported; typical observations made on 60 isolated hippocampal neurons per concentration	Exposure to SO_2 derivatives (sulfite, bisulfite) reversibly increased the amplitude of potassium channel TOCs in a dose-dependent and voltage-dependent manner. Compared to controls, 10 µM SO_2 shifted inactivation of depolarization toward more positive potentials without significantly affecting the activation process. **By increasing maximal TOC conductance and delaying TOC inactivation, micromolar concentrations of SO_2 derivatives may increase the excitability of hippocampal neurons and thus contribute to the enhanced neuronal activity associated with SO_2 intoxication.**	Du and Meng (2004a)
1 or 10 µM SO_2 derivatives (1:3, $NaHSO_3$ to Na_2SO_3)	2-4 min	Wistar rat, both sexes, 10-15 days old, weight and number not reported; n = 6-13 isolated dorsal root ganglion neurons avgd per endpoint	Maximum sodium current amplitudes for both TTX-S and TTX-R channels were increased by exposure to SO_2 derivatives (10 or 1 µM, respectively), with amplitudes diminished at more negative evoking potentials and enhanced at less negative or positive potentials. SO_2 derivatives (a) slowed both current activation and inactivation for both types of sodium channels; (b) shifted activation currents to more positive potentials, increasing threshold voltages for action potential generation and contributing to reduced neuron excitability; and (c) caused even larger counteracting positive shifts in inactivation voltages tending to increase dorsal root ganglion neuron excitability. **On balance, the data suggest micromolar concentrations of sulfite/bisulfite can increase the excitability of dorsal root ganglion neurons, providing a basis for SO_2-associated neurotoxicity.**	Du and Meng (2004b)

TABLE AX4-6 (cont'd). NERVOUS SYSTEM—NEUROPHYSIOLOGY AND BIOCHEMISTRY EFFECTS OF SO_2 AND DERIVATIVES

Concentration	Duration	Species	Effects	Reference
In Vitro/Ex Vivo				
0.01, 0.1, 0.5, or 1 µM SO_2 derivatives (1:3, $NaHSO_3$ to Na_2SO_3)	Not specified, but brief ("added to the external solution just before each experiment")	Wistar rat, both sexes, 10-15 days old, weight and number not reported; n = 6-15 isolated dorsal root ganglion neurons avgd per endpoint	In isolated dorsal root ganglion neurons, SO_2 derivatives increased HVA-I_{Ca} amplitudes in a concentration- and depolarizing voltage-dependent manner (EC_{50} was ~0.4 µM) by altering Ca channel properties. This effect was partially reversible by SO_2 derivative washout, and was PKI-inhibitable, indicating involvement of PKA and secondary messengers. Additionally, exposure caused a positive shift in reversal potential. SO_2 derivatives also delayed activation and inactivation of Ca channels, but the latter was more pronounced, thus overall prolonging action potential duration and increasing HVA-I_{Ca}. Exposure also slowed the fast component and accelerated the slow component of recovery from Ca channel inactivation. **Thus, ≤1 µM sulfite/bisulfite caused prolonged opening and altered properties of Ca channels, elevated HVA-I_{Ca}, and abnormal Ca signaling with neuronal cell injury. Authors speculate these effects may correlate to SO_2 inhalation toxicity, perhaps leading to abnormal regulation via peripheral neuron Ca channels of nociceptive impulse transmission.**	Du and Meng (2006)
Acute/Subacute/Subchronic Exposure				
22, 64, or 148 mg/m^3 (8.4, 24.4, or 56.5 ppm); whole body	6 h/day for 7 days	Kunming-strain mice, male, age not reported, 18-20 g, n = 10/group	Decreased glutathione, glucose-6-phosphate dehydrogenase, and GST activities were observed in the brain at 64 and 148 mg/m^3.	Wu and Meng (2003)

TABLE AX4-6 (cont'd). NERVOUS SYSTEM—NEUROPHYSIOLOGY AND BIOCHEMISTRY EFFECTS OF SO_2 AND DERIVATIVES

Concentration	Duration	Species	Effects	Reference
10 ppm (26.2 mg/m^3); whole body	1 h/day for 21 or 24 days	Guinea pig, sex not reported, adult, 250-500 g, n = 12/group (6/subgroup)	The effects of SO_2 exposure on lipid profiles, lipid peroxidation and lipase activity in three regions of the brain (cerebral hemisphere, CH; cerebellum, CB; brain stem, BS) were examined. Significant ($p < 0.001$-0.05) findings include reductions in total lipids (CH, BS; also CB, but nonsignificant) and free fatty acids (CH, CB, BS). PL were elevated in CH, but reduced in CB; Chol was elevated in CH, but reduced in CB and BS; and esterified fatty acids were elevated in CB, but reduced in CH and BS. Levels of malonaldehyde and lipase activity were elevated in all regions. **Results indicate that subacute brief exposures to SO_2 can lead to degradation of brain lipids, with the exact nature of the lipid alterations dependent upon brain region.**	Haider et al. (1981)
10 ppm (26.2 mg/m^3); whole body	1 h/day for 30 days	Charles Foster rat, male, adult, 150-200 g, n = 12/group (6/subgroup)	The effects of SO_2 exposure on lipid profiles, lipid peroxidation and lipase activity in three regions of the brain (cerebral hemisphere, CH; cerebellum, CB; brain stem, BS) were examined. Significant ($p < 0.001$-0.05) findings include reductions in total lipids (CH, BS, CB), while PL were elevated only in CB. Chol was elevated in CH and CB, but not BS; and gangliosides were elevated in CB and BS, but reduced in CH. Lipid peroxidation (malonaldehyde formation) was elevated in whole brain and all regions (although nonsignificantly in BS), as was lipase activity in CH, the only tissue examined. Despite regional differences in PL and Chol changes, Chol/PL ratios were elevated in all three brain regions (again nonsignificantly in BS). **Results are somewhat different than those seen in guinea pig (Haider et al., 1981), but again suggest that subacute brief exposures to SO_2 can lead to degradation of brain lipids, with the exact nature of the lipid alterations dependent upon brain region.**	Haider et al. (1982)

TABLE AX4-6 (cont'd). NERVOUS SYSTEM—NEUROPHYSIOLOGY AND BIOCHEMISTRY EFFECTS OF SO_2 AND DERIVATIVES

Concentration	Duration	Species	Effects	Reference
10 ppm (26.2 mg/m^3) SO_2 alternated with 20 ppm (14.7 mg/m^3) H_2S; whole body	1 h/day for 30 days (alternating SO_2 or H_2S)	Guinea pig, sex and age not reported, 250-400 g, n = 18/group in 2 groups (6/group in some subgroups)	The effects of alternating SO_2 + H_2S exposure on lipid profiles, lipid peroxidation and lipase activity in four regions of the brain (cerebral hemisphere, CH; basal ganglia, BG; cerebellum, CB; brain stem, BS) and in the spinal cord (SC) were examined. Significant ($p < 0.001$-0.05) findings include reductions in total lipids and Chol, and elevated lipid peroxidation (malonaldehyde formation) and lipase activity, in all brain regions and SC. Chol/PL ratios were also reduced in all tissues (but nonsignificantly in BG and CB). For other parameters (PL, free fatty acids, esterified fatty acids, and gangliosides), changes were observed in most tissues but were region-specific. **Results indicate that subacute brief, alternating exposures to SO_2 or H_2S lead to degradation of brain lipids, again with the exact nature of the lipid alterations dependent upon brain/spinal cord region. Additionally, some of the effects observed for this mixture vary from those seen with SO_2 alone (Haider et al., 1981, 1982).**	Haider and Hasan (1984)
10 ppm (26.2 mg/m^3) (± iv alloxan to induce experimental type 1 diabetes); whole body	1 h/day, 7 days/wk for 6 wks	Swiss albino rat, male, 3 mos old, weight not reported, n = 10/group in 4 groups	In retina tissue, exposure elevated SOD activity and reduced GPx and catalase activities. TBARS were elevated only in non-diabetic rats exposed to SO_2. In brain tissue, exposure elevated SOD and reduced GPx activities in both non-diabetics and diabetics, while catalase activities were not affected; TBARS were elevated in both non-diabetics and diabetics. With respect to VEPs, exposure prolonged latencies in 4 of 5 VEP components in non-diabetics and 5 of 5 in diabetics, while reducing virtually all peak-to-peak amplitudes in non-diabetics and diabetics. For many endpoints, SO_2 effects were additive to those resulting from the induced diabetic condition. **In summary, brain and retinal anti-oxidant and lipid peroxidation status, as well as neuro-visual performance were affected by subchronic exposure to brief periods of 10 ppm SO_2, and these effects were exacerbated by a diabetic condition.**	Ağar et al. (2000)

TABLE AX4-6 (cont'd). NERVOUS SYSTEM—NEUROPHYSIOLOGY AND BIOCHEMISTRY EFFECTS OF SO_2 AND DERIVATIVES

Concentration	Duration	Species	Effects	Reference
Subchronic/Chronic Exposure				
10 ppm (26.2 mg/m^3) (± iv alloxan to induce experimental type 1 diabetes); whole body	1 h/day, 7 days/wk for 6 wks	Rat, male, 3 mos old, weight not reported, n = 10/group in 4 groups	In brain tissue, SO_2 exposure elevated SOD and reduced GPx activities in both non-diabetics and diabetics, while catalase activities were not affected; TBARS were elevated in both non-diabetics and diabetics. With respect to afferent peripheral nerve pathways (SEPs), exposure prolonged latencies in 4 of 4 SEP components in both non-diabetics and diabetics; also altered were some inter-peak latencies (non-diabetics and diabetics) and some peak-to-peak amplitudes (non-diabetics only). In some cases, SO_2 effects were additive to those resulting from the induced diabetic condition. **In summary, brain anti-oxidant and lipid peroxidation status, as well as afferent peripheral nerve pathways, were affected by subchronic exposure to 10 ppm SO_2, and these effects were exacerbated by a diabetic condition. Authors suggest that SO_2 exposure could potentiate the incidence and/or severity of diabetes.**	Küçükatay et al. (2003)
10 ppm (26.2 mg/m^3); whole body	1 h/day, 7 days/wk for 6 wks	Swiss albino rat, male, 3, 12, or 24 mos old, weight not reported, n = 10/group in 6 groups	Effects of aging ± SO_2 exposure on levels of lipid peroxidation (TBARS), antioxidant enzyme status (catalase, GPx, SOD), and afferent peripheral nerve pathways (SEPs) were monitored in the brain of young (Y, 3 mo), middle-aged (M, 12 mo) and old (O, 24 mo) rats. In addition to age-related changes, SO_2 exposure significantly ($p < 0.0001$-0.02) elevated TBARS and SOD, while reducing GPx (Y, M, O); catalase levels were not affected. Of 4 monitored SEP component peaks, SO_2 significantly ($p < 0.01$-0.05) prolonged latencies in groups Y (4/4) and M (1/4), but not in O (0/4). Peak-to-peak amplitudes were decreased in Y, (2/3) and increased in M (1/3), but not affected in O (0/3). **Taken together, these data indicate that subchronic exposure to brief periods of 10 ppm SO_2 can impact afferent peripheral nerve pathways and the lipid peroxidation and antioxidant enzyme status of the brain.**	Yargiçoğlu et al. (1999)

TABLE AX4-6 (cont'd). NERVOUS SYSTEM—NEUROPHYSIOLOGY AND BIOCHEMISTRY EFFECTS OF SO_2 AND DERIVATIVES

Concentration	Duration	Species	Effects	Reference
Subchronic/Chronic Exposure				
10 ppm (26.2 mg/m^3); whole body	1 h/day, 7 days/wk for 6 wks	Swiss albino rat, male, 3, 12, or 24 mos old, weight not reported, n = 10/group in 6 groups	Effects of aging ± SO_2 exposure on levels of lipid peroxidation (TBARS), antioxidant enzyme status (catalase, GPx, SOD), and visual system function (VEPs) were monitored in the brain and eye (retina and lens) of young (Y, 3 mo), middle-aged (M, 12 mo) and old (O, 24 mo) rats. In addition to age-related changes, SO_2 exposure significantly ($p < 0.0001$-0.04) elevated TBARS in brain and lens (Y, M, O), and in retina (Y); reduced GPx in brain (Y) and lens (Y, M, O); reduced catalase in retina (Y, M, O); and elevated SOD in brain (Y, M), retina (Y, M, O) and lens (M, O). Of 5 monitored VEP component peaks, SO_2 prolonged latencies in groups Y (4/5), M (3/5) and O (1/5). **Taken together, these data indicate that subchronic exposure to brief periods of 10 ppm SO_2 can impact the visual system and the lipid peroxidation and antioxidant enzyme status of the brain and eye**.	Kilic (2003)
Neurodevelopment/Neurobehavior				
32 or 65 ppm (83.8 or 170 mg/m^3); whole body	Gestation day 7-18	CD-1 mouse dams were exposed; numbers of dams exposed and offspring evaluated not indicated	Righting and negative geotaxis reflexes were delayed at both concentrations.	Singh (1989)
5, 12, or 30 ppm (13.1, 31.4, or 78.6 mg/m^3); whole body	Near continuous (80% of time) exposure from 9 days before mating through the 12-14th day of pregnancy	CD-1 mouse, adult male and female parental animals were exposed (n = 10/group/sex) and male and female offspring (n = 8 litters/group, fostered by unexposed dams at birth) were evaluated at 2-18 days of age; adult male offspring also evaluated (n = 8/group)	Offspring: No effects observed for birth weight, postnatal body weight gain, somatic and neurobehavioral development (e.g., eyelid and ear opening, incisor eruption, and reflex development); no postnatal developmental data were shown by study authors. No effects observed in passive avoidance testing of adult males. Adults: Observation of behavior outside the exposure chamber on exposure days 3, 6, and 9 revealed dose-related increases in digging and decreases in grooming by females in the 30 ppm group on exposure day 9; non-dose related increases were observed for crossing and wall rearing by females in the 30 ppm group on exposure day 9. Observance of behaviors in 2 breeding pairs/group in the 12 and 30 ppm groups revealed increased rearing and social interaction in the 30 ppm group shortly after the start of exposure, followed by return to baseline levels; effects were generally of greater magnitude in males.	Petruzzi et al. (1996)

TABLE AX4-6 (cont'd). NERVOUS SYSTEM—NEUROPHYSIOLOGY AND BIOCHEMISTRY EFFECTS OF SO_2 AND DERIVATIVES

Concentration	Duration	Species	Effects	Reference
Neurodevelopment/Neurobehavior				
5, 12, or 30 ppm (13.1, 31.4, or 78.6 mg/m^3); whole body	Near continuous (90% of time) exposure from 9 days before mating through the 14th day of pregnancy	CD-1 mouse, adult male and female parental animals were exposed and adult male offspring (fostered by unexposed dams at birth) were evaluated at ~120 days of age, n = 11-12 offspring/group	In 20-min encounters with unexposed males, prenatally-exposed males compared to controls displayed (dose(s) of effect, time of testing effect observed) increased duration of self grooming (5 ppm, 15-20 min), decreased frequency and duration of tail rattling (≥5 ppm at 5-10 min and 12 ppm at 10-15 min), and decreased duration of defensive postures (≥12 ppm, 0-5 min). Study authors also noted a non-significant decrease in freezing (apparently at all dose levels) and non-significant increases in social exploration (apparently at all doses) and rearing (apparently at ≥12 ppm).	Fiore et al. (1998)

CAT = catalase
Chol = cholesterol
GPx = Se-dependent glutathione peroxidase
GST = glutathione-S-transferase
HVA-I_{Ca} = high-voltage activated calcium currents
PKA = cyclic AMP-dependent protein kinase A
PKI = synthetic peptide inhibitor of PKA
PL = phospholipids
SEPs = somatosensory-evoked potentials
SOD = Cu,Zn-superoxide dismutase
TBARS = thiobarbituric acid-reactive substances
TOC = potassium channel transient outward currents
TTX = tetrodotoxin
TTX-R = tetrodotoxin-resistant
TTX-S = tetrodotoxin-sensitive
VEPs = visual-evoked potentials

TABLE AX4-7. REPRODUCTIVE AND DEVELOPMENTAL EFFECTS OF SO_2

Concentration ppm	Duration	Species	Effects	Reference
Reproductive Organ Effects - Subacute/Subchronic				
22, 56, or 112 mg/m^3 (8.4, 21, or 43 ppm); whole body	6 h/day for 7 days	Kunming albino mice, male, 5 wks old, 19 ± 2 g, n = 10/group	Changes observed in mouse testes (concentrations of effects) included decreased activities of SOD (43 ppm, possibly at 21 ppm according to text) and GPx (≥21 ppm), increased catalase activity (8.4 and 21 ppm), decreased GSH level (≥21 ppm), and increased TBARS levels (≥8.4 ppm). **The study authors concluded that SO_2 can induce oxidative damage in testes of mice.**	Meng and Bai (2004)
10 or 30 ppm (26.2 or 78.6 mg/m^3); whole body	6 h/day, ~5 days/wk for 21 wks (total of 99 days)	Sprague-Dawley CD rat, male, 8 wks old, weight not reported, n = 70/group in 3 groups (inhalation series)	No significant ($p < 0.05$) effect on testes histopathology was found, although there was a very slight and probably biologically insignificant increase in relative testes weight. (0.61 ± 0.02 vs. 0.56 ± 0.02, % body weight.).	Gunnison et al. (1987)
Developmental/Reproductive				
32 or 65 ppm (83.8 or 170 mg/m^3); whole body	Gestation day 7-18	CD-1 mouse dams were exposed; numbers of dams exposed and offspring evaluated not indicated	No significant effects were observed for number of live pups born/litter. Pup birth weight was lower at 65 ppm. Righting and negative geotaxis reflexes were delayed at both concentrations.	Singh (1989)
5, 12, or 30 ppm (13.1, 31.4, or 78.6 mg/m^3); whole body	Near continuous (80% of time) exposure from 9 days before mating through the 12-14th day of pregnancy	CD-1 mouse, adult male and female parental animals were exposed (n = 10/group/sex) and male and female offspring (n = 8 litters/group, fostered by unexposed dams at birth) were evaluated at 2-18 days of age; adult male offspring also evaluated (n = 8/group)	Decreased food and water intake were observed in parental males and females of the 12 and 30 ppm groups at the start of mating (exposure days 9-13). No effects observed for mating or successful pregnancies. There were no effects on litter sizes, sex ratio, or neonatal mortality (data not shown by study authors). No effects observed for birth weight, postnatal body weight gain, somatic and neurobehavioral development (e.g., eyelid and ear opening, incisor eruption, and reflex development); no postnatal developmental data were shown by study authors. No effects observed in passive avoidance testing of adult males.	Petruzzi et al. (1996)

TABLE AX4-7 (cont'd). REPRODUCTIVE AND DEVELOPMENTAL EFFECTS OF SO_2

Concentration ppm	Duration	Species	Effects	Reference
Developmental/Reproductive				
5, 12, or 30 ppm (13.1, 31.4, or 78.6 mg/m^3); whole body	Near continuous (90% of time) exposure from 9 days before mating through the 14th day of pregnancy	CD-1 mouse, adult male and female parental animals were exposed and adult male offspring (fostered by unexposed dams at birth) were evaluated at ~120 days of age, n = 11-12 offspring/group	In 20-min encounters with unexposed males, prenatally-exposed males compared to controls displayed (dose(s) of effect, time of testing effect observed) increased duration of self grooming (5 ppm, 15-20 min), decreased frequency and duration of tail rattling (≥5 ppm at 5-10 min and 12 ppm at 10-15 min), and decreased duration of defensive postures (≥12 ppm,0-5 min). Study authors also noted a non-significant decrease in freezing (apparently at all dose levels) and non-significant increases in social exploration (apparently at all doses) and rearing (apparently at ≥12 ppm).	Fiore et al. (1998)
5 ppm (13.1 mg/m^3); whole body	2 h/day for 13 wks	New Zealand White rabbit, male and female, n = 3-4/group, 1-day-old, immunized against Alternaria tenuis	Following subchronic exposure beginning in the neonatal period, there were no effects on lung resistance, dynamic compliance, transpulmonary pressure, tidal volume, respiration rate, or min volume.	Douglas et al. (1994)

GPx = glutathione peroxidase
GSH = glutathione
SOD = superoxide dismutase
TBARS = thiobarbituric acid-reactive substances

TABLE AX4-8. HEMATOLOGICAL EFFECTS OF SO_2

Concentration	Duration	Species	Effects	Reference
Acute/Subacute Exposure				
0.87 ppm (2.36 mg/m^3); whole body	24 h	Swiss Albino rat, male, age not reported, 250-300 g, n = 51, 50	Effects of SO_2 exposure included increased hematocrit, sulfhemoglobin and osmotic fragility and decreased whole blood and packed cell viscosities. RBC number, hemoglobin, mean corpuscular volume, mean corpuscular hemoglobin concentration, and plasma viscosity were not significantly altered.	Baskurt (1988)
Subchronic Exposure				
286 mg/m^3 (100 ppm); whole body. The units were initially reported as µg/m^3 but were corrected per correspondence with the study author.	5 h/day for 28 days	Wistar rat, male, 7 wks old, weight not reported, n = 4-16	Dams were fed diets containing casein at 180 [control], 120, 90, or 60 g/kg during pregnancy and their offspring were exposed to air or SO_2 as adults. In blood of offspring, SO_2 exposure significantly reduced the numbers of circulating total leukocytes and lymphocytes in the 180 and 120 g/kg dietary groups; neutrophils numbers were not affected in any group. GSH levels in the 180 and 60 g/kg (but not the two intermediate) dietary groups were reduced by SO_2 exposure. **This study provides information for an extremely high concentration level but is being acknowledged here with the unit corrected to verify that a low-concentration level study was not missed**.	Langley-Evans et al. (1997); Langley Evans (2007)
10 ppm (26.2 mg/m^3); whole body	1 h/day for 30 days	Guinea pig, sex and age not reported, 250-450 g, n = 12/group	SO_2 exposure resulted in RBC membrane lipoperoxidation (elevated levels of malonyldialdehyde) and other oxidative damage (elevated osmotic fragility ratios and levels of methemoglobin and sulfhemoglobin). All these effects were significantly ($p < 0.05$) mitigated by injections of Vitamin E+C three times per wk.	Etlik et al. (1995)
10 ppm (26.2 mg/m^3); whole body	1 h/day, 7 days/ wk for 6 wks	Swiss Albino rat, male, 3 mos old, weight not reported, n = 10 per group in 4 groups	RBC parameters were monitored in non-diabetic rats, non-diabetic rats exposed to SO_2, alloxan-induced diabetic rats, and diabetic rats exposed to SO_2. In both non-diabetic and diabetic rats exposed to SO_2, levels of GPx, catalase, GSH, GST, and TBARS were elevated in RBC while those of SOD were reduced.	Ağar et al. (2000)
10 ppm (26.2 mg/m^3); whole body	1 h/day for 45 days	Rat, sex and age not reported, 214-222 g, n = 6-8 per group	SO_2 exposure significantly elevated levels of methemoglobin, sulfhemoglobin and malonyldialdehyde, the latter of which was substantially reversed by Vitamin E+C treatment. RBC osmotic fragility was increased by SO_2, and again partially mitigated by Vitamin E+C. SO_2 elevated RBC, white blood cell, hemoglobin and hematocrit values, but not mean corpuscular volume, mean corpuscular hemoglobin or mean corpuscular hemoglobin concentration. Vitamin E+C exposure did not affect these parameters.	Etlik et al. (1997)

TABLE AX4-8 (cont'd). HEMATOLOGICAL EFFECTS OF SO_2

Concentration	Duration	Species	Effects	Reference
Acute/Subacute Exposure				
10 ppm (26.2 mg/m^3); whole body	1 h/day, 7 days/wk for 8 wks	Swiss-Albino rat, male, 2.5-3.0 mos old, weight not reported, n = 30 (14 controls, 16 treated)	Decreased Cu,Zn- SOD activity, increased GPx and GST activity, and increased TBARS formation were observed in RBC of treated rats. No significant effect on glucose-6-phosphate dehydrogenase or catalase levels was observed.	Gümüşlü et al. (1998)
10 ppm (26.2 mg/m^3); whole body	1 h/day, 7 days/wk for 6 wks	Albino rat, male, 3, 12, and 24 mos old, mean weight 213-448 g, n = 10/group	Enzyme and GSH activity (GPx, catalase, GSH, and GST) were increased and copper-zinc SOD activity was decreased in RBCs of all experimental groups compared to controls. RBCs in older rats had lower levels of all antioxidants enzymes and increased TBARS activity compared to younger rats.	Yargiçoğlu et al. (2001)

GSH = glutathione
GPx = glutathione peroxidase
GST = glutathione-S-transferase
HP = hydrolyzed protein
RBC = red blood cell or erythrocyte
SOD = superoxide dismutase
TBARS = thiobarbituric acid-reactive substance

TABLE AX4-9. ENDOCRINE SYSTEM EFFECTS OF SO_2

Concentration	Duration	Species	Effects	Reference
5 or 10 ppm (13.1 or 26.2 mg/m^3); whole body	24 h/day for 15 days	Sprague-Dawley CD rat, male, age not reported, 250-275 g, n = 9/subgroup in 9 subgroups	Subjects were rats fed standard diet (normal) or high cholesterol diet, and rats with streptozotocin-induced diabetes fed standard diet. In diabetic rats, there was no effect on glucose levels. Exposure to ≥5 ppm lowered plasma insulin level in normal and hypercholesterolemic diet groups, but elevated it (non-significantly) in diabetic rats. **In each rat model, inhalation of SO_2 at levels without overt effects affected insulin levels. Specific effects varied according to diet or diabetes**.	Lovati et al. (1996)
10 ppm (26.2 mg/m^3); whole body	1 h/day, 7 days/wk for 6 wks	Swiss Albino rat, male, 3 mos old, weight not reported, n = 10/group	Effects were compared in non-diabetic rats and rats with alloxan induced diabetes. SO_2 increased blood glucose in diabetic and non-diabetic rats.	Ağar et al. (2000)
10 ppm (26.2 mg/m^3); whole body	1 h/day, 7 days/wk for 6 wks	Rat, male, 3 mos old, weight not reported, n = 10/group in 4 groups	Effects were compared in normal rats and rats with alloxan induced diabetes. SO_2 elevated blood glucose levels in both non-diabetics and diabetics.	Küçükatay et al. (2003)

TABLE AX4-10. EFFECTS OF SO_2 EXPOSURE ON RESPIRATORY SYSTEM MORPHOLOGY

Concentration	Duration	Species	Effects	Reference
Acute/Subacute Exposure				
1 ppm (2.6 mg/m^3); nose only	3 h/day for 6 days; animals evaluated for up to 72 h following exposure	Hartley guinea pig, male, age not reported, 250-320 g, n = 14/group/time point	In combined group of SO_2 exposed animals and furnace gas controls, no alveolar lesions were observed.	Conner et al. (1985)
Subchronic/Chronic Exposure				
5 ppm (13 mg/m^3); nose only	2 h/day, 5 days/wk for 4 wks	F344/Crl rat, male and female, 10-11 wks old, weight not reported, n = 3/sex/group	No nasal or pulmonary lesions.	Wolff et al. (1989)
1 ppm (2.62 mg/m^3); whole body	5 h/day, 5 days/wk for 4 or 8 mos; half the animals in the 8-mo group were allowed to recover for 3 mos.	Sprague-Dawley rat, male, young adult, initial weight not reported, n = 12-15/data point	At 4 mos of SO_2 exposure, increases were observed for incidence of bronchial epithelial hyperplasia (80 vs. 40% in controls) and numbers of nonciliated epithelial cells (31.1 vs. 27.7% in controls); neither effect persisted past 4 mos of exposure.	Smith et al. (1989)

TABLE AX4-11. CARCINOGENIC EFFECTS OF SO_2

Concentration	Duration	Species	Effects	Reference
Pulmonary Effects - SO_2				
0, 10, or 30 ppm (0, 26.2, or 78.6 mg/m^3) SO_2 (whole body) ± 1 mg B[a]P 0, 100 or 400 ppm W, or [400 ppm W + 40 ppm Mo] in a low-Mo diet, ± B[a]P (See Effects column) ± B[a]P	SO_2: 21 wk, 5 day/wk (minus holidays), 6 h/day High W, low Mo diet: 21 wk, 7 day/wk B[a]P: 15 wk, once per wk starting wk 4	Rat, Sprague-Dawley, male, 9 wk old, ~315-340 g, n = 20-74/group	Purpose was to investigate carcinogenic/cocarcinogenic effects of SO_2 inhalation or dietary-induced high levels of systemic sulfite/bisulfite in conjunction with tracheal installation of B[a]P. High drinking water levels of W in conjunction with low-Mo feed induce sulfite oxidase deficiency in rats, and thus high systemic levels of sulfite and bisulfite (at 0, 100 or 400 ppm W, mean plasma sulfite was 0, 0 or 44 µM, while mean tracheal sulfite + bisulfite was 33, 69 or 550 nmol/g wet wt). Mortality in B[a]P groups (~50% after ~380-430 d) was due almost exclusively to SQCA of the respiratory tract; survival rate was excellent for other groups (~50% mortality after ~620-700 d). **Results indicate no SQCA was induced in any of the SO_2 inhalation or systemic sulfite + bisulfite groups, nor were incidences in the B[a]P groups enhanced by such coexposures. This lack of cocarcinogenicity does not support the hypothesis that SO_2 exposure could elevate systemic sulfite/bisulfite, generating $GSSO_3H$, which would inhibit GST and reduce intracellular GSH, thus interfering with a major detoxication pathway for B[a]P and enhancing its carcinogenicity. Authors note that due to the high incidence of animals with tumors in the B[a]P only groups (65/72 and 63/72), cocarcinogenicity of SO_2 or sulfite + bisulfite could only have been demonstrated by shortening of tumor induction time and/or increased rate of SQCA appearance—neither were observed.**	Gunnison et al. (1988)

TABLE AX4-11 (cont'd). CARCINOGENIC EFFECTS OF SO_2

Concentration	Duration	Species	Effects	Reference
Pulmonary Effects - SO_2				
0, 0.2 mL C, or {0.2 mL DEP+C ± [4 ppm (10.48 mg/m^3) SO_2 or 6 ppm (11.28 mg/m^3) NO_2 or 4 ppm SO_2 + 6 ppm NO_2]}; whole body [Note: 0.2 mL CBP = 1mg; 0.2 mL DEcCBP = 1 mg CBP + 2.5 mg DEP)]	SO_2 and/or NO_2: 10 mo, 16 h/day CBP or DEcCBP: 4 wk, once/wk by intratracheal infusion	Rat, SPF F344/Jcl, male, 6 wk old, wt not reported, n = 23-30 per group in 6 groups	Purpose was to study effects of DEP on rat lung tumorigenesis and possible tumor promoting effects of SO_2 or NO_2 singly or together. Alveolar hyperplasia and adenoma were significantly ($p < 0.01$-0.05) increased over controls in the CBP group, but not the DEcCBP group. This was ascribed to induction of alveolitis and AM infiltration (a tumor response specific to rat and of questionable relevance to humans) in the former group, but apparently prevented by DEP in the latter. Alveolar bronchiolization near small hyaline masses of deposited DEcCBP was observed in all DEcCBP groups, the masses presumably allowing long-term exposure to DEP extracts by contacted alveolar epithelium. DNA adducts were found only in the three gas-exposed groups. Discounting the CBA group, elevated alveolar hyperplasia was seen only in the DEcCBP + NO_2 group, and elevated incidences of alveolar adenoma in the DEcCBP + SO_2 and particularly the DEcCBP + NO_2 groups; neither effect was observed with coexposure to both gases—speculated by the authors to perhaps result from inhibition of the stronger NO_2 promotion by HSO_3^-. **Thus, SO_2 appears to have weaker capacity than NO_2 for promoting tumor induction (and perhaps genotoxicity) by DEP extract, and may antagonize such effects by NO_2 during coexposure of the gases.**	Ohyama et al. (1999)
0, C, or {25 mg SPM+C ± [4 ppm (10.48 mg/m^3) SO_2 or 6 ppm (11.28 mg/m^3) NO_2 or 4 ppm SO_2 + 6 ppm NO_2]}; whole body	SO_2 and/or NO_2: 11 mo, 16 h/day C ± SPM: 4 wk, once/wk by intratracheal injection	Rat, SPF Fisher 344, male, 5 wk old, wt not reported, n = 5 per group in 6 groups	Purpose was to study effects of Tokyo air SPM, with or without coexposure to SO_2 or NO_2 or their combination, on the development of proliferative lesions of PEC. **PEC hyperplasia was significantly ($p < 05$) increased by exposure to SPM, but coexposure to either gas or their mixture was without additional effect. No PEC papillomas were observed in control groups, while a few were seen in the SPM groups, irrespective of gas coexposures. Thus, SO_2 demonstrated no tumor promotion or cocarcinogenic properties. [Study did not describe the nature of the carbon (C) used.]**	Ito et al. (1997)

TABLE AX4-11 (cont'd). CARCINOGENIC EFFECTS OF SO_2

Concentration	Duration	Species	Effects	Reference
Pulmonary Effects - SO_2				
0 or [10 ppm (26.2 mg/m^3) SO_2 + 5 ppm (9.4 mg/m^3) NO_2] ± [3 or 6 mg/kg bw of DEN]; exposure to gases whole body	SO_2 + NO_2: 6, 10.5, 15, or 18 mo, 5 day/wk, 19 h/day DEN: once by s.c. injection, ~2 wk after the start of inhalation exposure	Hamster, Syrian golden, both sexes, 10 wk old, bw not reported, n = 40/sex per each of 12 exposure groups	The principle focus of this large study was to examine whether two inhaled diesel-exhaust emission preparations (± particulates) could enhance the tumorigenesis of injected DEN. An ancillary aim was to see whether inhalation of the irritant SO_2 + NO_2 mixture could cause similar enhancement of DEN tumorigenicity. Gas mixture exposure did not affect bw gain, but slightly shortened survival times (although significantly only for females). Apart from effects attributed to DEN, serial sacrifices showed progressive increases in ciliated tracheal cell aberrations and in number of tracheal mucosal cells. In the lung, gas mixture-related effects were limited to a progressing alveolar lesion involving lining with bronchiolar epithelium and the presence of some pigment-containing AM, and to a mild, diffuse thickening of the alveolar septa. **SO_2 + NO_2 exposure did not by itself elevate tumor rate in the upper respiratory tract, nor did it enhance increases induced by DEN. Thus the mixture appeared to have no tumor inducing or promoting effects.**	Heinrich et al. (1989)
Nonpulmonary Effects - SO_2				
0 or 6 ppm (0 or 15.72 mg/m^3) SO_2, ± 0.2 ppm (600 µg/m^3); whole body; NDMA	20 mo, 5 day/wk, 4 h/day	Rat, Sprague-Dawley, female, age and wt not reported, n = 36 per group in 4 relevant groups	This is a preliminary report for observations after 20 mo (800 h inhalation in 200 exposures, with calculated inhaled cumulative doses of 77 mg SO_2 and 2-3 mg NDMA per rat). The effects of NDMA ± SO_2 inhalation were studied. Group mortality was as follows: control (3/36), SO_2 (5/36), NDMA (4/36), NDMA + SO_2 (7/36). The only tumors observed were nasal: control (0), SO_2 (0), NDMA (1), NDMA + SO_2 (3). **No observable parameters, including body wt gain, were affected by the additional SO_2 exposure; assessment of tumor incidence effects could not yet be performed**.	Klein et al. (1989)

D_{ae} = aerodynamic diameter
AM = alveolar macrophage
B[a]P = benzo[a]pyrene
BHPN = N-bis(2-hydroxypropyl) nitrosamine
C = carbon or carbon black particles
DEN = diethylnitrosamine
DEP+C = DEP extract-coated C
DEcCBP = DEP extract coated carbon black particles
DEP = diesel exhaust particles
GSH = glutathione
$GSSO_3H$ = glutathione S-sulfonate
GST = glutathione-S-transferase
NDMA = N-nitroso-dimethylamine
Mo = molybdenum
PEC = pulmonary endocrine cells
SPM = suspended particulate matter extract
SPF = specific pathogen free
SQCA = squamous cell carcinoma
W = tungsten

TABLE AX4-12. RESPIRATORY SYSTEM BIOCHEMISTRY EFFECTS OF SO_2

Concentration	Duration	Species	Effects	Reference
Oxidation and Antioxidant Defenses - Subacute/Subchronic Exposure				
22, 56, or 112 mg/m^3 (8.4, 21, or 43 ppm); whole body	6 h per day for 7 days	Kunming albino mice, male and female, 5 wks old, 19 ± 2 g, n = 10/sex/group	Changes observed in lung tissue (concentrations of effect) included higher SOD activity in males (8.4 ppm) and females (8.4 and 21 ppm), lower SOD activity in males (21 and 43 ppm) and females (43 ppm), increased GPx activity in males and females (8.4 ppm), decreased GPx activity in males and females (≥21 ppm), decreased catalase activity in males (43 ppm), decreased reduced GSH level in males and females (≥8.4 ppm), increased TBARS level in males (≥8.4 ppm) and females ≥21 ppm). **Study authors concluded that sulfur dioxide induced oxidative damage in lungs of mice.**	Meng et al. (2003a)
22, 64, or 148 mg/m^3 (8.4, 24.4, or 56.5 ppm); whole body	6 h/day for 7 days	Kunming-strain mice, male, age not reported, 18-20 g, n = 10/group	Glucose-6-phosphate dehydrogenase and GST activity were decreased in lung at 64 and 148 mg/m^3. Lung GSH levels were reduced in the 22 and 148 mg/m^3 exposure groups. Administration of buckthorn seed oil increased GST and decreased TBARS activity compared to mice exposed to 42 mg/m^3 SO_2 alone.	Wu and Meng (2003)

TABLE AX4-12 (cont'd). RESPIRATORY SYSTEM BIOCHEMISTRY EFFECTS OF SO_2

Concentration	Duration	Species	Effects	Reference
Oxidation and Antioxidant Defenses - Subacute/Subchronic Exposure				
5, 50, or 100 ppm (13.1, 131, or 262 mg/m^3); whole body	5 h/day for 7-28 days	Wistar rat, male, 7 wks old, weight not reported, n = 4-5/treatment group, 8 controls	In the 5 and 100 ppm groups, GSH in BAL fluid decreased at 7 days and increased at 21 days; at 28 days GSH returned to normal in the 5 ppm group and further increased in the 100 ppm group. GSH was depleted in the lung, at 5 and 100 ppm but not at 50 ppm. With respect to GSH-related enzymes, exposure to 5 ppm lowered GCS, GPx, GST, and GRed activity in the lung. Effects in the 100 ppm group were similar to the 5 ppm group, except that lung GPx was not reduced. Exposure to 50 ppm did not affect lung GST, but reduced the number of inflammatory cells in circulation and decreased GCS, GPx, GRed, and GT in the lung. **Study authors concluded that sulfitolysis of glutathione disulphide occurs *in vivo* during SO_2 exposure and that SO_2 is a potent glutathione depleting agent, even in the absence of pulmonary injury**.	Langley-Evans et al. (1996)
10 ppm (26.2 mg/m^3); whole body	1 h/day, 7 days/wk for 6 wks	Swiss albino rat, male, 3, 12, or 24 mos old, 210-450 g, n = 9-11/group in 6 groups	Effects of age on SO_2-induced oxidative effects in lung tissue were observed in young (3-mo-old), middle aged (12-mo-old), and old (24-mo old) rats. SO_2 exposure significantly elevated TBARS, SOD, GPx, and GST in all age groups; reduced catalase in young and middle-aged rats, but did not affect catalase in old rats. In rats not exposed to SO_2, SOD, GPx and GST increased with age and catalase decreased with age. General observations in SO_2-exposed animals were increases in SOD, GPx, and TBARS with age. The authors of the AQCD toxicology chapter noted that while lipid peroxidation increased with age, relative TBARS increases in response to SO_2 were inversely correlated with age (i.e., largest percent increase seen in young rats).	Gümüşlü et al. (2001)

TABLE AX4-12 (cont'd). RESPIRATORY SYSTEM BIOCHEMISTRY EFFECTS OF SO_2

Concentration	Duration	Species	Effects	Reference
Oxidation and Antioxidant Defenses - Subacute/Subchronic Exposure				
286 mg/m^3 (~101 ppm by study author calculations); whole body **Note: The study mistakenly listed units of µg/m^3 and it was verified with the study authors that the units should have been listed as mg/m^3.**	5 h/day for 28 days	Wistar rat, male, 7 wks old, weight not reported, n = 4-16	This study explored the effects of maternal diet protein restriction during gestation on offspring lung enzyme responses after SO_2 exposure in adulthood. Adult offspring representing different maternal dietary concentrations of casein (180 [control], 120, 90 or 60 g/kg) were exposed either to air or SO_2. GSH levels in BAL fluid and the lung were not affected either by maternal diet or SO_2 exposure. In the lung GRed and GT were not affected by SO_2 in any maternal diet group; GPx was reduced only in the 120 g/kg maternal diet group; GCS was elevated in the 180 and 60 g/kg groups; and GST was reduced in the 180, 120 and 90 g/kg groups (to the level seen in both the air- and SO_2-exposed 60 g/kg maternal diet groups). **This study does not provide information relevant to ambient exposures, but is being mentioned in this table to record that a low-concentration level study was not overlooked.**	Langley-Evans et al. (1997); Langley Evans et al. (2007)

TABLE AX4-12 (cont'd). RESPIRATORY SYSTEM BIOCHEMISTRY EFFECTS OF SO_2

Concentration	Duration	Species	Effects	Reference
Differential Gene Expression Subacute Exposure				
14, 28, or 56 mg/m^3 (5.35, 10.70, or 21.40 ppm); whole body	6 h/day for 7 days	Wistar Rat, male, age not reported, 180-200 g, n = 6/group in 4 groups	Repeated acute exposure caused significant ($p < 0.001$-0.05) concentration-dependent reductions in enzyme activities and gene expression in the lung for both CYP1A1 and CP1A2. Effects were seen at the mid and high concentrations, but not the low. Authors speculate that underlying mechanisms may involve oxidative stress and/or cytokine release, and may represent an adaptive response to minimize cell damage.	Qin and Meng (2005)
14, 28, or 56 mg/m^3 (5.35, 10.70, or 21.40 ppm); whole body	6 h/day for 7 days	Wistar rat, male, age not reported, 180-200 g, n = 6/group in 4 groups	SO_2 exposure caused significant concentration-dependent changes in the mRNA (mid and high concentrations) and protein expression (all concentrations in lung, but statistical significance not indicated) of apoptosis-related genes: increases for *bax* and *p53* apoptosis-promoting genes, and decreases for the apoptosis-repressing gene *bcl-2*. Caspase-3 activity (occurring early in apoptosis process) was also increased at the mid and high concentration.	Bai and Meng (2005a)

BAL = bronchoalveolar lavage
CYP = Cytochrome P450
GCS = γ-glutamylcysteine synthetase
GSH = glutathione
GT = γ-glutamyl transpeptidase
GST = glutathione S-transferase
GPx = glutathione peroxidase
GRed = glutathione reductase
SOD = superoxide dismutase
TBARS = thiobarbituric acid-reactive substances

TABLE AX4-13. RESPIRATORY SYSTEM EFFECTS OF SO_2 IN DISEASE MODELS

Concentration	Duration	Species	Effects	Reference
1 ppm (2.62 mg/m^3); whole body	5 h/day, 5 days/wk for 4 or 8 mos; half the animals in the 8-mo group were allowed to recover for 3 mos.	Sprague-Dawley rat, male, young adult, initial weight not reported, n = 12-15/data point	Respiratory system exposure effects on "normal" and emphysema-like lungs (elastase induced) were assessed by morphological (e.g., histopathology and morphometry) and physiological (e.g., lung function and volume measured during spontaneous breathing and paralysis) endpoints. At 4 mos of SO_2 exposure, bronchial alveolar hyperplasia was increased in normal animals, but reduced in elastase-treated animals, and numbers of nonciliated epithelial cells were increased (by 12%) in normal but not elastase-treated animals; neither morphological observation persisted past 4 mos of exposure. Physiological tests conducted at 4 mos of exposure revealed decreased residual volume and quasistatic compliance in normal SO_2-exposed animals during paralyses, and decreased residual volume/total lung capacity ratio during spontaneous breathing and decreased nitrogen washout slope during paralysis in elastase-treated, SO_2-exposed animals. After 8 mos of exposure, lung volume and incidence of alveolar emphysema were elevated by SO_2 only in the elastase-treated animals; those effects were not observed in the recovery period. **Authors concluded that elastase-induced emphysema persisted but obscured rather than enhanced SO_2 effects. It was indicated that the model lacked tar residues typically found in the lungs of smokers**.	Smith et al. (1989)

TABLE AX4-14. EFFECTS OF MIXTURES CONTAINING SO_2 AND OZONE

Concentration		Duration	Species	Endpoints	Interaction	Reference
SO_2 (ppm)	**Ozone (ppm)**					
Acute/Subacute Exposure						
3 ppm (7.9 mg/m^3); head only	0.3	5 h/day for 3 days	Sheep, sex not reported, adult, 23-50 kg, n = 6	Tracheal mucus velocity	Decreased by 40% immediately after exposure and 25% at 24 h postexposure to the mixture of the 2 compounds. The effects of either compound alone were not reported.	Abraham et al. (1986)
				Ciliary beat frequency	No effect	
Chronic/Subchronic Exposure						
13.2 mg/m^3 (5.0 ppm) in addition to 1.04 mg/m^3 ammonium sulfate; whole body	0.2 mg/m^3 (0.10 ppm)	5 h/day, 5 days/wk for up to 103 days	CD1 mice, female, 3-4 wks old, weight not reported, n = 360/group total (14-154/group in each assay)	Mortality rate after *Streptococcus* aerosol challenge	Increased in groups exposed to ozone alone and mixture of ozone, SO_2, and ammonium sulfate.	Aranyi et al. (1983)
				Alveolar macrophage bactericidal activity towards inhaled *K. pneumoniae*	Increased trend (non-significant) in ozone group but significantly increased in mixture group.	
				Counts, viability, and ATP levels in cells obtained by pulmonary lavage	No effect of either treatment	

TABLE AX4-14 (cont'd). EFFECTS OF MIXTURES CONTAINING SO_2 AND OZONE

Concentration						
SO_2 (ppm)	**Ozone (ppm)**	**Duration**	**Species**	**Endpoints**	**Interaction**	**Reference**
1 ppm (2.62 mg/m^3); whole body	1 ppm in addition to 3 ppm trans-2-butene	23 h/day, 7 days/wk, for 4 wks	Golden hamster, male, age not reported, ~105 g, n = 14 or 15/group; mild emphysema was induced in some animals by intratracheal administration of elastase	Lung volumes	End expiratory volume, residual volume, total lung capacity and vital capacity were unaffected in the mixture versus air exposure group in normal or emphysematous hamsters.	Raub et al. (1983)
				Respiratory system compliance	Unaffected in the mixture versus air exposure group in normal or emphysematous hamsters.	
				Distribution of ventilation (N_2 washout slope)	The N_2 slope decreased in the mixture versus air exposure group in both normal and emphysematous hamsters.	
				Diffusion capacity for carbon monoxide	Significantly increased in the mixture versus air-exposed normal animals. Although the text reported an increase in the mixture versus air-exposed emphysematous animals, Figure 3 of the study indicated that the effect was very small and did not obtain statistical significance. Significantly lower in emphysematous versus normal hamsters exposed to the mixture. **The authors noted a significant interaction between exposure to the mixture and emphysema.**	

TABLE AX4-14 (cont'd). EFFECTS OF MIXTURES CONTAINING SO_2 AND OZONE

Concentration						
SO_2 (ppm)	**Ozone (ppm)**	**Duration**	**Species**	**Endpoints**	**Interaction**	**Reference**
				Histopathology	Inflammatory lesions were found in the lungs of emphysematous hamsters exposed to air or the mixture. Hyperplasia incidence was higher in emphysema hamsters exposed to the mixture versus air. Inflammatory lesions were similar in emphysematous hamsters exposed to air or the mixture. Data were not shown for histopathology data.	
				Overall author conclusion	**Animals with impaired lung function may have decreased capacity to compensate for the pulmonary insult caused by exposure to a complex pollutant mixture.**	

TABLE AX4-15. EFFECTS OF SO_2 LAYERED ON METALLIC OR CARBONACEOUS PARTICLES

Concentration		Duration	Species	Endpoints	Interaction	Reference
SO_2	**Metal (mg/m^3)**					
~ 1 ppm (2.6 mg/m^3); whole body	Zinc oxide: 0.8, 2.7, or 6.0 mg/m^3 (0.05 µM projected area diameter, GSD 2.0) (sulfate, sulfite, and sulfur trioxide detected)	3 h	Hartley guinea pig, male, age not reported, 240-300 g, n = 7-16/group	Vital capacity	No effect with exposure to 7.8 mg/m^3 zinc oxide alone and 2.7 mg/m^3 zinc oxide in combination with SO_2, but decreased with exposure to 0.8 and 6.0 mg/m^3 zinc oxide in combination with SO_2.	Lam et al. (1982)
0	7.8			Total lung capacity	No effect with exposure to 7.8 mg/m^3 zinc oxide alone, but decreased with exposure to 6.0 mg/m^3 zinc oxide in combination with SO_2.	
				Diffusion capacity for carbon monoxide and ratio of diffusion capacity for carbon monoxide to total lung capacity or alveolar volume.	No effect with exposure to 7.8 mg/m^3 zinc oxide alone, but decreased with exposure to 2.7 and 6.0 mg/m^3 zinc oxide in combination with SO_2.	
				Alveolar volume	No effect with exposure to 7.8 mg/m^3 zinc oxide alone, but decreased with exposure to 6.0 mg/m^3 zinc oxide in combination with SO_2.	
~1 ppm (2.6 mg/m^3); head only	0	1 h	Hartley guinea pig, male, age not reported, 200-300 g, n = 8-23/group	Pulmonary function	SO_2 exposure alone resulted in an 11% increase in resistance and 12% decrease in compliance.	Amdur et al. (1983)

TABLE AX4-15 (cont'd). EFFECTS OF SO_2 LAYERED ON METALLIC OR CARBONACEOUS PARTICLES

Concentration						
SO_2	Metal (mg/m^3)	Species	Endpoints	Interaction	Reference	Concentration
0	Zinc oxide: ~1-2 (0.05 µM projected area diameter, GSD 2.0); mixed at 24 °C and 30% RH			Pulmonary function	Zinc oxide exposure alone resulted in a 9% decrease in compliance that persisted 1 h after exposure.	
~1 ppm (2.6 mg/m^3)	~1-2; mixed at 24 °C and 30% RH			Pulmonary function	A 12% decrease in compliance and decreased tidal volume that persisted 1 h after exposure, and decreased min volume. **There was no evidence of new compound formation. Study authors concluded that effects on tidal volume and min volume mostly likely represented an additive effect.**	
~1 ppm (2.6 mg/m^3)	~1-2; mixed at 480 °C and 30% RH			Pulmonary function	A 12% decrease in compliance and decreased tidal volume that persisted 1 h after exposure and a 12% increase in resistance and decreased min volume. **There was no evidence of new compound formation.**	
~1 ppm (2.6 mg/m^3)	~1-2; mixed at 480 °C and 80% RH with addition of water vapor downstream			Pulmonary function	A 13% decrease in compliance that persisted 1 h after exposure and a 29% increase in resistance. **Sulfite formation was observed**.	
~1 ppm (2.6 mg/m^3)	~1-2; mixed at 480 °C and 30% RH with addition of water vapor during mixing.			Pulmonary function	A 19% increase in resistance that persisted 1 h after exposure, decreased tidal volume immediately after exposure, and a 26% decrease in compliance 1 h after exposure. **Sulfate, sulfite, and sulfur trioxide formation was observed.**	

TABLE AX4-15 (cont'd). EFFECTS OF SO_2 LAYERED ON METALLIC OR CARBONACEOUS PARTICLES

Concentration		Duration	Species	Endpoints	Interaction	Reference
SO_2	**Metal (mg/m^3)**					
1.10-1.25 ppm (2.9-3.3 mg/m^3); head only	Copper oxide: 1.16-2.70 (<0.1 µM)	1 h	Hartley guinea pig, male, age not reported, 275-375 g; n = 8/group	Pulmonary resistance	Increased 32-47% during exposure and at 1 and 2 h postexposure when SO_2 and copper oxide were mixed at 37 °C, a condition that resulted in formation of 0.36 µmol/m3 sulfite on the copper oxide particles. No effect was observed with the compounds were mixed at 1411 °C, a condition that led to the formation of sulfate on the copper oxide particles.	Chen et al. (1991)
				Dynamic lung compliance	No effect when mixed under conditions that led to the formation of either sulfate or sulfite on particles.	
1.02 ppm (2.7 mg/m^3); head only	Zinc oxide: 0 (0.05 µM median diameter, GSD 2.0)	1 h	Hartley guinea pig, male, age not reported, 290-410 g, n = 6-9/group	Baseline pulmonary resistance at 2 h following exposure	No effect in any group.	Chen et al. (1992)
0	2.76			Airway hyperresponsiveness to acetylcholine	No effect with exposure to SO_2 or zinc oxide alone; compared to furnace controls (3% argon). **Hyperresponsiveness increased in both groups exposed to SO_2-layered zinc oxide particles.**	
1.10 ppm (2.9 mg/m^3)	0.87					
1.08 ppm (2.8 mg/m^3)	2.34					

TABLE AX4-15 (cont'd). EFFECTS OF SO_2 LAYERED ON METALLIC OR CARBONACEOUS PARTICLES

Concentration						
SO_2	**Metal (mg/m^3)**	**Duration**	**Species**	**Endpoints**	**Interaction**	**Reference**
10 ppm (26.2 mg/m^3); nose only	0	4 h	Swiss mice, female, 5 wks old, 20-23 g, n = 5/group	AM F_c-receptor mediated phagocytosis of sheep red blood cells at 3 days after exposure	Dose-dependent reductions in AM phagocytosis were observed at each concentration of SO_2 mixed with carbon black aerosol at 85% relative humidity, the only conditions under which SO_2 significantly chemisorbed to carbon black aerosol and oxidized to sulfate. AM phagocytic activity was reduced somewhat immediately after exposure (Day 0), was minimal on Days 1 and 3, began increasing on Day 7, and was fully recovered by Day 14. No effects were observed with exposure to SO_2 or carbon black alone. **The data indicate that environmentally relevant respirable carbon particles can act as effective vectors for delivering toxic amounts of acid SO_4^{2-} to distal parts of the lung.**	Jakab et al. (1996)
0	Carbon black: 10 mg/m^3 (0.3 µM, GSD 2.7)					
5 ppm (13.1 mg/m^3)	10 mg/m^3 (formed 6 µg sulfate at 85% humidity)					
10 ppm (26.2 mg/m^3)	10 mg/m^3 (formed 13.7 µg sulfate at 85% humidity)					

TABLE AX4-15 (cont'd). EFFECTS OF SO_2 LAYERED ON METALLIC OR CARBONACEOUS PARTICLES

Concentration		Duration	Species	Endpoints	Interaction	Reference
SO_2	**Metal (mg/m^3)**					
20 ppm (52.4 mg/m^3)	10 mg/m^3 (formed 48.7 µg sulfate at 85% humidity)					
10 ppm (26.2 mg/m^3); nose only	0	4 h once or for 4, 5, or 6 days	Outbred Swiss mouse, female, age and weight not specified, n = 10 or 12 per experimental value.	Inflammatory response after a single 4-h exposure	There was no effect on total cell number, lymphocyte/PMN differentials, or total protein levels in BAL fluid in any group.	Clarke et al. (2000)
0	Carbon black: 10 mg/m^3 (10% humidity)			AM F_c-mediated phagocytosis after a single 4-h exposure	Suppressed by acid sulfate coated particles (at ~140 µg/m^3) at 1, 3, and 7 days postexposure; values returned to normal by Day 14.	
0	Carbon black: 10 mg/m^3 in 85% humidity to generate 8 µg/m^3 acid sulfate			Intrapulmonary bactericidal activity toward *Staphylococcus aureus*	Decreased by a single 4-h exposure to sulfate coated particles (at ~140 µg/m^3) at 1 and 3 days postexposure, with recovery by Day 7. Suppression was also observed after 5 and 6 days of repeated exposure to ~20 µg/m^3 sulfate coated particles a condition more relevant to potential ambient human exposures.	
10 ppm (26.2 mg/m^3)	Carbon black: 10 mg/m^3 in 10% humidity to generate 41 µg/m^3 acid sulfate					

TABLE AX4-15 (cont'd). EFFECTS OF SO_2 LAYERED ON METALLIC OR CARBONACEOUS PARTICLES

Concentration		Duration	Species	Endpoints	Interaction	Reference
SO_2	**Metal (mg/m^3)**					
10 ppm ($26.2\ mg/m^3$)	Carbon black: 10 mg/m^3 in 85% humidity to generate 137 $\mu g/m^3$ acid sulfate					
1 ppm ($2.62\ mg/m^3$)	Carbon black: 1 mg/m^3 in 85% humidity to generate 20 $\mu g/m^3$acid sulfate:					
1 ppm ($2.6\ mg/m^3$); nose only	Zinc oxide: 6 (0.05 µM projected area diameter, GSD 2.0)	3 h/day for 6 days; animals evaluated for up to 72 h following exposure	Hartley guinea pig, male, age not reported, 250-320 g, n = 5-18/group/ time point	Right lung to body weight ratio	No effect by SO_2. Increased for 48 h in group exposed to SO_2-layered zinc oxide.	Conner et al. (1985)

TABLE AX4-15 (cont'd). EFFECTS OF SO_2 LAYERED ON METALLIC OR CARBONACEOUS PARTICLES

Concentration						
SO_2	**Metal (mg/m^3)**	**Duration**	**Species**	**Endpoints**	**Interaction**	**Reference**
1 ppm (2.6 mg/m^3)	0			Right lung wet to dry weight ratio	No effect by SO_2. Increased at 1 h after exposure in SO_2-layered zinc oxide group.	
				Lung morphology	No lesions were observed in the SO_2 group. In the group exposed to SO_2-layered zinc oxide, there was increased incidence of alveolar duct inflammation consisting of interstitial cellular infiltrate, increased numbers of macrophages, and replacement of squamous alveolar epithelium with cuboidal cells. Frequency and severity of lesions were greatest immediately following exposure and by 72 h following exposure, lesions were mild and infrequent.	
				Tracheal secretory cell concentration.	No effects with either exposure scenario.	
				Epithelial permeability	No effects with either exposure scenario.	
				DNA synthesis (^{3}H-tymidien uptake) terminal bronchial cells	Unaffected by SO_2. Increased at 24 and 72 h after exposure to zinc oxide/SO_2.	
				Lung volumes	Unaffected by SO_2 exposure. Functional reserve capacity, vital capacity, and total lung capacity were decreased from 1 to 72 h following exposure to zinc oxide/SO_2.	
				Diffusion capacity for carbon monoxide	Unaffected by SO_2 exposure. Decreased by ~40-50% from 1 to 24 h following exposure to zinc oxide/SO_2.	
				Alveolar volume	Unaffected by SO_2 exposure. Decreased by ~10% from 1 to 24 h following exposure to zinc oxide/SO_2.	
				Pulmonary mechanics	Respiratory frequency, tidal volume, pulmonary resistance, and pulmonary compliance were unaffected by either exposure.	

TABLE AX4-15 (cont'd). EFFECTS OF SO_2 LAYERED ON METALLIC OR CARBONACEOUS PARTICLES

Concentration		Duration	Species	Endpoints	Interaction	Reference
SO_2	**Metal (mg/m^3)**					
1 ppm (2.6 mg/m^3)				Author conclusion	**Changes were identical to those reported in a previous study in which guinea pigs were exposed to zinc oxide alone. Sulfur compounds deposited on the surface are less important than the zinc oxide particle.**	
1 ppm (2.6 mg/m^3); head only	Zinc oxide: 1 or 2.5 (0.05 µM CMD, GSD 2.0) Sulfate was generated at 7 and 11 $\mu g/m^3$ at each respective dose; sulfuric acid level was reported at 21 and 33 $\mu g/m^3$ at each respective dose.	3 h/day for 5 days	Guinea pig, sex, age, and weight not reported, n = 8-9/group	Pulmonary diffusing capacity	No effect with exposure to 1 ppm SO_2 or 2.5 mg/m^3 zinc oxide alone (data not shown by study authors). Significant and dose related decreases on exposure days 4 and 5 at 7 $\mu g/m^3$ sulfate (20% less than control) and days 2-5 at 11 $\mu g/m^3$ sulfate (up to 40% less than control).	Amdur et al. (1988)
		1 h		Bronchial sensitivity to acetylcholine	No effect of 1 ppm SO_2 or 2.8 mg/m^3 zinc oxide alone. Increased with SO_2 administered in combination with either zinc oxide dose. **The study authors noted that responses were similar to those produced by 200 $\mu g/m^3$ sulfuric acid of similar particle size, thus indicating the importance of surface layer.**	

TABLE AX4-15 (cont'd). EFFECTS OF SO_2 LAYERED ON METALLIC OR CARBONACEOUS PARTICLES

Concentration						
SO_2	**Metal (mg/m^3)**	**Duration**	**Species**	**Endpoints**	**Interaction**	**Reference**
5 ppm (13 mg/m^3); nose only	22 mg/m^3 gallium oxide (0.2 µM volume median diameter, GSD not reported), with and without addition of 7 mg/m^3 benzo(a)pyrene	2 h/day for 4 days, followed by 2 days without exposure, followed by 5 more days of exposure; animals were evaluated for up to 28 days following exposure	Fischer-344, male and female, 18-19 wks old, weight not reported, n = 2/sex/group at each evaluation time period	Tracheal and large airways morphology	No effects observed with coexposure to gallium oxide and SO_2.	Shami et al. (1985)
				Pulmonary morphology	Increase numbers of non-ciliated cells in terminal bronchial epithelium was observed in the SO_2/gallium oxide/benzo(a)pyrene group. Mild peribronchial and perivascular mononuclear inflammatory cell infiltrate and small hyperplastic epithelial cells in alveoli, and alveolar septal hypertrophy was observed in the SO_2/gallium oxide group, with and without benzo(a)pyrene exposure; effects were more prominent with benzo(a)pyrene exposure.	
				Cell proliferation (^{3}H-thymidine intake) in trachea and large airways	In the SO_2/gallium oxide group: increased on days 1 and 14; basal cells were primarily labeled. In the SO_2/gallium oxide/benzo(a)pyrene group: increased on day 8.	

TABLE AX4-15 (cont'd). EFFECTS OF SO_2 LAYERED ON METALLIC OR CARBONACEOUS PARTICLES

Concentration		Duration	Species	Endpoints	Interaction	Reference
SO_2	**Metal (mg/m^3)**					
5 ppm (13 mg/m^3); nose only				Cell proliferation (^{3}H-thymidine intake) in terminal bronchioles	In the SO_2/gallium oxide group: increased on day 14; Clara cells were primarily labeled. In the SO_2/gallium oxide/benzo(a)pyrene group: increased on day 11.	
				Types of ^{3}H-thymidine-labeled cells in the alveolar region	In the SO_2/gallium oxide group: type II cells were primarily labeled in the alveolar region through 14 days of exposure.	
					In the SO_2/gallium oxide/benzo(a)pyrene group: labeling was increased in Type II, Type I, and endothelial cells on day 8.	
5 ppm (13 mg/m^3); nose only	Gallium oxide: 27 mg/m^3 (~0.20 µM MMD, GSD ~1.5-2), with and without 7.5 mg/m^3 of 1-nitropyrene and benzo[a]pyrene	2 h/day, 5 days/wk for 4 wks	F344/Crl rat, male and female, 10-11 wks old, weight not reported, n = 6/sex/group	Pulmonary particle clearance	No effect was observed with exposure to SO_2 alone; clearance was slowed only by gallium oxide, with or without coexposure to SO_2 or the other compounds; SO_2 in combination with the polyaromatic hydrocarbons had no effect on clearance rate. Study authors concluded that toxicity was dominated by gallium oxide.	Wolff et al. (1989)
5 ppm (13 mg/m^3)	0					

BAL = bronchoalveolar lavage fluid
CMD = count median diameter
GSD = geometric standard deviation
MMAD = mass median aerodynamic diameter
MMD = mass median diameter
RH = relative humidity

TABLE AX4-16. EFFECTS OF SO_2 AND SULFATE MIXTURES

Concentration		Duration	Species	Endpoints	Interaction	Reference
SO_2	Sulfate (mg/m^3)					
Acute						
5 ppm (13.1 mg/m^3); nose only	Sulfate aerosol 1.5 (0.5 µM MMAD, GSD 1.6)	4 h	Sprague Dawley rat, male, age not reported, ~200 g, n = 8/group	Lung clearance of radiolabeled tracer particles.	No significant effect was observed with the mixture of the two compounds at 80-85% humidity.	Mannix et al. (1982)
Chronic/Subchronic						
1 ppm (2.62 mg/m^3); whole body	0	5 h/day, 5 days/wk for 4 or 8 mos; half the animals in the 8-mo group were allowed to recover for 3 mos.	Sprague-Dawley rat, male, young adult, initial weight not reported, n = 12-15/data point	Morphological observations at 4 mos exposure in "normal" rats	Bronchiolar epithelial hyperplasia and increased numbers of non-ciliated epithelial cells were observed in rats exposed to either compound alone but coexposure to both compounds did not magnify the effects. An increase in alveolar chord length was observed in the $(NH_4)_2SO_4$ group and no further changes were observed with coexposure to SO_2.	Smith et al. (1989)
0	$(NH_4)_2SO_4$: 0.5 mg/m^3 (MMAD = 0.42-0.44 ± 0.04 µm, GSD 2.2-2.6)			Morphological observations at 4 mos exposure in rats treated with elastase to induce an emphysema-like condition	Bronchiolar epithelial hyperplasia was decreased in groups exposed to either compound alone or the mixture of the two compounds. A decrease in alveolar chord length was observed in the $(NH_4)_2SO_4$ group and no further changes were observed with coexposure to SO_2.	
1 ppm (2.62 mg/m^3)	0.5 mg/m^3			Morphological observations at 8 mos exposure in "normal" rats	An increase in non-ciliated epithelial cells and alveolar birefringence (an indication of alveolar interstitial fibrosis) was observed only in the group exposed to $(NH_4)_2SO_4$.	

TABLE AX4-16 (cont'd). EFFECTS OF SO_2 AND SULFATE MIXTURES

Concentration		Duration	Species	Endpoints	Interaction	Reference
SO_2	Sulfate (mg/m^3)					
Chronic/Subchronic						
				Morphological observations at 8 mos exposure in rats treated with elastase	An increase in lung volume per body weight and emphysema incidence was observed in groups treated with either compound alone or in combination; alveolar chord length was increased only in the group exposed to the mixture of compounds.	
				Morphological observations at 12 mos exposure in normal rats	Increased alveolar chord length was observed only in the $(NH_4)_2SO_4$ group.	
				Morphological observations at 12 mos exposure in rats treated with elastase	In increase in absolute lung volume was observed only in the group treated with the mixture of both compounds.	
				Lung function effects at 4 mos exposure in normal rats	A decrease in residual volume was observed in the SO_2 group and decreased quasistatic compliance was observed in the SO_2 group and in the $(NH_4)_2SO_4$ group, but the effects were not observed with the mixture.	
				Lung function effects at 4 mos exposure in elastase-treated rats	Ratio of residual volume/total lung capacity and N_2 washout was decreased in the SO_2 group and in the $(NH_4)_2SO_4$ group, but the effects were not observed with the mixture.	

TABLE AX4-16 (cont'd). EFFECTS OF SO_2 AND SULFATE MIXTURES

Concentration		Duration	Species	Endpoints	Interaction	Reference
SO_2	Sulfate (mg/m^3)					
Chronic/Subchronic						
				Overall conclusions	**In general, pollutant effects were minimal and transient, and appeared obscured or repressed in elastase-treated groups; $(NH_4)_2SO_4$ was more bioactive than SO_2, with little evidence of mixture additivity (in several instances, effects seen with one or both pollutants individually were not seen with the mixture).**	

GSD = geometric standard deviation
MMAD = mass median aerodynamic diameter

TABLE AX4-17. EFFECTS OF ACTUAL OR SIMULATED AIR POLLUTION MIXTURES

Concentration		Duration	Species	Endpoints	Effect	Reference
Exposed Group	**Control Group**					
Acute/Subactute						
Air pollutant mixture at full concentration (tested in two studies): 0.35 ppm ozone, 1.3 ppm nitrogen dioxide, 2.5 ppm (6.6 mg/m^3) SO_2, 10 µg/m^3 manganese sulfate, 500 µg/m^3 ferric sulfate, 500 µg/m^3 ammonium sulfate, 500 µg/m^3 carbon aerosol. The mixture was also tested at ½ and ¼ concentrations. For aerosols MMAD = 0.3-0.48 µM with GSD = 2.6-4.6. Nose-only exposure Compounds formed included sulfate, nitrate, hydrogen ion, and nitric acid.	Clean air	4 h	Sprague-Dawley rat, male, age not reported, 240-280 g, n = 6-9/group	Breathing pattern	Effect of full concentration mixture in two studies: increased breathing frequency, trend or significant decrease in tidal volume, decreased or unaffected oxygen consumption, and increased or unaffected ventilation equivalent for oxygen. Effect of half concentration mixture: increased min ventilation. Quarter concentration: no significant effects.	Mautz et al. (1988)
				Histopathology	Full concentration: Area of type 1 parenchymal lung lesions were increased in 1 of 2 experiments and area of type 2 parenchymal lung lesions were increased in both experiments. **Effects were equivalent to those observed with ozone exposure alone.** Half and quarter concentrations: No effects.	
				Mucociliary clearance	No effect on early or late clearance of ^{85}Kr-labeled polystyrene particles.	

TABLE AX4-17 (cont'd). EFFECTS OF ACTUAL OR SIMULATED AIR POLLUTION MIXTURES

Concentration						
Exposed Group	**Control Group**	**Duration**	**Species**	**Endpoints**	**Effect**	**Reference**
Acute/Subacute						
				Nasal epithelial injury (measured by tritiated thymidine uptake).	No effect at any concentration.	
2.55 ppm (6.7 mg/m^3) SO_2, 0.3 ppm ozone, 1.2 ppm nitrogen oxide, 150 µg/m^3 ferric oxide, 130 µg/m^3 nitric acid, 2.0 µM/m^3 hydrogen ion, and 500 µg/m^3 total Fe^{3+}, Mn^{2+}, and NH_4^{2+} combined; nose only	Purified air	4 h/day for 7 or 21 days	Sprague-Dawley rat, male, age not reported, 200-225 g, n = 5-13/group/ time period	Bronchoalveolar epithelial permeability to ^{99m}Tc-diethylenetriaminepentaacetate.	No effect at either time period.	Phalen and Kleinman (1987)
				Nasal mucosal permeability to ^{99m}Tc-diethylenetriaminepentaacetate.	No effect at either time period.	
				Macrophage rosette formation.	Rosette formation was decreased (indicating damage to F_c receptors) for up to 4 days after the 7- or 21-day exposure; magnitude of effect was greater following the 21-day exposure. By day 4 after exposure, numbers began increasing and by day 7 were equivalent to control values.	

TABLE AX4-17 (cont'd). EFFECTS OF ACTUAL OR SIMULATED AIR POLLUTION MIXTURES

Concentration						
Exposed Group	**Control Group**	**Duration**	**Species**	**Endpoints**	**Effect**	**Reference**
Acute/Subacute						
				Macrophage phagocytic activity	In rats exposed for 7 days, decreased activity was observed for 2 days following exposure. No effects were observed after the 21-day exposure period.	
Subchronic/Chronic						
Urban air: São Paulo, mean levels of air pollutants measured 200 m from the police station where rats were kept: 29.05 µg/m^3 (0.011 ppm) SO_2; 1.25 ppm carbon monoxide, 11.08 ppb ozone, 35.18 µg/m^3 particulates.	Rural air: Atibaia, an agricultural town 50 km from São Paulo was considered the control; air pollutant levels were not measured.	6 mos	Wistar rat, male, 2 mos old, weight not reported, n = 14-30/group	Death	37 of 69 rats housed in São Paulo died before the end of the study and autopsy of 10 animals identified pneumonia as the cause of death; 10 of 56 animals housed in Atibaia died.	Saldiva et al. (1992)
				Respiratory mechanics	Nasal resistance was higher in animals housed in Atibaia. No differences were observed for pulmonary resistance or dynamic lung elastance.	
				Mucus properties	In animals from São Paulo tracheal mucus output was lower, relative speed of tracheal mucus (as assessed by frog palate assay) was slower, ratio between viscosity and elasticity was higher for nasal mucus, and rigidity of tracheal mucus was increased.	
				Bronchoalveolar lavage	In lavage fluid from animals housed in São Paulo, there were increased numbers of cells, lymphocytes, and polymorphonuclear cells.	

TABLE AX4-17 (cont'd). EFFECTS OF ACTUAL OR SIMULATED AIR POLLUTION MIXTURES

Concentration						
Exposed Group	**Control Group**	**Duration**	**Species**	**Endpoints**	**Effect**	**Reference**
Subchronic/Chronic						
				Histochemical evaluation	Hyperplasia was observed in respiratory epithelium of rats housed in São Paulo.	
				Ultrastructural studies	Animals housed in São Paulo had a higher frequency of cilia abnormalities including composite cilia, microtubular defect, vesiculation, and decreased microvelocity of luminal membrane.	
Urban air: See description for Saldiva et al. (1992)	Rural air: See description for Saldiva et al. (1992)	6 mos	Rats were from the same cohort as Saldiva et al. (1992); n = 15/group	Nasal passage pathology	Rats housed in São Paulo had increased nasal epithelium volume, larger amounts of mucosubstances stored in epithelium, and more acidic mucus secretions in lamina propria glands.	Lemos et al. (1994)
Urban air: São Paulo, levels of air pollutants measured were: ~8-50 µg/m^3 (0.003-0.019 ppm) SO_2, ~0.1-0.45 ppm nitrogen dioxide, ~4.8-7 ppm carbon monoxide, and ~50-120 µg/m^3 particulate matter.	Rural air: Atibaia, an agricultural town 50 km from São Paulo was considered the control; air pollutant levels were not measured.	Four groups of rats were housed: 3 mos in São Paulo, 3 mos in São Paulo followed by 3 mos in Atibaia, 3 mos in Atibaia, or 6 mos at Atibaia.	Wistar rats, male, 1.0-1.5 mos old, weight not reported, n = 30/group	Lung responsiveness to methacholine	Increased respiratory system elastance resulting from increased sensitivity to methacholine in rats housed in São Paulo for 3 mos compared to all the other groups. No exposure-related effects were observed for respiratory system resistance.	Pereira et al. (1995)

TABLE AX4-18. EFFECTS OF METEOROLOGICAL CONDITIONS ON SO_2 EFFECTS

Concentration		Duration	Species	Endpoints	Interaction	Reference
SO_2 (ppm)	**Condition**					
0.5 or 5 ppm (1.31 or 13.1 mg/m^3); apperantly intratracheal	Drop in air temperature from 38 °C to 15 °C	45 min	Rabbit, sex not reported, adult, mean 2.0 kg, n = 5-10/group; animals were mechanically ventilated.	Lung resistance	Exposure to cool air for 20 min resulted in a ~54% mean increase in lung resistance. Exposure to SO_2 for 20 min increased lung resistance by 16% at 0.5 ppm and 50% at 5 ppm. **The difference in lung resistance from warm to cold air was halved (27%) by exposure to 0.5 ppm and was not significant at 5 ppm. The study authors concluded that transient alteration in tracheobronchial wall following SO_2 exposure may have reduced accessibility of airway nervous receptors to cold air.**	Barthélemy et al. (1988)
1.0, 2.5, or 5 ppm (2.62, 6.55, or 13.1 mg/m^3); apparently intratracheal	Drop in intratracheal temperatures from ~35.5 °C to ~27 °C	In pre-exposure period: 15-min exposure to warm humid air, 10-min exposure to cold dry air, and 15-min exposure to warm humid air. In the SO_2 exposure period: 10-min exposures to each SO_2 concentration in cold dry air or with cold dry air alone were preceded and followed by 15-min exposures to warm humid air.	Duncan-Hartley guinea pigs, male, age and weight not reported, n = 7-12/group, mechanically ventilated; animals were hyperventilated during cold air and SO_2 exposure to simulate exercise.	Peak expiratory flow	Percent decreases were significantly greater with exposures to SO_2 in dry air at concentrations of 1.0 ppm (~32.7%) and 2.5 ppm (~35.6%) than with exposure to cold dry air (~27%); decrease at 5 ppm SO_2 in cold dry air (~25.3%) was similar to that with cold dry air. The effects did not persist following exposures.	Hälinen et al. (2000a)

TABLE AX4-18 (cont'd). EFFECTS OF METEOROLOGICAL CONDITIONS ON SO_2 EFFECTS

Concentration						
SO_2 (ppm)	**Condition**	**Duration**	**Species**	**Endpoints**	**Interaction**	**Reference**
				Tidal volume	Percent decreases were significantly greater with exposure to SO_2 in cold dry air at concentrations of 1.0 ppm (~22.4%) and 2.5 ppm (~28.3%) than with exposure to cold dry air (~18.1%); decrease at 5 ppm SO_2 in cold dry air (~17.8%) was similar to that of cold dry air. The effects did not persist following exposures.	
				Bronchoalveolar lavage	The clean dry air group had significantly more macrophages, lymphocytes, and increased protein concentration in lavage than the warm humid air control. The cold dry air + SO_2 group had fewer macrophages than the clean dry air group and higher protein concentration than the unexposed controls.	
				Histopathology	Increased incidence of eosinophilic infiltration within and below tracheal epithelium with exposure to cold dry air or SO_2 in cold dry air.	

TABLE AX4-18 (cont'd). EFFECTS OF METEOROLOGICAL CONDITIONS ON SO_2 EFFECTS

Concentration						
SO_2 (ppm)	**Condition**	**Duration**	**Species**	**Endpoints**	**Interaction**	**Reference**
1 ppm (2.62 mg/m^3); apparently intratracheal	Drop in intratracheal temperatures from ~37 °C to ~26 °C	60 min	Duncan-Hartley guinea pigs, male, age and weight not reported, n = 8-9/group, mechanically ventilated; animals were hyperventilated during cold air and SO_2 exposure to simulate exercise.	Peak expiratory flow	Non-significant decreases compared to baseline (4.5-10.8%) at 10 and 20 min of exposure to cold dry air. With exposure to SO_2 in cold dry air: decreased significantly (11.4%, i.e., bronchoconstriction) compared to baseline at 10 min of exposure but recovered from 20 to 60 min of exposure. The effect with SO_2 exposure was not statistically significant compared to that of cold dry air alone.	Hälinen et al. (2000b)
				Tidal volume	Decreased from baseline throughout most of the exposure period with cold dry air or SO_2 in cold dry air; response with SO_2 was more shallow than that of cold dry air alone, but statistical significance compared to cold dry air was obtained only at 60 min of exposure.	
				Bronchoalveolar lavage	Decreased neutrophil numbers in the SO_2 group compared to the warm humid air group but no significant difference compared to the cold dry air group.	
				Histopathology	No effect in lung or tracheobronchial airways.	
				General conclusions	Functional effects on the lower respiratory tract were weaker than in the previous study with 10-min exposures (Hälinen et al., 2000a).	

GSD = geometric standard deviation
MMAD = mass median aerodynamic density

TABLE AX4-19. IN VITRO OR EX VIVO RESPIRATORY SYSTEM EFFECTS OF SO_2 AND METABOLITES

Concentration	Duration	Species	Effects	Reference
In Vitro—Primary/Nonprimary				
0, 5,10, 20, 30, or 50 ppm (0, 13.1, 26.2, 52.4, or 131 mg/m^3) SO_2	1 h	Fauve de Bourgogne rabbits, 1 mo old, tracheal epithelium explants	Relative to control cultures, cell viability was not reduced at 5 and 10 ppm, but was at 30 ppm (~70%) and 50 ppm (~60%). Ciliary beat frequency was significantly reduced ($p < 0.05$) at 10-30 ppm, and was correlated with swollen mitochondria and depletion of cellular ATP, as well as with blebbing of ciliated or microvilli-covered cells and with aggregation and flattening of cilia.	Blanquart et al. (1995)
0, 0.1, 2, 20, or 40 mM (0, 4, 80, 800, or 1600 µg/mL) SO_3^{2-}	~1 min - 96 h	Rat, Sprague-Dawley, 200-250g; sex, age, and n not reported; lung cells and liver cells. Human lung-derived cell line, A549	This study focused on intracellular covalent reactions of sulfite with primarily proteinaceous sulfhydryl compounds in cells isolated from rat lung and rat liver (for some comparative purposes), as well as in the human lung-derived cell line, A549. Sulfitolysis of protein disulfide bonds results in formation of cysteine S-sulfonate, and sulfitolysis of GSSG in formation of $GSSO_3H$. The latter was formed in dose-dependent fashion upon the addition of sulfite to A549 cells. In addition to fibronectin and albumin, this study identified a third sulfite-binding protein in rat lung cytosol. $GSSO_3H$ was shown to be a potent competitive inhibitor of GST in rat lung, liver and A549 cells. **Results suggest that SO_2 could affect the detoxication of PAHs and other xenobiotics via formation of $GSSO_3H$ and subsequent inhibition of GST and enzymatic conjugation of GSH with reactive electrophiles.**	Menzel et al. (1986)

TABLE AX4-19 (cont'd). IN VITRO OR EX VIVO RESPIRATORY SYSTEM EFFECTS OF SO_2 AND METABOLITES

Concentration	Duration	Species	Effects	Reference
Ex Vivo				
7.5, 15, 22.5, 30, or 37.5 mg/m^3 (2.9, 5.7, 8.6, 11.5, or 14.3 ppm); ex vivo expsoure of trachea	30 min	Guinea pig, sex, age, and weight not reported, n = 4-8/group	No remarkable morphologic abnormalities in the tracheal mucociliary system of the 2.9 ppm group, though slight vacuolization, rare membrane blebs, and slightly widened intercellular spaces were observed. Abnormalities in the 5.7 and 8.6 ppm groups were similar and included loosened contact to the basal membrane, extensive intracellular edema and vacuolization, swollen mitochondria, polypoid extrusions and huge blebs in the cell membrane and ciliary membrane, widened intercellular space, and disrupted tight junctions. Additional abnormalities in the 11.5 and 14.3 ppm groups included marked epithelial sloughing, occasionally disrupted cell membranes and microtubules, and frequently disrupted ciliary membranes. Tracheal mucociliary activity was significantly decreased in all exposure groups (from 8.7 ± 1.0 Hz [controls] to 4.0 ± 1.1, 3.4 ± 2.7, 1.8 ± 2.2, 1.5 ± 1.8, and 2.0 ± 1.2 Hz in the 7.5, 15, 22.5, 30, and 37.5 mg/m^3 groups, respectively).	Riechelmann et al. (1995)
2.5, 5.0, 7.5, 10.0, or 12.5 ppm (6.6, 13.1, 19.7, 26.2, or 32.8 mg/m^3); ex vivo exposure of trachea	30 min	Guinea pig, sex, age, and weight not reported, n = 4-7/group	63% decrease in tracheal mucociliary activity at 2.5 ppm with dose-dependent decrease to 81% at 7.5 ppm; higher concentrations did not further decrease mucociliary activity. Ciliary beat frequency decreased by 45% at 5.0 ppm with dose-dependent decrease to 72% at 12.5 ppm. All reductions are relative to baseline values; no effect on controls for either parameter.	Knorst et al. (1994)

GSH = glutathione
GSSG = glutathione disulfide
$GSSO_3H$ = glutathione S-sulfonate
GST = glutathione-S-transferase
PAH = polycyclic aromatic hydrocarbons
AM = alveolar macrophages
BAL = bronchoalveolar lavage

TABLE AX4-20. GENOTOXIC EFFECTS OF SO_2 AND METABOLITE

Concentration	Duration	Species/System	Effects	Reference
"*Point Mutation*"[1] In Vitro				
0 or 50 ppm (131 mg/m^3) SO_2 or the equivalent agar concentration of SO_3^{2-}, 15 µg/ml)	48 h	Rat, Sprague-Dawley, female, liver enzyme preparations	In vitro induction of reverse mutation in cultures of *S. typhimurium* strain TA98 was not affected by incubating the bacterial-B(a)P-liver S9 enzyme activation system in the presence of SO_2/sulfite. An ancillary finding from the 0 µg B(a)P control exposures is that SO_2/sulfite itself did not appear mutagenic.	Pool-Zobel et al. (1990)
Cytogenetic and DNA Damage[2] In Vitro				
0, 20, 50 or 200 ppm (0, 52.4, 131 or 524 mg/m^3) SO_2; 0, 0.1, 0.2 or 0.4 mM SO_3^{2-} 0 or 2.5 µmol HSO_3^- per microtiter plate well 0, 0.1, 0.2 or 0.4 mM SO_4^{2-} 0 or 10 µmol $MgSO_4$ per tube	1-24 h	Hamster, Syrian golden, fetal lung cells (FHLC, gestational Day 15) Rat, Sprague-Dawley, male, age not reported, ~200g, hepatocytes Chinese hamster ovary cell line transformed by SV40, CO60 cells Precinorm U (human serum standard)	Toxicity and genotoxicity of SO_2, sulfite/bisulfite and sulfate (also NO_2/NO_x) were variously assessed in several in vitro test systems. It was noted that medium pH remained stable at $[SO_2] \leq 200$ ppm. Precinorm LDH activity was substantially inhibited by 50 ppm SO_2 after 1-3 h, and by 0.1 mM sulfite ion almost immediately, but not by 0.1 mM sulfate ion; AST was modestly inhibited after 5 h by 200 ppm SO_2; other monitored enzymes were not affected. While trypan blue exclusion was not affected, SO_2 cytotoxicity to FHLC was demonstrated at 20 ppm by reduced plating efficiency; at 50 ppm, enzyme activity leaked into culture medium was reduced only for AP and especially LDH (not other enzymes). 200 ppm SO_2 did not induce DNA damage (single-strand breaks) by itself in either FHLC or rat hepatocytes, but did somewhat reduce that induced by AMMN. In hepatocytes, incubation with $MgSO_4$ also caused a small reduction in AMMN-induced DNA damage. A 1-h exposure to 200 ppm SO_2 did not induce selective amplification of SV40 DNA in CO60 cells, nor affect that induced by DMBA or B[a]P. However, while also not affecting induction by DMBA or B[a]P, HSO_3^- added directly to the medium for 24 h did induce SV40 DNA amplification on its own—authors appear to suggest this might result from arrest of cells in mid-S phase, which leads to DNA amplification. **Thus, principal findings include inhibition of LDH by SO_2 or sulfite that could impair the cellular energy system; such an impairment could be responsible (possibly along with SO_4^{2-} conjugation of reactive intermediates) for the observed inhibition of AMMN-induced DNA damage by SO_2. Further, SO_2 does not appear by itself to induce DNA damage.**	Pool et al. (1988a)

TABLE AX4-20 (cont'd). GENOTOXIC EFFECTS OF SO_2 AND METABOLITE

Concentration	Duration	Species/System	Effects	Reference
Cytogenetic and DNA Damage[2] In Vitro				
3 mM SO_3^{2-}	40 min (test tube reactions)	dG or DNA	Test tube reaction mixtures that caused sulfite to oxidize to sulfur trioxide radical (SO_3^-) resulted in the hydroxylation of dG (8-OHdG) and the generation of DNA double strand breaks.	Shi and Mao (1994)
5 mM SO_3^{2-} (as Na_2SO_3)	1.5 h (test tube reaction)	dG	Test tube reaction of sulfite ion with H_2O_2 shown to generate OH radicals capable of hydroxylating dG to the DNA damage marker, 8-OHdG. Furthermore, incubation of sulfite with nitrite or various transition metal ions was shown to generate sulfur trioxide anion radical (SO_3^-).	Shi (1994)
Cytogenetic and DNA Damage[2] Acute/Subacute Exposure				
0 mg/m^3 (0 ppm) SO_2 (+ 0 or 8 mg/kg bw SSO) or 28 mg/m^3 (10.7 ppm) SO_2 (+ 0, 2, 4, 6 or 8 mg/kg bw SSO); whole body	± SSO ip on Days 1-3; then SO_2 for 5 day (Days 4-8), 6 h/day	Kunming mouse, male and female, ~6 wk old, 20-25 g, n = 6/sex/conc.	**Subacute inhalation of 28 mg/m^3 SO_2 induced a significant ($p < 0.001$) 10-fold increase in mouse bone marrow MNPCE, which was partially mitigated in dose-dependent fashion by pretreatment with SSO, a complex natural anti-oxidant substance**. SO_2 exposure also resulted in organ:bw ratios that increased for liver and kidney, decreased for lung and spleen, and remained unchanged for heart. Such ratio changes were largely mitigated by SSO pretreatment.	Ruan et al. (2003)
0, 14, 28, 56, or 84 mg/m^3 (0, 5.35, 10.7, 21.4, or 32.1 ppm) SO_2; whole body	7 day, 4 h/day	Kunming mouse, male and female, ~6 wk old, 20-25 g, n = 10/sex/conc.	In vivo exposure caused significantly ($p < 0.01$-0.001) increased frequencies of bone marrow MNPCE similarly in both sexes at all concentrations in a dose-dependent manner, and with only minimal cytotoxicity at the 3 highest concentrations. The level of MNPCE (%) even at the low SO_2 conc. was triple that of the control value. **Thus, subacute inhalation of SO_2 at noncytotoxic concentrations (though still notably higher than most human exposures) was clastogenic in mice.**	Meng et al. (2002)

TABLE AX4-20 (cont'd). GENOTOXIC EFFECTS OF SO_2 AND METABOLITE

Concentration	Duration	Species/System	Effects	Reference
Cytogenetic and DNA Damage[2] Acute/Subacute Exposure				
0, 14, 28, 56, or 84 mg/m^3 (0, 5.35, 10.7, 21.4, or 32.1 ppm) SO_2; whole body	7 day, 6 h/day	Kunming mouse, male and female, ~5 wk old, 18-20 g, n = 6/sex/conc.	Following in vivo exposure to SO_2, it was shown by the single cell gel electrophoresis (comet) assay that such exposure induced significant ($p < .001$-$.05$) dose-dependent DNA damage (presumed mostly to be single-strand breaks and alkali-labile sites) in cells isolated from brain, lung, liver, intestine, kidney, spleen, and testicle, as well as in lymphocytes, and beginning at the lowest concentration (except male intestine—lowest response at 28 mg/m^3). **Results demonstrate that SO_2, can cause systemic DNA damage in many organs, not just the lung. Authors note that potential occupational exposures and the fact that the obligate nose-breathing mouse removes ~95% of inhaled SO_2 in its nasal passages make this experimental concentration range relevant to possible human exposures.**	Meng et al. (2005b)
0 or 50 ppm (131 mg/m^3) SO_2	2 wk, 7 day/wk, 24 h/day	Rat, Sprague-Dawley, female, 4 mo old, wt not reported, n = 5 per group	Assessments were conducted on isolated primary lung and liver cells, or on blood serum. In vivo SO_2 exposure did not affect viability (trypan blue exclusion) of cells either immediately after isolation or after 1 h incubation with 1% DMSO (used for enzyme leakage assays). In contrast to controls, hepatocytes from SO_2-exposed rats released no LDH activity into DMSO-medium after 1 h, and AST activity was reduced. Other enzyme (AP, ALT, GT) activity releases were not affected in lung cells, and none were in hepatocytes. In blood serum, the only effect was a marked increase in LDH activity. The only significant ($p < 0.001$-0.01) exposure effects on lung or liver activities (in x 9000 g supernatants of cell homogenates) of xenobiotic metabolizing enzymes (AHH, NDMA-D, GST) were elevated NDMA-D in the liver and reduced GST in the lung. **Single-strand DNA breakage induced by three nitroso compounds (AMMN, NDMA, NMBzA) was reduced in hepatocytes from SO_2-exposed rats**. Authors discuss possible mechanisms for the observed effects, and note they are similar to in vitro effects reported elsewhere (see above, Pool et al., 1988a).	Pool et al. (1988b)

TABLE AX4-20 (cont'd). GENOTOXIC EFFECTS OF SO_2 AND METABOLITE

Concentration	Duration	Species/System	Effects	Reference
Cytogenetic and DNA Damage[2] Subchronic/chronic				
0, 0.2 mL C, or {0.2 mL DEP+C ± [4 ppm (10.48 mg/m^3) SO_2 or 6 ppm (11.28 mg/m^3) NO_2 or 4 ppm SO_2 + 6 ppm NO_2]}; whole body [Note: 0.2 mL C = 1 mg; 0.2 mL DEcCBP = 1 mg C + 2.5 mg DEP)]	SO_2 and/or NO_2: 10 mo, 16 h/day C or DEP+C: 4 wk, once/wk by intratracheal infusion	Rat, SPF F344/Jcl, male, 6 wk old, wt not reported, n = 23-30 per group in 6 groups	Purpose was to study effects of DEP on rat lung tumorigenesis and possible tumor promoting effects of SO_2 or NO_2 singly or together. [See Table AX4-17 for tumor-related effects.] DEP extract-DNA adducts were found only in the three gas-exposed groups. Chromatograms revealed two different adducts, one of which appears somewhat more abundant with SO_2 coexposure, the other substantially more so with NO_2; combined coexposure of both gases with DEP+C produced an adduct chromatogram appearing to be a composite of those for the individual gases. **Thus, SO_2 and NO_2 appear capable of promoting the genotoxicity of DEP extract, though perhaps not in identical fashion.**	Ohyama et al. (1999)

[1]Encompasses classical mutant selection assays based upon growth conditions under which mutants (or prototrophic revertants), but not the wild type (or auxotrophic) population treated with the test agent, can successfully grow (e.g., "Ames test", CHO/HGRPT or mouse lymphoma L5178Y/TK mammalian cell systems, various yeast and *Drosophila* systems, etc.); while most viable mutation events detected in these assays are typically "point" mutations (DNA base substitutions, small deletions or frameshifts, etc.), some may involve larger losses/rearrangements of genetic material.

[2]Encompasses CA, induction of MN or SCE, aneuploidy/polyploidy, DNA adduct and crosslink formation, DNA strand breakage, etc.

AHH = aryl hydrocarbon hydroxylase
AP = alkaline phosphatase
AMMN = N-nitroso-acetoxymethylmethylamine
ALT = alanine-amino-transferase
AST = aspartate-amino-transferase
B[a]P = benzo[a]pyrene
bw = body weight
C = carbon or carbon black particles
CA = chromosome aberrations
DEcCBP = DEP extract coated carbon black particles
DEP+C = diesel exhaust particle extract adsorbed to C
DMBA = 7, 12-dimethylbenzanthracene
DMSO = dimethyl sulfoxide
dG = 2′-deoxyguanosine
8-OHdG = 8-hydroxy-2′-deoxyguanosine
FHLC = fetal hamster lung cells
GT = γ-glutamyltransferase
GST = glutathione-S-transferase;
LDH = lactate dehydrogenase
MN = micronuclei
MNPCE = micronucleated PCE
NDMA = N-nitrosodimethylamine
NDMA-D = N-nitrosodimethylamine demethylase
NMBzA = N-nitrosomethylbenzylamine
PCE = polychromatic erythrocytes
SSO = seabuckthorn seed oil
SCE = sister chromatid exchanges
SV40 = simian virus 40

TABLE AX4-21. LIVER AND GASTROINTESTINAL EFFECTS OF SO_2

Concentration	Duration	Species	Effects	Reference
Subacute/Subchronic Exposure				
22, 56, or 112 mg/m^3 (7.86, 20, or 40 ppm per author conversion); whole body	6 h/day for 7 days	Kunming albino mouse, male and female, 5 wks old, 19 ± 2 g, n = 6/sex/subgroup	Effects observed in stomach (concentration of effect) included: increase in SOD activity (7.86 ppm, males only) and TBARS level (≥7.86 ppm) and decreases in SOD (≥20 ppm, males only) and GPx activities (≥20 ppm, males only) and GSH level (40 ppm). Effects observed in intestine were increases in catalase activity (≥20 ppm in males, 40 ppm in females) and TBARS level (≥20 ppm) and decreases in SOD (≥7.86 ppm) and GPx (≥20 ppm) activities and GSH level(≥7.86 ppm).	Meng et al. (2003c)
22, 64, or 148 mg/m^3 (8.4, 24.4, or 56.5 ppm); whole body	6 h/day for 7 days	Kunming-strain mice, male, age not reported, 18-20 g, n = 10/group	No effects were observed in the liver at 22 or 64 mg/m^3. GST and glucose-6-phosphate dehydrogenase activities and GSH level were decreased at 148 mg/m^3.	Wu and Meng (2003)
14, 28, or 56 mg/m^3 (5.35, 10.70, or 21.40 ppm); whole body	6 h/day for 7 days	Wistar rat, male, age not reported, 180-200 g, n = 6/group in 4 groups	Significant and concentration-dependent changes in mRNA (mid and high concentrations) and protein expression (all concentrations) included increases for *bax* and p53 apoptosis-promoting genes, and decrease for *bcl-2* apoptosis-repressing gene. **Authors speculated potential impact on human apoptosis-deficient diseases**.	Bai and Meng (2005b)
14, 28, or 56 mg/m^3 (5.35, 10.70, or 21.40 ppm); whole body	6 h/day for 7 days	Wistar rat, male, age not reported, 180-200 g, n = 6/group in 4 groups	SO_2 caused significant concentration-dependent reductions in liver enzyme activities and gene expression for CYP1A1 and CYP1A2. Effects were seen at the mid and high concentrations (only high for CYP1A1 enzyme activity), but not the low. Authors speculate that underlying mechanisms may involve oxidative stress and/or cytokine release, and may represent an adaptive response to minimize cell damage.	Qin and Meng (2005)

TABLE AX4-21 (cont'd). LIVER AND GASTROINTESTINAL EFFECTS OF SO_2

Concentration	Duration	Species	Effects	Reference
Subacute/Subchronic Exposure				
5 or 10 ppm (13.1 or 26.2 mg/m^3); whole body	24 h/day for 15 days	Sprague-Dawley CD rat, male, age not reported, 250-275 g, n = 9/subgroup	Subjects were rats fed standard diet (normal) or high cholesterol diet, and rats with streptozotocin-induced diabetes fed standard diet. SO_2 (≥5 ppm) elevated plasma triglycerides in normal and hypercholesterolemic groups, while 10 ppm lowered plasma high density lipoprotein cholesterol in hypercholesterolemic rats. In diabetic rats, 10 ppm SO_2 lowered triglycerides and free fatty acids without affecting high density lipoprotein cholesterol or total cholesterol. In the liver, SO_2 elevated triglycerides in normal and hypercholesterolemic groups (at 10 ppm), but lowered it in diabetic rats (at ≥5 ppm); esterified cholesterol was elevated in normal rats (at 10 ppm), but lowered in diabetic rats (at ≥ 5ppm), and free cholesterol was unchanged in all groups. In normal rats, triglycerides secretion rate was inhibited by 10 ppm SO_2. SO_2 caused several changes in plasma apolipoprotein composition in normal and hypercholesterolemic groups, but not in diabetic rats. Leukotriene parameters were not affected. **Thus, in each rat model, inhalation of SO_2 at levels without overt effects affected plasma and tissue lipid content. Specific effects varied according to diet or diabetes**.	Lovati et al. (1996)
5, 50, or 100 ppm (13.1, 131, or 262 mg/m^3); whole body	5 h/day for 7-28 days	Wistar rat, male, 7 wks old, weight not reported, n = 4-5/treatment group, 8 controls	GSH was depleted in the liver at 5 and 100 ppm but not at 50 ppm. With respect to GSH-related enzymes, exposure to 5 ppm decreased GRed and GST activity in the liver. Exposure to 50 ppm did not affect liver GST, but decreased liver GRed and GPx.	Langley-Evans et al. (1996)
286 mg/m^3 (100 ppm); whole body Units were incorrectly reported as µg/m^3 in the study but were corrected according to information provided by study author	5 h/day for 28 days	Wistar rat, male, 7 wks old, weight not reported, n = 4-16	Adult rats exposed to air or SO_2 were born to dams fed diets with varying casein contents (180 [control], 120, 90 or 60 g/kg) during gestation. In the liver, SO_2 exposure elevated GSH level in the 120 g/kg dietary group but lowered it in the 60 g/kg dietary group. SO_2 did not affect liver GST in any group. SO_2 increased GCS levels in the 180 and 90 g/kg groups, GPx in the 60 g/kg group, and GRed in the 120 and 90 g/kg groups. This study provides information for an extremely high concentration level but is being acknowledged here with the unit corrected to verify that a low-concentration level study was not missed.	Langley-Evans et al. (1997); Langley-Evans 2007

TABLE AX4-21 (cont'd). LIVER AND GASTROINTESTINAL EFFECTS OF SO_2

Concentration	Duration	Species	Effects	Reference
Subacute/Subchronic Exposure				
10 or 30 ppm (26.2 or 78.6 mg/m^3); whole body	6 h/day, ~5 days/wk for 21 wks (total of 99 days)	Sprague-Dawley CD rat, male, 8 wks old, weight not reported, n = 70/group in 3 groups (inhalation series)	No effects on relative liver weight or histopathology were found.	Gunnison et al. (1987)
10 ppm (26.2 mg/m^3); whole body	1 h/day, 7 days/wk for 6 wks	Swiss Albino rat, male, 3 mos old, weight not reported, n = 10/group	Effects were compared in non-diabetic rats, non-diabetic rats exposed to SO_2, alloxan-induced diabetic rats, and diabetic rats exposed to SO_2. SO_2 increased blood glucose in all groups, but did not affect total cholesterol, high density lipoprotein cholesterol, low density lipoprotein cholesterol, very low density lipoprotein cholesterol, or triglyceride levels in either normal or diabetic rats.	Ağar et al. (2000)
10 ppm (26.2 mg/m^3); whole body	1 h/day, 7 days/wk for 6 wks	Rat, male, 3 mos old, weight not reported, n = 10/group in 4 groups	Effects compared in normal rats and rats with alloxan induced diabetes. Among the significant effects observed, SO_2 exposure enhanced the body weight loss seen in the diabetic group, but did not affect body weight gain in the control group. SO_2 elevated blood glucose levels in both controls and diabetics, but lowered triglycerides only in diabetics. Cholesterol parameters were not affected.	Küçükatay et al. (2003)

GST = glutathione S-transferase
GT = γ-glutamyltranspeptidase
SOD = Cu,Zn-superoxide dismutase
TBARS = thiobarbituric acid-reactive substances

TABLE AX4-22. RENAL EFFECTS OF SO_2

Concentration	Duration	Species	Effects	Reference
22, 64, or 148 mg/m^3 (8.4, 24.4, or 56.5 ppm)	6 h/day for 7 days	Kunming-strain mice, male, age not reported, 18-20 g, n = 10/group	GST was decreased in the kidney at 64 and 148 mg/m^3 and glucose-6-phosphate dehydrogenase activity was decreased at 148 mg/m^3. Kidney GSH levels were reduced at all exposure levels.	Wu and Meng (2003)
5, 50, or 100 ppm (13.1, 131, or 262 mg/m^3)	5 h/day for 7-28 days	Wistar rat, male, 7 wks old, weight not reported, n = 4-5/treatment group, 8 controls	GSH was depleted in the kidney in the 5 and 100 ppm groups but not in the 50 ppm group. No effects were observed for other GSH-related enzymes.	Langley-Evans et al. (1996)

TABLE AX4-23. LYMPHATIC SYSTEM EFFECTS OF SO_2 AND SO_2 MIXTURE

Concentration	Duration	Species	Effects	Reference
Subchronic/Chronic Exposure				
1 ppm (2.62 mg/m^3); whole body	5 h/day, 5 days/wk for 4 mos.	Sprague-Dawley rat, male, young adult, initial weight not reported, n = 12-15/data point	No significant effects were reported for spleen weight or mitogen-induced activation of peripheral blood lymphocytes or spleen cells (data not shown by study authors).	Smith et al. (1989)
13.2 mg/m^3 (5.0 ppm) SO_2 + 1.04 mg/m^3 ammonium sulfate + 0.2 mg/m^3 (0.10 ppm) ozone; whole body	5 h/day, 5 days/wk for up to 103 days	CD1 mice, female, 3-4 wks old, weight not reported, n = 360/group total (14-154/group in each assay)	Cytostasis of MBL-2 leukemia target cells by peritoneal macrophage was increased in groups exposed to ozone alone or a mixture of the three compounds but was significantly higher with the mixture than with ozone alone at a macrophage:target cell ratio of 10:1; no significant effects were observed with macrophage:target cell ratio of 20:1. A reduction in splenic lymphocyte blastogenesis in response to phytohemagglutinin and concanavalin A occurred after exposure to ozone alone, but increased response occurred after exposure to the mixture; no response to alloantigen occurred after exposure to ozone alone but increased response occurred after exposure to mixture; there were no effects on *S. typhosa* lipopolysaccharide with either exposure scenario.	Aranyi et al. (1983)

B(a)P = benzo(a)pyrene
GCS = γ-glutamylcysteine synthetase
GPx = glutathione peroxidase
GRed = glutathione reductase
GSH = glutathione
GSH = glutathione
GST = glutathione-S-transferase
GPx = glutathione peroxidase
GSH = glutathione
SOD = superoxide dismutase
TBARS = thiobarbituric acid-reactive substances
GST = glutathione S-transferase
GT = γ-glutamyltranspeptidase
SOD = Cu,Zn-superoxide dismutase
TBARS = thiobarbituric acid-reactive substances

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AX5. CHAPTER 5 ANNEX – EPIDEMIOLOGICAL STUDIES OF HUMAN HEALTH EFFECTS ASSOCIATED WITH EXPOSURE TO AMBIENT SULFUR OXIDES

TABLE AX5-1. ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH RESPIRATORY MORBIDITY IN FIELD/PANEL STUDIES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean SO_2 Levels	Copollutants Considered	Findings & Interpretation	Effect Estimates (95% CI)
UNITED STATES					
Mortimer et al. (2002) Eight urban areas in the U.S.: St. Louis, MO; Chicago, IL; Detroit, MI; Cleveland, OH; Washington, DC; Baltimore, MD; East Harlem, NY; Bronx, NY Jun-Aug 1993	Panel study of 846 asthmatic children aged 4-9 yrs from the National Cooperative Inner-City Asthma Study (NCICAS). Study children either had physician-diagnosed asthma and symptoms in the past 12 mos or respiratory symptoms consistent with asthma that lasted more than 6 wks during the previous yr. Respiratory symptoms recorded in daily diary and included cough, chest tightness, and wheeze. Mixed effects models and GEE models used to evaluate the effect of air pollutants on PEF and respiratory symptoms. Models adjusted for day of study, previous 12-h mean temperature, urban area, diary number, rain in the past 24 h.	3-h avg SO_2 (8 a.m.-11 a.m.) for all 8 areas (shown in figure): 22 ppb Avg intradiary range: 53 ppb	O_3 (r = 0.29) NO_2 PM_{10}	None of pollutants associated with evening PEF or evening symptoms. Using single-pollutant model, SO_2 had little effect on morning PEF (data not shown). Significant associations between moving avg of 1- to 2-day lag of SO_2 and incidence of morning asthma symptoms.	OR for morning symptoms associated with 20-ppb increase in 3-h avg SO_2 concentration (Lag 1-2 day): 8 urban areas: Single-pollutant model: 1.19 (1.06, 1.35) SO_2 with O_3 model: 1.18 (1.05, 1.33) 7 urban areas: Single-pollutant model: 1.22 (1.07, 1.40) SO_2 with O_3 and NO_2 model: 1.19 (1.04, 1.37) 3 urban areas: Single-pollutant model: 1.32 (1.03, 1.70) SO_2 with O_3, NO_2, and PM_{10} model: 1.23 (0.94, 1.62)

TABLE AX5.1 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH RESPIRATORY MORBIDITY IN FIELD/PANEL STUDIES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean SO_2 Levels	Copollutants Considered	Findings & Interpretation	Effect Estimates (95% CI)
UNITED STATES (cont'd)					
Schildcrout et al. (2006) Albuquerque, NM; Baltimore MD; Boston MA; Denver, CO; San Diego, CA; Seattle, WA; St. Louis, MO; Toronto, Ontario, Canada Nov 1993-Sept 1995	Meta-analysis of 8 panel studies with 990 children of the Childhood Asthma Management Program (CAMP), during the 22-mo prerandomization phase to investigate effects of criteria pollutants on asthma exacerbations (daily symptoms and use of rescue inhalers). Poisson regression and logistic regression models used in analyses. Within city models controlled for day of wk, ethnicity, annual family income, flexible functions of age and log-transformed sensitivity to the methacholine challenge using natural splines with knots fixed at 25th, 50th, and 75th percentiles. Also controlled for confounding due to seasonal factors. All city-specific estimates included in calculations of study-wide effects except Albuquerque where SO_2 data were not collected.	24-h avg SO_2: Median (10th, 25th, 75th, 90th percentile): Albuquerque: NA Baltimore: 6.7 ppb (3.2, 4.7, 9.8, 14.2) Boston: 5.8 ppb (2.7, 3.7, 9.1, 14.1) Denver: 4.4 ppb (1.2, 2.5, 6.7, 9.5) San Diego: 2.2 ppb (1.2, 1.7, 3.1, 4.4) Seattle: 6.0 ppb (3.7, 4.7, 7.5, 9.5) St. Louis: 7.4 ppb (3.9, 5.3, 10.7, 13.6) Toronto: 2.5 ppb (0.2, 1.0, 4.8, 8.8)	O_3 ($-0.03 \leq r \leq 0.44$) NO_2 ($0.23 \leq r \leq 0.68$) PM_{10} ($0.31 \leq r \leq 0.65$) CO ($0.19 \leq r \leq 0.67$)	All SO_2 Lags positively related to increased risk of asthma symptoms, but only the 3-day moving avg was statistically significant. Stronger associations observed for CO and NO_2. Data analyzed using 2-pollutant models based on the sum of the 2 within-subject pollutant effects, which were intended to provide insight into the increased risk of asthma symptoms associated with simultaneous shift in 2-pollutants. In 2-pollutant models with CO, NO_2, and PM_{10}, the SO_2 effect estimates remained robust. SO_2 not associated with rescue inhaler use rates.	OR for daily symptoms associated with 10-ppb increase in within-subject 24-h avg SO_2 concentration: Lag 0: 1.06 (0.99, 1.13) Lag 1: 1.05 (0.95, 1.16) Lag 2: 1.06 (0.99, 1.12) 3-day moving sum : 1.04 (1.00, 1.08) Rate ratio for number of rescue inhaler used associated with 10-ppb increase within-subject concentration of SO_2 Lag 0: 1.01 (0.97, 1.06) Lag 1: 1.01 (0.97, 1.06) Lag 2: 1.04 (0.99, 1.09) 3-day moving sum: 1.02 (0.99, 1.05) Results for 2-pollutant models shown in figure.

TABLE AX5.1 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH RESPIRATORY MORBIDITY IN FIELD/PANEL STUDIES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean SO_2 Levels	Copollutants Considered	Findings & Interpretation	Effect Estimates (95% CI)
UNITED STATES (cont'd)					
Schwartz et al. (1994) Watertown, MA (Apr-Aug 1985); Kingston-Harriman, TN (Apr-Aug 1986); St. Louis, MO; (Apr-Aug 1986); Steubenville, OH; (Apr-Aug 1987); Portage, WI; (Apr-Aug 1987); Topeka, KS (Apr-Aug 1988)	Longitudinal study of 1,844 children in grades 2-5 from the Six Cities Study to examine the effects of PM and SO_x on respiratory health. Daily diaries completed by parents, recording symptoms, such as cough, chest pain, phlegm, wheeze, sore throat, and fever. Logistic regression models adjusting for aurocorrelation were used for the analysis. To examine possible non-linearity in the relationship, smooth functions of the air pollution variables were fit using GAM and the significance of the deviation from linearity was tested.	24-h mean SO_2: Median: 4.1 ppb IQR: 1.4, 8.2 Max: 81.9	O_3 (r = −0.09) NO_2 (r = 0.51) PM_{10} (r = 0.53) $PM_{2.5}$ (r = 0.55) $PM_{2.5}$ sulfur (r = 0.50) H^+ (r = 0.23)	SO_2 associated with incidence of cough and lower respiratory symptoms. Local smooth showed increased cough incidence for only above a 4-day avg of 20 ppb (less than 5% of data). Test for nonlinearity was significant (p = 0.002). No increase in incidence of lower respiratory symptoms was seen until 24-h avg SO_2 concentrations exceeded 22 ppb. ORs for cough and lower respiratory symptoms related to were substantially reduced after adjustment for PM_{10}, suggesting the SO_2 associations might be confounded by particles.	OR for cough incidence associated with 10-ppb increase in 4-day avg SO_2 concentration: Single-pollutant model: 1.15 (1.02, 1.31) SO_2 with PM_{10} model: 1.08 (0.93, 1.25) SO_2 with O_3 model: 1.15 (1.01, 1.31) SO_2 with NO_2 model: 1.09 (0.94, 1.30) OR for lower respiratory symptoms associated with 10-ppb increase in 24-h avg SO_2 concentration: Single-pollutant model: 1.28 (1.13, 1.46) SO_2 with PM_{10} model: Not presented. Stated as not statistically significant.

TABLE AX5.1 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH RESPIRATORY MORBIDITY IN FIELD/PANEL STUDIES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean SO_2 Levels	Copollutants Considered	Findings & Interpretation	Effect Estimates (95% CI)	
UNITED STATES (cont'd)						
Delfino et al. (2003) Los Angeles, CA Nov 1999-Jan 2000	Panel study of 22 Hispanic children with asthma aged 10 to 16 yrs. Participants performed twice-daily PEF measurements and filled out symptom diaries. Analyses of symptoms conducted using GEE with exchangeable correlation. Linear mixed model used for PEF analyses. GEE models controlled for respiratory infections (data available for 20 subjects) and temperature.	1-h max SO_2: 7.0 ppb (SD 4.0) IQR: 4.0 8-h max SO_2: 4.6 ppb (SD 3.0) IQR: 2.5	O_3 (r = −0.19) NO_2 (r = 0.89) CO (r = 0.69) PM_{10} (r = 0.73) EC (r = 0.87) OC (r = 0.83) VOCs	None of the VOCs or gaseous pollutants associated with PEF. Current-day, but not previous-day, SO_2 concentrations associated with symptom score >1 and >2.	OR for symptom score >1 per IQR increase in SO_2: 1-h max SO_2: Lag 0: 1.31 (1.10, 1.55) Lag 1: 1.11 (0.91, 1.36) 8-h max SO_2: Lag 0: 1.23 (1.06, 1.41) Lag1: 1.11 (0.97, 1.28)	OR for symptom score >2 per IQR increase in SO_2: 1-h max SO_2: Lag 0: 1.37 (0.87, 2.18) Lag 1: 0.76 (0.35, 1.64) 8-h max SO_2: Lag 0: 1.36 (1.08, 1.71) Lag 1: 0.91 (0.51, 1.60)
Neas et al. (1995) Uniontown, PA Summer 1990	Panel study of 83 fourth and fifth grade students in Uniontown, Pennsylvania. Participants reported twice-daily PEF and the presence of cold, cough, or wheeze. During the summer of 1990, there were 3,582 child-days. PEF analyzed with autoregressive linear regression model that included a separate intercept for evening measurements, trend, temperature and 12-h avg air pollutant concentration, weighted by the number of hours child spent outdoors during the previous 12 h.	12-h avg SO_2: 10.2 ppb Max: 44.9 IQR: 11.1 Daytime 12-h avg SO_2 (8 a.m.-8 p.m.): 14.5 ppb Overnight 12-h avg SO_2 (8 p.m.-8 a.m.): 5.9 ppb	PM_{10} $PM_{2.5}$ O_3 total sulfate particles particle-strong acidity (r = 0.44)	Incidence of new evening cough episodes significantly associated with the preceding daytime 12-h avg SO_2. Mean deviation in PEF not associated with SO_2.	Effects associated with 10-ppb increase in 12-h avg SO_2: Change in mean deviation in PEF: −0.63 L/min (−1.33, 0.07) OR for evening cough: 1.19 (1.00, 1.42) Concentration weighted by proportion of hours spent outdoors during prior 12 h: Change in mean deviation in PEF: −1.25 L/min (−2.75, 0.25) OR for evening cough: 1.53 (1.07, 2.20)	

TABLE AX5.1 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH RESPIRATORY MORBIDITY IN FIELD/PANEL STUDIES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean SO_2 Levels	Copollutants Considered	Findings & Interpretation	Effect Estimates (95% CI)
UNITED STATES (cont'd)					
Newhouse et al. (2004) Tulsa, OK Sep-Oct 2000	Panel study of 24 patients aged 9 to 64 yrs with physician-diagnosed asthma. Subjects performed twice-daily PEF (morning and evening) measurements, and recorded medications taken and symptoms. Simple linear regression, forward stepwise multiple regression and correlation analysis performed. Multiple regression analyses used to develop predictive models for other environmental factors. Analyses produced complex models with different predictor variables for each symptom.	24-h avg SO_2: 0.01 ppm Range: 0.00, 0.02	$PM_{2.5}$ CO O_3 pollen fungal spores	Of the atmospheric pollutants, avg and max O_3 were most significant factors that influenced symptoms. Quantitative results not provided for SO_2. Avg or max SO_2 found to be negative predictors of asthma in subgroup analyses of women and nonsmokers and rhinitis in all patients. Avg SO_2 also negative predictor of evening PEF.	Not quantitatively useful.
Ross et al. (2002) East Moline, IL May-Oct 1994	Panel study of 59 asthmatic subjects aged 5 to 49 yrs. Analysis based on 40 subjects, due to withdrawal or failure to provide requested health data. Study assessed the effect of single and combined exposures to air pollutants and airborne allergens on PEF, symptom scores and medication use frequency. Multivariate linear-regression models with 1st order autoregression used for analysis of daily means of mean - standardized PEF, symptom scores and asthma medication use; logistic regression used for dichotomized data for symptom score and medication use, log-linear models for log-transformed symptom scores and medication use frequency.	24-h avg SO_2: 3.4 ppb (SD 3.1) Median: 2.8 IQR: 2.4 Range: 0, 27.3	PM_{10} O_3 NO_2 pollen fungi	No associations observed with SO_2.	No effect estimates provided.

TABLE AX5.1 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH RESPIRATORY MORBIDITY IN FIELD/PANEL STUDIES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean SO_2 Levels	Copollutants Considered	Findings & Interpretation	Effect Estimates (95% CI)
EUROPE					
Boezen et al. (1998) Amsterdam and Meppel, the Netherlands winter of 1993-1994	Panels study of 189 adults (48 to 73 yrs) with and without chronic respiratory symptoms in urban and rural areas to investigate whether bronchial hyperresponsiveness and PEF variability can be used to identify subjects who are susceptible to air pollution. Spirometry and methacholine challenge were performed and subjects with a fall in FEV_1 of 20% or greater were considered BHR. Subjects performed twice-daily peak flow for 3 mos. A subject's basal PEF variability was calculated over an 8-day period with low air pollution. PEF variability was expressed as (highest PEF-lowest PEF/mean) or amplitude % mean (ampl%mean) PEF. After calculation of the daily PEF variability, the number of days where the ampl% mean was greater than 5% was determined. This resulted in two groups of subjects; those with ampli%mean PEF of 5% or less every day in the 8-day period, and those with an ampl%mean PEF greater than 5% on at least 1 day. Effects of air pollutants on prevalence of symptoms assessed with logistic regression models that adjusted for autocorrelation of the residuals, daily min temp, time trend and weekends/holidays.	24-h avg SO_2 Urban Mean: 11.8 µg/m^3 Range: 2.7, 33.5 Rural Mean: 8.2 Range: 0.8, 41.5	PM_{10} BS NO_2	No association between SO_2 and respiratory symptoms in subjects with no BHR, BHR at < cum 2.0 methacholine or BHR at < cum 1.0 methacholine. In subjects with ampl%mean PEF > 5% and those with ampli%mean PEF > 5% for > 33% of days, SO_2 was associated with the prevalence of phlegm.	Odds ratio (per 40 µg/m^3 SO_2) Subjects with no BHR URS: 0.86 (0.73, 1.03) LRS: 1.15 (0.90, 1.46) Cough: 1.01 (0.84, 1.21) Phlegm: 1.01 (0.86, 1.20) BHR at ≤cum 2.0 Methacholine URS: 1.11 (0.78, 1.56) LRS: 1.03 (0.72, 1.47) Cough: 0.89 (0.66, 1.19) Phlegm: 1.03 (0.78, 1.37) BHR at ≤1.0 Methacholine URS: 1.02 (0.65, 1.61) LRS: 0.96 (0.63, 1.47) Cough: 0.96 (0.64, 1.44) Phlegm: 1.00 (0.68, 1.46) Ampl%mean PEF ≤5% URS: 0.82 (0.62, 1.08) LRS: 1.38 (0.93, 2.03) Cough: 0.72 (0.52, 0.98) Phlegm: 0.79 (0.59, 1.05) Ampl%mean PEF > 5% URS: 1.04 (0.88, 1.23) LRS: 1.14 (0.96, 1.36) Cough: 1.07 (0.90, 1.26) Phlegm: 1.23 (1.05, 1.43)

TABLE AX5.1 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH RESPIRATORY MORBIDITY IN FIELD/PANEL STUDIES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean SO_2 Levels	Copollutants Considered	Findings & Interpretation	Effect Estimates (95% CI)
EUROPE (cont'd)					
Boezen et al. (1998) (cont'd)					Ampl%mean PEF > 5%, >33% of days URS: 1.10 (0.85, 1.41) LRS: 1.14 (0.91, 1.42) Cough: 1.14 (0.89, 1.47) Phlegm: 1.36 (1.14, 1.63)
Boezen et al. (1999) Bodegraven, Meppel, Nuspeet, Rotterdam, Amsterdam, The Netherlands 3 winters of 1992-95	Panel study of 632 children (7 to 11 yrs) living in rural and urban areas of the Netherlands, to investigate whether children with bronchial hyperresponsiveness (BHR) and relatively high serum concentrations of total IgE were susceptible to air pollution. Methacholine challenge performed to determine bronchial hyperresponsiveness. Serum total IgE higher than the median (60kU/L) were defined as relatively high. Peak flow was measured twice daily and lower and upper respiratory symptoms were recorded daily for 3 mos. Association between symptoms and air pollutants assessed using logistic regression that adjusted for daily min temp, linear, quadratic and cubic time trend and weekends and holidays, and incidence of influenza. Examined 0, 1, 2 Lags and 5 day mean of air pollutants.	1992-9: Urban areas- Mean: 22.5 µg/m^3, Range: (1.4, 61.3) Rural areas- Mean: 9.8 Range: (1.3, 34.2) 1993-4: Urban areas- Mean: 11.8, Range: (2.7, 33.5) Rural areas- Mean: 8.2, Range: (0.8, 41.5) 1994-5: Urban areas- Mean: 8.3, Range: (0.6, 24.4); Rural areas- Mean: 4.3, Range: (0.5,17.0)	PM_{10} Black smoke NO_2	459 children had complete data. For children with BHR and relatively high serum total IgE, the prevalence of LRS was associated with increases in PM_{10}, BS, SO_2, and NO_2. In the group with no BHR and relatively low IgE, and the group with BHR and low IgE, there was no consistent association between air pollutants with symptoms or decreased PEF. In children with no BHR but relatively high serum total IgE, there was a 28% to 149% increase in the prevalence of LRS per 40 µg/m^3 SO_2.	Odds ratio (per 40 µg/m^3 SO_2) Children with BHR and relatively high IgE (n = 121) LRS Lag0: 1.45 (1.13, 1.85) Lag 1: 1.41 (1.09, 1.82) Lag 2: 1.40 (1.10, 1.79) 5-day mean: 2.25 (1.42, 3.55) URS Lag 0: 1.17 (0.99, 1.38) Lag 1: 1.06 (0.90, 1.25) >10% morning PEF decrease Lag 0: 1.09 (0.89, 1.34) Lag 1: 1.00 (0.81, 1.23) >10% evening PEF decrease Lag 0: 1.06 0.86, 1.30) Lag 1: 0.83 (0.68, 1.02)

TABLE AX5.1 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH RESPIRATORY MORBIDITY IN FIELD/PANEL STUDIES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean SO_2 Levels	Copollutants Considered	Findings & Interpretation	Effect Estimates (95% CI)
EUROPE (cont'd)					
Boezen et al. (1999) (cont'd)					NO BHR and low IgE (n = 167) LRS Lag 0: 1.12 (0.76, 1.66) Lag 1: 0.61 (0.39, 0.94) URS Lag 0: 1.01 (0.89, 1.13) Lag 1: 1.08 (0.96, 1.22) >10 morning PEF decrease Lag 0: 1.02 (0.89, 1.16) Lag 1: 1.00 (0.87, 1.15) >10% evening PEF decrease Lag 0: 1.10 (0.97, 1.25) Lag 1: 1.06 (0.93, 1.21) With BHR and low IgE (n = 67) LRS Lag 0: 0.72 (0.41, 1.28) Lag 1: 1.03 (0.56, 1.91) URS Lag 0: 0.82 (0.62, 1.09) Lag 1: 0.84 (0.64, 1.12) >10% morning PEF decrease Lag 0: 0.74 (0.51, 1.07) Lag 1: 0.96 (0.67, 1.37) >10% evening PEF decrease Lag 0: 1.23 (0.88, 1.73) Lag 1: 1.32 (0.96, 1.82)

TABLE AX5.1 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH RESPIRATORY MORBIDITY IN FIELD/PANEL STUDIES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean SO_2 Levels	Copollutants Considered	Findings & Interpretation	Effect Estimates (95% CI)
EUROPE (cont'd)					
Boezen et al. (1999) (cont'd)					With BHR and low IgE (n = 67) LRS Lag 0: 0.72 (0.41, 1.28) Lag 1: 1.03 (0.56, 1.91) URS Lag 0: 0.82 (0.62, 1.09) Lag 1: 0.84 (0.64, 1.12) >10% morning PEF decrease Lag 0: 0.74 (0.51, 1.07) Lag 1: 0.96 (0.67, 1.37) >10% evening PEF decrease Lag 0: 1.23 (0.88, 1.73) Lag 1: 1.32 (0.96, 1.82) No BHR and high IgE (n = 104) LRS Lag 0: 1.44 (1.17,1.77) Lag 1: 1.28 (1.00, 1.64) Lag 2: (1.38 (1.08, 1.77) 5-day mean: 2.49 (1.54, 4.04) URS Lag 0: 0.98 (0.84, 1.14) Lag 1: 1.01 0.87, 1.18) >10% morning PEF decrease Lag 0: 0.92 (0.79, 1.08) Lag 1: 1.03 (0.89, 1.21) >10% evening PEF decrease Lag 0: 1.00 (0.85, 1.17) Lag 1: 1.05 (0.90, 1.23)

TABLE AX5.1 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH RESPIRATORY MORBIDITY IN FIELD/PANEL STUDIES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean SO_2 Levels	Copollutants Considered	Findings & Interpretation	Effect Estimates (95% CI)
EUROPE (cont'd)					
Boezen et al. (2005) Meppel, Nunspeet, Amsterdam, The Netherlands two winters 1993-1995	Panel study of 327 elderly patients (50 to 70 yrs) to determine susceptibility to air pollution by airway hyperresponsiveness (AHR), high total immunoglobulin (IgE), and sex. Methacholine challenges were performed and subjects with greater than or equal to 20% fall in FEV_1 after inhalation of up to 2.0 mg methacholine were considered AHR+. Subjects with total serum IgE > 20 kU/L were defined as high total IgE (IgE+). Twice daily PEF measurements and daily symptoms recorded for 3 mos. Data analysis performed using logistic regression with modeling of first-order autocorrelation in the residuals that adjusted for daily minimum temperature, time trend, weekend/holidays and influenza incident for the rural and urban areas and the two winters separately. Subjects were classified as IgE+ AHR+, IgE+ AHR−, IgE− AHR+ or IgE− AHR+. Examined effects of pollutants on the same day, Lag 1, Lag 2 and the 5-day mean concentration of Lag 0 to Lag 4 preceding that day. Groups that had effect estimates for PM_{10}, BS, SO_2, and NO_2 that were outside the 95% CI of the effect estimates for the AHR−/IgE− (control group) were considered to have increased susceptibility to air pollution.	24-h mean SO_2 ($\mu g/m^3$) in winter Winter 1993/1994 Urban: Mean: 11.8 $\mu g/m^3$ Median: 10.2 Range: 2.7, 33.5 Rural: Mean: 8.2 Median: 4.4 Range: 0.8, 41.5 Winter 1994/1995 Urban: Mean: 8.3 Median: 7.4 Range: 0.6, 24.4 Rural: Mean: 4.3 Median: .7 Range: 0.5, 17.0	PM_{10} BS NO_2	No consistent associations between the prevalence of LRS or >10% fall in evening PEF and air pollution in any of the four groups. In the AHR+/IgE group, the prevalence of URS was associated with SO_2 at 1 day Lag, and the prevalence of >10% fall in morning PEF with SO_2 at Lag 1, Lag 2 and 5-day mean (avg of Lag 0 to Lag 4). For females who were AHR+/IgE+, the prevalence of >10% fall in PEF was associated with SO_2 Lag 1, Lag 2 and 5-day mean. In subjects with AHR−/IgE+ the prevalence of URS was associated with SO_2 the previous day and the mean of Lag 0 to Lag 4. The effect estimate was outside the 95% CI of	Odds ratio (per 10 $\mu g/m^3$ SO_2) AHR−/IgE− URS Lag 0: 0.99 (0.93, 1.05) Lag 1: 1.02 (0.97, 1.08) Cough: Lag 0: 1.03 (0.98, 1.08) Lag 1: 0.97 (0.93, 1.02) >10% fall in morning PEF Lag 1: 1.00 (0.92, 1.08) AHR−/IgE+ URS Lag 0: 0.98 (0.92, 1.03) Lag 1: 1.07 (1.01, 1.12) 5-day mean 1.15 (1.02, 1.29), OR outside 95% CI of control group Cough: Lag 0: 1.01 (0.95, 1.07) Lag 1: 1.02 (0.96, 1.08) >10 % fall in morning PEF Lag 1: 1.00 (0.92, 1.08) AHR+/IgE− Lag 0: 1.05 (0.94, 1.17) Lag 1: 1.07 (0.96, 1.19) Cough: Lag 0: 1.03 (0.95, 1.12) Lag 1: 1.01 (0.93, 1.09)

TABLE AX5.1 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH RESPIRATORY MORBIDITY IN FIELD/PANEL STUDIES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean SO_2 Levels	Copollutants Considered	Findings & Interpretation	Effect Estimates (95% CI)
EUROPE (cont'd)					
Boezen et al. (2005) (cont'd)				The estimate for the control group AHR−/IgE−. No consistent positive associations found between prevalences of URS, cough or >10% fall in morning PEF and air pollutants in subjects with AHR+/IgE− or AHR−/IgE−. Based on results of the study, authors conclude that subjects with AHR+/IgE+ were the most responsive to air pollution.	>10 % fall in morning PEF Lag 1: 0.99 (0.87, 1.12) 5-day mean: 0.78 (0.61, 0.98), OR outside 95% CI of control group AHR+/IgE+ Lag 0: 1.06 (0.97, 1.15) Lag 1: 1.13 (1.05, 1.23) Cough: Lag 0: 1.02 (0.94, 1.11) Lag 1: 1.02 (0.94, 1.10) >10 % fall in morning PEF Lag 1: 0.99 (0.87, 1.12) AHR+/IgE+ URS Lag 0: 1.06 (0.97, 1.15) Lag 1: 1.13 (1.05, 1.23), OR outside 95% CI of control group Cough: Lag 0: 1.02 (0.94, 1.11) Lag 1: 1.02 (0.94, 1.10) >10 % fall in morning PEF Lag 1: 1.15 (1.04, 1.27), OR outside 95% CI of control group Lag 2 : 1.18 (1.07, 1.30), OR outside 95% CI of control group 5-day mean : 1.26 (1.07, 1.49), OR outside 95% CI of control group

TABLE AX5.1 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH RESPIRATORY MORBIDITY IN FIELD/PANEL STUDIES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean SO_2 Levels	Copollutants Considered	Findings & Interpretation	Effect Estimates (95% CI)
EUROPE (cont'd)					
Cuijpers et al. (1994) Maastricht, the Netherlands Nov-Dec 1990 (baseline) Aug 8-16 (smog episode)	The effects of exposure to summer smog on respiratory health were studied in 535 children (age unspecified). During a smog episode, 212 children were randomly chosen to be reexamined for lung function and symptoms. Only 112 of the children had adequately completed summer questionnaires and were used for the symptom analysis. Lung function measurements made with forced oscillation technique were available for 212 children and valid spirometry was available for 208 children. Corrected baseline lung function compared using paired t test and difference in the prevalence in symptoms during baseline and episode compared.	24-h avg SO_2 Baseline 55 µg/m^3 Summer episode 23 µg/m^3	NO_2 BS O_3 PM_{10} Acid aerosol H^+	Small decrements in FEV_1 and FEF_{25-75} found in the 212 children during the episode compared to baseline. However, there was also a significant decrease in resistance parameters. No increases observed in the prevalence of acute respiratory symptoms.	Change in lung function and impedance between baseline and smog episode: FEV_1: −0.032 L (SD 0.226), $p <= 0.05$ FEF_{25-75}: −0.086 L/s (SD 0.415), $p <= 0.01$ Resistance at 8 Hz: −0.47 cm H_2O (L/s) (SD 1.17), $p <= 0.05$
Hoek and Brunekreff (1995) Deurne and Enkhuizen, The Netherlands Mar-Jul 1989	Panel study of 300 children (7-11 yrs) to examine the effects of photochemical air pollution on acute respiratory symptoms. Occurrence of respiratory symptoms recorded by parents in daily diary. Symptoms included cough, shortness of breath, upper and lower respiratory symptoms, throat and eye irritation, headache and nausea. Association of symptom prevalence and incidence assessed using first order autoregressive, logistic regression model.	Daily concentration of $SO_2 < 43$ µg/m^3	O_3 PM_{10} SO_4^{2} NO_3^-	Same day concentrations of SO_2 and NO_2 not associated with symptom prevalence.	No effect estimates for SO_2 provided

TABLE AX5.1 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH RESPIRATORY MORBIDITY IN FIELD/PANEL STUDIES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean SO_2 Levels	Copollutants Considered	Findings & Interpretation	Effect Estimates (95% CI)
EUROPE (cont'd)					
Kopp et al. (1999) Two towns in Black Forest, Germany Villingen and Freudenstadt Mar-Oct 1994	Panel study of 170 children (median age 9.1 yrs) to investigate nasal inflammation and subsequent adaptation after ambient ozone exposures. Nasal lavage was sampled over 11 time points, and skin prick tests performed. Nasal lavage samples were analyzed for eosinophil cationic protein, albumen, and leukocytes as markers of nasal inflammation. To avoid confounding with allergens, the study population was restricted to only children with no positive reaction to any of the tested inhalant allergens. GEE used in analysis.	Mean SO_2 (mg/m^3) Villingen Mean: 3 5%: 0 95%: 9 Freudenstadt Mean: 3 5%: 0 95%: 9	O_3, NO_2, TSP, PM_{10}	Results for only O_3. Authors noted that since there were very low concentrations of NO_x and SO_2, the confounding effects of these components in ambient air were negligible. Eosinophil cationic protein and leukocyte levels peaked after the first increase in ambient ozone levels.	

TABLE AX5.1 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH RESPIRATORY MORBIDITY IN FIELD/PANEL STUDIES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean SO_2 Levels	Copollutants Considered	Findings & Interpretation	Effect Estimates (95% CI)
EUROPE (cont'd)					
Peters et al. (1996) Erfurt and Weimar, former German Democratic Republic; Sokolov, Czech Republic Sept 1990 to June 1992	Panel study of 102 adult (32 to 80 yrs) and 155 children (7 to 15 yrs) with asthma from the former German Democratic Republic and Czech Republic to investigate the acute effects of winter type air pollution on symptoms, medication intake and PEF. Used regression analyses and distributed Lag models.	Winter 1990/1991 Erfurt Mean: 125 µg/m^3, Max: 564 µg/m^3, IQR: 113 µg/m^3 Weimar Mean: 236 µg/m^3, Max: 1018 µg/m^3, IQR: 207 µg/m^3 Sokolov Mean: 90 µg/m^3, Max: 492 µg/m^3, IQR: 94 µg/m^3 Winter 1991/1992 Erfurt Mean: 96 µg/m^3, Max: 462 µg/m^3, IQR: 80 µg/m^3 Weimar Mean: 153 µg/m^3, Max: 794 µg/m^3, IQR: 130 µg/m^3 Sokolov Mean: 71 µg/m^3, Max: 383 µg/m^3, IQR: 66 µg/m^3	TSP, PM_{10}, SO_4, PSA (particle strong acidity)	5-day mean concentration of SO_2 associated with PEF and symptoms in children (combined analysis from former German Democratic Republic and Czech Republic). Correlation coefficient between SO_2 and TSP in Erfurt was r = 0.8, 0.9 during both winters and in Weimar during the first winter. Correlation with TSP in Sokolov and in Weimar during the second winter was r = 0.4, 0.5.	Combined analysis for children Change in PEF Concurrent day 0.18 (−0.44, 0.09) per 133 µg/m^3 5-day mean −.90 (−1.35, −0.46) per 128 µg/m^3 Change in symptom score Concurrent day −0.1 (−5.9, 5.7) per 133 µg/m^3 5-day mean 14.7 (0.8, 28.6) per 128 µg/m^3 Combined analysis for adults Change in PEF Concurrent day −0.20 (−0.53, 0.12) per 133 µg/m^3 5-day mean −0.28 (−0.72, 0.16) per 128 µg/m^3

TABLE AX5.1 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH RESPIRATORY MORBIDITY IN FIELD/PANEL STUDIES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean SO_2 Levels	Copollutants Considered	Findings & Interpretation	Effect Estimates (95% CI)
EUROPE (cont'd)					
Pinter et al. (1996) Tata Area, Hungary winter mos between Dec 1993-Mar 1994	Longitudinal (children <14 yrs) and cross-sectional study (9 to 11 yrs) to examine air pollution and respiratory morbidity in children. In the longitudinal prospective study, respiratory morbidity was evaluated daily and on a weekly basis. In cross-sectional study, anthropometric parameters, physical status, pulse and blood pressure, lung function parameters, eosinophils in the nasal smear, hematological characteristics and urinary excretion of some metabolites were examine and measured. Anova and linear regression used in analysis.	Mean SO_2 exceeded the limit of yearly avg 150 µg/m^3 Daily peaks reached as high as 450 µg/m^3 No specific values given	NO_2	Significant correlation between SO_2 levels and acute daily respiratory morbidity, but no correlation with weekly incidence. Authors stated that in the cross-sectional study, almost all health parameters were impaired but no results were shown.	Results only provided in graph. No p-values provided

TABLE AX5.1 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH RESPIRATORY MORBIDITY IN FIELD/PANEL STUDIES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean SO_2 Levels	Copollutants Considered	Findings & Interpretation	Effect Estimates (95% CI)
EUROPE (cont'd)					
Roemer et al. (1993) Wageningen and Bennekom, Netherlands	Panel of 73 children (mean age 9.3 yrs, range 6 to 12 yrs) with chronic respiratory symptoms to investigate effects of winter air pollution on lung function, symptoms and medication use. Subjects performed twice-daily PEF measurements, largest of three PEF readings used in regression analysis. Both incidence and prevalence of symptoms analyzed, using logistic regression.	Daily concentrations of SO_2 shown in graph Highest 24-h avg concentration SO_2: 105 µg/m^3	NO_2 PM_{10} BS	Positive association between incidence of phlegm and runny nose with SO_2 on the same day. Significant association also found between evening PEF and SO_2 on, the same day, previous day and 1 wk (avg of same day and 6 days before). The use of bronchodilators also associated with SO_2. Correlation with copollutants: NO_2: r = 0.26 PM_{10}: r = 0.65 BS: r = 0.63	Mean of individual regression coefficient Morning PEF Same day: −0.021 (0.024) Lag 1: −0.024 (0.031) Wk: −0.50 (0.069) Evening PEF Same day: −0.048 (0.018) p < 0.05 Lag 1: −0.039 (0.021) p < 0.10 Wk: −0.110 (0.055) p < 0.05 Prevalence of symptoms (per 50 µg/m^3 SO_2) Asthma attack Same day: 0.008 (0.012) Lag 1: 0.016 (0.011) 1 wk: 0.058 (0.027) p < 0.05 Wheeze Same day: 0.033 (0.17) p < 0.10 Lag 1: 0.042 (0.016) p < 0.05 Wk: 0.069 (0.032) p < 0.05 Waken with symptoms Same: day 0.033 (0.019) p < 0.10 Lag 1: 0.032 (0.018) p < 0.10 Wk: 0.058 (0.045) Shortness of breath Same: day 0.029 (0.016) p < 0.10 Lag 1: 0.016 (0.015) Wk: 0.044 (0.035)

TABLE AX5.1 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH RESPIRATORY MORBIDITY IN FIELD/PANEL STUDIES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean SO_2 Levels	Copollutants Considered	Findings & Interpretation	Effect Estimates (95% CI)
EUROPE (cont'd)					
Roemer et al. (1993) (cont'd)					Cough Same day 0.018 (0.025) Lag 1: 0.012 (0.023) Wk 0.072 (0.066) Runny nose Same day 0.070 (0.026) $p < 0.05$ Lag 1: −0.11 (0.025) Wk 0.153 (0.074) $p < 0.05$ Phlegm Same day 0.011 (0.022) Lag 1: 0.014 (0.020) Wk −0.005 (0.056)
Roemer et al. (1998) 14 European Centers: Umea, Sweden; Malmo, Sweden; Kuopi, Finland; Oslo, Norway; Amsterdam , The Netherlands; Berlin, Germany; Katowice, Poland; Cracow, Poland; Teplice, Czech Republic; Prague, Czech Republic; Budapest, Hungary; Pisa, Italy; Athens, Greece Winter 1993-1994	Multicenter panel study of the acute effects of air pollution on respiratory health of 2010 children (aged 6 to 12 yrs) with chronic respiratory symptoms. Results from individual centers were reported by Kotesovec et al. (1998), Kalandidi et al. (1998), Haluszka et al. (1998), Forsberg et al. (1998), Clench-Aas et al. (1998), and Beyer et al. (1998). Calculated effect estimates of air pollution on PEF or the daily prevalence of respiratory symptoms and bronchodilator use from the panel-specific effect estimates	Range: –2.7 µg/m^3 (Umea, urban), 113.9 µg/m^3 (Prague, urban)	PM_{10}, BS NO_2	No clear associations between PM_{10}, BS, SO_2, or NO_2 and morning PEF, evening PEF, prevalence of respiratory symptoms, or bronchodilator use could be detected. Previous day PM_{10} was negatively associated with evening PEF, but only in locations where BS was high compared to PM_{10} concentrations. No consistent differences in effect estimates between subgroups based on urban versus suburban, geographical location or mean levels of PM_{10}, BS, SO_2, and NO_2.	Combined effect estimates with 95% CI of air pollution on PEF Morning Lag 0: 0.2 (−0.2, 0.6) Lag 1: 0.2 (−0.2, 0.6) Lag 2: 0.6 (0.2, 1.0) 7-day mean 0.6 (−1.3, 2.5) Afternoon Lag 0: 0.1 (−0.3, 0.5) Lag 1: 0.0 (−0.4, 0.4) Lag 2: 0.1 (−0.4, 0.6) 7-day mean 0.2 (−0.5, 0.9)

TABLE AX5.1 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH RESPIRATORY MORBIDITY IN FIELD/PANEL STUDIES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean SO_2 Levels	Copollutants Considered	Findings & Interpretation	Effect Estimates (95% CI)
EUROPE (cont'd)					
Taggart et al. (1996) Runcorn and Widnes in NW England Jul-Sep 1993	Panel study of 38 nonsmoking asthma subjects (18 to 70 yrs) to investigate the relationship between asthmatic bronchial hyperresponsiveness and pulmonary function (PEF, FEV_1, FVC) and summertime ambient air pollution. Used univariate nested (hierarchical) analysis of variance to test hypothesis that BHR or spirometry measurements varied with air pollution levels. Analysis was limited to within-subject variation of (BHR, FEV_1, or FVC).	24-h avg SO_2 Max: 103.7 µg/m^3	NO_2 O_3 smoke	No association between SO_2 and FEV_1 or FVC. Changes in BHR correlated significantly with changes in 24-h mean SO_2, NO_2, and smoke. Correlation with copollutants: O_3: r = 0.13 NO_2: r = 0.65 Smoke: r = 0.48	Percentage change in BHR per 10 µg/m^3 SO_2 24-h mean SO_2 −6.3 % (−13.6, 0.6) 48-h mean −2.9 % (−12.8, 8.2) 24-h Lag 7.4 % (−4.5, 20.8)

TABLE AX5.1 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH RESPIRATORY MORBIDITY IN FIELD/PANEL STUDIES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean SO_2 Levels	Copollutants Considered	Findings & Interpretation	Effect Estimates (95% CI)	
EUROPE (cont'd)						
Ward et al. (2002) Birmingham and Sandwell, England Jan-Mar 1997 May-Jul 1997	Panel study of 162 children (9 yrs at time of enrollment) from two inner city locations to investigate the association between ambient acid species with PEF and symptoms. Daily symptoms and twice-daily peak flow measurements were recorded over 8 wk periods in the summer and winter. 39 of the children reported wheezing in the past 12 mos. Linear regression used for PEF and logistic regression for symptoms.	24-h avg SO_2 Winter: Jan 13-Mar 10, 1997 Median: 5.4 ppb Range: 2, 18 ppb Summer: May 19-July 14, 1997 Median: 4.7 ppb Range: 2, 10 ppb	NO_2 O_3 PM_{10} H^+ Cl^- HCL HNO_3 NH_3 NH_4^+ NO_3^- SO_4^{2-}	In the summer, changes in morning PEF were associated with SO_2 at 3-days lag and the 7-day mean SO_2. Prevalence of cough associated with SO_2 on the same day. In the winter SO_2 was only associated with symptom of feeling ill on the same day.	24-h avg SO_2 (per 4.0 ppb in winter; per 2.2 ppb in summer) Data also available for 3-,4-, and 7-day Lag Change in PEF (L/min) Morning- Lag 0-day Winter −0.60 (−2.51, 1.32) Summer 0.91 (−0.95, 2.78) Afternoon- Lag 0-day Winter −0.32 (−2.71, 2.04) Wummer −0.89 (−2.61, 0.83) Odds ratio for symptoms Cough-Lag 0-day Winter 0.92 (0.81, 1.05) Summer 1.08 (1.02, 1.15) Ill-Lag 0-day Winter 1.09 (1.01, 1.18) Summer 1.05 (0.96, 1.14) Shortness of breath-Lag 0-day Winter 1.02 (0.93, 1.13) Summer 0.98 (0.87,1.10)	Morning- Lag 1-day Winter 0.08 (−1.67,1.86) Summer 0.29 (−1.56, 2.14) Afternoon- Lag 1-day Winter −0.88 (−2.87, 1.10) Summer −0.02 (−1.68, 1.65) Cough-Lag 1-day Winter 1.00 (0.87, 1.15) Summer 1.04 (0.97, 1.11) Ill-Lag 1-day Winter 1.03 (0.95, 1.11) Summer 1.02 (0.94, 1.12) Shortness of breath-Lag 1-day Winter 1.00 (0.90, 1.09) Summer 1.00 (0.89, 1.13)

TABLE AX5.1 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH RESPIRATORY MORBIDITY IN FIELD/PANEL STUDIES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean SO_2 Levels	Copollutants Considered	Findings & Interpretation	Effect Estimates (95% CI)	
EUROPE (cont'd)						
Ward et al. (2002) (cont'd)					Wake at night with cough- Lag 0 day Winter 1.00 (0.91, 1.10) Summer 1.00 (0.87, 1.14)	Wake at night with cough- Lag 1 day Winter 1.05 (0.96, 1.15) Summer 1.02 (0.89, 1.16)
					Wheeze- Lag 0 day Winter 0.96, (0.85, 1.07) Summer 1.05 (0.92, 1.19)	Wheeze-Lag 1 day Winter 0.96 (0.86, 1.07) Summer 1.00 (0.88, 1.13
					Summer change in PEF 2.7 (1.03, 4.38) per 2.2 ppb SO_2 Lag 3 days ($p < 0.05$)	
					Summer change in PEF 6.83 (0.98, 12.69) per 2.2 ppb SO_2 Lag 0-6 days ($p < 0.05$)	

TABLE AX5.1 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH RESPIRATORY MORBIDITY IN FIELD/PANEL STUDIES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean SO_2 Levels	Copollutants Considered	Findings & Interpretation	Effect Estimates (95% CI)
EUROPE (cont'd)					
van der Zee et al. (1999) Netherlands, 3 winters from 1992 to 1995 Rotterdam and Bodegrven/Reeuwijk (1992-1993) Amsterdam and Meppel (1993-1994) Amsterdam and Nunspeet (1994-1995)	Panel study of 633 children (aged 7 to 11 yrs) with and without chronic respiratory symptoms, living in urban and nonurban areas in the Netherlands. Volunteers measured daily PEF and reported the occurrence of respiratory symptoms and bronchodilator use in a diary. Association between air pollution and decrements in PEF, symptoms and bronchodilator use evaluated with logistic regression models that adjusted for first order autocorrelation, min daily temperature, day of wk, time trend, incidence of influenza and influenza-like illness.	Median and max 24-h mean concentration ($\mu g/m^3$) 1992-1993 Urban 23 (152); Nonurban 8.9 (43) 1993-1994 Urban 11 (34); Nonurban 5.0 (42) 1994-1995 Urban 6.0 (24); Nonurban 3.6 (17)	PM_{10} Black smoke Sulfate NO_2	The correlation between SO_2 and PM varied from 0.5 to 0.8 during first two winters. Correlation with NO_2 about 0.50. In the urban areas, SO_2 was associated with >10% decrements in evening PEF, LRS and use of bronchodilator in children with symptoms. Most consistent associations found with PM_{10}, BS, and sulfate. No association found between SO_2 and prevalence of URS, cough, phlegm, and >10% decrements in morning PEF. In the nonurban areas, no associations found with SO_2. In children without symptoms, no consistent associations with SO_2. Authors concluded that children with symptoms are more susceptible to particulate air pollution effects and that use of medication for asthma did not prevent the adverse effects of PM in children with symptoms.	Odds ratio (per 40 $\mu g/m^3$ SO_2) Children with symptoms Urban areas Evening PEF Lag 0: 1.32 (0.96, 1.80) Lag 1: 0.83 (0.60, 1.14) Lag 2: 1.67 (1.28, 2.19) Symptoms of lower respiratory tract Lag 0: 1.35 (1.01, 1.79) Lag 1: 1.23 (0.93, 1.64) Symptoms of upper respiratory tract Lag 0: 0.97 (0.82, 1.14) Lag 1: 1.10 (0.94, 1.28) Cough Lag 0: 0.90 (0.77, 1.05) Lag 1: 1.12 (0.96, 1.30) Use of bronchodilator Lag 0: 0.92 (0.72, 1.18) Lag 1: 1.45 (1.13, 1.86) Nonurban areas Evening PEF Lag 0: 1.20 (0.91, 1.58) Lag 1: 0.89 (0.68, 1.17) Symptoms of lower respiratory tract Lag 0: 0.91 (0.69, 1.19) Lag 1: 0.91 (0.69, 1.22) Symptoms of upper respiratory Lag 0: 0.94 (0.81, 1.09) Lag 1: 0.97 (0.83, 1.13) 5-day mean: 0.67 (0.47, 0.94) Cough Lag 0: 1.08 (0.94, 1.23) Lag 1: 0.98 (0.85, 1.12) Use of bronchodilator Lag 0: 0.86 (0.59, 1.25) Lag 1: 1.18 (0.80, 1.74)

TABLE AX5.1 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH RESPIRATORY MORBIDITY IN FIELD/PANEL STUDIES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean SO_2 Levels	Copollutants Considered	Findings & Interpretation	Effect Estimates (95% CI)	
EUROPE (cont'd)						
van der Zee et al. (1999) (cont'd)					Odds ratio (per 40 µg/m^3 SO_2) Children without symptoms	
					Urban areas	Nonurban areas
					Evening PEF Lag 0: 1.13 (0.88, 1.47) Lag 1: 1.16 (0.90, 1.50)	Evening PEF Lag 0: 1.10 (0.87, 1.39) Lag 1: 1.07 (0.85, 1.35)
					URS Lag 0: 0.92 (0.76, 1.11) Lag 1: 1.10 (0.91, 1.34) Lag 2: 0.83 (0.70, 0.99)	URS Lag 0: 1.07 (0.92, 1.25) Lag 1: 0.85 (0.72, 1.00)
					Cough Lag 0: 0.93 (0.78, 1.11) Lag 1: 1.02 (0.84, 1.23)	Cough Lag 0: 0.86 (0.76, 0.97) Lag 1: 0.95 (0.83, 1.08)

TABLE AX5.1 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH RESPIRATORY MORBIDITY IN FIELD/PANEL STUDIES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean SO_2 Levels	Copollutants Considered	Findings & Interpretation	Effect Estimates (95% CI)	
EUROPE (cont'd)						
van der Zee (2000) Netherlands, 3 winters from 1992 to 1995 Rotterdam 1992-1993	Panel study of 489 adults (aged 50 to 70 yrs) with and without chronic respiratory symptoms, living in urban and nonurban areas in the Netherlands. Volunteers measured daily PEF and reported the occurrence of respiratory symptoms and bronchodilator use in a diary. Association between air pollution and decrements in PEF, symptoms and bronchodilator use evaluated with logistic regression models that adjusted for first order autocorrelation, min daily temperature, day of wk, time trend, incidence of influenza and influenza-like illness.	Median (max) conc 1992/1993: Urban 25 (61) µg/m^3 1993/1994 Urban 11 (34) µg/m^3, Nonurban 5.0 (42) µg/m^3 1994/1995 Urban 6.0 (24), Nonurban 3.6 (17) µg/m^3	PM_{10} BS Sulfate NO_2	Among symptomatic adults living in urban areas, the prevalence of >20% decrement in morning PEF was associated with SO_2. Moreover, there were no associations found with prevalence of bronchodilator use, LRS, >10% decrement in morning PEF and >10% and >20% decrement in evening PEF. In the nonurban areas, there was no consistent association between air pollution and respiratory health. In the nonsymptomatic adults, no consistent associations observed between health effects and air pollutants, but a significant and positive association was observed with URS in the nonurban area at 1 day Lag. Range of Spearman correlation coefficients between 24-h avg conc SO_2 and copollutants : PM_{10}: 0.31, 0.78 BS: 0.21, 0.75 Sulfate: 0.29, 0.69 NO_2: 0.47, 0.51	Odds ratio (per 40 µg/m^3 SO_2) symptomatic adults In urban areas >10% decline in PEF Morning Lag 0: 0.86 (0.60, 1.23) Lag 1: 0.97 (0.68, 1.39) >20% decline in PEF Morning Lag 0: 1.33 (0.66, 2.71) Lag 1: 1.98 (1.03-3.79) LRS Lag 0: 1.01 (0.84, 1.20) Lag1: .97 (0.82, 1.16) 5-day mean: 0.71 (95% CI: 0.53 to 0.95) URS Lag 0: 1.15 (0.97, 1.37) Lag 1: 1.06 (0.90, 1.26) Bronchodilator use Lag 0: 1.09 (0.93, 1.28) Lag 1: 1.05 (0.89, 1.24) Lag 2: 0.85 (0.72, 0.99)	 In nonurban areas >10 % decline in PEF Morning Lag 0: 79 (0.48, 1.29) Lag 1: 1.08 (0.68, 1.72) >20% decline in PEF Morning Lag 0: 0.79 (0.22, 2.88) Lag 1: 71 (0.13, 4.02) LRS Lag 0: 1.11 (0.94, 1.30) Lag 1: 1.04 (0.88, 1.22) URS Lag 0: 0.97 (0.79, 1.20) Lag 1: 1.20 (0.98, 1.47) Bronchodilator use Lag 0: 1.04 (0.91, 1.18) Lag 1: 1.08 (0.95, 1.22)

TABLE AX5.1 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH RESPIRATORY MORBIDITY IN FIELD/PANEL STUDIES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean SO_2 Levels	Copollutants Considered	Findings & Interpretation	Effect Estimates (95% CI)	
EUROPE (cont'd)						
van der Zee (2000) (cont'd)					Nonsymptomatic adults	
					Urban areas	Nonurban areas
					>10% decline in PEF Morning Lag 0: 0.77 (0.39, 1.52) Lag 1: 0.94 (0.51, 1.73)	>10% decline in PEF Morning Lag 0: 2.12 (0.98, 4.62) Lag 1: 0.87 (0.38, 1.99) Lag 2: 0.13 (0.04, 0.36) 5-day mean: 0.03 (0.00, 0.24)
					URS Lag 0: 1.10 (0.81, 1.48) Lag 1: 1.23 (0.92, 1.65)	URS Lag 0: 0.73 (0.49, 1.07) Lag 1: 1.71 (1.18, 2.46) Lag 2: 0.65 (0.44, 0.97)

TABLE AX5.1 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH RESPIRATORY MORBIDITY IN FIELD/PANEL STUDIES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean SO_2 Levels	Copollutants Considered	Findings & Interpretation	Effect Estimates (95% CI)
EUROPE (cont'd)					
Desqueyroux et al. (2002) Paris, France Nov 1995-Nov 1996	Panel study of 60 patients with moderate to severe physician-diagnosed asthma (mean age 55 yrs). Asthma attacks were noted by physician at each consultation (regular or emergency). Asthmatic attacks defined as need to increase twofold the dose of beta2 agonist.	24-h avg SO_2 Summer 7 (5) µg/m^3 Range: 2, 27 Winter 19 (12) µg/m^3 Range: 3, 81	PM_{10} NO_2 O_3	No association between asthma attacks and SO_2 for any Lag or season.	Mean 24-h SO_2 (per 10 µg/m^3) OR on incident of asthma attacks Lag 1: day 0.98 (0.76, 1.27) Lag 2: day 0.92 (0.72, 1.19) Lag 3: day 1.01 (0.82, 1.23) Lag 4: day 1.01 (0.86, 1.19) Lag 5: day 1.05 (0.85, 1.29) Cumulative exposure mean (−1 to −5 days) 0.99 (0.76, 1.30)
Forsberg et al. (1993) Pitea, Northern Sweden March to April	Panel study of 31 asthmatic patients (9 to 71 yrs) to assess relationship between daily occurrence of asthma symptoms and fluctuations in air pollution and meteorological conditions. Subjects recorded symptoms (shortness of breath, wheezing, cough, and phlegm) for 14 consecutive days.	24-h avg SO_2 (µg/m^3) Mean: 5.7 Range: 1.3, 12.9	NO_2, BS	No significant association observed with SO_2. Positive association between severe shortness of breath and black smoke. Correlation with copollutants: NO_2: r = 0.24 BS: r = 0.70	Regression coefficient and 90% CI Subjects with shortness of breath (n = 28) 0.0345 (−0.49, 0.118) Subjects with 5 or more incident episodes of severe shortness of breath (n = 10) −0.0266 (−0.140, 0.087)

TABLE AX5.1 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH RESPIRATORY MORBIDITY IN FIELD/PANEL STUDIES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean SO_2 Levels	Copollutants Considered	Findings & Interpretation	Effect Estimates (95% CI)	
EUROPE (cont'd)						
Higgins et al. (1995) United Kingdom	Panel study of 75 patients with physician diagnosed asthma or chronic bronchitis (mean age 50, range 18 to 82 yrs) to determine if air pollution affects respiratory function and symptoms. Subjects asked to keep symptom records and perform PEF for 28 days. PEF values recorded every 2 h beginning at 02.00 our each day. Methacholine challenge performed on each subjects. Those with PM_{20} FEV_1 of <12.25 µmol were considered as methacholine reactors. PEF variability was calculated as the amplitude % mean: (highest-lowest PEF value/mean) ×100. 75 patients had PEF records, 65 completed symptom questionnaires.	Maximum 24-h SO_2 117 µg/m^3	O_3 NO_2	The amplitude % mean was significantly associated with increasing levels of SO_2, on the same day for all subjects and among reactors. Mean daily PEF and minimum PEF associated with SO_2 among reactors only. Significant associations also observed with wheeze and SO_2 on the same day, at 24-h Lag, and 48-h Lag for all subjects and meta-choline reactors; and with bronchodilator use for all subjects at 24-h Lag.	Regression coefficient per 10 µg/m^3 SO_2 All subjects Mean PEF (L/min) Same day −0.021 (0.031) 24-h Lag 0.003 (0.033) 48-h Lag 0.021 (0.032) Minimum PEF(L/min) Same day −0.062 (0.039) 24-h Lag −0.048 (0.041) 48-h Lag −0.001 (0.040)	Reactors Mean PEF (l/min) Same day −0.087 (0.054) 24-h Lag −0.44 (0.058) 48-h Lag 0.012 (0.057) Minimum PEF(L/min) Same day −0.168 (0.071) 24-h Lag −0.078 (0.076) 48-h Lag −0.026 (0.075)

TABLE AX5.1 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH RESPIRATORY MORBIDITY IN FIELD/PANEL STUDIES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean SO_2 Levels	Copollutants Considered	Findings & Interpretation	Effect Estimates (95% CI)	
EUROPE (cont'd)						
Higgins et al. (1995) (cont'd)					Amplitude (% mean) Same day: 0.167 (0.072) 24-h Lag 0.191 (0.76) 48-h Lag 0.022 (0.075)	Amplitude (% mean) Same day: 0.157 (0.120) 24-h Lag 0.083 (0.127) 48-h Lag 0.005 (0.126)
					Wheeze Same day: 1.14 (1.03, 1.26) 24-h Lag 1.22 (1.09, 1.37) 48-h Lag 1.14 (1.02, 1.27)	Wheeze Same day: 1.26 (1.08, 1.47) 24-h Lag 1.57 (1.30, 1.89) 48-h Lag 1.24 (1.06, 1.45)
					Dyspnoea Same day: 1.03 (0.94, 1.14) 24-h Lag 1.07 (0.96, 1.18) 48-h Lag 0.94 (0.85, 1.05)	Dyspnoea Same day: 1.04 (0.90, 1.20) 24-h Lag 1.17 (1.00, 1.37) 48-h Lag 1.03 (0.89, 1.20)
					Cough Same day: 1.03 (0.95, 1.12) 24-h Lag 1.04 (0.95, 1.13) 48-h Lag 1.02 (0.94, 1.12)	Cough Same day: 1.09 (0.96, 1.24) 24-h Lag 1.05 (0.91, 1.20) 48-h Lag 1.00 (0.87, 1.15)

TABLE AX5.1 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH RESPIRATORY MORBIDITY IN FIELD/PANEL STUDIES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean SO_2 Levels	Copollutants Considered	Findings & Interpretation	Effect Estimates (95% CI)	
EUROPE (cont'd)						
Higgins et al. (1995) (cont'd)					Throat symptoms Same day: 1.01 (0.92, 1.11) 24-h Lag 1.00 (0.91, 1.10) 48-h Lag 0.96 (0.87, 1.06)	Throat symptoms Same day: 1.06 (0.92, 1.21) 24-h Lag 1.06 (0.91, 1.23) 48-h Lag 1.01 (0.87, 1.17)
					Eye symptoms Same day: 1.08 (0.97, 1.20) 24-h Lag 1.11 (0.99, 1.24) 48-h Lag 1.10 (0.99, 1.21)	Eye symptoms Same day: 1.19 (1.01, 1.40) 24-h Lag 1.21 (1.01, 1.45) 48-h Lag 1.08 (0.91, 1.28)
					Bronchodilator use Same day 1.11 (0.97, 1.26) 24-h Lag 1.16 (1.01, 1.34) 48-h Lag 1.12 (0.98, 1.27)	Bronchodilator use Same day 1.18 (0.99, 1.42) 24-h Lag 1.23 (1.02, 1.50) 48-h Lag 1.31 (1.09, 1.58)

TABLE AX5.1 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH RESPIRATORY MORBIDITY IN FIELD/PANEL STUDIES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean SO_2 Levels	Copollutants Considered	Findings & Interpretation	Effect Estimates (95% CI)
EUROPE (cont'd)					
Hiltermann et al. (1998) Bilthoven, The Netherlands Jul-Oct 1995	Panel study of 60 adult (18 to 55 yrs) nonsmoking patients with intermittent to severe persistent asthma to examine the association of summertime air pollution (ozone and PM_{10}) with respiratory symptoms, medication use and PEF. Subjects were followed over 96 days. Twice daily PEF, respiratory symptoms, and medication use and whether they were exposed to environmental tobacco smoke were recorded daily. Analysis controlled for time trends, aeroallergens, environmental tobacco smoke exposures, day of wk and temperature. Examined Lag effects of 0 to 2 days.	24-h avg SO_2 ($\mu g/m^3$) Mean: 6.2 Range: 0.1, 16.2 Correlation with BS r = 0.53	O_3 PM_{10} NO_2 BS	SO_2 not included in the analysis since levels were negligible during the study period (<17 $\mu g/m^3$) Correlation with copollutants: O_3: r = 0.30 PM_{10}: r = 0.37 NO_2: r = 0.49 BS: r = 0.53	None provided

TABLE AX5.1 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH RESPIRATORY MORBIDITY IN FIELD/PANEL STUDIES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean SO_2 Levels	Copollutants Considered	Findings & Interpretation	Effect Estimates (95% CI)
EUROPE (cont'd)					
Hoek and Brunekreff (1993) Wageningen, The Netherlands	Panel study of 112 children (7 to 12 yrs, non-urban) to assess effects of winter air pollution pulmonary function and respiratory symptoms. Parents filled out symptom diary that was turned in every 2 wks. Pulmonary function test performed by technician every 3 wks. Additional pulmonary function tests performed when SO_2 was predicted to be higher than 125 µg/m^3 or NO_2 >90 µg/m^3.	Daily concentrations presented in graph; Highest 24-h avg conc SO_2: 105 µg/m^3 (air pollution episode)	PM_{10}, BS, NO_2	During the winter episode, pulmonary function of schoolchildren was significantly lower than baseline. Significant negative associations between SO_2 and FVC, FEV_1 and MMEF. No significant associations found with prevalence of respiratory symptoms. Authors noted that it is not clear which components of episode mix responsible for association and that the concentrations of acid aerosol and SO_2 were too low for direct effects to be likely. SO_2 moderately correlated with PM_{10} (r = 0.69) and black smoke (r = 0.63) but not NO_2 (r = 0.28).	Mean of individual regression slopes and SE FVC Same day −0.55 (0.10), p < 0.05 Lag 1: −0.74 (0.15) p < 0.05 1 wk −0.94 (0.20) p < 0.05 FEV_1 Same day −0.51 (0.09) p < 0.05 Lag 1: −0.21 (−0.63) p < 0.05 1 wk −0.78 (0.18) p < 0.05 PEF Same day −0.64 (−0.44) Lag 1: −0.21 (0.63) 1 wk −0.34 (0.81) p < 0.05 MMEF Same day −0.54 (0.20) Lag 1: −0.40 (0.29) 1 wk −0.61 (0.37) Prevalence of acute respiratory symptoms regression coefficient from time-series model and SE Cough Same day 0.02 (0.18) Lag 1: −0.14 (0.19) 1 wk 0.13 (0.76)

TABLE AX5.1 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH RESPIRATORY MORBIDITY IN FIELD/PANEL STUDIES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean SO_2 Levels	Copollutants Considered	Findings & Interpretation	Effect Estimates (95% CI)
EUROPE (cont'd)					
Hoek and Brunekreff (1993) (cont'd)					Upper respiratory symptoms Same day 0.12 (0.16) Lag 1: −0.02 (0.17) 1 wk −0.24 (0.76) Lower respiratory symptoms Same day 0.06 (0.26) Lag 1: −0.11 (0.29) 1 wk −0.54 (0.92) Any respiratory symptoms Same day 0.01 (0.13) Lag 1: −0.03 (0.13) 1 wk −0.11 (0.60)
Lagorio et al. (2006) May 24 to June 24, 1999 and Nov 18 to Dec 22, 1999 Rome, Italy	Panel study of 29 patients with either COPD (n = 11, mean age 67 yrs), asthma (n = 11, mean age 33 yrs) or ischemic heart disease (n = 7, mean age 63 yrs) to evaluate whether daily levels of air pollutants have a measurable impact on lung function in adults with preexisting lung or heart disease.	24-h mean SO_2 ($\mu g/m^3$) Spring mean 4.7 SD 1.8 Winter mean 7.9 SD 2.2 Overall mean 6.4 SD 2.6	$PM_{2.5}$ $PM_{10-2.5}$ PM_{10} CD Cr FE NI PB PT V Zn NO_2 CO O_3	Because avg 24-h concentrations of SO_2 were low and showed little variability, SO_2 was not considered in the analysis Correlation with copollutants: $PM_{2.5}$: r = 0.34 $PM_{10-2.5}$: r = −0.16 PM_{10}: r = 0.21 NO_2: r = 0.01 O_3: r = −0.61 CO: r = 0.65	No data available

TABLE AX5.1 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH RESPIRATORY MORBIDITY IN FIELD/PANEL STUDIES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean SO_2 Levels	Copollutants Considered	Findings & Interpretation	Effect Estimates (95% CI)
EUROPE (cont'd)					
Neukirch et al. (1998) Paris, France Nov 15, 1992 to May 9, 1993	Panel study of 40 nonsmoking, mild to moderate asthmatics (16 to 70 yrs, mean 46) to examine the short-term effects of winter air pollution in asthma symptoms and three daily peak flow measurements. Patients were followed for 23 wks. Used GEE models that controlled for autocorrelation of responses, weather, and time trends. Analysis conducted on entire study population and for subgroup of subjects who took inhaled B2 agonists as needed. Assessed air pollution effect on both incident and prevalence of symptoms, Z-transformed morning PEF and daily PEF variability.	24-h avg SO_2 Mean: 21.7 (13.5) µg/m^3 Range: 4.4, 83.8	NO_2, PM_{13}, Black smoke	Significant effects on incidence and prevalence of symptoms. Effects at Lag days 3-6 and weekly avg exposures. Based on group avg PEF of 407 l/min, a 50 µg/m^3 increase SO_2 caused a maximum decrease in morning PEF of 5.5%. Correlation with copollutants: NO_2: r = 0.54 PM_{13}: r = 0.83 BS: r = 0.89	24-h avg SO_2 (per 50 µg/m^3) Odds ratio: all subjects Incident episodes: Wheeze: Lag 5: 1.66 (1.01, 2.70) Nocturnal cough: Lag 3: 1.60 (0.98, 2.62) Lag 4: 1.71 (0.86, 3.40) Lag 6: 1.72 (1.16, 2.55) Respiratory infections: Lag 3: 3.14 (1.30, 7.59) Lag 4: 2.70 (1.36, 5.37) Lag 5: 2.79 (0.95, 8.21) Wk: 8.52 (1.20, 60.5) Odds ratio: all subjects Prevalent episodes: Wheeze: Lag 5: 1.35 (1.01, 1.81) Lag 6: 1.39 (1.04, 1.87) Wk: 1.64 (0.91, 2.94) Nocturnal cough: Lag 6: 1.34 (1.00, 1.79) Shortness of breath: Wk: 1.56 (1.06, 2.32) Respiratory infections: Lag 4: 2.40 (1.33, 4.33) Lag 5: 2.72 (1.67, 4.44) Lag 6: 2.94 (1.80, 4.79) Wk: 6.30 (1.31, 30.2)

TABLE AX5.1 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH RESPIRATORY MORBIDITY IN FIELD/PANEL STUDIES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean SO_2 Levels	Copollutants Considered	Findings & Interpretation	Effect Estimates (95% CI)
EUROPE (cont'd)					
Neukirch et al. (1998) (cont'd)					Odds ratio: Subjects taking B2 agonists Incident episodes: Asthma attacks: Lag 6: 2.19 (0.91, 5.29) Wheeze: Lag 5: 1.84 (1.13, 3.00) Nocturnal cough: Lag 3: 2.41 (1.47, 3.93 Lag 4: 2.35 (0.88, 6.26) Lag 6: 1.86 (1.14, 3.04) Odds ratio: Subjects taking B2 agonists Prevalent episodes: Asthma attacks: Lag 5: 1.88 (0.95, 3.73) Lag 6: 2.82 (1.57, 5.07) Wheeze: Lag 5: 1.51 (1.02, 2.23) Lag 6: 1.57 (1.06, 2.32) Nocturnal cough: Lag 3: 1.73 (1.06, 2.82) Lag 4: 2.28 (1.27, 4.11) Lag 5: 1.91 (1.17, 3.12) Lag 6: 1.91 (1.17, 3.12)

TABLE AX5.1 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH RESPIRATORY MORBIDITY IN FIELD/PANEL STUDIES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean SO_2 Levels	Copollutants Considered	Findings & Interpretation	Effect Estimates (95% CI)
EUROPE (cont'd)					
Neukirch et al. (1998) (cont'd)					Shortness of breath: Lag 4: 1.81 (1.22, 2.67) Lag 5: 1.65 (1.11, 2.44) Lag 6: 1.61 (1.20, 2.16) Wk: 3.03 (1.26, 7.33) Regression coefficients of the effects and SE (per 1 µg/m^3) Z-transformed morning PEF Lag 5: −0.450 (0.138) p = 0.001 Lag 6: −0.337 (0.164) p = 0.03 PEF daily variability Lag 2: 0.025 (0.013) p = 0.05

TABLE AX5.1 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH RESPIRATORY MORBIDITY IN FIELD/PANEL STUDIES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean SO_2 Levels	Copollutants Considered	Findings & Interpretation	Effect Estimates (95% CI)
EUROPE (cont'd)					
Peacock et al. (2003) Southern England Nov 1, 1996 to Feb 14, 1997	Panel study of 177 children (mean age 10.7 yrs, range 7 to 13) from three schools (two urban and 1 rural location) to investigate effects of winter air pollution on respiratory function. Children were followed for 13 wks. Used two sources of air pollution in the rural area, one that was "locally validated" and the other "nationally validated".	24-h avg SO_2 (ppb) Rural (nationally validated) Mean 5.1 (4.7) Range 0.0, 35.6 Rural (locally validated) Mean 5.4 (5.1) Range 0.0, 39.1 Urban 1 Mean 6.0 (6.0) Range 0.5, 32.5	O_3 NO_2 PM_{10} SO_4	No statistically significant association between winter SO_2 and PEFR, 0.70% decline in PEFR for a 10-ppb increase in the five-day mean concentration of SO_2 (community monitor)	24-h avg SO_2 change in PEF per 1 ppb SO_2 - community monitor Lag 0: 0.05 (−0.05, 0.16) Lag 1: −0.04 (−0.13, 0.06) Lag 2: −0.08 (−0.19, 0.04) Mean (0-4) −0.23 (−0.65, 0.18) Change in PEF per 1 ppb SO_2 - local Lag 0: −0.01 (−0.10, 0.07) Lag 1: 0.02 (−0.05, 0.10) Lag 2: −0.09 (−0.18, 0.01) Mean (0-4) −0.09 (−0.25, 0.07) Odds of 20% decrement in PEF below the median-all children Lag 0 0.987 (0.958, 1.017) Lag 1 1.007 (0.986, 1.030) Lag 2 0.992 (0.963, 1.023) Mean (0-4) 0.972 (0.887, 1.066) Odds of 20% decrement in PEF below the median-wheezy children Lag 0 0.981 (0.925, 1.041) Lag 1 0.999 (0.957, 1.042) Lag 2 0.995 (0.939 1.054) Mean (0-4) 1.019 (0.890 to 1.167)

TABLE AX5.1 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH RESPIRATORY MORBIDITY IN FIELD/PANEL STUDIES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean SO_2 Levels	Copollutants Considered	Findings & Interpretation	Effect Estimates (95% CI)
EUROPE (cont'd)					
Ponka A. (1990) Helsinki, Finland 1991	Survey study to compare weekly changes in ambient SO_2, NO_2, and temperature and the incidence of respiratory diseases, and absenteeism for children in day-care centers and schools and for adults in the work place during a 1-yr period (1987).	Mean weekly concentration of SO_2 ($\mu g/m^3$) Mean: 21.1 SD = 11.7 Median: 17.0 Range: 9, 61.5 Mean of daily max Mean: 53 SD = 20.8 Median: 48 Range: 25.9, 130.3	NO_2	Mean SO_2 concentration correlated with the incidences of URI and tonsillitis reported from health centers. SO_2 also correlated with absenteeism due to febrile illness among children in day care centers and adults. When comparing incidences during the low and high levels of SO_2, the number of cases of URI and tonsillitis reported from health centers increased as well as absenteeism. After standardization for temperature, the only difference that was statistically significant was the occurrence of URI diagnosed at health centers. Frequency of URI was 15% higher during high levels of SO_2 compared to low.	Statistical significance (p) of product moment correlation coefficients (correlation coefficient) between SO_2 and respiratory disease and absenteeism Respiratory tract infections diagnosed at health centers: URI SO_2 arithmetic mean $p < 0.001$ (0.553) SO_2 mean of daily maximums: $p = 0.0012$ (0.437) Tonsillitis Arithmetic mean: 0.0098 (0.355) Mean of daily maximums: NS Absenteeism due to febrile illness: Day care centers SO_2 arithmetic mean: $p = 0.012$ (0.404) Mean of daily maximums: $p = 0.048$ (0.323) School children SO_2 arithmetic mean: NS Mean of daily maximums: NS Adults SO_2 arithmetic mean: $p < 0.0001$ (0.644) Mean of daily maximums: $p < 0.0001$ (0.604) No significant correlation between SO_2 and URI, tonsillitis, otitis, or LRI in day care center children

TABLE AX5.1 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH RESPIRATORY MORBIDITY IN FIELD/PANEL STUDIES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean SO_2 Levels	Copollutants Considered	Findings & Interpretation	Effect Estimates (95% CI)
EUROPE (cont'd)					
Ponka A. (1990) (cont'd)					Statistical significance of weekly frequency of respiratory tract disease and absenteeism during low and high levels of SO_2: Respiratory infections diagnosed at health centers: URI SO_2 arithmetic mean: $p < 0.001$ Mean of daily max: $p = 0.0005$ Tonsillitis SO_2 arithmetic mean: 0.0351 SO mean of daily max: NS Absenteeism due to febrile illness Day care center children: $p = 0.0256$ School children: $p = 0.0014$ Adults: $p = 0.0005$

TABLE AX5.1 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH RESPIRATORY MORBIDITY IN FIELD/PANEL STUDIES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean SO_2 Levels	Copollutants Considered	Findings & Interpretation	Effect Estimates (95% CI)	
EUROPE (cont'd)						
Segala et al. (1998) Paris, France Nov 15, 1992 to May 9, 1993	Panel study of 84 children (7 to 15 yrs) with physician diagnosed asthma to examine the effects of winter air pollution on childhood asthma. For 25 wks, parents recorded the presence or absence of asthma attacks, upper or lower respiratory infections with fever, the use of supplementary inhaled B2 agonist, the severity of symptoms (wheeze, nocturnal cough and shortness of breath). Children also recorded PEF three times a day. GEE models adjusted for age, sex, weather and time trend. Investigated effects of SO_2 at 0 to 6 day Lags.	SO_2 mean (SD): 21.7 (13.5) µg/m^3 Range: (4.4, 83.8) µg/m^3	NO_2 PM_{13} BS	SO_2 associated with both incident and prevalent episodes of asthma, use of supplementary beta 2 agonist, incident episodes of nocturnal cough, prevalent episodes of shortness of breath and respiratory infection. Correlation with copollutants: NO_2: r = 0.54 PM_{13}: r = 0.43 BS: r = 0.89	OR per 50 µg/m^3 SO_2 (Only effects at 0 and 1-days Lag shown below unless statistically significant) Incident episodes: Mild asthmatics (n = 43) Asthma: Lag 0: OR 2.86 (1.31, 6.27) Lag 1: 2.45 (1.01, 5.92) Wheeze: Lag 0: 1.47 (0.90, 2.41) Lag1: 1.27 (0.48, 3.38) Nocturnal cough: Lag 3: 1.93 (1.18, 3.15) Lag 4: 2.12 (1.43, 3.13) Respiratory infections Lag 1: 1.52 (0.38, 5.98)	Prevalent episodes Mild asthmatics (n = 43) Asthma: Lag 0: 1.71 (1.15, 2.53) Lag 1: 1.55 (0.86, 2.78) Wheeze: Lag 4: 1.48 (0.90, 2.41) Shortness of breath : Lag 1: 1.36 (0.92, 2.01) Lag 2: 1.45 (0.98, 2.14) Lag 3: 1.52 (1.03, 2.25) Lag 4: 1.51 (1.02, 2.24) Respiratory infections: Lag 0: 1.58 (0.72, 3.46) Lag 1: 1.91 (0.79, 4.62) Lag 2: 2.13 (0.97, 4.67) Lag 3: 2.09 (1.05, 4.15) Lag 4: 2.05 (1.14, 3.68)

TABLE AX5.1 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH RESPIRATORY MORBIDITY IN FIELD/PANEL STUDIES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean SO_2 Levels	Copollutants Considered	Findings & Interpretation	Effect Estimates (95% CI)
EUROPE (cont'd)					
Segala et al. (1998) (cont'd)					Beta2 agonist: Lag 4: 1.63 (1.00, 2.66) Beta2 agonist: Lag 4: 2.02 (1.02, 4.01) Lag 5: 1.96 (0.99, 3.88) Moderate asthmatics (n = 41) Statistically significant (only) prevalent episodes: Beta2 agonist: Lag 0: 3.67 (1.25, 10.8) Lag 1: 4.60 (2.10, 10.1) Lag 2: 7.01 (3.53, 13.9) Lag 3: 4.74 (1.96, 11.5)
Timonen and Pekkanen (1997) Kuopio, Finland 1994	Panel study of 169 children (7 to 12 yrs) with asthma or cough symptoms living in urban and suburban areas of Kuopio, Finland to determine association between air pollution and respiratory health. In the urban areas there were 39 asthmatics and 46 with cough only; in the suburban areas there were 35 asthmatics and 49 with cough who were included in the final analysis. Twice daily PEF and daily symptoms were recorded for 3 mos. First order autoregressive models used to assess associations between air pollutants and PEF and logistic regression models used for symptom prevalences and incidences. Analysis conducted on daily mean PEF deviations. Mean morning or evening PEF calculated for each child was subtracted from the daily value of morning or evening PEF. The daily deviations were then Avgd to obtain daily mean PEF deviation for morning or evening PEF.	Avg daily SO_2 ($\mu g/m^3$) Urban area: Mean: 6.0 25th percentile: 2.6 50th percentile: 3.6 75th percentile: 7.1 Max: 32	PM_{10} BS NO_2	Among children with cough only, morning and evening deviations in PEF in the urban panel was negatively associated with SO_2. SO_2 was also associated with an increase in the incidence of URS in children with cough only in the urban area. When excluding the three highest SO_2 days, these effects were no longer statistically significant. No associations found between SO_2 and morning or evening PEF or respiratory symptoms in children with cough only in the suburban panel.	Correlation coefficient with SO_2: PM_{10} r = 0.21 BS r = 0.20 NO_2 r = 0.22 Regression coefficient (SE) (per 10 $\mu g/m^3$ SO_2) Morning PEF deviations Children with cough alone Lag 0: −0.229 (0.608) Lag 1: −1.38 (0.564) Lag 2: −0.683 (0.523) 4-day mean: −1.28 (0.633) Evening PEF deviations Children with cough alone Lag 0: −1.84 (0.673) Lag 1: −0.144 (0.711) Lag 2: −0.291 (0.613) 4-day mean: −0.878 (0.868)

TABLE AX5.1 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH RESPIRATORY MORBIDITY IN FIELD/PANEL STUDIES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean SO_2 Levels	Copollutants Considered	Findings & Interpretation	Effect Estimates (95% CI)	
EUROPE (cont'd)						
Timonen and Pekkanen (1997) (cont'd)				Correlation with copollutants (urban area): PM_{10}: r = 0.21 BS: r = 0.20 NO_2: r = 0.22	Asthmatic Lag 0: 0.198 (0.804) Lag 1: 0.382 (0.789) Lag 2: 0.648 (0.715) 4 day mean: 1.39 (1.14) Odds ratio (per 10 μg/m^3) URS Lag 1: 1.46 (1.07, 2.00) Lag 2: 1.46 (1.14, 1.87) 4-day mean: 1.55 (1.08, 2.24) Odds ratio when excluded 3 highest SO_2 days (no 95% CI provided, but effects were not significant) Lag 1: 1.13 Lag 2: 1.46 4-day mean: 1.12	Asthmatics Lag 0: 1.28 (0.711) Lag 1: 0.575 (0.727) Lag 2: 0.819 (0.642) 4-day mean: 1.34 (1.05)

TABLE AX5.1 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH RESPIRATORY MORBIDITY IN FIELD/PANEL STUDIES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean SO_2 Levels	Copollutants Considered	Findings & Interpretation	Effect Estimates (95% CI)
LATIN AMERICA					
Pino et al. (2004) Santiago, Chile 1995-1997	Cohort study of 492 infants recruited at 4 mos of age and followed through the first yr of life to determine the association between air pollution on wheezing bronchitis.	Mean concentration of SO_2 (ppb) Mean: 11.6 SD = 8.1 Median: 10.0	$PM_{2.5}$ NO_2	No consistent association was found between the 24-h avg SO_2 and risk of wheezing bronchitis. However, after a 7-day lag, a 10-ppb increase in the 24-h avg SO_2 was associated with a 21% increase in risk of wheezing bronchitis.	Increase in wheezing bronchitis (95% CI) per 10 ppb SO_2 21% (8, 39%)
Romieu et al. (1996) Mexico City, Mexico April-Jul 1991 Nov 1991-Feb 1992	Panel study of 71 mildly asthmatic children (5 to 13 yrs) to assess the relationship between air pollution and childhood asthma exacerbation. Children measured PEF three times daily and recorded daily symptoms and medication use. Examined both incidence and prevalence of symptoms. Lower respiratory symptoms, cough, phlegm, wheeze, and/or difficulty breathing.	24-h avg SO_2 (ppm) Mean: 0.09 SD = 0.05 Range: 0.02, 0.20	O_3 PM_{10} $PM_{2.5}$ NO_2	SO_2 concentrations were not related to changes in PEF or respiratory symptoms	Change in PEF per 10-ppb increase in SO_2 0.26 (−0.35, 0.88, 1.01) L/min Odds ratio per 10 ppb SO_2 Coughing: 0.96 (0.92, 1.01) Lower respiratory symptoms: 0.97 (0.94, 1.01)

TABLE AX5.1 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH RESPIRATORY MORBIDITY IN FIELD/PANEL STUDIES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean SO_2 Levels	Copollutants Considered	Findings & Interpretation	Effect Estimates (95% CI)
ASIA					
Chen et al. (1999) Three towns in Taiwan: Sanchun, Taihsi, Linyuan May1995-Jan 1996	Cross-sectional panel study of 895 children (8 to 13 yrs) to evaluate the short-term effect of ambient air pollution on pulmonary function. Single and multipollutant models adjusted for sex, height, BMI, community, temperature, and rainfall. Examined 1, 2, and 7-day lag effects.	Peak concentrations of SO_2 Range: 0, 72.4 ppb Day-time avg and 1-day lag SO_2 correlated with PM_{10} (r = 0.68) SO_2 correlated with NO_2 (r = 0.71)	CO NO_3 PM_{10} NO_2	Daytime peak SO_2 at 2 days lag significantly associated with FVC using the single-pollutant model. Association also observed with NO_2 and CO with FVC. No PM_{10} effects. Only O_3 effects significant in multipollutant models.	Change in FVC (mL) daytime avg SO_2 Lag 1: −3.18 (1.80) Lag 2: −2.70 (1.49) Lag 7: 0.61 (2.59) Daytime peak SO_2 Lag 1: −0.91 (0.73) Lag 2: −1.27 (0.59), $p < 0.05$ Lag 7: −1.05 (1.29) Change in FEV_1 (mL) daytime avg SO_2 Lag 1: −1.95 (1.69) Lag 2: −1.12 (1.41) Lag 7: −1.48 (2.44) Daytime peak SO_2 Lag 1: −0.57 (0.68) Lag 2: −0.64 (0.56) Lag 7: −1.96 (1.22)
Xu et al. (1991) Beijing, China Three areas: industrial, residential and suburban (control) August 1986	Cross sectional survey of 1140 adults (40 to 69 yrs) who had never smoked living in three areas of Beijing, to determine respiratory health effects of indoor and outdoor air pollution. A trained interviewer obtained pulmonary function measurements and determined history of chest illnesses, respiratory symptoms, cigarette smoking, occupational exposure, residential history, education level and type of fuel used for cooking and heating.	Annual mean concentration of SO_2 ($\mu g/m^3$) Residential: 128 Industrial: 57 Suburban: 18	TSPM	An inverse linear association found between Ln outdoor SO_2 and FEV_1 and FVC after adjusting for age, height and sex.	Regression estimate and standard error per Ln SO_2 ($\mu g/m^3$) Height-adjusted FEV_1 (mL): −35.6 (17.3) Height-adjusted FVC (mL): −131.4 (18.8)

TABLE AX5.1 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH RESPIRATORY MORBIDITY IN FIELD/PANEL STUDIES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean SO_2 Levels	Copollutants Considered	Findings & Interpretation	Effect Estimates (95% CI)
ASIA (cont'd)					
Park et al. (2002) Seoul, Korea Mar 2, 1996 to Dec 22, 1999	Time series analysis of school absenteeism due to illness and air pollution in one elementary school in Seoul. School located in area with heavy traffic. Avg enrollment in 1996 was 1,264.	24-h avg SO_2 Mean: 9.19 ppb SD=4.61 Range: 2.68, 28.11 SO_2 correlated with CO (r = 0.67)	PM_{10} NO_2 CO O_3	SO_2, $PM_{10,}$ and O_3 associated with illness related school absenteeism. SP2 and O_3 are protective for non-illness related absences.	Relative risk per IQR SO_2 (5.68 ppb) Total absences: 1.03 (1.02, 1.05) Non-illness related absences: 0.95 (0.92, 0.99) Illness related absences: 1.09 (1.07, 1.12) 2-pollutant model with O_3: 1.10 (1.08, 1.13)
Park et al. (2005a) Korea March to June 2002	Panel study of 69 patients (16 to 75 yrs) diagnosed with asthma by bronchial challenge or by bronchodilator response. Patients recorded twice-daily PE, symptoms at the end of each day (cough, wheeze, chest tightness, shortness of breath, sputum changes and the next morning, night awakenings). During the study period, 14 Asian dust days were identified. GEE and generalized additive Poisson regression model used in analysis.	Daily avg SO_2 Control days: 0.0069 (0.0019) ppm Dust days: 0.0052 (0.0010) ppm	PM_{10} NO_2 CO O_3	During the dust days, SO_2 levels were significantly lower compared to control days. SO_2 had no significant effect on PEF variability or night symptoms.	Relative risk based on Poisson log-linear regression analysis PEF variability (>20%) 0.76 (0.37, 1.56) Night symptoms: 0.98 (0.59, 1.51)

TABLE AX5.2. ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR RESPIRATORY DISEASES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean Levels & Monitoring Stations	Copollutants & Correlations	Method, Findings, Interpretation	Effects: Relative Risk or % Change & Confidence Intervals (95%)
UNITED STATES					
Jaffe et al. (2003) 3 cities, Ohio, United States (Cleveland, Columbus, Cincinnati) Period of Study: 7/91-6/96	ED Visits Outcome (ICD9): Asthma (493) Age Groups Analyzed: 5-34 Study design: Time series N: 4,416 Statistical analyses: Poisson regression using a standard GAM approach Covariates: City, day of wk, wk, yr, minimum temperature, overall trend, dispersion parameter Season: June to Aug only Dose-response investigated: Yes Statistical package: NR Lag: 0-3 days	24-h avg: Cincinnati: 35.9 (25.1) µg/m^3 Range: 1.7, 132 Cleveland: 39.2 (25.3) µg/m^3 Range: 2.6, 167 Columbus: 11.1 (8.5) µg/m^3 Range: 0, 56.8	Cincinnati: $PM_{2.5}$; r = 0.31 NO_2; r = 0.07 O_3; r = 0.14 Cleveland: $PM_{2.5}$; r = 0.29 NO_2; r = 0.28 O_3; r = 0.26 Columbus: $PM_{2.5}$; r = 0.22 NO_2; r = NR O_3; r = 0.42	Wide confidence intervals for data from Cleveland and Columbus make these data not significant and unstable. Only data for Cincinnati was considered statistically significant and demonstrated a concentration response function that was positive. No multipollutant models were utilized.	Increment: 50 µg/m^3 Cincinnati: 35% [9, 21] lag 2 Cleveland: 6% [−7, 21] lag 2 Columbus: 26% [−25, 213] lag 3 All cities: 12% [1, 23] Attributable risk from SO_2 increment: Cincinnati: 4.2% Cleveland: 0.66% Columbus: 2.94%

TABLE AX5.2 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR RESPIRATORY DISEASES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean Levels & Monitoring Stations	Copollutants & Correlations	Method, Findings, Interpretation	Effects: Relative Risk or % Change & Confidence Intervals (95%)
UNITED STATES (cont'd)					
Moolgavkar* et al. (1997) United States: Minneapolis-St. Paul; Birmingham Period of Study: 1986-1991	Hospital Admissions Outcomes (ICD 9 codes): COPD including asthma (490-496), Pneumonia (480-487) Age groups analyzed: 65+ Study design: Time series Statistical analyses: Semi-parametric Poisson regression, GAM Covariates: day of wk, season, temporal trends, temperature Statistical package: S Plus Lag: 0-3 days	SO_2 24-h avg (ppb): Minneapolis: Mean: 4.82 10th: 1.9 25th: 2.66 50th: 4.02 75th: 6.0 90th: 8.5 Birmingham: Mean: 6.58 10th: 2.2 25th: 3.7 50th: 6.0 75th: 8.6 90th: 11.6	Minneapolis: $PM_{2.5}$; r = 0.08 NO_2; r = 0.09 CO; r = 0.07 O_3; r = −0.12 Birmingham: $PM_{2.5}$; r = 0.17 CO; r = 0.16 O_3; r = 0.02	SO_2 with NO_2 and $PM_{2.5}$ were associated with hospital admissions. Evidence of mixture effects was found. No single-pollutant was more important than the other for respiratory admissions. Each pollutant was associated with admissions except CO. Consideration of four pollutants together showed the strongest association with ozone. No pollutant other than O_3 was stable in its association with hospital admissions. No effects were reported for Birmingham. Positive results were only observed in Minneapolis.	Increment: 3.5 ppb Sum of Pneumonia and COPD 1.6% [−0.1, 3.3] lag 2 Pneumonia Only Minneapolis: 65+ 0.9% [−1.1, 2.9] lag 2 20 df 0.5% [−1.5, 2.5] lag 2 130 dfS

TABLE AX5.2 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR RESPIRATORY DISEASES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean Levels & Monitoring Stations	Copollutants & Correlations	Method, Findings, Interpretation	Effects: Relative Risk or % Change & Confidence Intervals (95%)
UNITED STATES (cont'd)					
Moolgavkar (2000) Reanalysis (2003) Multicity, United States: Chicago, Los Angeles, Maricopa County, (Phoenix) Period of Study: 1987-1995	Hospital Admissions Outcomes (ICD 9 codes): COPD including asthma (490-496) Age groups analyzed: 0-19, 20-64, 65+ (LA only) Study design: Time series Statistical analyses: Poisson regression, GAM Covariates: Day of wk, temporal trends, temperature, relative humidity Lag: 0-5 days	Chicago: Median: 6 ppb 25th: 4 75th: 8 Range: 0.5, 36 Los Angeles: Median: 2 ppb 25th: 1 75th: 4 Range: 0, 16 Maricopa: Median: 2 ppb 25th: 0.5 75th: 4 Range: 0, 14	Chicago: $PM_{2.5}$; r = 0.42 CO; r = 0.35 NO_2; r = 0.44 O_3; r = 0.01 Los Angeles: $PM_{2.5}$; r = 0.42 $PM_{2.5}$; r = 0.41 CO; r = 0.78 NO_2; r = 0.74 03; r = –0.21 Maricopa: $PM_{2.5}$; r = 0.11 CO; r = 0.53 NO_2; r = 0.02 O_3; r = –0.37	In Los Angeles there was a significant association with and hospital admissions for COPD. SO_2 may be acting as a surrogate for other pollutants since heterogeneous responses found in different cities are inconsistent with a cause-effect model.	Increment: 10 ppb COPD, >65 yrs Chicago lag 0: 4.87 (t = 3.18) GAM-100 LA lag 0: 2.84 (t = 13.32) GAM-30 LA lag 0: 1.80 (t = 9.60) GAM-100 LA lag 0: 1.78 (t = 7.72) NS-100

TABLE AX5.2 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR RESPIRATORY DISEASES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean Levels & Monitoring Stations	Copollutants & Correlations	Method, Findings, Interpretation	Effects: Relative Risk or % Change & Confidence Intervals (95%)
UNITED STATES (cont'd)					
Schwartz (1995) New Haven, CT Tacoma, WA United States Period of Study: 1988-1990	Hospital Admissions Outcomes (ICD 9 codes): All respiratory admissions (460-519) Age groups analyzed: ≥65 Study design: Time series N: 13,470 Statistical analyses: Poisson regression, log linear regression using GLM and GAM Covariates: dewpoint, temp, long-term trends, days of wk Statistical package: S- Plus Lag: 0-1	24-h avg New Haven Mean 78 µg/m^3 (29.8 ppb) 10th: 23 25th: 35 50th: 78 75th: 100 90th: 159 Tacoma 44 µg/m^3 (16.8 ppb) 10th: 15 25th: 26 50th: 40 75th: 56 90th: 74	$PM_{2.5}$ O_3	In New Haven, risk associated with SO_2 was not affected by inclusion of $PM_{2.5}$ in the model and the effect of $PM_{2.5}$ was not strongly affected by inclusion of SO_2. This suggests that in New Haven, SO_2 and $PM_{2.5}$ acted independently. In Tacoma 2-pollutant model analysis showed risk associated with SO_2 was attenuated by $PM_{2.5}$. This suggested risks associated with SO_2 and $PM_{2.5}$ were not independent. Possible SO_2 acts as a surrogate for $PM_{2.5}$ in this city.	Increment: 50 µg/m^3 or 18.8 ppb New Haven, CT RR = 1.03 [CI 1.02,1.05], lag 0-1 $p < 0.001$ 2-pollutant model with $PM_{2.5}$: RR = 1.04 [CI 1.02, 1.06] $p < 0.001$ Tacoma, WA RR = 1.06 [CI 1.01, 1.12], lag 0-1 $p > 0.02$ 2-pollutant model with $PM_{2.5}$: RR = 0.99 [CI 0.93, 1.06] $p > 0.5$

TABLE AX5.2 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR RESPIRATORY DISEASES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean Levels & Monitoring Stations	Copollutants & Correlations	Method, Findings, Interpretation	Effects: Relative Risk or % Change & Confidence Intervals (95%)
UNITED STATES (cont'd)					
Wilson et al. (2005) Multicity, United States (Portland, ME and Manchester, NH) Period of Study: 1996-2000 (Manchester) 1998-2000 (Portland)	ED Visits Outcomes (ICD 9 codes): All respiratory (460-519); Asthma (493) Age groups analyzed: 0-14 yrs; 15-64 yrs; ≥65 yrs Study design: Time series Statistical analyses: Multiple regression analysis standard GAM with more stringent criteria parameters Covariates: Time-trend, season, influenza, temperature, humidity, precipitation Stat package: S-Plus Lag: 0-2	SO_2 1-h max: Mean, (SD) (ppb) Portland All yr: 11.1 (9.1) Winter: 17.1 (12.0) Spring: 10.0 (7.1) Summer: 9.1 (8.0) Fall: 9.7 (7.1) Manchester All yr: 16.5 (14.7) Winter: 25.7 (15.8) Spring: 14.8 (12.0) Summer: 10.6 (15.1) Fall: 14.6 (11.1)	O_3 $PM_{2.5}$	Elevated levels of SO_2 were positively associated with elevated respiratory and asthmatic ER visits. The significance of these relationships is not sensitive to analytic or smoothing techniques.	Increment: 6.3 ppb (IQR) for Portland; IQR for Manchester Portland: All respiratory All ages RR 1.05 [1.02, 1.07] lag 0 0-14 yrs RR 0.98 [0.93, 1.02] lag 0 15-64 yrs RR 1.06 [1.03, 1.09] lag 0 >65 yrs RR 1.10 [1.05, 1.15] lag 0 Asthma All ages RR 1.06 [1.01, 1.12] lag 2 0-14 yrs RR 1.03 [0.93, 1.15] lag 2 15-64 yrs 1.07 [1.01, 1.15] lag 2 >65 yrs RR 1.07 [0.90, 1.26] lag 2 Manchester: All respiratory All ages RR 1.01 [0.99, 1.02] lag 0 0-14 yrs RR 1.00 [0.96, 1.04] lag 0 15-64 yrs RR 1.00 [0.98, 1.03] lag 0 >65 yrs RR 1.04 [0.97, 1.11] lag 0 Asthma All ages RR 1.03 [0.98, 1.09] lag 2 0-14 yrs RR 1.11 [0.98, 1.25] lag 2 15-64 yrs 1.02 [0.96, 1.08] lag 2 >65 yrs RR 1.06 [0.83, 1.36] lag 2

TABLE AX5.2 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR RESPIRATORY DISEASES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean Levels & Monitoring Stations	Copollutants & Correlations	Method, Findings, Interpretation	Effects: Relative Risk or % Change & Confidence Intervals (95%)
UNITED STATES (cont'd)					
Gwynn* et al. (2000) Buffalo, NY United States Period of Study: 1988-1990 Days: 1,090	Hospital Admissions Outcomes (ICD 9 codes): Respiratory admissions: Acute bronchitis/bronchiolitis (466); Pneumonia (480-4860); COPD and Asthma (490-493, 496) Age groups analyzed: 6 Study design: Time series N: 24, Statistical analyses: Poisson regression with GLM and GAM Covariates: season, day of wk, holiday, temperature, relative humidity Lag: 0-3 days	24-h avg SO_2 (ppb): Min: 1.63 25th: 8.4 Mean: 12.2 75th: 15.4 Max: 37.7	H^+ r = 0.06 SO_4^{2-} r = 0.19 $PM_{2.5}$ r = 0.19 O_3 r = 0.02 NO_2 r = 0.36 CO r = 0.11 COH r = 0.19	Significant associations observed between several pollutants and various health-effect outcomes make it difficult to discriminate the influence of a single-pollutant. This is likely the a result of the relatively high intercorrelations among the various pollutants, as well as the possible interactive role of several pollutants in the reported associations.	Increment: 25.5, 7.0 ppb (Max-Mean; IQR) SO_2 alone: Max-Mean RR 1.096 (t = 3.05) lag 0 IQR RR 1.025 (t = 3.05) lag 0

TABLE AX5.2 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR RESPIRATORY DISEASES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean Levels & Monitoring Stations	Copollutants & Correlations	Method, Findings, Interpretation	Effects: Relative Risk or % Change & Confidence Intervals (95%)
UNITED STATES (cont'd)					
Lin et al. (2004a) New York (Bronx County), United States Period of Study: 6/1991-12/1993	Hospital Admissions Outcomes (ICD 9 codes): Asthma (493) Age groups analyzed: 0-14 Study design: Case-control N: 2,629 cases; 2,236 controls Statistical analyses: logistic regression Covariates: Race and ethnicity, age, gender, season Statistical package: Lag: 0,1,2,3, 0-3	Cases: 24-h avg: 16.78 ppb 50th: 13.72 Range: 2.88, 66.35 Controls: 24-h avg: 15.57 ppb 50th: 13.08 Range : 2.88, 66.35 Quartile Concentrations (ppb) : Q1 : 2.88, 8.37 Q2: 9.37, 13.38 Q3: 13.5, 20.91 Q4: 20.21, 66.35		Odds ratios for risk of hospitalization for asthma increased with each quartile of SO_2 concentration. Lag 1, 2, or 3 all showed a concentration response that was positive for odds ratio as each quartile was compared to the total exposure group (trend p > 0.001).	Quartile (24-h avg) Q2 OR 1.26 lag 3 Q3 OR 1.45 lag 3 Q4 OR 2.16 [1.77, 2.65] lag 3 Quartile (1-h max) Q4 OR 1.86 [1.52, 2.27] lag 3 For a 4-ppb increase in SO_2 (24-h avg) RR 1.07 [1.04, 1.11]

TABLE AX5.2 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR RESPIRATORY DISEASES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean Levels & Monitoring Stations	Copollutants & Correlations	Method, Findings, Interpretation	Effects: Relative Risk or % Change & Confidence Intervals (95%)
UNITED STATES (cont'd)					
Michaud et al. (2004) Hilo, Hawaii 2/21/1997-5/31/2001	ED Visits Outcomes (ICD 9 codes): COPD (490-496); Asthma (493, 495); bronchitis (490, 491), other COPD (492, 494, 496) Age groups analyzed: All Study design: Time series Statistical analyses: Exponential regression models Covariates: temporal variables, day of wk, meteorology Stat package: Stata, SAS Lag: 0,1,2,3 days	1-h max: 1.92 (12.2) ppb Range: 0.0, 447 24-h avg: 1.97 (7.12) ppb Range: 0.0, 108.5	PM_1	The lack of organic carbon shows the pure SO_2 effect uncontaminated by vehicle emissions. Asthma is associated with Vog, but Vog is not a major cause of asthma in Hawaii. The strongest association was with the mo of the yr. Admission for asthma and respiratory conditions was higher in the winter compared to the summer, based on admission per day (observational- not statistical analysis).	Increment: 10 ppb COPD RR 1.04 [0.99, 1.09] lag 1 RR 1.04 [1.00, 1.09] lag 2 RR 1.07 [1.03, 1.11] lag 3 Asthma RR 1.01 [1.00, 1.10] lag 1 RR 1.02 [1.03, 1.12] lag 2 RR 1.02 [1.03, 1.12] lag 3 Bronchitis RR 1.01 [0.93, 1.13] lag 1 RR 0.99 [0.88, 1.05] lag 2 RR 1.01 [1.00, 1.14] lag 3 Other COPD RR 1.00 [0.78, 1.23] lag 1 RR 0.96 [0.62, 1.11] lag 2 RR 0.98 [0.75, 1.16] lag 3

TABLE AX5.2 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR RESPIRATORY DISEASES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean Levels & Monitoring Stations	Copollutants & Correlations	Method, Findings, Interpretation	Effects: Relative Risk or % Change & Confidence Intervals (95%)
UNITED STATES (cont'd)					
Peel et al. (2005) Atlanta, GA, United States Period of Study: 1/93-8/2000	ED Visits Outcome(s) (ICD 9): All respiratory (460-6, 477, 480-6, 480-6, 490-3, 496); Asthma (493); COPD (491-2, 496); Pneumonia (480-486); Upper Respiratory Infection (460-6, 477) Age groups analyzed: All Study design: Time series N: 484,830 # of Hospitals: 31 Statistical analyses: Poisson Regression, GEE, GLM, and GAM (data not shown for GAM) Covariates: Day of wk, hospital entry/exit, holidays, time trend; season, temperature, dew point temperature Statistical package: SAS, S-Plus Lag: 0 to 7 days. 3 day moving avgs.	1-h max: 16.5 (17.1) ppb 10th%: 2.0 90th%: 39.0	O_3 NO_2 CO $PM_{2.5}$ Evaluated multipollutant models (data not shown)	Estimates from distributed lag models (0-13 days) tend to be higher than for 3-day moving avg. Positive associations for URI and COPD with SO_2 were noted for unconstrained lags (0-13 days) that covered the previous two weeks of exposure.	Increment: 20 ppb All respiratory RR 1.008 [0.997, 1.019] lag 0-2, 3-day moving avg Upper Respiratory Infection (URI) RR 1.010 [0.998, 1.024] lag 0-2, 3-day moving avg Asthma All: 1.001 [0.984, 1.017] lag 0-2, 3-day moving avg Pneumonia RR 1.003 [0.984, 1.023] lag 0-2, 3-day moving avg COPD RR 1.016 [0.985, 1.049] lag 0-2, 3-day moving avg

TABLE AX5.2 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR RESPIRATORY DISEASES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean Levels & Monitoring Stations	Copollutants & Correlations	Method, Findings, Interpretation	Effects: Relative Risk or % Change & Confidence Intervals (95%)
UNITED STATES (cont'd)					
Schwartz et al. (1996) Cleveland, OH Period of Study: 1988-1990	Hospital Admissions Outcomes (ICD 9 codes): All respiratory disease Age groups analyzed: ≥65 Study design: Time series Statistical analyses: Poisson regression Covariates: Season, temperature, day of wk Statistical package: Lag: 0-1	24-h avg: 35 ppb 10th: 13 25th: 20 50th: 31 75th: 45 90th: 61	$PM_{2.5}$ O_3	Significant associations were seen for $PM_{2.5}$ and O_3, with somewhat weaker evidence for SO_2.	Increment: 100 µg/m^3 RR 1.03 [0.99, 1.06] lag 0-1

TABLE AX5.2 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR RESPIRATORY DISEASES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean Levels & Monitoring Stations	Copollutants & Correlations	Method, Findings, Interpretation	Effects: Relative Risk or % Change & Confidence Intervals (95%)
UNITED STATES (cont'd)					
Sheppard et al. (1999) Reanalysis (2003) Seattle, WA, United States Period of Study: 1987-1994	Hospital Admissions Outcomes (ICD 9 codes): Asthma (493) Age groups analyzed: <65 Study design: Time series N: 7,837 # of hospitals: 23 Statistical analyses: Poisson regression with adjustment for auto-correlation. Covariates: Statistical package: S-Plus Lag: 0,1,2,3	24-h avg: 8 ppb IQR: 5 ppb 10th: 3.0 25th: 5.0 50th: 8.0 75th: 10.0 90th: 13.0	$PM_{2.5}$; r = 0.31 $PM_{2.5}$; r = 0.22 O_3; r = 0.07 CO; r = 0.24	Sources of SO_2 adjacent or near to monitoring site. Low concentrations. No association with SO_2 for asthma but positive association for appendicitis.	Increment: 5 ppb (IQR) GAM with stricter criteria: 1.0% [−2.0, 3.0] lag 0 GLM with natural spline smoothing: 0.0% [−3.0, 4.0] lag 0

TABLE AX5.2 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR RESPIRATORY DISEASES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean Levels & Monitoring Stations	Copollutants & Correlations	Method, Findings, Interpretation	Effects: Relative Risk or % Change & Confidence Intervals (95%)
CANADA					
Bates et al. (1990) Vancouver Region, BC, Canada Period of Study: 7/1/1984-10/31/1986	ED Visits Outcome(s) (ICD 9): Asthma (493); Pneumonia (480-486); Chronic bronchitis (491,492,496); Other respiratory (466) Age groups analyzed: All; 15-60 Study design: # of Hospitals: 9 Statistical analyses: Pearson correlation coefficients were calculated between asthma visits and environmental variables Season: Warm (May-Oct); Cool (Nov-Apr) Covariates: NR Statistical package: NR Lag: 0, 1, 2	May-Oct SO_2 1-h max: Range: 0.0137, 0.0151 ppm Nov-Apr Range: 0.012, 0.0164 ppm Number of stations: 11	May-Oct. O_3; r = 0.23 NO_2; r = 0.67 CoH; r = 0.34 SO_4; r = 0.46 Nov-Apr O_3; r = 0.47 NO_2; r = 0.61 CoH; r = 0.64 SO_4; r = 0.54	SO_2 effects depend on the season. In the summer a rise in ambient SO_2 levels was seen to coincide with a rise in respiratory related hospital admissions.	Correlation Coefficients: Warm Season (May-Oct) Asthma (15-60 yrs) r = 0.118 lag 0 $p < 0.01$ r = 0.139 lag 1 Respiratory (15-60 yrs) r = 0.134 lag 0 $p < 0.001$ r = 0.164 lag 1 $p < 0.001$ Cool Season (Nov-Apr) Respiratory 1-14 yrs r = 0.205 lag 0 $p < 0.001$ r = 0.234 lag 1 $p < 0.001$ r = 0.234 lag 2 $p < 0.001$ 15-60 yrs r = 0.180 lag 0 $p < 0.001$ r = 0.214 lag 1 $p < 0.001$ r = 0.215 lag 2 $p < 0.001$ $\geq$61 yrs r = 0.257 lag 0 $p < 0.001$ r = 0.308 lag 1 $p < 0.001$ r = 0.307 lag 2 $p < 0.001$ Asthma ($\geq$61 yrs) r = 0.125 lag 0 $p < 0.001$ r = 0.149 lag 1 $p < 0.001$ r = 0.148 lag 2 $p < 0.001$ Total ER admissions ($\geq$61 yrs) r = 0.13 lag 1 $p < 0.01$ r = 0.13 lag 2 $p < 0.01$

TABLE AX5.2 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR RESPIRATORY DISEASES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean Levels & Monitoring Stations	Copollutants & Correlations	Method, Findings, Interpretation	Effects: Relative Risk or % Change & Confidence Intervals (95%)
CANADA (cont'd)					
Burnett et al. (1997a) 16 cities Canada Period of Study: 4/1981-12/1991 Days: 3,927	Hospital Admissions Outcomes (ICD 9 codes): All respiratory admissions (466, 480-6, 490-4, 496) Study design: Time series N: 720,519 # of hospitals: 134 Statistical analyses: random effects relative risk regression model Covariates: Long-term trend, season, day of wk, hospital, Statistical package: NR Lag: 0, 1, 2 day	1-h max SO_2 (ppb) Mean: 14.4 SD = 22.2 25th: 3 50th: 10 75th: 19 95th: 45 99th: 97	O_3 r = 0.04 CO NO_2 COH	Control of SO_2 reduced but did not eliminate the ozone association with respiratory hospital admissions.	Increment: 10 ppb Single-pollutant SO_2 and respiratory admissions, p = 0.134 Multipollutant model (adjusted for CO, O_3, NO_2, COH, dew point): RR 1.0055 [0.9982, 1.0128] lag 0

TABLE AX5.2 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR RESPIRATORY DISEASES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean Levels & Monitoring Stations	Copollutants & Correlations	Method, Findings, Interpretation	Effects: Relative Risk or % Change & Confidence Intervals (95%)
CANADA (cont'd)					
Stieb et al. (1996) St. John, New Brunswick, Canada Period of Study: 1984-1992 (May-Sept only)	ED Visits Outcome(s): Asthma ICD9 codes: NR Age groups analyzed: 0-15, >15 Study design: Time series N: 1,163 # of Hospitals: 2 Statistical analyses: SAS NLIN (Equivalent to Poisson GEE) Covariates: Day of wk, long-term trends, Season: Summers only (May-Sep) Dose-response investigated?: Yes Statistical package: SAS Lag: 0-3 days	1-h max SO_2 (ppb) Mean: 38.1 Range: 0, 390 95th 110	O_3; r = 0.04 NO_2; r = −0.03 SO_4^{2-}; r = 0.23 TSP; r = 0.16	SO_2 did not affect the rate of asthma ED visits when O_3 was included in the model.	Increment: NR $SO_2 + O_3$: β = −0.0030 (0.0027) lag 0

TABLE AX5.2 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR RESPIRATORY DISEASES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean Levels & Monitoring Stations	Copollutants & Correlations	Method, Findings, Interpretation	Effects: Relative Risk or % Change & Confidence Intervals (95%)
CANADA (cont'd)					
Stieb* et al. (2000) Saint John, New Brunswick, Canada Period of Study: Retrospective: 7/92-6/94 Prospective: 7/94-3/96	ED Visits Outcome(s): Asthma; COPD; Respiratory infection (bronchitis, bronchiolitis, croup, pneumonia); All respiratory ICD9 codes: NR Age groups analyzed: All Study design: Time series N: 19,821 Statistical analyses: Poisson regression, GAM Covariates: Day of wk, selected weather variables in each model Seasons: All yr, summer only Dose-response investigated: Yes Statistical package: S-Plus Lag: all yr = 0; summer only = 0-3	24-h avg: Annual mean: 6.7 (5.6) ppb 95th: 18.0 Max: 60.0 Warm season mean: 7.6 (5.2) ppb 95th: 18.0 Max: 29.0 1-h max: Annual mean: 23.8 (21.0) ppb 95th: 62.0 Max: 161.0 Warm season mean: 25.4 (17.8) ppb 95th: 62.0 Max: 137.0	CO; r = 0.31 O_3; r = 0.10 NO_2; r = 0.41 TRS; r = 0.08 $PM_{2.5}$; r = 0.36 $PM_{2.5}$; r = 0.31 H^+; r = 0.24 SO_4^{2-}; r = 0.26 COH; r = 0.31 H_2S; r = −0.01 Assessed multipollutant models	Non-linear effect of SO_2 on summertime respiratory visits observed and log transformation strengthened the association.	Increment: 23.8 ppb (mean) 1-h max: Respiratory visits: 3.9% lag 5 May to Sept: 3.9% lag 0-3 Multipollutant model (SO_2, O_3, NO_2) All yr: 3.7% [1.5, 6.0] lag 5 Multipollutant model (ln (NO_2), O_3, SO_2 COH) May to Sept: 3.9% [1.1, 6.7] lag 0-3

TABLE AX5.2 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR RESPIRATORY DISEASES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean Levels & Monitoring Stations	Copollutants & Correlations	Method, Findings, Interpretation	Effects: Relative Risk or % Change & Confidence Intervals (95%)
CANADA (cont'd)					
Burnett et al. (1997b) Toronto, Canada Period of Study: 1992-1994	Hospital Admissions Outcomes (ICD 9 codes): Respiratory tracheobronchitis (480-6), COPD (491-4, 496) Study design: Time series Statistical analyses: Poisson regression, GEE, GAM Covariates: Temperature, dew point temperature, Long-term trend, season, influenza, day of wk Seasons: Summers only Lag: 0,1,2,3,4 days	Mean SO_2: 7.9 ppb CV: 64 Range: 0, 26 5th: 1 25th: 4 50th: 7 75th: 11 95th: 18 Number of Stations: 6-11	CO; r = 0.37 H^+; r = 0.45 SO_4; r = 0.42 TP; r = 0.55 FP; r = 0.49 CP; r = 0.44 COH; r = 0.50 O_3; r = 0.18 NO_2; r = 0.46	Risks of hospitalization for respiratory disease were summed for O_3, NO_2, and SO_2 at 11% increase in admissions. The proportion associated with the single-pollutant SO_2 was 3.6%. CoH was the strongest predictor of hospitalization indicating particle associated pollutants are responsible for effects and outcomes measured.	Increment: 4.00 ppb (IQR) Respiratory-percent increase 4.0% (t = 4.14) lag 0 Copollutant and multipollutant models RR (t-statistic): SO_2, COH: 1.012 (1.10) SO_2, H^+: 1.022 (1.96) SO_2, SO_4: 1.021 (1.93) SO_2, TP: 1.021 (1.72) SO_2, FP: 1.022 (1.92) SO_2, CP: 1.023 (2.03) SO_2, O_3, NO_2: 1.019 (1.64)

TABLE AX5.2 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR RESPIRATORY DISEASES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean Levels & Monitoring Stations	Copollutants & Correlations	Method, Findings, Interpretation	Effects: Relative Risk or % Change & Confidence Intervals (95%)
CANADA (cont'd)					
Burnett et al. (1999) Metro Toronto, Canada Period of Study: 1980-1994	Hospital Admissions Outcomes (ICD 9 codes): Asthma (493); obstructive lung disease (490-2, 496); Respiratory infection (464, 466, 480-7, 494) Study design: Time series Statistical analyses: Poisson regression model with stepwise analysis Covariates: Long-term trends, season, day of wk, daily maximum temperature, daily minimum temperature, daily avg dew point temperature, daily avg relative humidity Statistical package: S-Plus, SAS Lag: 0,1,2 days, cumulative	24-h mean: 5.35 ppb, CV = 110; 5th: 0 25th: 1 50th: 4 75th: 8 95th: 17 100th: 57 Number of stations: 4	$PM_{2.5}$; r = 0.46 $PM_{2.5-2.5}$; r = 0.28 $PM_{2.5}$; r = 0.44 CO; r = 0.37 NO_2; r = 0.54 O_3; r = 0.02	The percent hospital admissions associated with SO_2 increased for: asthma, COPD, and respiratory infection. However, in multipollutant models significant increases were only seen in asthma and respiratory infection SO_2 effects could be largely explained by other variables in the pollution mix as demonstrated by the Multipollutant model. The greatest contribution of SO_2 is to respiratory infection. However, overall SO_2 is a small factor in total hospitalization response.	Increment: 5.35 ppb (Mean) Single-pollutant model percent increase (t statistic) Asthma: 1.01% (1.76) lag 0-2 OLD 0.03% (0.05) lag 0-1 Respiratory infection: 2.40% (5.04) lag 0-2 Multipollutant model percent increase (SE) Asthma: $SO_2 + CO + O_3$: 0.89% (SE < 2) $SO_2 + CO + O_3 + PM_{2.5}$: 0.69% (SE < 2) $SO_2 + CO + O_3 + PM_{2.5-2.5}$: 0.16% (SE < 2) $SO_2 + CO + O_3 + PM_{2.5}$: 0.76% (SE < 2) Respiratory infection: $SO_2 + NO_2 + O_3$: 1.85% $SO_2 + NO_2 + O_3 + PM_{2.5}$: 0.67 (SE < 2) $SO_2 + NO_2 + O_3 + PM_{2.5-2.5}$: 1.71 (SE ≥ 3) $SO_2 + NO_2 + O_3 + PM_{2.5}$: 1.00 (SE > 2)

TABLE AX5.2 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR RESPIRATORY DISEASES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean Levels & Monitoring Stations	Copollutants & Correlations	Method, Findings, Interpretation	Effects: Relative Risk or % Change & Confidence Intervals (95%)
CANADA (cont'd)					
Burnett* et al. (2001) Toronto, Canada Period of Study: 1980-1994	Hospital Admissions Outcomes (ICD 9 codes): Croup (464.4), pneumonia (480-486), asthma (493), acute bronchitis/bronchiolitis (466) Age groups analyzed: <2 yrs Study design: Time series Statistical analyses: Poisson regression with GAM Covariates: Temporal trend, day of wk, temperature, relative humidity Statistical package: S-Plus Lag: 0-5 days	1-h max SO_2 (ppb) Mean: 11.8 CV: 93 5th: 0 25th: 5 50th: 10 75th: 15 95th: 32 99th: 55 100th: 110 Number of stations: 4	O_3; r = 0.39 SO_2 CO $PM_{2.5}$ $PM_{2.5-2.5}$	SO_2 had the smallest effect on respiratory admissions of all pollutants considered.	Increment: NR All respiratory admissions: Single-pollutant: Percent increase: 3.1% (t = 1.900) lag 3 Multipollutant (adjusted for O_3): Percent increase: 1.21% (t = 0.67) lag 3

TABLE AX5.2 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR RESPIRATORY DISEASES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean Levels & Monitoring Stations	Copollutants & Correlations	Method, Findings, Interpretation	Effects: Relative Risk or % Change & Confidence Intervals (95%)
CANADA (cont'd)					
Fung et al. (2006) Vancouver, BC, Canada Period of Study: 6/1/95-3/31/99	Hospital Admissions Outcomes (ICD 9 codes): All respiratory hospitalizations (460-519) Age groups analyzed: 65+ Study design: (1) Time series (2) Case-crossover, (3) DM-models (Dewanji and Moolgavkar, 2000, 2002) N: 40,974 Statistical analyses: (1) Poisson, (2) conditional logistic regression, (3) DM method–analyze recurrent data in which the occurrence of events at the individual level over time is available Covariates: Day of wk Statistical package: S-Plus and R Lag: Current day, 3 and 5 day lag	SO_2 24-h avg: Mean: 3.46 ppb SD = 1.82 IQR: 2.50 ppb Range: 0.00, 12.50	CO; r = 0.61 COH; r = 0.65 NO_2; r = 0.57 $PM_{2.5}$; r = 0.61 $PM_{2.5}$; r = 0.42 $PM_{2.5-2.5}$; r = 0.57 O_3; r = −30.35	No significant association was found between hospital admissions and current day SO_2 levels (lag 0). Significant associations were found with SO_2 using a 3, 5, and 7 day moving avg, with the strongest association observed with a 7 day lag. The DM method produced slightly higher relative risks compared to the Time series and case crossover results.	Increment: 2.5 ppb (IQR) NO_2 Time series RR 1.013 [0.997, 1.028] lag 0 RR 1.030 [1.010, 1.051] lag 0-3 RR 1.032 [1.008, 1.056] lag 0-5 RR 1.031 [1.003, 1.060] lag 0-7 NO_2 Case-crossover RR 1.010 [0.992, 1.027] lag 0 RR 1.028 [1.005, 1.050] lag 0-3 RR 1.030 [1.004, 1.057] lag 0-5 RR 1.028 [0.998, 1.058] lag 0-7 NO_2 DM model RR 1.013 [0.998, 1.027] lag 0 RR 1.034 [1.015, 1.053] lag 0-3 RR 1.039 [1.016, 1.061] lag 0-5 RR 1.044 [1.018, 1.070] lag 0-7 DM method produced slightly higher RR estimates on O_3, SO_2 and $PM_{2.5}$ compared to time-series and case-crossover, and slightly lower RR estimates on COH, NO_2, and $PM_{2.5}$, though the results were not significantly different from one another.

TABLE AX5.2 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR RESPIRATORY DISEASES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean Levels & Monitoring Stations	Copollutants & Correlations	Method, Findings, Interpretation	Effects: Relative Risk or % Change & Confidence Intervals (95%)
CANADA (cont'd)					
Kesten et al. (1995) Toronto, ON, Canada Period of Study: 1991-1992	ED Visits Outcome(s) (ICD 9): Asthma (493) Age groups analyzed: Study design: Time series N: 854 # of Hospitals: 1 Statistical analyses: Auto regression Statistical package: SAS Lag: 1 or 7	SO_2 24-h avg No data was provided for concentration or for correlation with other pollutants.	NO_2 O_3 API (TRS, CO, TSP)	Fit of an auto-regression model with covariates linked to same day gave no evidence of association between asthma and SO_2. Despite multiple attempts to correlate individual or combinations of pollutants with air quality indices, no association was found between ER visits for asthma and ambient daily, weekly, or monthly levels of SO_2, NO_2, or O_3.	No relative risks were provided.

TABLE AX5.2 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR RESPIRATORY DISEASES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean Levels & Monitoring Stations	Copollutants & Correlations	Method, Findings, Interpretation	Effects: Relative Risk or % Change & Confidence Intervals (95%)
CANADA (cont'd)					
Lin et al. (2003) Toronto, ON Period of Study: 1981-1993	Hospital Admissions Outcomes (ICD 9 codes): Asthma (493) Age groups analyzed: 6-12 Study design: Bi-directional case-crossover N: 7,319 Statistical analyses: Conditional logistic regression Covariates: Daily maximum and minimum temperatures and avg relative humidity Lag: Cumulative lag of 1-7 days.	SO_2 24-h avg: 0.36 ppb SD = 5.90 Range: 0, 57.00 25th: 1.00 50th: 4.00 75th: 8.00 Number of Stations: 4	CO; r = 0.37 NO_2; r = 0.54 $PM_{2.5}$; r = 0.44 O_3; r = −0.01 $PM_{2.5}$; r = 0.46 $PM_{2.5-2.5}$; r = 0.28	SO_2 is positively associated with asthma hospitalizations, although the relationship varies in boys and girls.	Increment: 7 ppb (IQR) Boys 6-12 yrs; Girls 6-12 yrs Lag 0: OR 1.00 [0.95, 1.05]; 1.04 [0.97, 1.11] Lag 0-1: OR 0.99 [0.93, 1.06]; 1.04 [0.95, 1.13] Lag 0-2: OR 0.98 [0.90, 1.06]; 1.05 [0.95, 1.16] Lag 0-3: OR 0.96 [0.87, 1.05]; 1.09 [0.98, 1.22] Lag 0-4: OR 0.95 [0.86, 1.05]; 1.13 [1.00, 1.28] Lag 0-5: OR 0.93 [0.83, 1.03]; 1.17 [1.02, 1.34] Lag 0-6: OR 0.93 [0.83, 1.04]; 1.20 [1.04, 1.39] Multipollutant model with $PM_{2.5-2.5}$ and $PM_{2.5}$ Boys 6-12 yrs; Girls 6-12 yrs Lag 0: OR 0.98 [0.93, 1.04]; 1.06 [0.98, 1.14] Lag 0-1: OR 0.99 [0.91, 1.06]; 1.03 [0.93, 1.14] Lag 0-2: OR 0.96 [0.88, 1.05]; 1.04 [0.92, 1.17] Lag 0-3: OR 0.95 [0.85, 1.05]; 1.08 [0.95, 1.23] Lag 0-4: OR 0.94 [0.84, 1.06]; 1.12 [0.97, 1.29] Lag 0-5: OR 0.91 [0.80, 1.04]; 1.18 [1.00, 1.38] Lag 0-6: OR 0.91 [0.80, 1.04]; 1.28 [1.08, 1.51]

TABLE AX5.2 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR RESPIRATORY DISEASES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean Levels & Monitoring Stations	Copollutants & Correlations	Method, Findings, Interpretation	Effects: Relative Risk or % Change & Confidence Intervals (95%)
CANADA (cont'd)					
Lin* et al. (2004b) Vancouver, BC Canada Period of Study: 1987-1998	Hospital Admissions Outcomes (ICD 9 codes): Asthma (493) Age groups analyzed: 6-12 Study design: Time series N: 3,754 (2,331 male, 1,423 female) Statistical analyses: Semi-parametric Poisson regression with GAM (with default and more stringent criteria) Covariates: Trend, day of wk, Statistical package: S-Plus Lag: Cumulative 1-7 day	24-h avg SO_2 (ppb) Mean: 4.77 SD = 2.75 Min: 0 25th: 2.75 50th: 4.25 75th: 6.00 Max: 24.00 Number of stations: 30	CO; r = 0.67 NO_2; r = 0.67 O_3; r = −0.10 $PM_{2.5}$; r = $PM_{2.5}$; r =	Results presented are default GAM, but authors state that use of natural cubic splines with a more stringent convergence rate produced similar results	Increment: 3.3 ppb (IQR) Boys 6-12 yrs by SES status: Low; High Lag 0 RR 1.02[0.94, 1.10]; 1.03 [0.95, 1.12] Lag 0-1 RR 1.03 [0.94, 1.13]; 1.06 [0.96, 1.17] Lag 0-2 RR 1.03 [0.93, 1.15]; 1.06 [0.95, 1.18] Lag 0-3 RR 1.01 [0.90, 1.13]; 1.04 [0.92, 1.17] Lag 0-4 RR 0.98 [0.88, 1.10]; 1.02 [0.90, 1.14] Lag 0-5 RR 0.97 [0.86, 1.10]; 1.02 [0.89, 1.16] Lag 0-6 RR 0.98 [0.86, 1.12]; 1.05 [0.91, 1.21] Girls 6-12 yrs by SES status: Low; High Lag 0 RR 1.05 [0.95, 1.16]; 1.07 [0.96, 1.19] Lag 0-1 RR 1.11 [0.99, 1.25]; 1.07 [0.94, 1.21] Lag 0-2 RR 1.11 [0.97, 1.26]; 1.07 [0.93, 1.23] Lag 0-3 RR 1.18 [1.02, 1.36]; 1.02 [0.87, 1.19] Lag 0-4 RR 1.18 [1.02, 1.35]; 0.99 [0.85, 1.15] Lag 0-5 RR 1.19 [1.01, 1.40]; 0.95 [0.80, 1.13] Lag 0-6 RR 1.15 [0.97, 1.36]; 0.98 [0.81, 1.17] Multipollutant model (adjusted for NO_2) Girls, Low SES: 1.17 [1.00, 1.37] lag 0-3 1.19 [1.00, 1.42] lag 0-5

TABLE AX5.2 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR RESPIRATORY DISEASES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean Levels & Monitoring Stations	Copollutants & Correlations	Method, Findings, Interpretation	Effects: Relative Risk or % Change & Confidence Intervals (95%)
CANADA (cont'd)					
Lin et al. (2005) Toronto, ON, Canada Period of Study: 1998-2001	Hospital Admissions Outcomes (ICD 9 codes): Respiratory infections (464,466, 480-487) Age groups analyzed: 0-14 Study design: Case-crossover N: 6,782 # of Hospitals: Statistical analyses: Conditional logistic regression Covariates: Statistical package: SAS 8.2 Lag: 0-6 days	24-h avg: Mean: 4.73 ppb SD = 2.58 ppb Range: 1.00, 19.67 25th: 3.00 50th: 4.00 75th: 6.00 Number of monitors: 5	$PM_{2.5}$; r = 0.47 $PM_{2.5-2.5}$; r = 0.29 $PM_{2.5}$; r = 0.48 CO; r = 0.12 NO_2; r = 0.61	Asthma hospitalization for boys was associated with SO_2 before the adjustment for fine and coarse PM. Asthma hospitalization for girls was not associated with SO_2 for any lag.	Increment: 3 ppb (IQR) Unadjusted Boys only: OR 1.06 [0.97, 1.16] lag 0-3 OR 1.02 [0.92, 1.13] lag 0-5 Girls only: OR 1.05 [0.94, 1.16] lag 0-3 OR 1.07 [0.95, 1.21] lag 0-5 Boys and Girls OR 1.06 [0.99, 1.13] lag 0-3 OR 1.04 [0.96, 1.13] lag 0-5 Adjusted Boys only: OR 1.11 [1.01, 1.21] lag 0-3 OR 1.08 [0.97, 1.21] lag 0-5 Girls only: OR 1.07 [0.96, 1.19] lag 0-3 OR 1.12 [0.98, 1.28] lag 0-5 Boys and Girls OR 1.10 [1.02, 1.18] lag 0-3 OR 1.10 [1.01, 1.20] lag 0-5

TABLE AX5.2 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR RESPIRATORY DISEASES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean Levels & Monitoring Stations	Copollutants & Correlations	Method, Findings, Interpretation	Effects: Relative Risk or % Change & Confidence Intervals (95%)
CANADA (cont'd)					
Lin et al. (2005) (cont'd)					Multipollutant model with $PM_{2.5}$ and $PM_{2.5}$ Boys only: OR 1.02 [0.90, 1.15] lag 0-3 OR 0.99 [0.85, 1.16] lag 0-5 Girls only: OR 1.09 [0.0.94, 1.26] lag 0-3 OR 1.07 [0.90, 1.28] lag 0-5 Boys and Girls OR 1.05 [0.95, 1.15] lag 4 OR 1.03 [0.91, 1.16] lag 6

TABLE AX5.2 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR RESPIRATORY DISEASES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean Levels & Monitoring Stations	Copollutants & Correlations	Method, Findings, Interpretation	Effects: Relative Risk or % Change & Confidence Intervals (95%)
CANADA (cont'd)					
Luginaah et al. (2005) Windsor, ON, Canada Period of Study: 4/1/95-12/31/00	Hospital Admissions Outcomes (ICD 9 codes): Respiratory admissions (460-519) Age groups analyzed: 0-14, 15-64, 65+, all ages Study design: (1) Time series and (2) case-crossover N: 4,214 # of Hospitals: 4 Statistical analyses: (1)Poisson regression, GAM with natural splines (stricter criteria), (2) conditional logistic regression with Cox proportional hazards model Covariates: Temperature, humidity, change in barometric pressure, day of wk Statistical package: S-Plus Lag: 1,2,3 days	SO_2 mean 1 h Max: 27.5 ppb, SD = 16.5; Range: 0, 129 IQR: Number of stations: 4	NO_2; r = 0.22 CO; r = 0.16 $PM_{2.5}$; r = 0.22 COH; r = 0.14 O_3; r = −0.02 TRS; r = 0.13	The effect of SO_2 on respiratory hospitalization varies considerably, especially at low levels of exposure.	Increment: 19.25 ppb (IQR) Time-series, females; males All ages, 1.041 [0.987, 1.098]; 0.953 [0.900, 1.009] lag 1 0-14 yrs, 1.111 [1.011, 1.221] ; 0.952 [0.874, 1.037] lag 1 15-65 yr, 1.031 [0.930, 1.144] ; 0.971 [0.845, 1.15] lag 1 65+ yr, 1.030 [0.951, 1.115] ; 0.9409 [0.860, 1.029] lag 1 Case-crossover, females; males All ages, 1.047 [0.978, 1.122]; 0.939 [0.874, 1.009] lag 1 0-14 yrs, 1.119 [0.995, 1.259] ; 0.923 [0.831, 1.025] lag 1 15-65 yr, 1.002 [0.879, 1.141] ; 0.944 [0.798, 1.116] lag 1 65+ yr, 1.020 [0.924, 1.126] ; 0.968 [0.867, 1.082] lag 1

TABLE AX5.2 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR RESPIRATORY DISEASES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean Levels & Monitoring Stations	Copollutants & Correlations	Method, Findings, Interpretation	Effects: Relative Risk or % Change & Confidence Intervals (95%)
CANADA (cont'd)					
Villeneuve et al., 2006 Toronto, ON, Canada Period of Study: 1995-2000 Days: 2,190	GP Visits Outcome(s) (ICD9): Allergic Rhinitis (177) Age groups analyzed: ≥65 Study design: Time series N: 52,691 Statistical analyses: GLM, using natural splines (more stringent criteria than default) Covariates: Day of wk, holiday, temperature, relative humidity, aero-allergens Season: All Yr; Warm, May-Oct; Cool, Nov-Apr Statistical package: S-Plus Lag: 0-6	24-h avg: 4.7 ppb SD = 2.8 IQR: 3.2 ppb Range: 0, 24.8 Number of stations: 9	NO_2 O_3 CO $PM_{2.5}$ $PM_{2.5\text{-}2.5}$ $PM_{2.5}$	There were positive associations between allergic rhinitis and SO_2 for exposures occurring on the same day as physician visits, but only during the winter time.	Increment: 10.3 ppb (IQR) All results estimated from Stick Graph: All Yr: Mean increase: 1.7% [−0.4, 2.8] lag 0 Warm: Mean increase: 0.3% [−1.9, 2.5] lag 0 Cool: Mean increase: 1.9% [−0.2, 4.1] lag 0

TABLE AX5.2 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR RESPIRATORY DISEASES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean Levels & Monitoring Stations	Copollutants & Correlations	Method, Findings, Interpretation	Effects: Relative Risk or % Change & Confidence Intervals (95%)
CANADA (cont'd)					
Yang et al. (2003a) Vancouver, Canada Period of Study: 1986-1998 Days: 4748	Hospital admissions outcomes (ICD 9 codes): All respiratory admissions (460-519) Study design: Case-crossover Age groups analyzed: <3, ≥65 Statistical analyses: conditional logistic regression Statistical package: NR Lag: 0-5 days	24-h avg SO_2 (ppb): Mean: 4.84 SD = 2.84 5th: 1.50 25th: 2.75 50th: 4.25 75th: 6.25 100th: 24.00 IQR: 3.50 Number of stations: 30	CO NO_2 O_3; r = −0.37 COH	SO_2 showed the weakest effect among children and the second weakest effect among older adults when compared to all other pollutants considered in the study.	Increment: 3.50 ppb (IQR) All respiratory admissions <3 yrs: SO_2 alone: OR 1.01 [0.98, 1.05] lag 2 $SO_2 + O_3$: OR 1.01 [0.97, 1.04] lag 2 $SO_2 + O_3 + CO + COH + NO_2$: OR 0.98 [0.94, 1.03] lag 2 All respiratory admissions ≥65 yrs: SO_2 alone: OR 1.02 [1.00, 1.04] lag 0 $SO_2 + O_3$: OR 1.02 [1.00, 1.04] lag 0 $SO_2 + O_3 + CO + COH + NO_2$: OR 1.01 [0.98, 1.03] lag 0

TABLE AX5.2 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR RESPIRATORY DISEASES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean Levels & Monitoring Stations	Copollutants & Correlations	Method, Findings, Interpretation	Effects: Relative Risk or % Change & Confidence Intervals (95%)
CANADA (cont'd)					
Yang et al. (2005) Vancouver, BC, Canada Period of Study: 1994-1998 Days: 1826	Hospital admissions outcomes (ICD 9 codes): COPD excluding asthma (490-2, 494, 496) Age groups analyzed: 65+ Study design: Time series N: 6,027 Statistical analyses: Poisson regression with GAM (with more stringent criteria) Covariates: Temperature, relative humidity, day of wk, temporal trends, season Statistical package: S-Plus Lag: 0-6 days, moving averages	24-h avg: 3.79 ppb, SD = 2.12; IQR: 2.75 ppb; Range: 0.75, 22.67 Winter: 4.10 (2.87) Spring: 3.40 (1.58) Summer: 4.10 (1.79) Fall: 3.56 (1.92) Number of Stations: 31	$PM_{2.5}$; r = 0.62 NO_2; r = 0.61 CO; r = 0.67 O_3; r = −0.34	This study produced a marginally significant association between COPD hospitalization and 6-day SO_2 exposure. Most previous studies have not detected a significant effect of SO_2 on respiratory ED visits or hospitalizations.	Increment: 2.75 ppb (IQR) COPD > 65 yrs, yr round RR 1.00 [0.97, 1.04] lag 0 RR 1.02 [0.98, 1.06] lag 0-1 RR 1.04 [0.99, 1.08] lag 0-2 RR 1.04 [0.99, 1.09] lag 0-3 RR 1.05 [0.99, 1.11] lag 0-4 RR 1.06 [1.00, 1.13] lag 0-5 RR 1.06 [0.99, 1.13] lag 0-6 2-pollutant model NO_2: RR 0.99 [0.91, 1.08] lag 0 CO: RR 0.97 [0.87, 1.07] lag 0-6 O_3: RR 1.07 [1.00, 1.14] lag 0-6 $PM_{2.5}$: 0.97 [0.88, 1.06] lag 0-6 Multipollutant models SO_2, CO, NO_2, O_3, $PM_{2.5}$: RR 0.94 [0.85, 1.05] SO_2, CO, NO_2, O_3: RR 0.96 [0.86, 1.06]

TABLE AX5.2 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR RESPIRATORY DISEASES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean Levels & Monitoring Stations	Copollutants & Correlations	Method, Findings, Interpretation	Effects: Relative Risk or % Change & Confidence Intervals (95%)
AUSTRALIA/NEW ZEALAND					
Barnett et al. (2005) Multicity, Australia/New Zealand; (Auckland, Brisbane, Canberra, Christchurch, Melbourne, Perth, Sydney) Period of Study: 1998-2001	Hospital admissions outcomes (ICD 9/ICD 10): All respiratory (460-519/J00-J99 excluding J95.4-J95.9, RO9.1, RO9.8), asthma (493/J45, J46, J44.8), COPD (490-492, 494-496/J40-J44, J47, J67), pneumonia with bronchitis (466, 480-486/J12-17, J18.0 j18.1 J18.8 J18.9 J20 J21) Age groups analyzed: 0, 1-4, 5-14 Study design: Case-crossover Statistical analyses: Conditional logistic regression, random effects meta-analysis Covariates: Temperature, current-previous day temperature, relative humidity, pressure, extremes of hot and cold, day of wk, holiday, day after holiday Season: Cool, May-Oct; Warm, Nov-Apr Statistical package: SAS Lag: 0-1 days	24-h avg (ppb) (range): Auckland: 4.3 (0, 24.3) Brisbane: 1.8 (0, 8.2) Canberra: NA Christchurch: 2.8 (0, 11.9) Melbourne: NA Perth: NA Sydney: 0.9 (0, 3.9) Daily 1-h max (range): Auckland: NA Brisbane: 7.6 (0, 46.5) Canberra: NA Christchurch: 10.1 (0.1, 42.1) Melbourne: NA Perth: NA Sydney: 3.7 (0.1, 20.2) IQR: 5.4 ppb	BS; r = 0.07, 0.29 $PM_{2.5}$; r = 0.12, 0.35 $PM_{2.5}$; r = 0.17, 0.33 CO; r = 0.25, 0.41 NO_2; r = 0.15, 0.58 O_3; r = −0.12, 0.16	Increased hospital admissions were significantly associated with SO_2 for acute bronchitis, pneumonia, and respiratory diseases. In multipollutant models the impacts of particulate matter and NO_2 were isolated. There were seasonal impacts on pneumonia and acute bronchitis admissions in the 1- to 4-yr-old age group for SO_2.	Increment: 5.4 ppb (1-h max IQR) Pneumonia and acute bronchitis 0 yrs 3.5% [−0.3, 7.3] lag 0-1 1-4 yrs 6.9% [2.3, 11.7] lag 0-1 Respiratory 0 yrs 3.2% [0.3, 6.3] lag 0-1 1-4 yrs 2.7% [0.6, 4.8] lag 0-1 5-14 yrs 2.0% [−5.5, 10.1] lag 0-1 Asthma 0 yrs No analysis (poor diagnosis) 1-4 yrs 3.4% [−4.3, 11.6] lag 0-1 5-14 yrs 3.3% [−5.6, 13.0] lag 0-1

TABLE AX5.2 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR RESPIRATORY DISEASES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean Levels & Monitoring Stations	Copollutants & Correlations	Method, Findings, Interpretation	Effects: Relative Risk or % Change & Confidence Intervals (95%)
AUSTRALIA/NEW ZEALAND (cont'd)					
Petroeschevsky et al. (2001) Brisbane, Australia Period of Study: 1987-1994 Days: 2922	Hospital admissions outcomes (ICD 9): All respiratory (460-519); Asthma (493) Age groups analyzed: 0-4, 5-14, 15-64, 65+, all ages Study design: Time series N: 33,710 (13,246 = asthma) Statistical analyses: APHEA protocol, Poisson regression, GEE Covariates: Temperature, humidity, season, infectious disease, day of wk, holiday Season: Summer, Autumn, Winter, Spring, All yr Dose-response investigated?: Yes Statistical package: SAS Lag: Single: 1,2,3 day Cumulative: 0-2, 0-4	Mean: 24-h avg: Overall: 4.1 ppb Summer: 3.9 ppb Autumn: 4.2 ppb Winter: 4.8 ppb Spring: 3.7 ppb Mean: 1-h max Overall: 9.2 ppb Summer: 7.8 ppb Autumn: 9.3 ppb Winter: 11.3 ppb Spring: 8.4 ppb # of stations: 3	Bsp O_3 NO_2	SO_2 was highly correlated with maximum daily ER admissions for respiratory conditions. The highest association was observed in the winter followed by autumn, spring, and summer. For asthma, the highest association was observed in the winter and autumn. No statistically significant contributions for respiratory admissions were reported for the age group 5-14 yr olds for any pollutant.	Increment: 0 ppb Respiratory: 0-4 yrs 24-h avg 1.224 [1.087, 1.377] lag 0-4 5-14 yrs 1-h max 1.049 [0.986, 1.116] lag 0-4 15-64 yrs 24-h avg 1.033 [0.895, 1.118] lag 1 65+ yrs 24-h avg 1.121 [1.019, 1.234] lag 0 All ages 24-h avg 1.080 [1.030, 1.131] lag 1 Asthma: 0-14 yrs 24-h avg 1.080 [0.971, 1.201] lag 0 15-64 yrs 1-h max 0.941 [0.900, 0.984] lag 0 All ages 24-h avg 0.941 [0.876, 1.011] lag 2

TABLE AX5.2 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR RESPIRATORY DISEASES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean Levels & Monitoring Stations	Copollutants & Correlations	Method, Findings, Interpretation	Effects: Relative Risk or % Change & Confidence Intervals (95%)
EUROPE					
Anderson et al. (1997) Multicity, Europe (Amsterdam, Barcelona, London, Paris, Rotterdam) Period of Study: 1977-1989 for Amsterdam and Rotterdam 1986-1992 for Barcelona 1987-1991 for London 1980-1989 for Milan 1987-1992 for Paris	Hospital admissions outcomes (ICD 9): COPD–unspecified bronchitis (490), chronic bronchitis (491), emphysema (492), chronic airways obstruction (496) Study design: Time series Statistical analyses: APHEA protocol, Poisson regression, meta-analysis Covariates: Trend, season, day of wk, holiday, influenza, temperature, humidity Season: Cool, Oct-Mar; Warm, Apr-Sep Statistical package: NR Lag: 0,1,2 days and 0-3 cumulative	24-h all yr avg ($\mu g/m^3$): Amsterdam: 21 Barcelona: 40 London: 31 Milan: 53 Paris: 23 Rotterdam: 32 1-h max Amsterdam: 50 Barcelona: 60 London: NR Milan: NR Paris: 47 Rotterdam: 82	NO_2 BS TSP O_3	The effect of SO_2 varied considerably across the cities; however, the summer estimate was significantly associated with COPD for the 1-h measure and borderline significant for the daily mean. Both 24-h and 1-h SO_2 concentrations were significantly associated with COPD ER admissions in the warm season. Only cumulative lags of SO_2 showed borderline significance.	Increment: 50 $\mu g/m^3$ COPDC-Warm season 24 h 1.05 [1.01, 1.10] 1 h 1.02 [1.00, 1.04] COPD-Cool season 24 h 1.02 [0.98, 1.05] 1 h 1.01 [0.99, 1.03] COPD-All yr 24-h avg 1.022 [0.981, 1.055] lag 1 24-h avg 1.021 [0.998, 1.054] lag 0-3, cumulative 1-h max 1.01 [0.994, 1.029] lag 1 1-h max 1.015 [1.003, 1.027] lag 0-3, cumulative

TABLE AX5.2 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR RESPIRATORY DISEASES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean Levels & Monitoring Stations	Copollutants & Correlations	Method, Findings, Interpretation	Effects: Relative Risk or % Change & Confidence Intervals (95%)
EUROPE (cont'd)					
Atkinson et al. (2001) Multicity, Europe (Barcelona, Birmingham, London, Milan, Netherlands, Paris, Rome, Stockholm) Period of Study: 1998-1997	Hospital admissions outcomes (ICD 9): Asthma (493), COPD (490-496), All respiratory (460-519) Study design: Time series Statistical analyses: APHEA protocol, Poisson regression, meta-analysis Covariates: Season, temperature, humidity, holiday, influenza Statistical package: NR Lag: NR	1-h max of SO_2 (µg/m^3) Barcelona: NR Birmingham: 24.3 London: 23.6 Milan: 29.1 Netherlands: 8.5 Paris: 17.7 Rome: 9.8 Stockholm: 3.8	NO_2, O_3, CO, BS $PM_{2.5}$; r = Barcelona: 0.32 B'gham: 0.77 London: 0.72 Milan: 0.64 Netherlands: 0.67 Paris: 0.63 Rome: 0.15 Stockholm: 0.36	The inclusion of SO_2 in the models only modified $PM_{2.5}$ associations in the 0- to 14-yr age group.	Increment: 10 µg/m^3 for $PM_{2.5}$; change in SO_2 not described. Asthma, 0 to 14 yrs: For $PM_{2.5}$: 1.2 [0.2, 2.3] For $PM_{2.5}$ + SO_2: 0.8 [−3.7, 5.6] Asthma, 15 to 64 yrs: For $PM_{2.5}$: 1.1 [0.3, 1.8] For $PM_{2.5}$ + SO_2: 1.6 [0.6, 2.6] COPD + Asthma, ≥65 yrs For $PM_{2.5}$: 1.0 [0.4, 1.5] For $PM_{2.5}$ + SO_2: 1.3 [0.7, 1.8] All respiratory, ≥65 yrs of age For $PM_{2.5}$: 0.9 [0.6, 1.3] For $PM_{2.5}$ + SO_2: 1.1 [0.7, 1.4]

TABLE AX5.2 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR RESPIRATORY DISEASES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean Levels & Monitoring Stations	Copollutants & Correlations	Method, Findings, Interpretation	Effects: Relative Risk or % Change & Confidence Intervals (95%)
EUROPE (cont'd)					
Schouten et al. (1996) Multicity, The Netherlands (Amsterdam, Rotterdam) Period of Study: 04/01/77-09/30/89	Hospital admissions outcomes (ICD 9): All respiratory (460-519), COPD (490-2, 494, 496), Asthma (493) Age groups analyzed: 15-64, 65+, all ages Study design: Time series Statistical analyses: APHEA protocol, Poisson regression Covariates: Long-term trend, season, influenza, day of wk, holiday, temperature, humidity Season: Cool, Nov-Apr; Warm: May-Oct Statistical package: NR Lag: 0,1,2 days; and cumulative 0-1 and 0-3 day lags	24-h avg SO_2 Amsterdam Mean/Med: 28/21 µg/m^3 Rotterdam Mean: 40/32 µg/m^3 Daily 1-h max Amsterdam Mean/Med: 65/50 µg/m^3 Rotterdam Mean/Med: 99/82 µg/m^3 # of stations: 1 per city	NO_2 BS O_3	The relationship between short-term air pollution and hospital admissions was not always consistent at low levels of exposure. One statistically significant association between hospital admissions and asthma (all ages) occurred in Amsterdam after a cumulative lag of 1-3 days in the summer. Higher SO_2 levels were reported for the winter; therefore, this association was not a concentration response.	Increment: 100 µg/m^3 increment. All respiratory, Amsterdam 24-h avg 15-64 yrs RR 0.944 [0.864, 1.032] lag 2 RR 0.915 [0.809, 1.035] lag 0-3 >65 yrs RR 1.046 [0.965, 1.134] lag 2 RR 1.008 [0.899, 1.131] lag 0-3 1-h max 15-64 yrs RR 0.989[0.952, 1028] lag 2 RR 0.977 [0.927, 1.030] lag 0-3 >65 yrs RR 1.022 [0.985, 1060] lag 2 RR 1.010 [0.955, 1.068] lag 0-3 RR 0.941 [0.863, 1.026] lag 0-3

TABLE AX5.2 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR RESPIRATORY DISEASES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean Levels & Monitoring Stations	Copollutants & Correlations	Method, Findings, Interpretation	Effects: Relative Risk or % Change & Confidence Intervals (95%)
EUROPE (cont'd)					
Schouten et al. (1996) (cont'd)				In Rotterdam neither 1 day nor cumulative lags in the summer or winter increased asthma admissions to statistical significance. Rotterdam had much higher mean SO_2 concentrations. There were no significant associations to hospital admissions when higher pollution levels were prevalent.	COPD, Amsterdam 24-h avg–all ages RR 0.907 [0.814, 1.011] lag 0 RR 0.948 [0.838, 1.072] lag 0-1 1-h max–all ages RR 0.978 [0.933, 1.026] lag 0 RR 0.995 [0.940, 1.053] lag 0-1 Asthma, Amsterdam 24-h avg–all ages RR 0.802 [0.696, 0.924] lag 1 RR 0.792 [0.654, 0.958] lag 0-3 1-h max–all ages RR 0.995 [0.942, 1.051] lag 0

TABLE AX5.2 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR RESPIRATORY DISEASES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean Levels & Monitoring Stations	Copollutants & Correlations	Method, Findings, Interpretation	Effects: Relative Risk or % Change & Confidence Intervals (95%)
EUROPE (cont'd)					
Schouten et al. (1996) (cont'd)				The analysis of all respiratory hospital admissions for all ages in the entire country (Netherlands) produced a statistically significant association for both 1-h and 24-h periods (100 μg/m^3).	All respiratory, Rotterdam 24-h avg 15-64 yrs RR 0.941 [0.855, 1.036] lag 1 RR 0.895 [0.787, 1.019] lag 0-2 >65 yrs 1977-1981 RR 1.027 [0.904, 1.165] lag 2 RR 1.011 [0.834, 1.227] lag 0-3 >65 yrs 1982-1984 RR 1.087 [0.890, 1.328] lag 0 RR 1.258 [0.926, 1.710] lag 0-3 >65 yrs 1985-1989 RR 1.045 [0.908, 1.204] lag 0 RR 0.968 [0.787, 1.190] lag 0-3 1-h max 15-64 yrs RR 0.989[0.953, 1025] lag 1 RR 0.965 [0.915, 1.018] lag 0-2 >65 yrs 1977-1981 RR 0.892 [0.842, 0.945] lag 0 RR 0.987 [0.907, 1.074] lag 0-3 >65 yrs 1982-1984 RR 1.005 [0.933, 1.081] lag 0 RR 1.062 [0.938, 1.202] lag 0-3 >65 yrs 1985-1989 RR 1.010 [0.955, 1.068] lag 0 RR 1.064 [0.992, 1.141] lag 0-1

TABLE AX5.2 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR RESPIRATORY DISEASES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean Levels & Monitoring Stations	Copollutants & Correlations	Method, Findings, Interpretation	Effects: Relative Risk or % Change & Confidence Intervals (95%)
EUROPE (cont'd)					
Schouten et al. (1996) (cont'd)					COPD, Rotterdam 24-h avg–all ages RR 0.963 [0.874, 1.059] lag 2 RR 1.019 [0.887, 1.172] lag 0-3 1-h max–all ages RR 0.991 [0.955, 1.029] lag 2 RR 1.013 [0.953, 1.076] lag 0-3
Spix et al. (1998) Multicity (London, Amsterdam, Rotterdam, Paris, Milan), Europe Period of Study: 1977 and 1991	Hospital Admissions Outcomes (ICD 9 codes): All respiratory (460-519); Asthma (493) Age groups analyzed: 15-64, 65+ Study design: Time series # of Hospitals: Statistical analyses: Poisson regression following APHEA protocol. Pooled meta-analysis adjusted for heterogeneity Covariates: trend, seasonality, day of wk, holiday, temperature, humidity, unusual events (strikes, etc.) Statistical package: Lag: 1 to 3 days	SO_2 daily mean (µg/m^3) London: 29 Amsterdam: 21 Rotterdam: 25 Paris: 23 Milan: 66	NO_2, O_3, BS, TSP	Daily counts of adult respiratory admissions were not consistently associated with daily mean levels of SO_2. Heterogeneity between cities was likely due to the number of stations or temperature. Only hospital admissions for ≥65 yr olds were significantly associated with SO_2 in the warm season.	Increment: 50 µg/m^3 All cities, yr round 15-64 yrs RR 1.009 [0.992, 1.025] Warm RR 1.01 [0.98, 1.04] Cold RR 1.01 [0.97, 1.07] ≥65 yrs RR 1.02 [1.005, 1.046] Warm RR 1.06 [1.01, 1.11] Cold RR 1.02 [0.99, 1.04] APHEA protocol pooled result from ≥65 yrs old from Europe All respiratory RR 1.02 [1.00, 1.05]

TABLE AX5.2 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR RESPIRATORY DISEASES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean Levels & Monitoring Stations	Copollutants & Correlations	Method, Findings, Interpretation	Effects: Relative Risk or % Change & Confidence Intervals (95%)
EUROPE (cont'd)					
Sunyer et al. (1997) Multicity, Europe (Barcelona, Helsinki, Paris, London) Period of Study: 1986-1992	Hospital admissions/ED visits outcomes (ICD 9): Asthma (493) Age groups analyzed: <15, 15-64 Study design: Time series Statistical analyses: APHEA protocol, Poisson regression, GEE; meta-analysis Covariates: Humidity, temperature, influenza, soybean, Long-term trend, season, day of wk Season: Cool, Oct-Mar; Warm: Apr-Sep Statistical package: NR Lag: 0,1,2,3 and cumulative 1-3	24-h median (range) ($\mu g/m^3$) Barcelona: 41 (2, 160) Helsinki: 16 (3, 95) London: 31 (9, 100) Paris: 23 (1, 219) # of stations: Barcelona: 3 London: 4 Paris: 4 Helsinki: 8	NO_2 black smoke O_3	SO_2 alone or as part of a mixture was a factor that exacerbated asthma admissions. In 2-pollutant models with SO_2 and BS, the association of BS with SO_2 was attenuated for <15 yr olds, compared to single-pollutant model associations. In addition, the association of NO_2 was also attenuated by the inclusion of SO_2.	Increment: 50 $\mu g/m^3$ of 24-h avg for all cities combined. Asthma 15-64 yrs 0.997 [0.961, 1.034] lag 2 1.003 [0.959, 1.050] lag 0-3, cum <15 yrs 1.075 [1.026, 1.126] lag 1 1.061 [0.996, 1.131]lag 2-3, cum 2-pollutant models: SO_2/Black smoke <15 yrs 1.092 [1.031, 1.156] lag 0-1 SO_2/NO_2 <15 yrs 1.075 [1.019, 1.135]

TABLE AX5.2 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR RESPIRATORY DISEASES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean Levels & Monitoring Stations	Copollutants & Correlations	Method, Findings, Interpretation	Effects: Relative Risk or % Change & Confidence Intervals (95%)
EUROPE (cont'd)					
Sunyer et al. (2003) Multicity study (Birmingham (B), London (L), Milan (M), Netherlands (N), Paris (P), Rome (R) and Stockholm (S), Europe Period of Study: 1992 and 1997	Hospital admissions/ED visits outcome(s) (ICD 9): Asthma (493); COPD and Asthma (490-496); All respiratory (460-519) Age groups analyzed: All, 0-14 yrs; 16-64 yrs; ≥65 yrs Study design: Time series Poisson regression with GAM following APHEA 2 protocol Covariates: temperature, humidity, Long-term trend, season Statistical package: NR Lag: 0, 1	SO_2 24-h avg and SD ($\mu g/m^3$) B 24.3 (12.7) L 23.6 (23.7) M 32.5 (37.5) N 8.5 (7.7) P 17.7 (12.5) R 9.8 (9.9) S 6.8 (6.2)	$PM_{2.5}$; r = 0.64 CO; r = 0.53	The magnitude of association with asthma across the seven cities was comparable to earlier studies of London, Helsinki and Paris. Exposure factors may be important. Children may spend greater time outdoors compared with adults. Pneumonia requires chronic exposure to produce inflammatory response and infection, whereas asthma is an acute response.	Increment: 10 $\mu g/m^3$ Asthma 0-14 yrs 1.3% [0.4, 2.2] 15-64 yrs 0.0% [−0.9, 1.00] COPD and Asthma ≥65 yrs 0.6% [0.0, 1.2] All Respiratory ≥65 yrs 0.5% [0.1, 0.9] Asthma 0-14 yrs SO_2 + $PM_{2.5}$: −3.7% (p > 0.1) SO_2 + CO: −0.7% (p > 0.1)

TABLE AX5.2 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR RESPIRATORY DISEASES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean Levels & Monitoring Stations	Copollutants & Correlations	Method, Findings, Interpretation	Effects: Relative Risk or % Change & Confidence Intervals (95%)
EUROPE (cont'd)					
Anderson et al. (1998) London, England Period of Study: Apr 1987-Feb 1992 Days: 1,782	Hospital admissions outcomes (ICD 9): Asthma (493) Age groups analyzed: <15, 15-64, 65+ Study design: Time series Statistical analyses: APHEA protocol, Poisson regression Covariates: Time trends, seasonal cycles, day of wk, public holidays, influenza epidemics, temperature, humidity Season: Cool (Oct- Mar); Warm (Apr-Sep) Statistical package: NR Lag: 0, 1, 2 days	24-h avg SO_2 ($\mu g/m^3$) Mean: 32.0 SD = 11.7 Range: 9, 100 5th: 16 10th: 18 25th: 24 50th: 31 75th: 38 90th: 46 95th: 52 # of monitors: 2	O_3 NO_2 BS	The strongest association between SO_2 and asthma admissions was for those ≥65 yrs in the cool season. A weaker association was observed for children in the warm season and all yr. The adult population showed no association. In 2-pollutant models ozone was overall the strongest pollutant associated with hospital admission with weaker associations with NO_2 and BS. The most consistent yr-round association for All ages was found with BS. When looking at all ages combined, SO_2 association remained significant in all 2-pollutant models except with NO_2, both for all yr and the summer (warm) season.	Increment: 10 ppb in 24-h SO_2 0-14 yrs Whole yr 1.64% [0.29, 3.01] lag 1 2.04% [0.29, 3.83] lag 0-3 + O_3 1.77% [0.22, 3.36] lag 1 + NO_2 1.23% [−0.22, 2.69] lag 1 + BS 1.66% [0.23, 3.12] lag 1 Warm season 3.33% [1.09, 5.63] lag 1 3.40% [0.41, 6.48] lag 0-3 + O_3 3.35% [0.89, 5.87] lag 1 + NO_2 2.92% [0.58, 5.32] lag 1 + BS 3.66% [1.35, 6.02] lag 1 Cool season 0.56% [−1.16, 2.32] lag 1 1.24% [−0.95, 3.49] lag 0-2 15-64 yrs Whole yr −0.69% [−2.28, 0.94] lag 2; −0.71% [−2.69, 1.30] lag 0-2 Warm −1.39% [−3.97, 1.27] lag 0; −2.2% [−5.46, 11.8] lag 0-2 Cool season −0.24% [−2.28, 1.84] lag 0 0.20% [−2.28, 2.74] lag 0-2

TABLE AX5.2 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR RESPIRATORY DISEASES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean Levels & Monitoring Stations	Copollutants & Correlations	Method, Findings, Interpretation	Effects: Relative Risk or % Change & Confidence Intervals (95%)
EUROPE (cont'd)					
Anderson et al. (1998) (cont'd)					65+ yrs Whole yr 2.82% [−0.82, 5.96] lag 2; 3.06% [−0.72, 6.98] lag 0-3 Warm −2.62% [−7.31, 2.31] lag 2; −4.27% [−9.89, 1.71] lag 0-3 Cool season 5.85% [1.81, 10.05] lag 2; 7.28% [2.19, 12.62] lag 0-3 + O_3 7.84% [2.48, 13.48] lag 1 + NO_2 4.19% [−0.53, 9.13] lag 1 + BS 5.29% [0.42, 10.40] lag 1 All Ages Whole yr 1.64% [0.54, 2.75] lag 1; 2.75% [1.22, 4.30] lag 0-3 + O_3 1.48% [0.24, 2.73] lag 1 + SO_2 1.14% [−0.04, 2.33] lag 1 + BS 1.54%[0.36, 2.73] lag 1 Warm 2.02% [0.22, 3.85] lag 1; 2.60% [0.02, 5.25] lag 0-3 + O_3 1.91% [0.05, 3.81] lag 1 + NO_2 1.64% [−0.23, 3.56] lag 1 + BS 2.18% [0.32, 4.07] lag 1 Cool season 1.41% [0.0, 2.83] lag 1; 2.83% [0.89, 4.81] lag 0-3 + O_3 −0.09% [−1.61, 1.82] lag 1 + NO_2 0.83% [−0.67, 2.34] lag 1 + BS 1.11% [−0.41, 2.66] lag 1

TABLE AX5.2 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR RESPIRATORY DISEASES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean Levels & Monitoring Stations	Copollutants & Correlations	Method, Findings, Interpretation	Effects: Relative Risk or % Change & Confidence Intervals (95%)
EUROPE (cont'd)					
Anderson et al. (2001) West Midlands conurbation, United Kingdom Period of Study: 10/1994-12/1996	Hospital admissions outcomes (ICD 9 codes): All respiratory (460-519), Asthma (493), COPD (490-496, excluding 493) Age groups analyzed: 0-14, 15-64, 65+ Study design: Time series Statistical analyses: followed APHEA 2 protocol, GAM Covariates: Season, temperature, humidity, epidemics, day of wk, holidays Statistical package: S-Plus 4.5 Pro Lag: 0,1,2,3, 0-1, 0-2, 0-3	24-h avg: 7.2 ppb, 4.7 (SD) Min: 1.9 ppb Max: 59.8 ppb 10th: 3.3 ppb 90th: 12.3 ppb #of monitors: 5	$PM_{2.5}$; r = 0.55 $PM_{2.5-10}$; r = 0.31 BS; r = 0.50 SO_4; r = 0.19 NO_2; r = 0.52 O_3; r = 0.22	When admissions were analyzed by subgroups, respiratory and asthma admissions were positively correlated with SO_2. SO_2 significantly associated with asthma and respiratory admissions for the 0 to 14-yr-age group; however, little evidence of a seasonal interaction was observed.	Increment: 9 ppb (90th-10th) All respiratory All ages 1.3% [−0.7, 3.4] lag 0-1 0-14 yrs 4.6% [1.40, 7.8] lag 0-1 15-64 yrs −0.9% [−4.8, 3.3] lag 0-1 ≥65 yrs −2.0% [−4.9, 1.1] lag 0-1 COPD with asthma 0-14 yrs 10.9% [4.50, 17.8] lag 0-1 15-64 yrs 2.4% [−5.5, 10.9] lag 0-1 ≥65 yrs −4.2% [−8.9, 0.8] lag 0-1

TABLE AX5.2 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR RESPIRATORY DISEASES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean Levels & Monitoring Stations	Copollutants & Correlations	Method, Findings, Interpretation	Effects: Relative Risk or % Change & Confidence Intervals (95%)
EUROPE (cont'd)					
Atkinson et al. (1999a) London, England Period of Study: 1992-1994	Hospital admissions outcomes (ICD 9 codes): All respiratory (460-519); Asthma (493); Asthma and COPD (490-496); LRD (466,480-486) Age groups analyzed: all ages, 0-14 yr, 15-64 yr and ≥65 yr Study design: Time series N: 165,032 Statistical analyses: Poisson regression following APHEA protocol Covariates: Long-term seasonal patterns, day of wk, temperature, humidity, influenza. Statistical package: SAS Investigated Dose/Response: Yes Lag: 0,1,2,3 days	SO_{2-} 24-h (µg/m^3) Mean: 21.2 (7.8) µg/m^3 Min: 7.4 10th: 13 50th: 19.8 90th: 31 Max: 82.2 # of monitors: 5	O_3,CO, $PM_{2.5}$, BS, NO_2 Correlation coefficients ranged between r = 0.5 and 0.6	Asthma was closely linked with PM, CO, NO_2, and traffic pollution. When SO_2 and $PM_{2.5}$ were included in the same model, the magnitude of the individual associations was reduced, as were their statistical significance. This reduction occurred in children, adults and the elderly. The other pollutants all had the effect of reducing the magnitude of the individual SO_2 and $PM_{2.5}$ associations, although their statistical significance was unaffected. This indicates that both SO_2 and $PM_{2.5}$ were indicators of the same pollutant mixture.	Increment: 18 µg/m^3 All respiratory All ages 2.01% [0.29, 3.76] lag 1 0-14 yrs 5.14% [2.59, 7.76] lag 0 15-64 yrs 1.90% [−0.79, 4.660 lag 3 ≥65 yrs 2.25 [−0.09, 4.65] lag 3 Asthma All ages 3.38 [0.42, 6.43] lag 1 0-14 yrs 6.74% [2.92, 10.69] lag 1 15-64 yrs 4.58% [−0.18, 9.57] lag 3 ≥65 yrs 6.31% [−1.59, 14.83] lag 2 COPD and Asthma ≥65 yrs 1.53% [−1.83, 5.00] lag 3 Lower Respiratory ≥65 yrs 5.16% [1.19, 9.28] lag 3

TABLE AX5.2 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR RESPIRATORY DISEASES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean Levels & Monitoring Stations	Copollutants & Correlations	Method, Findings, Interpretation	Effects: Relative Risk or % Change & Confidence Intervals (95%)
EUROPE (cont'd)					
Atkinson et al. (1999b) London, United Kingdom Period of Study: 1/92-1294	ED visits outcome(s) (ICD 9): Respiratory ailments (490-496), including asthma, wheezing, inhaler request, chest infection, COPD, difficulty in breathing, cough, croup, pleurisy, noisy breathing Age groups analyzed: 0-14; 15-64; ≥65; All ages Study design: Time series N: 98,685 # of Hospitals: 12 Statistical analyses: Poisson regression, APHEA protocol Covariates: Long-term trend, season, day of wk, influenza, temperature, humidity Statistical package: SAS Lag: 0,1,0-2 and 0-3 days	24-h avg: 21.2 µg/m^3, SD = 7.8 10th: 13.0 50th: 19.8 90th: 31.0 Range: 7.4, 82.2 # of Stations: 5	SO_2 O_3 (8 h) CO (24 h), $PM_{2.5}$ (24 h) BS	SO_2 was closely related to $PM_{2.5}$, but 2-pollutant models showed that the effect of SO_2 was decreased by NO_2 and $PM_{2.5}$ inclusion. Inclusion of other pollutants did not significantly decrease the influence of SO_2 on ER admissions in 2-pollutant models.	Increment: 18 µg/m^3 in 24-h Single-pollutant model Asthma only 0-14 yrs 9.92% [4.75, 15.34] lag 1 15-64 yrs 4.19% [−0.53, 9.13] lag 1 All ages 4.95% [1.53, 8.48] lag 1 All respiratory 0-14 yrs 6.01% [2.98, 9.12] lag 2 15-64 yrs 2.72% [−0.18, 5.70] lag 3 65+ yrs −1.82% [−5.72, 2.25] lag 3 All Ages 2.81% [0.72, 4.93] lag 1 Copollutant models for asthma among children: SO_2 + NO_2: 5.42% [0.18, 10.93] SO_2 + O_3: 8.39% [3.82, 13.17] SO_2 + CO: 8.05% [3.45, 12.86] SO_2 + $PM_{2.5}$: 5.63 [0.53, 10.98] SO_2 + BS: 8.03 [3.32, 12.96]

TABLE AX5.2 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR RESPIRATORY DISEASES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean Levels & Monitoring Stations	Copollutants & Correlations	Method, Findings, Interpretation	Effects: Relative Risk or % Change & Confidence Intervals (95%)
EUROPE (cont'd)					
Boutin-Forzano et al. (2004) Marseille, France Period of Study: 4/97-3/98	ED visits outcome(s): Asthma ICD 9 Code(s): NR Age groups analyzed: 3-49 Study design: Case-crossover N: 549 Statistical analyses: Logistic regression Covariates: Minimal daily temperature, maximum daily temperature, minimum daily relative humidity, maximum daily relative humidity, day of wk Statistical package: NR Lag: 0-4 days	Mean: SO_2: 22.5 µg/m^3 Range: 0.0, 94.0	NO_2; r = 0.56 O_3; r = –0.25	No association was observed between ER visits for asthma and SO_2 levels. Only single-pollutant models were utilized.	Increment: 10 µg/m^3 Increased ER visits OR 1.0023 [0.9946, 1.0101] lag 0 OR 0.9995 [0.9923, 1.0067] lag 1 OR 0.9996 [0.9923, 1.0069] lag 2 OR 0.9970 [0.9896, 1.0045] lag 3 OR 0.9964 [0.9889, 1.0040] lag 4

TABLE AX5.2 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR RESPIRATORY DISEASES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean Levels & Monitoring Stations	Copollutants & Correlations	Method, Findings, Interpretation	Effects: Relative Risk or % Change & Confidence Intervals (95%)
EUROPE (cont'd)					
Buchdahl et al. (1996) London, United Kingdom Period of Study: 3/1/92-2/28/93	ED visits outcomes: Daily acute wheezy episodes ICD9: NR Age groups analyzed: ≤16 Study design: Case-control N: 1,025 cases, 4,285 controls Number of hospitals: 1 Statistical analyses: Poisson regression Covariates: Season, temperature, wind speed Season: Spring (Apr-Jun), Summer (Jul-Sep), Autumn (Oct-Dec), Winter (Jan-Mar) Statistical package: Stata Lag: 0-7 days	SO_2 24-h yr round Mean: 22 µg/m^3, SD = 14 IQR: µg/m^3 Spring: 20 (14) Summer: 18 (22) Fall: 24 (14) Winter: 25 (14)	NO_2; r = 0.62 O_3; r = −0.28	Variations in SO_2 could not explain the U-shaped relationship between ozone and incidence of asthma.	Increment: 14 µg/m^3 (Std. Dev.) No adjustments to model RR 1.16 [1.10, 1.23] lag not specified Adjusted for temperature and season. RR 1.12 [1.06, 1.19] lag not specified Adjusted for temperature, season and wind speed. RR 1.08 [1.00, 1.16] lag not specified

TABLE AX5.2 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR RESPIRATORY DISEASES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean Levels & Monitoring Stations	Copollutants & Correlations	Method, Findings, Interpretation	Effects: Relative Risk or % Change & Confidence Intervals (95%)
EUROPE (cont'd)					
Castellsague et al. (1995) Barcelona, Spain Period of Study: 1986-1989	ED visits outcome(s): Asthma ICD 9 Code(s): NR Age groups analyzed: 15-64 Study design: Time series # of Hospitals: 4 Statistical analyses: Poisson regression covariates: Long time trend, day of wk, temperature, relative humidity, dew point temperature Seasons : Winter : Jan-Mar; Summer : Jul-Sep Dose-response investigated: Yes Statistical package: NR Lag: 0, 1-5 days and cumulative. Summer: lag 2 days Winter: lag 1 day	Mean SO_2 ($\mu g/m^3$) Summer: 40.8 25th: 25 50th: 36 75th: 54 95th: 82 Winter: 52.0 25th: 36 50th: 49 75th: 67 95th: 94 # of Stations: 15 manual, 3 automatic	NO_2 O_3	Interaction between pollutants and asthma emergency room visits was influenced by soy-bean dust in the air. The daily mean of asthma visits and level of SO_2 were higher in the winter than in the summer. A positive but not statistically significant increase in relative risk was found for SO_2 in the summer. SO_2 levels were higher in the winter, but the RR was lower compared to the RR in the summer. SO_2 was not significantly associated with asthma related ER visits.	Increment: 25 $\mu g/m^3$ Seasonal differences Summer: RR 1.052 [0.980, 1.129] lag 2 Winter: RR 1.020 [0.960, 1.084] lag 1

TABLE AX5.2 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR RESPIRATORY DISEASES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean Levels & Monitoring Stations	Copollutants & Correlations	Method, Findings, Interpretation	Effects: Relative Risk or % Change & Confidence Intervals (95%)
EUROPE (cont'd)					
Dab[+] et al. (1996) Paris, France Period of Study: 1/1/87-9/30/92	Hospital admissions outcomes (ICD 9): All respiratory (460-519), Asthma (493), COPD (490-496) Age groups analyzed: All ages Study design: Time series Number of hospitals: 27 Statistical analyses: Poisson regression, followed APHEA protocol Covariates: Temperature, relative humidity, influenza, Long-term trend, season, holiday, medical worker strike Lag: 0,1,2 days, 0-3 cumulative	All Yr: 24-h avg: 29.7 μg/m^3 Median: 23.0 5th: 7.0 99th: 125.0 1-h max: 59.9 Median: 46.7 5th: 14.0 99th: 232.7 Warm season 24-h avg: 20.1 Median: 18.3 5th: 6.0 99th: 49.3 1-h max: 42.7 Median: 37.0 5th: 13.0 99th: 133.7 Cold season 24-h avg: 40.1 μg/m^3 Median: 31.3 5th: 8.7 99th: 149.0 1-h max: 78.3 Median: 60.7 5th: 17.0 99th: 268.3	NO_2 O_3 PM_{13} BS	1-h maximum SO_2 levels yielded lower relative risk when compared to 24-h avg levels. COPD effects were only significantly associated with SO_2 with no lag. The strongest association was observed with PM_{13}; 4.5% increase in respiratory admission per 100 ug/m^3 increment. SO_2 was a close second. Neither analysis by age or by season showed a significant sensitivity for hospital admissions. The strongest association for asthma admission for all pollutants was with SO_2 24-h avg of 7% [0.14, 14.10], but one hour maximum level was not significant. The strongest association for admission with COPD diagnosis was also for 24-h avg of SO_2 (9.9% [2.3, 18]).	Increment: 100 μg/m^3 All respiratory (1987-1990) 24-h avg RR 1.042 [1.005, 1.080] lag 0-2 1-h max RR 1.018 [0.988, 1.048] lag 0-2 Asthma (1987-1992) 24-h avg RR 1.070 [1.004, 1.141] lag 2 1-h max RR 1.047 [0.998, 1.098] lag 2 COPD 24-h avg RR 1.099 [1.023, 1.180] lag 0 1-h max RR 1.051 [1.025, 1.077] lag 0

TABLE AX5.2 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR RESPIRATORY DISEASES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean Levels & Monitoring Stations	Copollutants & Correlations	Method, Findings, Interpretation	Effects: Relative Risk or % Change & Confidence Intervals (95%)
EUROPE (cont'd)					
de Diego Damiá et al. (1999) Valencia, Spain 3/1994-3/1995	ED visits outcome(s) (ICD 9): Asthma (493) Age groups analyzed: >12 Study design: N: 515 # of Hospitals: 1 Statistical analyses: Stepwise regression and ANOVA; Linear regression Covariates: Season and temperature Statistical package: SPSS Lag:	24-h avg SO_2 ($\mu g/m^3$) Winter Mean: 56 Range: 30, 86 Spring Mean: 47 Range: 34, 75 Summer Mean: 40 Range: 12, 62 Autumn Mean: 50 Range: 42, 59 Number of monitors: 1	BS; r = 0.54	The SO_2 concentration was averaged for each season and quartiles of concentration determined. Asthma visits that occurred in each season were examined. There were no significant associations with asthma ER visits with any season or with any quartile of SO_2 exposure.	Mean number of asthma-related ED visits based on quartile of SO_2 All yr: <41 $\mu g/m^3$: 8.6 41-50 $\mu g/m^3$: 9.1 51-56 $\mu g/m^3$: 11.6 >56 $\mu g/m^3$: 11.9

TABLE AX5.2 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR RESPIRATORY DISEASES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean Levels & Monitoring Stations	Copollutants & Correlations	Method, Findings, Interpretation	Effects: Relative Risk or % Change & Confidence Intervals (95%)
EUROPE (cont'd)					
Fusco et al. (2001) Rome, Italy Period of Study: 1/1995-10/1997	Hospital admissions outcomes (ICD 9 codes): All Respiratory (460-519, excluding 470-478); Acute respiratory infections including pneumonia (460-466, 480-486), COPD (490-492, 494-496), asthma (493) Age groups analyzed: All ages, 0-14 Study design: Time series # of Hospitals: Statistical analyses: Poisson regression with GAM	24-h avg: 9.1 (5.8) $\mu g/m^3$ 25th: 5.1 50th: 7.9 75th: 12.0 # of monitors: 5	O_3; r = −0.35 CO; r = 0.56 NO_2; r = 0.33 Particles; r = 0.25	SO_2 did not have an effect on respiratory hospitalizations.	Increment: 6.9 $\mu g/m^3$ (IQR) Respiratory conditions: All ages: 0.4% [−1.3, 2.2] lag 0 0.8% [−0.9, 2.4] lag 1 0.3% [−1.3, 1.8] lag 2 0-14 yrs: −0.7% [−4.0, 2.7] lag 0 −2.0 [−5.2, 1.3] lag 1 −0.8 [−3.8, 2.3] lag 2 Acute respiratory infections: All ages: 0.4% [−2.1, 3.0] lag 0 1.4% [−1.0, 3.9] lag 1 1.2% [−1.0, 3.5] lag 2 0-14 yrs: −0.1% [−3.9, 3.8] lag 0 −2.7% [−6.3, 1.0] lag 1 −1.2% [−4.5, 2.2] lag 2

TABLE AX5.2 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR RESPIRATORY DISEASES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean Levels & Monitoring Stations	Copollutants & Correlations	Method, Findings, Interpretation	Effects: Relative Risk or % Change & Confidence Intervals (95%)
EUROPE (cont'd)					
Fusco et al. (2001) (cont'd)	Covariates: Influenza epidemics, day of study, temperature, humidity, day of wk, holidays Statistical package: S-Plus 4 Lag: 0, 1, 2, 3, 4				Asthma: All ages: −1.5% [−6.6, 3.9] lag 0 −1.5% [−6.5, 3.7] lag 1 2.5% [−2.2, 7.4] lag 2 0-14 yrs: −2.6 [−10.4, 6.0] lag 0 4.3% [−3.5, 12.7] lag 1 5.5% [−1.8, 13.2] lag 2 COPD: All ages: 1.0% [−1.9, 4.0] lag 0 −1.1% [−3.9, 1.8] lag 1 −0.5% [−3.1, 2.1] lag 2

TABLE AX5.2 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR RESPIRATORY DISEASES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean Levels & Monitoring Stations	Copollutants & Correlations	Method, Findings, Interpretation	Effects: Relative Risk or % Change & Confidence Intervals (95%)
EUROPE (cont'd)					
Galan et al. (2003) Madrid, Spain Period of Study: 1995-1998	ED visits outcome(s) (ICD9): Asthma (493) Age groups analyzed: All Study design: Time series N: 4,827 Statistical analyses: Poisson regression, (1) classic APHEA protocol and (2) GAM with stringent criteria Covariates: Trend, yr, season, day of wk, holidays, temperature, humidity, influenza, acute respiratory infections, pollen Statistical package: NR Lag: 0-4 days	24-h mean: 23.6 µg/m^3 SD = 15.4 10th: 9.2 25th: 12.3 50th: 18.7 75th: 31.3 90th: 43.9 Range: 5, 121.2 # of Stations: 15	$PM_{2.5}$; r = 0.581 NO_2; r = 0.717 O_3; r = −0.188	SO_2 registered a predominately winter based pattern, and was positively correlated with $PM_{2.5}$, NO_2. The lag that described the strongest association was 3 days. Multipollutant models were fitted for cold season pollutants. SO_2 was the most affected when $PM_{2.5}$ was included in the model. Parametric estimates using APHEA protocol produced similar results as GAM. The SO_2 association may be due to the concealing effects of other pollutants. $PM_{2.5}$ accounted for most of the observed effects.	Increment : 10 µg/m^3 Asthma : RR lag 0 1.018 [0.984, 1.054] RR lag 1 1.005 [0.972, 1.039] RR lag 2 1.002 [0.970, 1.036] RR lag 3 1.029 [0.997, 1.062] RR lag 4 1.025 [0.994, 1.058] Multipollutant model: SO_2/$PM_{2.5}$ 0.966 [0.925, 1.009]

TABLE AX5.2 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR RESPIRATORY DISEASES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean Levels & Monitoring Stations	Copollutants & Correlations	Method, Findings, Interpretation	Effects: Relative Risk or % Change & Confidence Intervals (95%)
EUROPE (cont'd)					
Garty et al. (1998) Tel Aviv, Israel 1993	ED visits outcome(s): Asthma ICD 9 Code(s): NR Age groups analyzed: 1-18 Study design: Descriptive study with correlations N: 1,076 Statistical analyses: Pearson correlation and partial correlation coefficients Covariates: Maximum and minimum ambient temperatures, relative humidity and barometric pressure Statistical package: Statistix	24-h mean of SO_2 (estimated from histogram): 27 µg/m^3 Range: 11, 64	NO_x SO_2 O_3	Asthma morbidity was higher in the autumn and winter than the rest of the yr. The number of ER visits is September was exceptionally high. The percent of total variance showed positive correlation between asthma ER visits in children and high levels of NO_x, SO_2, and increased barometric pressure. NO_x enhances the effects of SO_2, whereas O_3 had a reverse relation to SO_2. Air borne pollen was not a significant contributor to ER visits.	Correlation between SO_2 and ER visits for asthma: All Yr: Daily data r = 0.24 Running mean for 7 days r = 0.53 Excluding September: Daily data r = 0.31 Running mean for 7 days r = 0.64

TABLE AX5.2 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR RESPIRATORY DISEASES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean Levels & Monitoring Stations	Copollutants & Correlations	Method, Findings, Interpretation	Effects: Relative Risk or % Change & Confidence Intervals (95%)
EUROPE (cont'd)					
Hagen et al. (2000) Drammen, Norway Period of Study: 1994-1997	Hospital admissions outcomes (ICD 9): All respiratory admissions (460-519) Age groups analyzed: All ages Study design: Time series Number of hospitals: 1 Statistical analyses: Poisson regression with GAM (adhered to HEI phase 1.B report) Covariates: Time trends, day of wk, holiday, influenza, temperature, humidity Lag: 0,1,2,3 days	SO_2 24-h avg ($\mu g/m^3$): 3.64, SD = 2.41 25th: 2.16 50th: 2.92 75th: 4.38 # of Stations: 2	$PM_{2.5}$; r = 0.42 NO_2; r = 0.58 benzene; r = 0.29 NO; r = 0.47 O_3; r = −0.24 Formaldehyde; r = 0.54 Toluene; r = 0.48	SO_2 was significantly associated with respiratory hospital admissions. This relationship was robust to the inclusion of $PM_{2.5}$, but attenuated when both $PM_{2.5}$ and benzene were included in the model.	Increment: SO_2: 2.22 $\mu g/m^3$ (IQR) Single-pollutant model Respiratory disease only 1.056 [1.013, 1.101] All disease 0.990 [0.974, 1.007] 2-pollutant model with $PM_{2.5}$ 1.051 [1.005, 1.099] 3-pollutant model with $PM_{2.5}$ + Benzene 1.040 [0.993, 1.089]

TABLE AX5.2 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR RESPIRATORY DISEASES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean Levels & Monitoring Stations	Copollutants & Correlations	Method, Findings, Interpretation	Effects: Relative Risk or % Change & Confidence Intervals (95%)
EUROPE (cont'd)					
Hajat et al. (1999) London, United Kingdom Period of Study: 1992-1994	GP visits outcome (ICD9): Asthma (493); Lower respiratory disease (464, 466, 476, 480-3, 490-2, 485-7, 4994-6, 500, 503-5, 510-5) Age groups analyzed: 0-14; 15-64; 65+; all ages Study design: Time-series analysis Statistical analysis: Poisson regression, APHEA protocol Covariates: Long-term trends, seasonality, day of wk, temperature, humidity Seasons: Warm, Apr-Sep; Cool, Oct-Mar; All-yr Dose-response investigated? Yes Statistical package: SAS Lag: 0-3 days, cumulative	All yr 24-h avg: 21.2 μg/m^3, SD = 7.8 10th: 13.0 90th: 31.0 Warm: 24-h avg: 20.5 μg/m^3, SD = 6.5 10th: 13.4 90th: 28.4 Cool: 24-h avg: 22.0 μg/m^3, SD = 9.0 10th: 12.8 90th: 33.3	NO_2; r = 0.61 BS; r = 0.57 CO; r = 0.51 $PM_{2.5}$; r = 0.63 O_3; r = −0.11	This study showed weak, but consistent associations between SO_2 and consultations for asthma and other LRD, especially in children. Bubble plot suggests a concentration-response relationship.	Increment: 18 μg/m^3 (90th-10th percentile) Asthma All ages 3.6% [0.3, 6.9] lag 2; 4.4% [0.9, 7.9] lag 0-2 0-14 yrs 4.9% [0.1, 9.8] lag 1; 4.4% [−0.7,9.7] lag 0-2 Warm: 9.0% [2.2, 16.2] lag 1 Cool: 2.0% [4.5, 8.9] lag 1 15-64 yrs 3.6% [−0.6, 8.0] lag 2; 3.5% [−1.0, 8.2] lag 0-3 Warm: 2.5% [−3.3, 8.7] lag 2 Cool : 4.5% [−1.4, 10.7] lag 2 65 + yrs 4.5% [−3.5, 13.1] lag 1; 4.8% [−2.9, 13.2] lag 0-1 Warm: 7.5% [−4.0, 20.3] lag 1 Cool: 2.0% [−8.6, 13.9] lag 1 Lower respiratory disease All ages 1.8% [0.2, 3.4] lag 2; 2.2% [0.4, 4.1] lag 0-2 0-14 yrs 4.5% [1.4, 7.8] lag 2; 5.7% [1.7, 9.7] lag 0-3 Warm: 2.4% [−2.6, 7.7] lag 2 Cool: 5.8% [1.6, 10.2] lag 2

TABLE AX5.2 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR RESPIRATORY DISEASES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean Levels & Monitoring Stations	Copollutants & Correlations	Method, Findings, Interpretation	Effects: Relative Risk or % Change & Confidence Intervals (95%)
EUROPE (cont'd)					
Hajat et al. (1999) (cont'd)					15-64 yrs 1.5% [−0.7, 3.7] lag 1; 1.6% [−0.9, 4.1] lag 0-3 Warm: −0.5% [−3.8, 2.9] lag 1 Cool: 2.5% [−0.5, 5.5] lag 1 65 + −2.2% [−4.9, 0.6] lag 0; −1.4% [−4.4, 1.7] lag 0-1 Warm: −3.1% [−6.9, 0.9] lag 0 Cool: −1.6 % [−5.3, 2.3] lag 0 2-pollutant model – Asthma SO_2 alone 4.9% [0.1, 9.8] SO_2/O_3 5.9% [1.1, 10.9] SO_2/NO_2 2.7% [−2.7, 8.4] $SO_2/PM_{2.5}$ 3.4% [−3.0, 10.2] 2-pollutant model-Lower respiratory disease SO_2 alone 4.5% [1.4, 7.8] SO_2/O_3 4.8% [1.6, 8.1] SO_2/NO_2 3.1% [−0.6, 6.9] $SO_2/PM_{2.5}$ 3.8% [0.4, 7.2]

TABLE AX5.2 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR RESPIRATORY DISEASES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean Levels & Monitoring Stations	Copollutants & Correlations	Method, Findings, Interpretation	Effects: Relative Risk or % Change & Confidence Intervals (95%)
EUROPE (cont'd)					
Hajat* et al. (2001) London, United Kingdom Period of Study: 1992-1994	GP visits outcome (ICD9): Allergic Rhinitis (477) Age groups analyzed: 0-14; 15-64; 65+; all ages Study design: Time series analysis N: 4,214 Statistical analysis: Poisson regression, GAM Covariates: Long-term trends, seasonality, day of wk, temperature, humidity, variation in practice population, counts for lagged allergic pollen measures, daily number of consultations for influenza Dose-response investigated? Yes Statistical package: S-Plus Lag: 0-6 days, cumulative	24-h avg: 21.2 µg/m^3, SD = 7.8 10th: 13.0 90th: 31.0	NO_2; r = 0.61 BS; r = 0.57 CO; r = 0.51 $PM_{2.5}$; r = 0.63 O_3; r = −0.11	The number of allergic rhinitis admissions peaked in April and June. After 2-pollutant model analysis, SO_2 still remained highly significant in the presences of other pollutants. For both children and adults exposure-response associations showed that risk levels off at higher SO_2 levels.	Increment: 18 µg/m^3 (90th-10th percentile) Single-pollutant model <1 to 14 yrs 24.5% [14.6, 35.2] lag 4 24.9% [11.9, 39.4] lag 0-4 15 to 64 yrs 14.3% [6.2, 23.0] lag 3 15.5% [9.1, 22.3] lag 0-5 >64 yrs-too small for analysis 2-pollutant models <1 to 14 yrs SO_2 & O_3: 22.1% [12.0, 33.1] SO_2 & NO_2: 28.5% [15.5, 42.9] SO_2 & $PM_{2.5}$: 27.2% [15.3, 40.2] 15 to 64 yrs SO_2 & O_3: 8.5% [3.4, 13.9] SO_2 & NO_2: 8.3% [1.7, 15.3] SO_2 & $PM_{2.5}$: 6.7% [0.7, 13.0]

TABLE AX5.2 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR RESPIRATORY DISEASES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean Levels & Monitoring Stations	Copollutants & Correlations	Method, Findings, Interpretation	Effects: Relative Risk or % Change & Confidence Intervals (95%)
EUROPE (cont'd)					
Hajat* et al. (2002) London, United Kingdom Period of Study: 1992-1994	GP visits outcome (ICD9): Upper respiratory disease, excluding Rhinitis (460-3, 465, 470-5, 478) Age groups analyzed: 0-14; 15-64; 65+; all ages Study design: Time series analysis Statistical analysis: Poisson regression, GAM Covariates: Long-term trends, seasonality, day of wk, holidays, temperature, humidity, variation in practice population, counts for lagged allergic pollen measures, daily number of consultations for influenza Seasons: Warm, Apr-Sep; Cool, Oct-Mar Dose-response investigated? Yes Statistical package: S-Plus Lag: 0,1,2,3 days	All yr 24-h avg: 21.2 µg/m^3, SD = 7.8 10th: 13.0 90th: 31.0 Warm: 24-h avg: 20.5 µg/m^3, SD = 6.5 10th: 13.4 90th: 28.4 Cool: 24-h avg: 22.0 µg/m^3, SD = 9.0 10th: 12.8 90th: 33.3 # of Stations: 3	NO_2; r = 0.61 BS; r = 0.57 CO; r = 0.51 $PM_{2.5}$; r = 0.63 O_3; r = −0.11	Increased consultations for URD were most strongly associated with SO_2 in children. For adults and the elderly the strongest associations were for $PM_{2.5}$ and NO_2. The most consistent lag in adults and the elderly for development of URD was 2 days (one day after a pollution event).	Increment: 18 µg/m^3 (90th-10th percentile) Single-pollutant model All yr 0-14 yr 3.5% [1.4, 5.8] lag 0 15-64 yrs 3.5% [0.5, 6.5] lag 1 >65 yrs 4.6% [0.4, 9.0] lag 2 Warm 0-14 yrs 3.2% [−0.5, 7.0] lag 0 15-64 yrs 4.6% [1.5, 7.7] lag 1 ≥65 yrs 1.6% [−4.8, 8.5] lag 2 Cool 0-14 yrs 5.5% [2.4, 8.7] lag 0 15-64 yrs 2.7 [0.0, 5.4] lag 1 >65 yrs 5.7% [0.4, 11.4] lag 2 2-pollutant models 0-14 yrs SO_2 & O_3: 1.0% [−2.2, 4.2] SO_2 & NO_2: 4.7% [2.2, 7.4] SO_2 & $PM_{2.5}$: 4.6% [2.1, 7.2] For 15-64 yrs SO_2 & O_3: 3.7% [0.6, 7.0] SO_2 & NO_2: 2.6% [−0.0, 5.2] SO_2 & $PM_{2.5}$: 2.4% [−0.1, 5.0] For >65 yrs SO_2 & O_3: 9.0% [1.7, 16.9] SO_2 & NO_2: 4.3% [−1.2, 10.2] SO_2 & $PM_{2.5}$: 3.2% [−1.9, 8.7]

TABLE AX5.2 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR RESPIRATORY DISEASES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean Levels & Monitoring Stations	Copollutants & Correlations	Method, Findings, Interpretation	Effects: Relative Risk or % Change & Confidence Intervals (95%)
EUROPE (cont'd)					
Llorca et al. (2005) Torrelavega, Spain Period of Study: 1992-1995 Days: 1,461	Hospital admissions outcomes (ICD 9): All respiratory admissions (460-519) Age groups analyzed: All ages Study design: Time series Number of hospitals: 1 Statistical analyses: Poisson regression Covariates: Short and Long-term trends Statistical package: Stata Lag: NR	24-h avg SO_2: 13.3 µg/m^3, SD = 16.7 # of Stations: 3	NO_2; r = 0.588 NO; r = 0.544 TSP; r = –0.40 SH_2; r = 0.957	Associations between SO_2 and admissions observed in the Single-pollutant model disappear in a 5-pollutant model. Only NO_2 was significantly associated with admissions. No relation was described for sulphur compounds including H_2S or SO_2. The concentration of SO_2 changes with temperature changes, which may be responsible for cardiac stress. SO_2 was not significantly associated with cardiac respiratory or cardio-respiratory admissions	Increment: 100 µg/m^3 Single-pollutant model All cardio-respiratory admissions: RR 0.98 [0.89, 1.07] Respiratory admissions: 1.04 [0.90, 1.19] 5-pollutant model All cardio-respiratory admissions: RR 0.98 [0.80, 1.21] Respiratory admissions: 0.89 [0.64, 1.24]

TABLE AX5.2 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR RESPIRATORY DISEASES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean Levels & Monitoring Stations	Copollutants & Correlations	Method, Findings, Interpretation	Effects: Relative Risk or % Change & Confidence Intervals (95%)
EUROPE (cont'd)					
Oftedal et al. (2003) Drammen, Norway Period of Study: 1994-2000	Hospital admissions outcomes (ICD 10): All respiratory admissions (J00-J99) Age groups analyzed: All ages Study design: Time series Statistical analyses: Semi-parametric Poisson regression, GAM with more stringent criteria Covariates: Temperature, humidity, influenza Lag: 2,3 days	Mean: 2.9 µg/m^3, SD = 2.1 IQR: 2.03 µg/m^3	$PM_{2.5}$ NO_2 O_3 Benzene Formaldehyde Toluene	The study found positive associations between daily number of hospital admissions for acute respiratory diseases and concentrations of SO_2; associations did not change substantially from the first to the second 3-yr period.	Increment: 2.03 µg/m^3 (IQR) All respiratory disease 1.042 [1.011, 1.073]

TABLE AX5.2 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR RESPIRATORY DISEASES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean Levels & Monitoring Stations	Copollutants & Correlations	Method, Findings, Interpretation	Effects: Relative Risk or % Change & Confidence Intervals (95%)
EUROPE (cont'd)					
Ponce de Leon et al. (1996) London, England Period of Study: 04/1987-1988; 1991-02/1992	Hospital admissions outcomes (ICD 9): All respiratory (460-519) Age groups analyzed: 0-14, 15-64, 65+, all ages Study design: Time series N: 19,901 Statistical analyses: APHEA protocol, Poisson regression GAM Covariates: Long-term trend, season, influenza, day of wk, holiday, temperature, humidity Season: Cool, Oct-Mar; Warm: Apr-Sep Dose-response Investigated?: Yes Statistical package: SAS Lag: 0, 1, 2 days, 0-3 cumulative avg.	SO_2 24-h avg: 32.2 µg/m^3, SD = 12.6 5th: 15 10th: 18 25th: 24 50th: 31 75th: 39 90th: 47 95th: 54 # of stations: 2	NO_2; r = 0.44 BS; r = 0.44 O_3; r = –0.067	Though significant effects were observed with SO_2 in some age groups, they were not consistent or similar in magnitude to those of O_3.	Increment: 90th-10th percentile (24-h avg: 29 µg/m^3). All yr All ages 1.0092 [0.9926, 1.0261] lag 1 0-14 yrs 1.0093 [0.9837, 1.0356] lag1 15-64 yr 1.0223 [0.9942, 1.0511] lag 1 ≥65 yr 1.0221 [0.9970, 1.0478] lag 2 Warm season All ages 1.0111 [0.9864, 1.0364] lag 1 0-14 yrs 1.0468 [1.0066, 1.0885] lag 1 15-64 yr 0.9996 [0.9596, 1.0411] lag 1 >65 yr 1.0124 [0.9772, 1.0489] lag 2 Cool season All ages 1.0079 [0.9857, 1.0306] lag 1 0-14 yrs 0.9848 [0.9515, 1.0192] lag 1 15-64 yr 1.0389 [1.0010, 1.0783] lag 1 >65 yr 1.0280 [0.9945, 1.0625] lag 2

TABLE AX5.2 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR RESPIRATORY DISEASES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean Levels & Monitoring Stations	Copollutants & Correlations	Method, Findings, Interpretation	Effects: Relative Risk or % Change & Confidence Intervals (95%)
EUROPE (cont'd)					
Pönkä (1991) Helsinki, Finland Period of Study: 1987-1989	Hospital admissions outcomes (ICD 9 codes): Asthma (493) Age groups analyzed: 0-14; 15-64; ≥65 yrs Study design: Time series N: 4,209 Statistical analyses: Correlations and partial correlations Covariates: Minimum temperature Statistical package: Lag: 0-1	24-h avg: 19.2 (12.6) µg/m^3 Range: 0.2, 94.6 Number of monitors: 4	NO_2; r = 0.4516 NO; r = 0.4773 O_3; r = 0.1778 TSP; r = 0.1919 CO	The frequency of all admissions for asthma was significantly correlated to SO_2. Child asthma admissions were not significantly correlated with SO_2, but were correlated to O_3 and NO. SO_2 was also significantly correlated with elderly admissions. Increased hospitalization correlated with SO_2 was also observed for adults. Hospital admissions were more strongly correlated with SO_2 than other pollutants. ER visits were more strongly correlated with a mixture of pollutants (TSP, SO_2, O_3, and temperature). Multipollutant model co-linear results of SO_2, CO, NO_2, and NO suggest a mixture of pollutants is responsible for asthma admissions.	Correlations between hospital admissions (HA) for asthma and pollutants and temperature by ages. 0-14 yrs HA: −0.01391 Emergency HA: 0.0332 15-64 yrs HA: 0.1039 p = 0.0006 Emergency HA: 0.1199 p < 0.0001 ≥65 yrs HA: 0.0796 p = 0.0085 Emergency HA: 0.1169 p < 0.0001 Partial correlations between admissions for asthma and SO_2 were standardized for temperature. HA: 0.0770 p = 0.0172 Emergency HA: 0.1050 p = 0.0011

TABLE AX5.2 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR RESPIRATORY DISEASES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean Levels & Monitoring Stations	Copollutants & Correlations	Method, Findings, Interpretation	Effects: Relative Risk or % Change & Confidence Intervals (95%)
EUROPE (cont'd)					
Pönkä and Virtanen (1994) Helsinki, Finland Period of Study: 1987-1989 Days: 1096	Hospital admissions outcomes (ICD 9): Chronic bronchitis and emphysema (493) Age groups analyzed: <65, ≥65 Study design: Time series Statistical analyses: Poisson regression Covariates: Season, day of wk, yr, influenza, humidity, temperature Season: Summer (Jun-Aug), Autumn (Sep-Nov), Winter (Dec-Feb), Spring (Mar-May) Lag: 0-7 days	24-h mean: 19 µg/m^3, SD = 12.6; Range: 0.2, 95 # of stations: 2	NO_2 O_3 TSP	SO_2 was significantly associated with increased admissions for chronic bronchitis and emphysema for patients <65 yrs of age with a lag of 0 and 3 days. In the steps leading to regression analysis no association was observed between SO_2 levels and the ≥65 population. Multipollutant models were only used to examine NO_2 and SO_2. SO_2 had no significant association with morbidity caused by chronic bronchitis and emphysema in the ≥65 yr old population.	Increment: NR Chronic bronchitis and emphysema <65 yrs RR 1.31 [1.01, 1.70] lag 0 RR 0.96 [0.73, 1.27] lag 1 RR 0.78 [0.59, 1.03] lag 2 RR 1.39 [1.05, 1.86] lag 3 RR 0.89 [0.68, 1.16] lag 4 RR 1.28 [0.97, 1.70] lag 5 RR 0.91 [0.69, 1.20] lag 6 RR 1.09 [0.84, 1.40] lag 7 65+ yrs NR

TABLE AX5.2 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR RESPIRATORY DISEASES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean Levels & Monitoring Stations	Copollutants & Correlations	Method, Findings, Interpretation	Effects: Relative Risk or % Change & Confidence Intervals (95%)
EUROPE (cont'd)					
Pönkä and Virtanen, (1996) Helsinki, Finland Period of Study: 1987-1989	Hospital admissions outcomes (ICD 9 codes): Asthma (493) Age groups analyzed: 0-14, 15-64, 65+ Study design: Time series Statistical analyses: Covariates: Long-term trend, season, epidemics, day of wk, holidays, temperature, relative humidity Statistical package: Lag: 0-2	24-h avg (μg/m^3): Winter: 26 Spring: 22 Summer: 13 Fall: 15	NO_2 O_3 TSP	Significant associations were observed between daily SO_2 concentrations and daily counts of hospitalizations among 15- to 64-yr-old patients and among those over 64 years old, but not among children. These effects were observed when mean daily SO_2 values were lower than the maximum value recommended by WHO (125 μg/m^3).	Parameter estimates (PE) and standard erro (SE) for a 1-unit increase: Asthma 15-64 yrs : PE 0.2176 (0.1081) p = 0.44 lag 2 PE 0.3086 (0.1545) p = 0.046 lag 0-3 Asthma 65+ yrs : PE 0.2412 (0.0956) p = 0.012 lag 2

TABLE AX5.2 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR RESPIRATORY DISEASES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean Levels & Monitoring Stations	Copollutants & Correlations	Method, Findings, Interpretation	Effects: Relative Risk or % Change & Confidence Intervals (95%)
EUROPE (cont'd)					
Prescott et al. (1998) Edinburgh, United Kingdom Period of Study: 10/92-6/95	Hospital admissions outcomes (ICD 9): Pneumonia (480-7), COPD + Asthma (490-496) Age groups analyzed: <65, 65+ Study design: Time series Statistical analyses: Poisson log linear regression Covariates: Trend, seasonal and weekly variation, temperature, wind speed, day of wk Lag: 0,1, or 3 day rolling avg	SO_2: 14.5 (9.0) ppb Min: 0 ppb Max: 153 ppb # of Stations: 1	CO $PM_{2.5}$ NO_2 O_3 BS	No effect of SO_2 on hospitalizations observed in either age category.	Increment: 10 ppb Respiratory admissions >65 yrs −2.5 [−11.0, 6.9] lag 0-2 < 65 yrs 0.0 [−8.3, 9.1] lag 0-2

TABLE AX5.2 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR RESPIRATORY DISEASES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean Levels & Monitoring Stations	Copollutants & Correlations	Method, Findings, Interpretation	Effects: Relative Risk or % Change & Confidence Intervals (95%)
EUROPE (cont'd)					
Rossi et al. (1993) Oulu, Finland Period of Study: 10/1/1985-9/30/1986	ED visits outcome(s) (ICD 9): Asthma (493) Age groups analyzed: 15-85 Study design: Time series N: 232 Statistical analyses: Pearson's and partial correlation coefficients and multiple regression with stepwise discriminate analysis Covariates: Temperature, humidity Statistical package: BMDP software Lag: 0,1,2,3	24-h mean: 10.0 µg/m^3 Range: 0, 56 1-h max: 31.0 µg/m^3 Range: 1, 24 # of monitoring stations: 4	NO_2; r = 0.48 TSP; r = 0.31 H_2S	Same day ER visits were correlated to daily SO_2 levels, but the significance was lost with longer lag periods. When asthma visits were analyzed, SO_2 was positively and significantly correlated with asthma visits in the same wk and the wk after. After regression analyses, SO_2 became insignificant.	Pearson correlation coefficients ED asthma visits and same day SO_2: r = 0.13 p < 0.01 lag 0 Weekly ED asthma visits and same wk SO_2: r = 0.28 p < 0.05 Weekly ED asthma visits and previous wk SO_2: 0.30 p < 0.05 Multipollutant (NO_2; TSP; H_2S) Regression coefficient: All yr: β = 0.037, p = 0.535 Winter: β = –0.024, p = 0.710 Summer: β = –0.003, p = 0.991

TABLE AX5.2 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR RESPIRATORY DISEASES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean Levels & Monitoring Stations	Copollutants & Correlations	Method, Findings, Interpretation	Effects: Relative Risk or % Change & Confidence Intervals (95%)
EUROPE (cont'd)					
Sunyer et al. (1991) Barcelona, Spain Period of Study: 1985-1986	ED visits outcome(s) COPD (ICD 9): 490-496 Age groups analyzed: >14 Study design: Time series # of Hospitals: 4 Statistical analyses: multivariate linear regression Covariates: Meteorology, season, day of wk Statistical package: Lag: 0 to 2 days	24-h avg (SD): 56.5 (22.5) µg/m^3 98th: 114.3 Range: 17, 160 1-h max (SD): 141.9 (98.8) µg/m^3 98th: 461.3 Range: 17, 160 Number of monitors: 14-720	BS, CO, NO_2, O_3	An incremental change of 25 µg/m^3 in SO_2 was correlated with an adjusted increase of 0.5 daily visits due to COPD. SO_2 and ER visits were more strongly correlated in warm weather. Even at 24-h avg levels less than 100 µg/m^3, effects of SO_2 were statistically significant for COPD admissions.	Change in 24-h SO_2 daily ER µg/m^3 admissions P-value 150 0.55 < 0.01 100 0.7 < 0.01 72 0.7 0.04 52 0.41 > 0.05 39 −1.27 > 0.05 0.5 excess daily admissions per 25 µg/m^3 increment of SO_2.

TABLE AX5.2 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR RESPIRATORY DISEASES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean Levels & Monitoring Stations	Copollutants & Correlations	Method, Findings, Interpretation	Effects: Relative Risk or % Change & Confidence Intervals (95%)
EUROPE (cont'd)					
Sunyer et al. (1993) Barcelona, Spain Period of Study: 1985-1989	ED visits outcome(s) (ICD 9): COPD (490-492; 494-496) Study design: Time series Statistical analyses: Autoregressive linear regression Statistical package: Lag: 1,2	SO_2, 24-h Winter Tertiles (µg/m^3) <40.4 40.4, 61 >61 Winter Tertiles (µg/m^3) <28.1 28.1, 46.1 >46.1	BS	SO_2 concentrations were associated with the number of COPD ER admissions in the winter and summer. An increase of 25 µg/m^3 in SO_2 produced an adjusted change of ~6% and 9%, respectively, in the number of COPD emergencies in the winter and summer. Controlling for particulate matter resulted in a loss of significance. Co linearity of BS with SO_2 was observed.	Effects were expressed as adjusted changes in daily COPD ER admissions based on an increment of 25 µg/m^3. Winter: 6% Summer: 9% Mean ER admissions for COPD (winter) were 15.8 (range 3, 34) and 8.3 (range 1, 24) in the summer.

TABLE AX5.2 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR RESPIRATORY DISEASES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean Levels & Monitoring Stations	Copollutants & Correlations	Method, Findings, Interpretation	Effects: Relative Risk or % Change & Confidence Intervals (95%)
EUROPE (cont'd)					
Tenias et al. (1998) Valencia, Spain Period of Study: 1993-1995 Seasons: Cold: Nov-Apr Warm: May-Oct	ED visits outcome(s): Asthma ICD 9 Code(s): NR Age groups analyzed: >14 Study design: Time series N: 734 Statistical analyses: Poisson regression, APHEA protocol Covariates: seasonality, temperature, humidity, long-term trend, day of wk, holidays, influenza Seasons: Cold: Nov-Apr; Warm: May-Oct Dose-Response Investigated: Yes Statistical package: NR Lag: 0-3 days	24 h: 26.6 µg/m^3 25th: 17.9 50th: 26.2 75th: 34.3 95th: 42.6 Cold: 31.7 Warm: 21.7 1-h max: 56.3 µg/m^3 25th: 36.3 50th: 52.2 75th: 72.2 95th: 95.2 Cold: 64.6 Warm: 48.2 # of Stations: 2	24 h: O_3; r = −0.431 NO_2 (24 h); r = 0.265 NO_2 (1 h); r = 0.199 1 h: O_3; r = −0.304 NO_2 (24 h); r = 0.261 NO_2 (1 h); r = 0.201	SO_2 showed the strongest correlation to asthma admissions during the warm months. Multipollutant models showed that O_3 and black smoke had a small effect on the association between SO_2 and asthma ER visits while NO_2 greatly depressed these effects. It is likely that NO_2 was the dominant pollutant for respiratory outcomes. SO_2 was the "most vulnerable pollutant" to the presence of other pollutants.	Increment: 10 µg/m^3 SO_2 24-h avg All yr 1.050 [0.973, 1.133] lag 0 Cold 1.032 [0.937, 1.138] lag 0 Warm 1.070 [0.936, 1.224] lag 0 SO_2 1-h max All yr 1.027 [0.998, 1.057] lag 0 Cold 1.018 [0.980, 1.057] lag 0 Warm 1.038 [0.990, 1.090] lag 0

TABLE AX5.2 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR RESPIRATORY DISEASES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean Levels & Monitoring Stations	Copollutants & Correlations	Method, Findings, Interpretation	Effects: Relative Risk or % Change & Confidence Intervals (95%)
EUROPE (cont'd)					
Tenias et al. (2002) Valencia, Spain Period of Study: 1994-1995	ED visits outcome(s): COPD ICD 9 Code(s): NR Age groups analyzed: >14 Study design: Time series N: 1,298 # of Hospitals: 1 Statistical analyses: Poisson regression, APHEA protocol; basal models and GAM Covariates: Seasonality, annual cycles, temperature, humidity, day of wk, feast days Seasons: Cold, Nov-Apr; Warm, May-Oct Dose-response Investigated: Yes Statistical package: NR Lag: 0-3 days	24 h: 26.6 µg/m^3 25th: 17.9 50th: 26.2 75th: 34.3 95th: 42.6 Cold: 31.7 Warm: 21.7 1-h max: 56.3 µg/m^3 25th: 36.3 50th: 52.2 75th: 72.2 95th: 95.2 Cold: 64.6 Warm: 48.2	BS; r = 0.687 NO_2; r = 0.194 CO; r = 0.734 O_3; r = −0.431	SO_2 did not show any significant association with COPD ER visits for all seasons analyzed. SO_2 did not affect O_3 or CO association to ER admission for COPD when assessed together in the Multipollutant model. Possibility of a linear relationship between pollution and risk of emergency cases could not be ruled out.	Increment: 10 µg/m^3. 24-h avg SO_2 All yr RR 0.971 [0.914, 1.031] lag 0 Cold, 24-h avg: RR 0.970 [0.905, 1.038] lag 0 Warm, 24-h avg: RR 0.982 [0.885, 1.090] lag 0 1-h max SO_2 All yr RR 0.981 [0.958, 1.027] lag 3 Cold, 24-h avg: RR 0.972 [0.945, 1.000] lag 3 Warm, 24-h avg: RR 1.003 [0.979, 1.056] lag 3

TABLE AX5.2 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR RESPIRATORY DISEASES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean Levels & Monitoring Stations	Copollutants & Correlations	Method, Findings, Interpretation	Effects: Relative Risk or % Change & Confidence Intervals (95%)
EUROPE (cont'd)					
Thompson et al. (2001) Belfast, Northern Ireland Period of Study: 1993-1995	Hospital admissions/ED visits Outcome(s): Asthma ICD 9 Code(s): NR Age groups analyzed: Children Study design: Time series N: 1,044 Statistical analyses: Followed APHEA protocol, Poisson regression analysis Covariates: Season, long-term trend, temperature, day of wk, holiday Season: Warm (May-Oct); Cold (Nov-Apr) Statistical package: Stata Lag: 0-3	Warm Season SO_2 (ppb): Mean: 12.60; SD = 10.60; IQR: 6.0, 16.0 Cold Season SO_2 (ppb): Mean: 20.40; SD = 17.90; IQR: 11.0, 24.0	$PM_{2.5}$; r = 0.66 NO_2; r = 0.82 NO_x; r = 0.83 NO; r = 0.76 O_3; r = −0.58 CO; r = 0.64 Benzene; r = 0.80	This study found weak, positive associations for SO_2 and adverse respiratory outcomes in asthmatic children.	SO_2 Increment: Per doubling (ppb) Lag 0 RR 1.07 [1.03, 1.11] Lag 0-1 RR 1.09 [1.04, 1.15] Lag 0-2 RR 1.08 [1.02, 1.15] Lag 0-3 RR 1.08 [1.01, 1.15] Warm only Lag 0-1 RR 1.11 [1.04, 1.19] Cold only Lag 0-1 RR 1.07 [1.00, 1.15] Adjusted for Benzene Lag 0-1 RR 0.99 [0.90, 1.09]

TABLE AX5.2 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR RESPIRATORY DISEASES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean Levels & Monitoring Stations	Copollutants & Correlations	Method, Findings, Interpretation	Effects: Relative Risk or % Change & Confidence Intervals (95%)
EUROPE (cont'd)					
Tobías et al. (1999) Barcelona, Spain Period of Study: 1986-1989	ED visits outcome(s): Asthma ICD9: NR Age groups analyzed: >14 Study design: Time series Statistical analyses: Poisson regression, followed APHEA protocol Covariates: Temperature, humidity, long-term trend, season, day of wk Statistical package: NR Lag: NR	24-h avg SO_2 µg/m^3 Non-epidemic days: 85.8 (62.4) Epidemic days: 116.3 (79.3)	BS NO_2 O_3	The study failed to find a significant association between SO_2 and asthma ED visits.	β x 104 (SE × 104) using Std Poisson Without modeling asthma epidemics: 3.99 (4.14) Modeling epidemics with 1 dummy variable: 1.64 (2.76) Modeling epidemics with 6 dummy variables: 1.53 (2.75) Modeling each epidemic with dummy variable: 2.20 (2.65) β × 104 (SE × 104) using Autoregressive Poisson Without modeling asthma epidemics: 6.99 (14.37) Modeling epidemics with 1 dummy variable: 1.68 (2.77) Modeling epidemics with 6 dummy variables: 1.72 (2.75) Modeling each epidemic with dummy variable: 2.85 (2.89)

TABLE AX5.2 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR RESPIRATORY DISEASES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean Levels & Monitoring Stations	Copollutants & Correlations	Method, Findings, Interpretation	Effects: Relative Risk or % Change & Confidence Intervals (95%)
EUROPE (cont'd)					
Vigotti et al. (1996) Milan, Italy Period of Study: 1980-1989	Hospital admissions outcomes (ICD 9 codes): Respiratory disease (460-519). Age groups analyzed: 15-64 yrs and >64 yrs Study design: Time series N: >73,000 # of Hospitals: Statistical analyses: APHEA protocol Covariates: Season: cold season (Oct. to March) and warm season (Apr to Sept.) Statistical package: Lag: 0, cumulative 4 day (0-3)	24-h avg: 117.7 µg/m^3 Range: 3.0, 827.8 5th: 15.0 25th: 34.0 50th: 65.5 75th: 162.5 95th: 376.3 Winter: 248.6 Range: 30.6, 827.8 5th: 78.8 25th: 138.5 50th: 216.0 75th: 327.8 95th: 527.0 Summer: 30.5 Range: 3.0, 113.8 5th: 9.1 25th: 18.5 50th: 27.8 75th: 39.2 95th: 62.7 # of monitors: 4; r = 0.89, 0.91	TSP; r = 0.63	The effect of single day or cumulative day exposure to SO_2 was more pronounced during the cool months. Interaction between seasons was not significant. SO_2 did not interact with TSP. No differences were noted between age groups. There were increased, but not significant (borderline), risks for increased hospital admissions based on an increment change in SO_2 of 125 µg/m^3 in the winter.	Increment: 100 µg/m^3 All respiratory 15-64 yrs All yr round: RR 1.05 [1.00, 1.10] lag 0 Warm: RR 1.04 [0.98, 1.11] lag 0 Cool: RR 1.06 [1.00, 1.13] lag 0 >64 yrs All yr: RR 1.04 [1.00, 1.09] lag 0 Warm: RR 1.02 [0.96, 1.08] lag 0 Cool: RR 1.05 [1.00, 1.11] lag 0

TABLE AX5.2 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR RESPIRATORY DISEASES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean Levels & Monitoring Stations	Copollutants & Correlations	Method, Findings, Interpretation	Effects: Relative Risk or % Change & Confidence Intervals (95%)
EUROPE (cont'd)					
Walters et al. (1994) Birmingham, United Kingdom Period of Study: 1988-1990	Hospital admissions outcomes (ICD 9 codes): Asthma (493) and acute respiratory conditions (466, 480-486, 490-496) Study design: Time series Statistical analyses: Least squares regression Covariates: Temperature, pressure, humidity Lag: 3 day moving avg.	SO_2 24-h mean (µg/m^3) All yr: 39.06 Max: 126.3 Spring: 42.9 Summer: 37.8 Autumn: 40.9 Winter: 34.2	BS	In 2-pollutant models BS remained significant but SO_2 was no longer associated significantly with admission. A 100 µg/m^3 increment in SO_2 might result in four (0-7) more asthma admissions and 15.5 (6-25) move respiratory admissions/day. Spring and autumn did not show associations with admissions for asthma or respiratory.	Increment of 100 µg/m^3 Asthma Summer: 1.4% [−10, 39] lag 0 Winter: 2.7% [−0.8, 6.1] lag 0 All respiratory Summer: 5.9% [1.1, 10.6] lag 0 ($p < 0.02$) Winter: 18% [8.8, 26.8] lag 0 ($p < 0.0002$)

TABLE AX5.2 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR RESPIRATORY DISEASES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean Levels & Monitoring Stations	Copollutants & Correlations	Method, Findings, Interpretation	Effects: Relative Risk or % Change & Confidence Intervals (95%)
LATIN AMERICA					
Braga* et al. (1999) São Paulo, Brazil Period of Study: 10/1992-10/1993	Hospital admissions outcomes (ICD 9 codes): All respiratory (466,480-486,491-492,496) Age groups analyzed: <13 yrs Study design: Time series N: 68,918 # of Hospitals: 112 Statistical analyses: Multiple linear regression models (least squares). Also used Poisson regression techniques. GLM and GAM using LOESS for smoothing. Covariates: Season, temperature, humidity, day of wk, Statistical package: SPSS, S-Plus Lag: 1,2,3,4,5,6,7 moving avgs	24-h avg 22.40 (9.90) µg/m^3 Min: 6.4 Max: 69.6 # of monitors: 13	$PM_{2.5}$; r = 0.73 CO; r = 0.62 NO_2; r = 0.53 O_3; r =	SO_2 did not show a correlation with respiratory hospital admissions with any lag structure.	Increment: 22.4 µg/m^3 0.12 [−0.04, 0.28] lag 0 0.18 [−0.00, 0.37] lag 0-1 0.19 [−0.01, 0.39] lag 0-2 0.18 [−0.04, 0.40] lag 0-3 0.18 [−0.05, 0.42] lag 0-4 0.12 [−0.13, 0.36] lag 0-5 0.08 [−0.18, 0.35] lag 0-6

TABLE AX5.2 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR RESPIRATORY DISEASES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean Levels & Monitoring Stations	Copollutants & Correlations	Method, Findings, Interpretation	Effects: Relative Risk or % Change & Confidence Intervals (95%)
LATIN AMERICA (cont'd)					
Braga* et al. (2001) São Paulo, Brazil Period of Study: 1/93-11/97	Hospital admissions outcomes (ICD 9): All respiratory admissions (460-519) Age groups analyzed: 0-19, ≤2, 3-5, 6-13, 14-19 Study design: Time series Statistical analyses: Poisson regression with GAM Covariates: Long-term trend, season, temperature, relative humidity, day of wk, holiday Statistical package: S-Plus 4.5 Lag: 0-6 moving avg	SO_2 mean: 21.4 µg/m^3; SD = 11.2 IQR: 14.4 µg/m^3 Range: 1.6, 76.1 # of stations: 5-6	$PM_{2.5}$; r = 0.61 NO_2; r = 0.54 CO; r = 0.47 O_3; r = 0.17	Children <2 yrs were most susceptible to the effect of each pollutant. Pneumonia and bronchopneumonia were the main cause of hospital admissions (71%) in the <2-yr-old group. Bronchitis/asthma were more important for the intermediate age groups. However, in all age groups the largest increase in admissions was caused by chronic disease in tonsils and adenoids. Multipollutant models rendered all pollutants except $PM_{2.5}$ and SO_2 from significance. The effect of $PM_{2.5}$ stayed relatively unchanged while SO_2 was reduced; however, it remained significant.	Increment: µg/m^3 (IQR) All respiratory admissions <2 yrs 5.9% [4.5, 7.4] 3-5 yrs 1.6% [−1.3, 4.4] 6-13 yrs 0.6% [−2.2, 3.5] 14-19 yrs 1.3% [−3.2, 5.8] All ages 4.5% [3.3, 5.8]

TABLE AX5.2 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR RESPIRATORY DISEASES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean Levels & Monitoring Stations	Copollutants & Correlations	Method, Findings, Interpretation	Effects: Relative Risk or % Change & Confidence Intervals (95%)
LATIN AMERICA (cont'd)					
Farhat* et al. (2005) São Paulo, Brazil Period of Study: 1996-1997	Hospital Admissions/ED Visits Outcome(s) (ICD9): Lower Respiratory Disease (466, 480-5) Age groups analyzed: <13 Study design: Time series N: 4,534 # of Hospitals: 1 Statistical analyses: 1) Poisson regression and 2) GAM – no mention of more stringent criteria Covariates: Long-term trends, seasonality, temperature, humidity Statistical package: S-Plus Lag: 0-7 days, 2,3,4 day moving avg	24-h avg: Mean: 23.7 μg/m^3 SD = 10.0 Range: 3.4, 75.2 IQR: 12.5 # of Stations: 6	$PM_{2.5}$; r = 0.69 NO_2; r = 0.66 CO; r = 0.49 O_3; r = 0.28	This study reports a significant effect of air pollution on respiratory morbidity, though several pollutants were associated with increased respiratory events, making it difficult to isolate a single agent as the main atmospheric contaminant.	Increment: 12.5 μg/m^3 (IQR) Single-pollutant models (estimated from graphs): Pneumonia ~21% [4.8, 37] Asthma ~12% [−10, 38] Pneumonia multipollutant models: Adjusted for: $PM_{2.5}$ 13.3 [−5.7, 32.3] 6-day avg NO_2 16.5 [−1.6, 34.6] 6-day avg CO 18.4 [0.5, 36.2] 6-day avg O_3 18.4 [0.5, 36.2] 6-day avg Multipollutant model 13.3 [−5.9, 32.6] 6-day avg Asthma multipollutant models: Adjusted for: $PM_{2.5}$ 3.8 [−23.3, 31.0] 2-day avg NO_2 −1.2 [−27.4, 25.0] 2-day avg CO 6.2 [−18.8, 31.2] 2-day avg O_3 9.4 [−14.6, 33.5] 2-day avg Multipollutant model −0.5 [−27.7, 26.6] 2-day avg

TABLE AX5.2 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR RESPIRATORY DISEASES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean Levels & Monitoring Stations	Copollutants & Correlations	Method, Findings, Interpretation	Effects: Relative Risk or % Change & Confidence Intervals (95%)
LATIN AMERICA (cont'd)					
Gouveia and Fletcher, (2000) São Paulo, Brazil Period of Study: 11/92-9/94	Hospital admissions outcomes (ICD 9): All respiratory; Pneumonia (480-486); asthma or bronchitis (466, 490, 491, 493) Age groups analyzed: <1; <5 years Study design: Time series Statistical analyses: Poisson regression Covariates: Long-term trend, season, temperature, relative humidity, day of wk, holiday, strikes in public transport or health services Season: Cool (May-Oct), Warm (Nov-Apr) Statistical package: SAS Lag: 0, 1, 2 days	24-h avg: Mean: 18.3 µg/m^3 SD = 9.0 Range: 3.2, 61.1 5th: 7.6 25th: 11.9 50th: 16.6 75th: 22.2 95th: 35.8 # of stations: 4	$PM_{2.5}$; r = 0.72 NO_2; r = 0.37 CO; r = 0.65 O_3; r = 0.08	Current ambient air pollution concentrations have short-term adverse effects on children's respiratory morbidity assessed through admissions to hospitals.	Increment: 27.1 µg/m^3 (90th – 10th) All Respiratory <5 yrs RR 1.038 [0.983, 1.096] lag 1 <5 yrs Cool RR 1.06 [0.99, 1.11] (estimated from graph) <5 yrs Warm RR 0.98 [0.89, 1.07] (estimated from graph) Pneumonia <5 yrs RR 1.024 [0.961, 1.091] lag 1 <1 yr RR 1.071 [0.998, 1.149] lag 0 Asthma <5 yrs RR 1.106 [0.981, 1.247] lag 2

TABLE AX5.2 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR RESPIRATORY DISEASES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean Levels & Monitoring Stations	Copollutants & Correlations	Method, Findings, Interpretation	Effects: Relative Risk or % Change & Confidence Intervals (95%)
LATIN AMERICA (cont'd)					
Ilabaca et al. (1999) Santiago, Chile Period of Study: 2/1/95–8/31/96 Days: 578	ED visits outcome(s) (ICD9): Upper respiratory illness (460-465, 487); Lower respiratory illness (466, 480-486, 490-494, 496, 519.1, 033.9); Pneumonia (480-486) Age groups analyzed: <15 Study design: Time series # of Hospitals: 1 Statistical analyses: Poisson regression Covariates: Long-term trend, season, day of wk, temperature, humidity, influenza epidemic Season: Warm (Sep-Apr), Cool (May-Aug) Statistical package: NR Lag: 0-3 days	24-h avg SO_2 (µg/m^3) Warm: Mean: 14.9 Median: 13.2 SD = 8.8 Range: 1.9, 60.2 5th: 5.6 95th: 32.0 Cool: Mean: 31.8 Median: 28.2 SD = 18.4 Range: 5.6, 92.1 5th: 9.4 95th: 75.2 # of stations: 4	Warm: NO_2; r = 0.6556 O_3; r = 0.1835 $PM_{2.5}$; r = 0.6687 $PM_{2.5}$; r = 0.5764 Cool: NO_2; r = 0.7440 O_3; r = 0.1252 $PM_{2.5}$; r = 0.7337 $PM_{2.5}$; r = 0.6874	SO_2 was related to the number of respiratory ED visits, but because of the high correlation between contaminants, it is difficult to establish independent health effects. These results support the fact that exposure to air pollution mixtures may decrease immune functions and increase the risk for respiratory infections among children.	Increment: IQR All respiratory Cool Lag 2 IQR: RR 1.0289 [1.0151, 1.0428] Lag 3 IQR: RR 1.0374 [1.0236, 1.0513] Lag avg 7 IQR: RR 1.0230 [1.0086, 1.0377] Warm Lag 2 IQR: RR 1.0029 [0.9860, 1.0200] Lag 3 IQR: RR 1.0108 [0.9937, 1.0282] Lag avg 7 IQR: RR 1.0108 [0.9756, 1.0473] Upper respiratory Cool Lag 2 IQR: RR 1.0584 [1.0394, 1.0778] Lag 3 IQR: RR 1.0513 [1.0324, 1.0706] Lag avg 7 IQR: RR 1.0316 [1.0120, 1.0515] Warm Lag 2 IQR: RR 1.0061 [0.9850, 1.0277] Lag 3 IQR: RR 1.0130 [0.9916, 1.0349] Lag avg 7 IQR: RR 0.9815 [0.9390, 1.0260]

TABLE AX5.2 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR RESPIRATORY DISEASES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean Levels & Monitoring Stations	Copollutants & Correlations	Method, Findings, Interpretation	Effects: Relative Risk or % Change & Confidence Intervals (95%)
LATIN AMERICA (cont'd)					
Ilabaca et al. (1999) (cont'd)					Pneumonia Cool Lag 2 IQR: RR 1.0164 [0.9757, 1.0587] Lag 3 IQR: RR 1.0342 [0.9938, 1.0762] Lag avg 7 IQR: RR 1.0291 [0.9850, 1.0751] Warm Lag 2 IQR: RR 1.1010 [1.0404, 1.1653] Lag 3 IQR: RR 1.0248 [0.9669, 1.0862] Lag avg 7 IQR: RR 1.2151 [1.0771, 1.3709]

TABLE AX5.2 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR RESPIRATORY DISEASES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean Levels & Monitoring Stations	Copollutants & Correlations	Method, Findings, Interpretation	Effects: Relative Risk or % Change & Confidence Intervals (95%)
LATIN AMERICA (cont'd)					
Lin et al. (1999) São Paulo, Brazil Period of Study: May 1991-Apr 1993 Days: 621	ED visits outcome(s): Respiratory disease, Upper respiratory illness, Lower respiratory illness, Wheezing ICD 9Code(s): NR Age groups analyzed: <13 Study design: Time series # of Hospitals: 1 Statistical analyses: Gaussian and Poisson regression Covariates: Long-term trend, seasonality, day of wk, temperature, humidity Statistical package: NR Lag: 5-day lagged moving avgs	SO_2 µg/m^3: Mean: 20 SD = 8 Range: 4, 60 Number of stations: 3	NO_2; r = 0.38 CO; r = 0.56 $PM_{2.5}$; r = 0.73 O_3; r = 0.21	The results of this study demonstrate a significant association between the increase in emergency visits for all respiratory illness, especially URI, and SO_2 levels.	Increment: 10 µg/m^3 All respiratory illness SO_2 alone RR 1.079 [1.052, 1.107] 5-day moving avg SO_2 + $PM_{2.5}$ + O_3 + NO_2 + CO RR 0.938 [0.900, 0.977] Lower respiratory illness SO_2 alone RR 1.052 [0.984, 1.125] 5-day moving avg SO_2 + $PM_{2.5}$ + O_3 + NO_2 + CO RR 0.872 [0.783, 0.971] Upper respiratory illness SO_2 alone RR 1.075 [1.044, 1.107] 5-day moving avg SO_2 + $PM_{2.5}$ + O_3 + NO_2 + CO RR 0.951 [0.906, 0.999] Wheezing SO_2 alone RR 1.034 [0.975, 1.096] 5-day moving avg SO_2 + $PM_{2.5}$ + O_3 + NO_2 + CO RR 0.908 [0.824, 1.002]

TABLE AX5.2 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR RESPIRATORY DISEASES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean Levels & Monitoring Stations	Copollutants & Correlations	Method, Findings, Interpretation	Effects: Relative Risk or % Change & Confidence Intervals (95%)
LATIN AMERICA (cont'd)					
Martins* et al. (2002) São Paulo, Brazil Period of Study: 5/96-9/98	ED visits outcome(s) (ICD10): Chronic Lower Respiratory Disease (CLRD) (J40-J47); includes chronic bronchitis, emphysema, other COPDs, asthma, bronchiectasia Age groups analyzed: >64 Study design: Time series N: 712 # of Hospitals: 1 Catchment area: 13,163 total ER visits Statistical analyses: Poisson regression and GAM – no mention of more stringent criteria Covariates: Weekdays, time, minimum temperature, relative humidity, daily number of non-respiratory emergency room visits made by elderly Statistical package: S-Plus Lag: 2-7 days and 3 day moving avgs	SO_2 24-h avg (μg/m^3): 18.7, SD = 10.6 Range: 2.0, 75.2 IQR: 15.1 μg/m^3 # of Stations: 13	O_3; r = 0.28 NO_2; r = 0.67 $PM_{2.5}$; r = 0.72 CO; r = 0.51	The results of the study show a significant association between SO_2 and CLRD among the elderly.	Increment: IQR of μg/m^3 Percent increase: 17.5 [5.0, 23.0] lag 3-day moving avg (estimated from graph) Single-pollutant model β = 0.0140 (0.0056) Multipollutant model (with ozone) β = 0.0104 (0.0059)

TABLE AX5.2 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR RESPIRATORY DISEASES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean Levels & Monitoring Stations	Copollutants & Correlations	Method, Findings, Interpretation	Effects: Relative Risk or % Change & Confidence Intervals (95%)
ASIA					
Wong et al. (2002a)* London England and Hong Kong Period of Study: London: 1992-1994 Hong Kong: 1995-1997 Days: 1,096	Hospital admissions outcomes (ICD 9): All respiratory admissions (460-519); asthma (493) Age groups analyzed: 15-64, 65+, all ages Study design: Time series Statistical analyses: APHEA protocol, Poisson regression with GAM Covariates: Long-term trend, season, influenza, day of wk, holiday, temperature, humidity, thunderstorms Season: Cool, Oct-Mar; Warm: Apr-Sep Dose-Response Investigated?: Yes Statistical package: S-Plus Lag: 0, 1, 2, 3, 4 days, 0-1 cum. avg.	24-h SO_2 µg/m^3 Hong Kong Mean: 17.7 Warm: 18.3 Cool: 17.2 SD = 12.3 Range: 1.1, 90.0 10th: 6.2 50th: 14.5 90th: 32.8 London Mean: 23.7 Warm: 22.2 Cool: 25.3 SD = 12.3 Range: 6.2, 113.6 10th: 13.2 50th: 20.6 90th: 38.1	Hong Kong $PM_{2.5}$; r = 0.30 NO_2; r = 0.37 O_3; r = −0.18 London $PM_{2.5}$; r = 0.64 NO_2; r = 0.71 O_3; r = −0.25	Similar non-statistically significant associations between asthma hospital admissions and SO_2 were found in both cities. The association between respiratory hospital admissions and SO_2 showed significance in the cold season in Hong Kong and on an all yr basis. Respiratory hospital admissions were not significantly associated with SO_2 in Britain. In the 2-pollutant model the association between respiratory hospital admission and SO_2 in London was insignificant, and remained insignificant after adjusted for the second pollutants.	Increment: 10 µg/m^3 Asthma, 15-64 years Hong Kong ER −0.1 [−2.4, 2.2] lag 0-1 ER −1.5 [-3.4, 0.5] lag 2 Warm ER 1.5 [−1.5, 4.6] lag 0-1 Cool ER −2.0 [−5.4, 1.4] lag 0-1 London ER 0.7 [−1.0, 2.5] lag 0-1 ER 2.1 [0.7, 3.6] lag 3 Warm ER -1.4 [−4.7, 1.9] lag 0-1 Cool ER 1.6 [−0.5, 3.8] lag 0-1 Respiratory 65+ years Hong Kong ER 1.8 [0.9, 2.6] lag 0-1 ER 1.7 [1.0, 2.4] lag 0

TABLE AX5.2 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR RESPIRATORY DISEASES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean Levels & Monitoring Stations	Copollutants & Correlations	Method, Findings, Interpretation	Effects: Relative Risk or % Change & Confidence Intervals (95%)
ASIA (cont'd)					
Wong et al. (2002a)* (cont'd)		# of stations: Hong Kong: 7, r London: 3, r =		In Hong Kong, the positive association of SO_2 was most affected by NO_2, losing statistical significance. The positive association remained robust when adjusted for O_3, and a slight decrease in association after adjusted for $PM_{2.5}$.	Warm ER 1.1 [0.0, 2.2] lag 0-1 Cool ER 2.7 [1.4, 4.0] lag 0-1 +O_3 ER 1.9 [1.1, 2.8] lag 0-1 +$PM_{2.5}$ ER 1.2 [0.3, 2.2] lag 0-1 +NO_2 ER 0.3 [−0.7, lag 1.4] lag 0-1 London ER 0.2 [−0.6, 1.1] lag 0-1 ER 1.2 [0.5, 2.0] lag 3 Warm ER 1.3 [−0.5, 3.1] lag 0-1 Cool ER −0.3 [−1.3, 0.8] lag 0- +O_3 ER 0.5 [−0.4, 1.5] lag 0-1 +$PM_{2.5}$ ER 1.2 [0.3, 2.2] lag 0-1 +NO_2 ER 0.5 [−0.7, 1.7] lag 0-1
Chew et al. (1999) Singapore Period of Study: 1990-1994	Hospital Admissions/ED Visits Outcome(s) (ICD 9): Asthma (493) Age groups analyzed: 3-12, 13-21 Study design: Time series N: 23,000 # of Hospitals: 2 Statistical analyses: Linear regression, GLM	24-h avg: 38.1 µg/m^3, SD = 21.8 Range: 3.0, 141.0 # of Stations: 15	NO_2; r = O_3; r = TSP; r =	SO_2 was positively correlated to daily ER visits and hospitalization for asthma in children (3-12 yrs), but not adolescents. The association of ER visits with SO_2 persisted after standardization for meteorological and temporal variables. An adjusted increase in 2.9 ER visits for every 20 µg/m^3 increase in ambient SO_2 levels with a lag of 1 was observed.	Categorical analysis (via ANOVA) p-value and Pearson correlation coefficient (r) using continuous data comparing daily air pollutant levels and daily number of ER visits Age Group: 3-12 13-21

TABLE AX5.2 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR RESPIRATORY DISEASES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean Levels & Monitoring Stations	Copollutants & Correlations	Method, Findings, Interpretation	Effects: Relative Risk or % Change & Confidence Intervals (95%)
ASIA (cont'd)					
Chew et al. (1999) (cont'd)	Covariates: variables that were significantly associated with ER visits were retained in the model Statistical package: SAS/STAT, SAS/ETS 6.08 Lag: 1, 2 days avgs			The increased number of ER visits/day for each quartile are listed below: Q1: <9 Q2: 10-12 Q3: 13-16 Q4: >16	Lag 0 r = 0.04 r = 0.05 p < 0.001 p = 0.086 Lag 1 r = 0.10 r = 0.06 p < 0.001 p = 0.016 Lag 2 r = 0.08 r = 0.07 p < 0.001 p = 0.019
Hwang and Chan (2002) Taiwan Period of Study: 1998	ED Visits Outcome(s) (ICD 9): Lower Respiratory Disease (LRD) (466, 480-6) including acute bronchitis, acute bronchiolits, pneumonia Age groups analyzed: 0-14, 15-64, ≥65, all ages Study design: Time series Catchment area: Clinic records from 50 communities Statistical analyses: Linear regression, GLM Covariates: temperature, dew point temperature, season, day of wk, holiday Statistical package: NR Lag: 0,1,2 days and avgs	24-h avg: 5.4 ppb, SD = 3.0 Range: 1.5, 16.9	NO_2 $PM_{2.5}$ O_3 CO No correlations for individual pollutants.	Colinearity of pollutants prevented use of multipollutant models	Increment: 10% change in SO_2 (natural avg) which is equivalent to 2.4 ppb. NOTE: The percent change is for the rate of clinic use NOT for relative risk for adverse effect. Increased clinic visits for lower respiratory disease (LRD) by age group 0-14 yrs Lag 0 0.5% [0.3, 0.6] 15-64 yrs Lag 0 0.7% [0.5, 0.8] ≥65 yrs Lag 0 0.8% [0.6, 1.1] All ages Lag 0 0.5% [0.4, 0.7]

TABLE AX5.2 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR RESPIRATORY DISEASES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean Levels & Monitoring Stations	Copollutants & Correlations	Method, Findings, Interpretation	Effects: Relative Risk or % Change & Confidence Intervals (95%)
ASIA (cont'd)					
Lee et al. (2006) Hong Kong, China Period of Study: 1997-2002 Days: 2,191	Hospital admissions outcomes (ICD 9): Asthma (493) Age groups analyzed: ≤18 Study design: Time series N: 26,663 Statistical analyses: Semi-parametric Poisson regression with GAM (similar to APHEA 2) Covariates: Long-term trend, temperature, relative humidity, influenza, day of wk, holiday Statistical package: SAS 8.02 Lag: 0-5 days	SO_2 24-h mean: 17.7 µg/m^3, SD = 10.7 IQR: 11.1 µg/m^3 25th: 10.6 50th: 15.2 75th: 21.7 # of stations: 9-10	$PM_{2.5}$; r = 0.37 $PM_{2.5}$; r = 0.47 NO_2; r = 0.49 O_3; r = −0.17	Absence of an association of SO_2 with asthma admissions was attributed to low ambient SO_2 levels during the study period due to restrictions on sulfur content in fuel.	Increment: 11.1 µg/m^3 (IQR) Asthma Single-pollutant model Lag 0 −1.57% [−2.87, −0.26] Lag 1 −1.77% [−3.06, −0.46] Lag 2 −1.15% [−2.42, 0.14] Lag 3 0.82% [−0.45, 2.11] Lag 4 1.40% [0.13, 2.69] Lag 5 1.46% [0.19, 2.74] Multipollutant model–including PM, NO_2, and O_3 0.81% [−0.75, 2.4] lag 5 Other lags NR

TABLE AX5.2 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR RESPIRATORY DISEASES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean Levels & Monitoring Stations	Copollutants & Correlations	Method, Findings, Interpretation	Effects: Relative Risk or % Change & Confidence Intervals (95%)
ASIA (cont'd)					
Lee* et al. (2002) Seoul, Korea Period of Study: 12/1/97-12/31/99 Days: 822	Hospital Admissions Outcomes (ICD 10): Asthma (J45–J46) Age groups analyzed: <15 Study design: Time series N: 6,436 Statistical analyses: Poisson regression, log link with GAM Covariates: Time, day of wk, temperature, humidity Season: Spring (Mar-May), Summer (Jun-Aug), Fall (Sep-Nov), Winter (Dec-Feb) Statistical package: NR Lag: 0-2 days cumulative	24-h SO_2 (ppb) Mean: 7.7 SD = 3.3 5th: 3.7 25th: 5.1 50th: 7.0 75th: 9.5 95th: 14.3 # of stations: 27	NO_2; r = 0.723 O_3; r = −0.301 CO; r = 0.812 $PM_{2.5}$; r = 0.585	This study reinforces the possible role of SO_2 on asthma attacks, although it should be interpreted with caution because the effect estimates are close to the null and because results in the multipollutant models are inconsistent.	Increment: 14.6 ppb (IQR) Asthma SO_2 RR 1.11 [1.06, 1.17] lag 0-2 SO_2 + $PM_{2.5}$ RR 1.08 [1.02, 1.14] lag 0-2 SO_2 + NO_2 RR 0.95 [0.88, 1.03] lag 0-2 SO_2 + O_3 RR 1.12 [1.06, 1.17] lag 0-2 SO_2 + CO RR 0.99 [0.92, 1.07] lag 0-2 SO_2 + O_3 + CO + $PM_{2.5}$ + NO_2 RR 0.949 [0.868, 1.033]
Tanaka et al. (1998) Kushiro, Japan Period of Study: 1992-1993	ED Visits Outcome(s): Asthma ICD 9Code(s): NR Age groups analyzed: 15-79 Study design: Time series N: 102 # of Hospitals: 1 Statistical analyses: Poisson regression Covariates: temperature, vapor pressure, barometric pressure, relative humidity, wind velocity, wind direction at maximal velocity Statistical package: NR	SO_2 24-h avg 3.2 (2.4) ppb in fog 3.7 (1.9) ppb in fog free days Max SO_2 24-h avg <11 ppb	NO_2; r = NR SPM (TSP); r = O_3; r = NR	The results reveal that ED visits by atopic subjects increased on low SO_2 days. This observation is inconsistent with most air pollution epidemiology, as high levels of air pollutants have conventionally been linked with asthma exacerbation.	Increment: 5 ppb Nonatopic OR 1.18 [0.96, 1.46] Atopic OR 0.78 [0.66, 0.93]

TABLE AX5.2 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR RESPIRATORY DISEASES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean Levels & Monitoring Stations	Copollutants & Correlations	Method, Findings, Interpretation	Effects: Relative Risk or % Change & Confidence Intervals (95%)
ASIA (cont'd)					
Tsai et al. (2006) Kaohsiung, Taiwan Period of Study: 1996-2003 Days: 2922	Hospital admissions outcomes (ICD 9): Asthma (493) Study design: Case-crossover N: 17,682 Statistical analyses: Conditional logistic regression Covariates: Temperature, humidity Season: Warm (≥25 ºC); Cool (< 25 ºC) Statistical package: SAS Lag: 0-2 days Cumulative	SO_2 24-h mean: 9.49 ppb Range: 0.92, 31.33 25th: 6.37 50th: 8.94 75th: 12.16 # of stations: 6	$PM_{2.5}$ NO_2 O_3 CO	Positive associations were observed between air pollutants and hospital admissions for stroke. In single-pollutant models SO_2 was not associated with either PIH or IS. The season did not affect these associations. SO_2 was also not significant in 2-pollutant models.	Increment: 5.79 ppb (IQR) Seasonality Single-pollutant model >25 °C 1.018 [0.956, 1.083] lag 0-2 <25 °C 1.187 [1.073, 1.314] lag 0-2 Dual pollutant model Adjusted for $PM_{2.5}$ >25 °C 0.993 [0.932, 1.058] lag 0-2 <25 °C 1.027 [0.921, 1.146] lag 0-2 Adjusted for CO >25 °C] 0.910 [0.847, 0.978] lag 0-2 <25 °C 1.036 [1.027, 1.046] lag 0-2 Adjusted for NO_2 >25 °C 0.967 [0.903, 1.035] lag 0-2 <25 °C 0.735 [0.646, 0.835] lag 0-2 Adjusted for O_3 >25 °C 1.055 [0.990, 1.123] lag 0-2 <25 °C 1.195 [1.080, 1.323] lag 0-2

TABLE AX5.2 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR RESPIRATORY DISEASES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean Levels & Monitoring Stations	Copollutants & Correlations	Method, Findings, Interpretation	Effects: Relative Risk or % Change & Confidence Intervals (95%)
ASIA (cont'd)					
Wong et al. (1999) Hong Kong, China Period of Study: 1994-1995	Hospital admissions outcomes (ICD 9): All respiratory admissions (460-6, 471-8, 480-7, 490-6); Asthma (493), COPD (490-496), Pneumonia (480-7) Age groups analyzed: 0-4, 5-64, ≥65, all ages # of hospitals: 12 Study design: Time series Statistical analyses: Poisson regression (followed APHEA protocol) Covariates: Trend, season, day of wk, holiday, temperature, humidity Statistical package: SAS 8.02 Lag: days 0-3 cumulative	Median 24-h SO_2: 17.05 µg/m^3 Range: 2.74, 68.49 25th: 12.45 75th: 25.01 # of stations: 7, r =	O_3 SO_2 $PM_{2.5}$	Adverse respiratory effects of SO_2 were noted at low concentrations. Results for respiratory outcomes were attributed to the elderly population. This was also true for the other pollutants. Therefore, it is difficult to be certain that the effects were due mainly to SO_2. Pair-wise comparisons in multipollutant models showed significant interactions of $PM_{2.5}$, NO_2, and O_3.	Increment = 10 µg/m^3 Overall increase in admissions: 1.013 [1.004, 1.021] lag 0 Respiratory relative risks (RR) 0-4 yrs: 1.005 [0.991, 1.018] lag 0 5-64 yrs: 1.008 [0.996, 1.021] lag 0 >65 yrs: 1.023 [1.012, 1.036] lag 0 Asthma: 1.017 [0.998, 1.036] lag 0 COPD: 1.023 [1.011, 1.035] lag 0 Pneumonia: 0.990 [0.977, 1.004] lag 4

TABLE AX5.2 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR RESPIRATORY DISEASES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean Levels & Monitoring Stations	Copollutants & Correlations	Method, Findings, Interpretation	Effects: Relative Risk or % Change & Confidence Intervals (95%)
ASIA (cont'd)					
Wong et al. (2001a) Hong Kong, China Period of Study: 1993-1994	Hospital admissions outcomes (ICD 9): Asthma (493) Age groups analyzed: ≤15 N: 1,217 # of hospitals: 1 Study design: Time series Statistical analyses: Poisson regression (followed APHEA protocol) Covariates: Season, temperature, humidity Season: Summer (Jun-Aug), Autumn (Sep-Nov), Winter (Dec-Feb), Spring (Mar-May) Lag: 0,1,2,3,4,5 days; and cumulative 0-2 and 0-3 days.	24-h avg SO_2 mean: 12.2 µg/m^3 SD = 12.9 Range: 0, 98 µg/m^3 Autumn: 10.6 (9.6) Winter: 10.0 (7.5) Spring: 9.6 (8.8) Summer: 18.5 (19.5) # of stations: 9	$PM_{2.5}$ NO_2	SO_2 levels were found to be the highest during the summer. There were consistent and statistically significant associations between asthma admission and increased daily levels of SO_2. No associations were noted in the spring or winter. No significant associations were found between hospital admissions and day of the wk, humidity, temperature or atmospheric pressure. Total admissions were limited to one hospital.	Increment: 10 µg/m^3 Asthma All yr: RR 1.06 p = 0.004 Autumn: NR Winter: NR Spring: NR Summer: NR

*Default GAM

[+]Did not report correction for over-dispersion

NR: Not Reported

APHEA: Air Pollution and Health: a European Approach

TABLE AX5.3. ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH CARDIOVASCULAR MORBIDITY IN FIELD/PANEL STUDIES

Reference, Study Location, and Period	Outcomes and Methods	Mean SO_2 Levels	Copollutants Considered	Findings, Interpretation	Effects
UNITED STATES					
Liao et al. (2004) Three locations in United States: Minneapolis, MN; Jackson, MS; Forsyth County, NC 1996-1998	Cross-sectional study of 6,784 cohort members of the Atherosclerosis Risk in Communities Study. Participants were 45-64 yrs of age; baseline clinical examinations conducted from 1987-1989. HRV data collected from 1996-1998. Air pollutants obtained form EPA AIRS for this same period. Resting, supine, 5-min beat-to-beat RR interval data were collected over a 4-h period. Multivariable linear regression models used to assess associations between pollutants measured 1-3 days prior to HRV measurements. Models controlled for age, ethnicity-center, sex, education, current smoking, BMI, heart rate, use of cardiovascular medication, hypertension, prevalent coronary heart disease, and diabetes.	Mean (SD) SO_2 measured 1 day prior to HRV measurement was 4 (4) ppb	PM_{10} O_3 CO NO_2	Significant interaction between SO_2 and prevalence of coronary heart disease for low-frequency power analyses SO_2 inversely associated with SD of normal R-R intervals and low-frequency power and positively associated with heart rate. SO_2 association with low-frequency power stronger among those with history of coronary heart disease. Effect size of PM_{10} larger than for gaseous pollutants.	Log-transformed low-frequency power effect estimate and SE per 1 SD increment (4 ppb) SO_2 lag 1 day: Log transformed high-frequency power −0.024 (SE 0.016) Standard deviation of normal R-R intervals −0.532 (SE 0.270), $p < 0.05$ Heart rate: 0.295 (SE 0.130), $p < 0.05$ Prevalent CHD: −0.122 (SE 0.056), $p < 0.01$ No prevalent CHD −0.012 (SE 0.016)
Liao et al. (2005) United States, 1996-1998	Cross-sectional survey 10,208 participants (avg age 54 yrs) from Atherosclerosis Risk in Communities (ARIC) study cohort to assess the association between criteria air pollutants and hemostatic and inflammatory markers. 57% of participants were female and 66% male. Used hemostatis/inflammation variables collected during the baseline examination and air pollution data 1-3 days prior to the event. Used multiple linear regression models that controlled for age, sex, ethnicity-center, education, smoking, drinking status, BMI, history of chronic respiratory disease, humidity, seasons, cloud cover, and temperature. Also history of CVD and diabetes if not effect modifier in a particular model.	SO_2 mean (SD) 0.0005 (0.004) ppm Q1-3: 0.005 (0.003) ppm Q4: 0.006 (0.005) ppm	PM_{10} CO NO_2 O_3	Significant curvilinear association between SO_2 with factor VIII-C, WBC, and serum albumin. Curvilinear association indicated threshold effect	Results shown in graph.

TABLE AX5.3 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH CARDIOVASCULAR MORBIDITY IN FIELD/PANEL STUDIES

Reference, Study Location, and Period	Outcomes and Methods	Mean SO_2 Levels	Copollutants Considered	Findings, Interpretation	Effects
UNITED STATES (cont'd)					
Dockery et al. (2005) Boston, MA Jul 1995-Jul 2002	Cohort study of 203 cardiac patients with implanted cardioverter defibrillators. Patients were followed for an avg of 3.1 yrs from 1995-2002 to assess the role of air pollution on the incidence of ventricular arrhythmias. The association of arrhythmic episode-days and air pollutions analyzed with logistic regression using GEE with random effects. Model adjusted for patient, season, minimum temperature, mean humidity, day of the wk, and previous arrhythmia within 3 days. Only effects of 2-day running mean of air pollution concentration reported.	48-h avg SO_2; Median: 4.9 ppb 25th%: 3.3 ppb 75%: 7.4 ppb 95%: 12.8 ppb	$PM_{2.5}$ BC SO_4 PN NO_2 CO O_3	No statistically significant association between any of the air pollutant and ventricular arrhythmias when all events were considered. However, ventricular arrhythmias within 3 days of a prior event were statistically significant with SO_2, $PM_{2.5}$, BC, NO_2, CO, and marginally with SO_4, but not with O_3 or PN. CO, NO_2, BC, and $PM_{2.5}$ correlated, thus it was impossible to differentiate the independent effects. Since the increased risk of ventricular tachyarrhythmia was associated with air pollution observed among patients with a recent tachyarrhythmia, it was suggested that air pollution acts in combination with cardiac electrical instability to increase risk of arrhythmia.	For IQR (4.0 ppb) increase in 48-h mean SO_2: All events: OR = 1.04 (0.94, 1.14), p = 0.28 Prior arrhythmia event <3 days: 1.30 (95% CI: 1.06, 1.61), p = 0.013 Prior arrhythmia event >3 days: 0.98 (0.87, 1.11) p = 0.78

TABLE AX5.3 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH CARDIOVASCULAR MORBIDITY IN FIELD/PANEL STUDIES

Reference, Study Location, and Period	Outcomes and Methods	Mean SO_2 Levels	Copollutants Considered	Findings, Interpretation	Effects
UNITED STATES (cont'd)					
Gold et al. (2000) Boston, MA Jun-Sep 1997	Panel study on 21 active Boston residents aged 53-87 yrs to investigate the association between short-term changes in ambient air pollution and short-term changes in cardiovascular function. Participants observed up to 12 times from June to Sep 1997 (163 observations made in total). Protocol involved 25 mins per wk of continuous ECG monitoring, that included 5 mins of rest, 5 mins of standing, 5 mins of exercise outdoors, 5 mins of recovery, and 20 cycles of slow breathing. Fixed effects models adjusted for time-varying covariates and individuals traits.	24-h avg mean 3.2 ppb Range: 0, 12.6 ppb IQR: 3.0 ppb	$PM_{2.5}$ coarse matter O_3 NO_2 CO	In single-pollutant models, 24-h mean SO_2 associated with reduced heart rate in the first rest period but not overall. Associations weaker for shorter averaging periods. Association between SO_2 and heart rate not significant with the multipollutant model (SO_2 and $PM_{2.5}$). SO_2 not associated with r-MSSD.	Heart rate, first rest period, mean 66.3 bpm single-pollutant model estimated effect (SE) −1.0 (0.5) % mean 1.5, p = 0.03 Heart rate, first rest period, mean 66.3 bpm Multipollutant model ($PM_{2.5}$ and SO_2): SO_2 estimated effect (SE) −0.8 (0.5) % mean 1.2, p = 0.09 $PM_{2.5}$ estimated effect (SE) −1.6 (0.7) % mean 2.5, p = 0.03 Overall heart rate, mean 74.9 bpm single-pollutant model estimated effect (SE) −0.5 (0.5), p = 0.30 Overall heart rate, mean 74.9 bpm Multipollutant model SO_2 estimated effect (SE) −0.2 (0.5), p = 0.6 $PM_{2.5}$ estimated effect (SE) −1.9 (0.7) p = 01% mean 2.6

TABLE AX5.3 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH CARDIOVASCULAR MORBIDITY IN FIELD/PANEL STUDIES

Reference, Study Location, and Period	Outcomes and Methods	Mean SO_2 Levels	Copollutants Considered	Findings, Interpretation	Effects
UNITED STATES (cont'd)					
Park et al. (2005b) Greater Boston area, MA Nov 2000-Oct 2003	Cross-sectional study of effect of ambient air pollutants on heart rate variability (HRV) in 497 men who were in the Normative Aging Study and who were examined from Nov 2000 and Oct 2003. HRV measured between 0600 and 1300 h after resting for 5 mins. 4-h, 24-h, and 48-h moving avgs of air pollution matched to time of ECG measurement. Linear regression models included: age, BMI, fasting blood glucose, cigarette smoking, use of cardiac medications, room temp, season, and the lagged moving avg of apparent temp corresponding to the moving avg period for the air pollutant. Mean arterial blood pressure (MAP) and apparent temperature also included. Assessed modifying effects of hypertension, IHD, diabetes or use of cardiac/antihypertensive meds.	24-h avg SO_2 4.9 ppb SD = 3.4 Range: 0.95, 24.7 ppb	$PM_{2.5}$ particle number concentration BC NO_2 O_3 CO	No significant association between HRV and SO_2 for any of the averaging periods, but positive relationship.	4-h moving avg SO_2 (per 1 SD, 3.4 ppb SO_2) Log10 SDNN: 2.3 (−1.7, 6.4) Log10 HF: 5.6 (−4.9, 17.3) Log10 LF: 2.2 (−5.9, 11.1) Log10 (LF:HF) −3.2 (−10.1, 4.2)

TABLE AX5.3 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH CARDIOVASCULAR MORBIDITY IN FIELD/PANEL STUDIES

Reference, Study Location, and Period	Outcomes and Methods	Mean SO_2 Levels	Copollutants Considered	Findings, Interpretation	Effects
UNITED STATES (cont'd)					
Peters et al. (2000a) Eastern Massachusetts, U.S. 1995-1997	Pilot study to test hypothesis that patients with implanted cardioverter defibrillators would experience potentially life-threatening arrhythmias associated with air pollution episodes. Records detected arrhythmias and therapeutic interventions downloaded from the implanted defibrillator. Mean age of patients 62.2 yrs. 100 patients followed for over 3 yrs for 63,628 person-days. 33 patients with any discharges and 6 patients with 10 or more events. Data analyzed by logistic regression models using fixed effects models with individual intercepts for each patient. Model controlled for trend, season, meteorologic conditions, and day of week. Evaluated air pollutants on same day, lags 1, 2, and 3 days, and 5-day mean.	24-h avg SO_2: 7 ppb Median: 5 ppb Max: 87 ppb	PM_{10} $PM_{2.5}$ BC CO O_3 NO_2	No association between increased defibrillator discharges and SO_2.	33 patients with at least 1 defibrillator discharge Lag 0 0.76 (0.48, 1.21) Lag 1 0.91 (0.60, 1.37) Lag 2 0.89 (0.59, 1.34) Lag 3 1.09 (0.78, 1.52) 5-day mean 0.85 (0.50, 1.43) 6 patients with at least 10 discharges Lag 0 0.72 (0.40, 1.31) Lag 1 0.77 (0.44, 1.37) Lag 2 1.01 (0.63, 1.61) Lag 3 1.08 (0.72, 1.62) 5-day mean 0.75 (0.38, 1.47)
Peters et al. (2001) Greater Boston area, MA Jan 1995-May 1996	Case cross over Study design used to investigate association between air pollution and risk of acute myocardial infarctions in 772 patients (mean age 61.6 yrs) with MI as part of the Determinants of Myocardial Infarction Onset Study. For each subject, one case period was matched to 3 control periods, 24 h apart. Used conditional logistic regression models that controlled for season, day of wk, temperature, and relative humidity.	24-h avg SO_2: 7 ppb SD = 7 ppb 1-h avg SO_2: 7 ppb SD = 10 ppb	$PM_{2.5}$ PM_{10} Coarse mass BC O_3 CO NO_2	SO_2 not statistically associated with risk of onset of MI. Limitation of study is only 1 air pollution monitoring site available.	OR for 2-h avg SO_2 and 24-h avg SO_2 estimated jointly: 2 h per 2-ppb increase SO_2 Unadjusted: 1.00 (0.87, 1.14) Adjusted: 0.96 (0.83, 1.12) 24 h per 2-ppb increase Unadjusted: 0.92 (0.71, 1.20) Adjusted: 0.91 (0.67, 1.23)

TABLE AX5.3 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH CARDIOVASCULAR MORBIDITY IN FIELD/PANEL STUDIES

Reference, Study Location, and Period	Outcomes and Methods	Mean SO_2 Levels	Copollutants Considered	Findings, Interpretation	Effects
UNITED STATES (cont'd)					
Rich et al. (2005) Boston, MA Jul 1995-Jul 2002	Case cross-over design used to evaluate association between ventricular arrhythmias detected by implantable cardioverter defibrillators and air pollution. Same study population as Dockery et al. (2005): 203 patients with ICD and residential zip codes within 40 km of central particle monitoring site. Analyses conducted on 84 subjects with confirmed ventricular arrhythmias during the follow-up. Case periods defined by time of each confirmed arrhythmic event. Control periods (3-4 per case) selected by matching on weekday and hour of the day within the same calendar mo. Used conditional logistic regression that controlled for temperature, dew point, barometric pressure, and a frailty term for each subject. ORs presented for IQR increase in mean concentration and averaging time. Moving avg of concentrations considered: lags 0-2, 0-6, 0-23, and 0-47 h.	1-h avg SO_2: Median: 4.3 ppb 25th %: 2.6 75th %: 7.5 Max: 71.6 24-h avg SO_2: Median: 4.8 25th %: 3.2 75th %: 7.3 Max: 31.4	$PM_{2.5}$ BC NO_2 CO O_3	An IQR increase in the 24-h moving avg SO_2 (4.1 ppb) marginally associated with a 9% increased risk of ventricular arrhythmia and an increased risk with 48-h moving avg. There was no risk associated with 24-h moving avg after controlling for $PM_{2.5}$ cases that had a prior ventricular arrhythmia within 72 h had greater risk associated with SO_2 compared to those without a recent event, suggesting that risk is greater among cases with more irritable or unstable myocardium.	Odds ratios- single-pollutant model 0-2-h lag (per 4.7 ppb) 1.07 (0.97, 1.18) 0-6-h lag (per 4.5 ppb) 1.09 (0.98, 1.20) 0-23-h lag (per 4.1 ppb) 1.09 (0.97, 1.22) 0-47-h lag (per 4.0 ppb) 1.17 (1.02, 1.34) Odds ratios- 2-pollutant model SO_2 and $PM_{2.5}$ Per 4.1 ppb SO_2: 1.00 (0.84, 1.20) SO_2 and O_3 Per 4.1 ppb SO_2: 1.12 (0.99, 1.27) Per 4.1-ppb increase SO_2 Prior arrhythmia event <3 days: 1.20 (1.01, 1.44) Prior arrhythmia event >3 days: 0.96 (0.83, 1.10)

TABLE AX5.3 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH CARDIOVASCULAR MORBIDITY IN FIELD/PANEL STUDIES

Reference, Study Location, and Period	Outcomes and Methods	Mean SO_2 Levels	Copollutants Considered	Findings, Interpretation	Effects
UNITED STATES (cont'd)					
Rich et al. (2006) St. Louis, Missouri, May 2001-Dec 2002	Case-crossover design study of 56 patients with implantable cardioverter defibrillators. Subjects ranged from 20 to 88 years (mean 63). Case period defined by time of confirmed ventricular arrhythmia. Control periods matched on weekday and hour of the day within the same calendar mo. Used conditional logistic regression model that included mean of the previous 24-h temperature, relative humidity, barometric pressure, mean pollutant concentration in the 24 h before the arrhythmia. Model also included a frailty term for each subject.	599 days 25th percentile: 2 ppb 50th percentile: 4 ppb 75th percentile: 7 ppb Daily IQR: 5 ppb Case/control IQR: 5 ppb	$PM_{2.5}$ EC OC NO_2 CO O_3	Statistically significant increase in risk of ventricular arrhythmias associated with each 5-ppm increase in 24-h moving avg SO_2.	OR for ventricular arrhythmia associated with IQR increase 6-h moving avg SO_2 per 4 ppb: 1.04 (95% CI: 0.96, 1.12) 12-h moving avg SO_2 per 5 ppb: 1.17 (95% CI: 1.04, 1.30) 24-h moving avg SO_2 per 5 ppb: 1.24 (95% CI: 1.07, 1.44) 48-h moving avg SO_2 per 4 ppb: 1.15 (95% CI: 1.00, 1.34)
Schwartz et al. (2005) Boston, MA 12 wks during the summer of 1999	Panel study of 28 subjects (aged 61-89 yrs) to examine association between summertime air pollution and HRV. Subjects examined once a wk up to 12 wks and HRV measured for approximately 30 mins. Analyses used hierarchical models that controlled for baseline medical condition, smoking history, day of wk and hour of day, indicator variable for whether subjects had taken their medication before they came, temperature and time trend.	24-h avg SO_2: 25th %: 0.017 ppm 50th %: 0.020 ppm 75th %: 0.54 ppm	O_3 NO_2 CO $PM_{2.5}$ black carbon	No significant association with SO_2	Percentage change in HRV associated with IQR (0.523 ppm) increase in SO_2 SDNN (ms) 0.4 (−1.3 to 2.1) RMSSD (ms) 1.4 (−2.6 to 5.5) PNN50 (ms) 3.8 (−12.1 to 22.5) for 1-h avg SO_2 SDNN (ms) 0.4 (−4.2 to 5.1) for 24-h avg SO_2 RMSSD (ms) −0.3 (−1.3 to 0.8) PNN50 (%) −0.2 (20.9 to 17.6) LFHFR 2.9 (−4.9 to 11.4)

TABLE AX5.3 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH CARDIOVASCULAR MORBIDITY IN FIELD/PANEL STUDIES

Reference, Study Location, and Period	Outcomes and Methods	Mean SO_2 Levels	Copollutants Considered	Findings, Interpretation	Effects
CANADA					
Rich et al. (2004) Vancouver, British Columbia, Canada Feb-Dec 2000	Case-crossover analysis used to investigate association between air pollution and cardiac arrhythmia in 34 patients (aged 15-85 yrs, mean 62) with implantable cardioverter defibrillators. Study included only patients who experienced at least 1 ICD discharge during the study period. Control days were 7 days before and 7 days after day of ICD discharge. Conditional logistic regression analyses were stratified by individual.	24-h avg: 2.6 ppb SD = 1.3 ppb IQR: 1.6 ppb	$PM_{2.5}$ EC OC SO_4^{2-} PM_{10} CO NO_2 O_3	No statistically significant association between SO_2 and implantable cardioverter defibrillator discharges. However, when an analysis was stratified by season, OR for SO_2 were higher in the summer compared to winter.	No quantitative results provided. Results shown in graph.
Vedal et al. (2004) Vancouver, British Columbia, Canada 1997-2000	Retrospective, longitudinal panel study of 50 patients, aged 12-77 yrs with implantable cardioverter defibrillators. Total of 40,328 person-days over 4-yr period. GEE used to assess associations between short term increases in air pollutants and implantable cardioverter defibrillator discharges. Models controlled for temporal trends, meteorology, and serial autocorrelation.	24-h mean (SD) SO_2: 2.4 (1.2) ppb Range: 0.3, 8.1 ppb Median: 2.2 ppb 25th percentile: 1.5 75th percentile: 3.1	PM_{10} O_3 NO_2 CO	Concluded that in general no consistent effect of air pollution on cardiac arrhythmias in this population. There were no statistically significant associations between SO_2 and cardiac arrhythmias at any lag day, but positive associations at lag 2. When analysis was restricted to only patients who had at least 2 arrhythmias per yr over their period of observation (n = 16), a positive and significant association was seen with SO_2 at 2 days lag. When analysis was restricted to patients averaging 3 or more arrhythmias per yr (n = 13), there was no significant association, but a positive association was seen at 2 days lag.	No quantitative results, but % change in arrhythmia event-day rate for each SD increase in pollution concentration on log scale provided in figures.

TABLE AX5.3 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH CARDIOVASCULAR MORBIDITY IN FIELD/PANEL STUDIES

Reference, Study Location, and Period	Outcomes and Methods	Mean SO_2 Levels	Copollutants Considered	Findings, Interpretation	Effects
CANADA (cont'd)					
Vedal et al. (2004) (cont'd)				When stratified by season, SO_2 effects were in the in the positive direction in the winter, but in the negative direction in the summer. Authors noted results may be due to chance because of multiple comparisons or SO_2 may be surrogate for some other factor. Summer analysis: significant negative association with SO_2 at lag days 2 and 3 (data not shown). When stratified to patients with 2 or more arrhythmia event-days per yr, significant negative associations observed with SO_2 at lag of 3 days. Winter analysis: significant positive effect of SO_2 at 3 days lag (data not shown). If restricted to patients with at least 2 arrhythmias per yr, a significant positive association was seen at lags 2 and 3 days. When restricted to patients with 3 or more arrhythmia event days per yr, positive associations observed for SO_2 at lags of 2 and 3 days.	

TABLE AX5.3 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH CARDIOVASCULAR MORBIDITY IN FIELD/PANEL STUDIES

Reference, Study Location, and Period	Outcomes and Methods	Mean SO_2 Levels	Copollutants Considered	Findings, Interpretation	Effects
EUROPE					
Ibald-Mulli et al. (2001) Augsburg, Germany 1984-85, 1987-88	Retrospective analysis of 2607 subjects (25-64 yrs, subset of the participants of first and second MONICA survey who had valid electrocardiograms recordings in both surveys and blood pressure measurements). Used regression models for repeated measures that controlled for age, current smoking, and cardiovascular medication, BMI, total and high density lipoprotein cholesterol, temp, RH, and barometric pressure.	24-h avg SO_2 ($\mu g/m^3$) 1984-1985: Mean: 60.2 SD = 47.4 Range: 13.0, 238.2 follow up 1987-1988 Mean: 23.8 SD = 12.3 Range: 5.6, 71.1	TSP, CO	SO_2 and TSP associated with increases in systolic blood pressure. In the multipollutant model with TSP, the effect of TPS remained significant, but the SO_2 effect was substantially reduced. No clear association between SO_2 and CO and diastolic blood pressure was observed.	Same day concentrations: mean change in systolic blood pressure per 5th to 95th percentile increase in SO_2 (per 80 $\mu g/m^3$) Same day concentrations (per 80 $\mu g/m^3$): Men (n = 1339): 0.96 (0.07, 1.85) Women (n = 1268): 0.96 (−0.46, 1.49) Men and women: 0.74 (0.08, 1.40) 5-day avgs: Mean change in systolic blood pressure per 5th to 95th percentile increase in SO_2 (per 75 $\mu g/m^3$) Men: 0.97 (0.09, 1.85) Women: 1.23 (0.23, 2.22) Men and women: 1.07 (0.41, 1.73) 2-pollutant model Men and women: 0.23 (−0.50, 0.96)

TABLE AX5.3 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH CARDIOVASCULAR MORBIDITY IN FIELD/PANEL STUDIES

Reference, Study Location, and Period	Outcomes and Methods	Mean SO_2 Levels	Copollutants Considered	Findings, Interpretation	Effects
EUROPE (cont'd)					
Peters et al. (1999) Augsburg, Germany winter 1984-1985 winter 1987-1988	Retrospective analysis on subsample of 2,681 subjects (25-64 yrs) of the MONICA cohort who had valid electrocardiogram readings from both surveys and no acute infections. GEE for clusters used to assess association between heart rate and air pollution. Analyses adjusted for temperature, relative humidity, and air pressure.	24-h avg SO_2 ($\mu g/m^3$) Winter 1984-1985 Outside episode: Mean: 48.1 SD = 23.1 Range: 13, 103 Winter 1984-1985 During episode: Mean: 200.3 SD = 26.6 Range: 160, 238 Winter: 1987-1988 Mean: 23.6 SD = 12.2 Range: 6, 71	CO TSP	Increases in SO_2 concentrations associated with increases in heart rate	Mean change in heart rate per 5th to 95th percentile SO_2 Same day concentrations (per 80 $\mu g/m^3$ SO_2) Men: 1.02 (0.41, 1.63) Women: 1.07 (0.41, 1.73) Men and women: 1.04 (0.60, 1.49) 5-day avg (per 75 $\mu g/m^3$ SO_2) Men: 1.29 (0.68, 1.90) Women: 1.26 (0.57, 1.95) Men and women: 1.28 (0.82, 1.74)

TABLE AX5.3 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH CARDIOVASCULAR MORBIDITY IN FIELD/PANEL STUDIES

Reference, Study Location, and Period	Outcomes and Methods	Mean SO_2 Levels	Copollutants Considered	Findings, Interpretation	Effects
EUROPE (cont'd)					
Ruidavets et al. (2005) Toulouse, France 1995-1997	Cross-sectional survey of 863 randomly chosen adults (35-65 yrs) living in Toulouse (MONICA center) to examine the relationship between resting heart rate and air pollution. Resting heart rate was measured twice in a sitting position after a five minute rest. Used polytomous logistic regression models with quintiles of RHR. Final model controlled for sex, physical activity, systolic blood pressure, cardiovascular drug use, CRP, relative humidity, and season mos.	Mean SO_2: 13.3 (7.5) µg/m^3 Range: 1.3, 47.7 µg/m^3	NO_2 O_3	Marginally significant association between SO_2 and RHR in Q5 compared with Q1. No association with SO_2 at 1, 2, or 3 days lag.	OR based on daily levels of SO_2 OR for resting heart rate = 1.19 (95% CI: 1.02, 1.39) in 5th quintile (>75 bpm) compared to first quintile (<60 bpm) for 5 µg/m^3 increase in SO_2 same day 0 am-12 pm OR for resting heart rate 1.14 (95% CI: 1.01 to 1.30) in 5th quintile (>75 bpm) compared to first quintile (<60 bpm) for 5µg/m^3 increase in SO_2 same day 12 am-12 pm Not-significant associations not listed
LATIN AMERICA					
Holguin et al. (2003) Mexico City, Mexico Feb 8 to April 30, 2000	Panel study of 34 nursing home residents (60-96 yrs) to assess association between heart rate variability and air pollution. Heart rate variability measured every alternate day for 3 mos. Thirteen of the subjects had hypertension. Used GEE models that controlled for age and avg heart rate during HRV measurement.	24-h mean SO_2 (ppb) Mean: 24 SD = 12 Range: 6, 85	Indoor $PM_{2.5}$ Outdoor $PM_{2.5}$ O_3 NO_2 CO	SO_2 not related to heart rate variability on the same day or lag 1 day	Change in HRV per 10 ppb HRV-HF −0.003 (−0.035, 0.035) HRV-LF −0.004 (−0.004, 0.003) HRV-LF/HF 0.012 (−0.060, 0.082)

TABLE AX5.4. ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR CARDIOVASCULAR DISEASES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean Levels & Monitoring Stations	Copollutants (Correlations)	Effects: Relative Risk or % Change & Confidence Intervals ([95% Lower, Upper])
UNITED STATES				
Morris et al. (1995) U.S. (Chicago, Detroit, LA, Milwaukee, NYC, Philadelphia) Study period: 1986-1989, 4 yrs	Outcome(s) (ICD9): CHF 428. Daily Medicare hospital admission records. Study design: Time series Statistical analyses: GLM, negative binomial distribution Age groups analyzed: ≥65 yrs Covariates: Temperature, indicator variables for mo to adjust for weather effects and seasonal trends, day of wk, yr Statistical software: S-PLUS Lag(s): 0-7 days	SO_2 1-h max (ppm) Mean (SD) LA: 0.010 (0.005) Chicago: 0.025 (0.011) Philadelphia: 0.029 (0.015) New York: 0.032 (0.015) Detroit: 0.025 (0.013) Houston: 0.018 (0.009) Milwaukee: 0.017 (0.013)	NO_2 1-h max O_3 1-h max CO 1-h max Correlations of SO_2 with other pollutants strong. Multipollutant models run.	Results reported for RR of admission for CHF associated with an incremental increase in SO_2 of 0.05 ppm. CHF: LA: 1.60 (1.41, 1.82) Chicago: 1.05 (1.00, 1.10) Philadelphia: 1.01 (0.96, 1.06) New York: 1.04 (1.01, 1.08) Detroit: 1.00 (0.95, 1.06) Houston: 1.07 (0.97, 1.17) Milwaukee: 1.07 (0.99, 1.15) RR diminished in multipollutant (4 copollutants) models for all cities.

TABLE AX5.4 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR CARDIOVASCULAR DISEASES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean Levels & Monitoring Stations	Copollutants (Correlations)	Effects: Relative Risk or % Change & Confidence Intervals ([95% Lower, Upper])
UNITED STATES (cont'd)				
Moolgavkar (2000)* Cook County IL, Los Angeles County, CA, Maricopa County, AZ 1987-1995	Outcome(s) (ICD9): CVD 390-429; Cerebrovascular disease 430-448. Hospital admissions from CA department of health database. Age groups analyzed: 20-64, 65+ yrs Study design: Time series N: 118 CVD admissions/days # Hospitals: NR Statistical analysis: Poisson regression, GAM Covariates: Adjustment for day of wk, long-term temporal trends, relative humidity, temperature Statistical package: SPLUS Lag: 0-5 days	SO_2 24-h avg (ppb) Cook County: Min: 0.5 Q1: 4 Median: 6 Q3: 8 Max: 36 LA County: Min: 0 Q1: 1 Median: 2 Q3: 4 Max: 16 Maricopa County: Min: 0 Q1: 0.5 Median: 2 Q3: 4 Max: 14	PM_{10} (0.11, 0.42) $PM_{2.5}$ (0.42) (LA only) CO (0.35, 0.78) NO_2 (0.02, 0.74) O_3 (−0.37, 0.01) 2-pollutant models (see results)	Results reported for percent change in hospital admissions per 10 ppb increase in SO_2. T statistic in parentheses. CVD, 65+: Cook County 4.0 (6.1), lag 0 3.1 (4.5), lag 0, 2-pollutant model (CO) 1.0 (1.4), lag 0, 2-pollutant model (NO_2) LA County 14.4 (15.2), lag 0 −2.5 (−1.6), lag 0, 2-pollutant model (CO) 7.7 (5.7), lag 0, 2-pollutant model (NO_2) Maricopa County 7.4 (4.5), lag 0 3.0 (1.8), lag 0, 2-pollutant model (CO) 3.9 (1.5), lag 0, 2-pollutant model (SO_2) Cerebrovascular Disease, 65+: Cook County 3.1 (3.3) LA County 6.5 (4.9) Lags 1-5 also presented. Effect size generally diminished with increasing lag time. Increase in hospital admissions (10.3 for CVD and 9.0 for cerebrovascular) also observed for the 20-64 age group.

TABLE AX5.4 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR CARDIOVASCULAR DISEASES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean Levels & Monitoring Stations	Copollutants (Correlations)	Effects: Relative Risk or Percent Change & Confidence Intervals ([95% Lower, Upper])
UNITED STATES (cont'd)				
Moolgavkar (2003) Cook County IL, Los Angeles County, CA, Maricopa County, AZ 1987-1995	Outcome(s) (ICD9): CVD 390-429; Cerebrovascular disease 430-448 was not considered in the reanalysis. Hospital admissions from CA department of health database. Age groups analyzed: 20-64, 65+ yrs Study design: Time series N: 118 CVD admissions/day # Hospitals: NR Statistical analysis: Poisson regression, GAM with strict convergence criteria (10-8), GLM using natural splines Covariates: Adjustment for day of wk, long-term temporal trends, relative humidity, temperature Statistical package: SPLUS Lag: 0-5 days	See original analysis (Moolgavkar, 2000) above.	See original analysis (Moolgavkar, 2000) above.	Use of stringent criteria in GAM did not alter results substantially. However, increased smoothing of temporal trends attenuated results for all gases and effect size diminished with increasing lag. Results reported for incremental increase of 10 ppb SO_2. Estimated coefficient and T statistic in parentheses. GLM with 100 df (LA County) 13.67 (11.82), lag 0 6.44 (5.23), lag 1 0.23 (0.18), lag 2

TABLE AX5.4 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR CARDIOVASCULAR DISEASES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean Levels & Monitoring Stations	Copollutants (Correlations)	Effects: Relative Risk or % Change & Confidence Intervals ([95% Lower, Upper])
UNITED STATES (cont'd)				
Wellenius et al. (2005a) Birmingham, Chicago, Cleveland, Detroit, Minneapolis, New Haven, Pittsburgh, Seattle Study period: Jan 1986-Nov 1999 (varies slightly depending on city)	Outcome(s) IS, primary diagnosis of acute but ill-defined cerebrovascular disease or occlusion of the cerebral arteries; HS, primary diagnosis of intracerebral hemorrhage. ICD codes not provided. Hospital admissions ascertained from the Centers for Medicare and Medicaid Services. Cases determined from discharge data were admitted from the ER to the hospital. N IS: 155,503 N HS: 19,314 Study design: Time-stratified Case-crossover. Control days chosen such that they fell in same mo and same day of wk. Design controls for seasonality, time trends, chronic and other slowly varying potential confounders. Statistical analysis: 2-stage hierarchical model (random effects), conditional logistic regression for city effects in the first stage Software package: SAS Covariates: Lag(s): 0-2, unconstrained distributed lags	SO_2 24 h (ppb) 10th: 2.17 25th: 3.57 Median: 6.22 75th: 10.26 90th: 16.17 SO_2 data not available for Birmingham, AL	PM_{10} (0.39) CO, NO_2 Correlation only provided for PM because study hypothesis involves PM	Results reported for percent increase in stroke admissions for an incremental increase in SO_2 equivalent to one IQR (6.69). Ischemic Stroke: 1.35 (0.43, 2.29), lag 0 Hemorrhagic Stroke: 0.68 (−1.77, 3.19) Multipollutant models not run.

TABLE AX5.4 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR CARDIOVASCULAR DISEASES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean Levels & Monitoring Stations	Copollutants (Correlations)	Effects: Relative Risk or % Change & Confidence Intervals ([95% Lower, Upper])
UNITED STATES (cont'd)				
Koken et al. (2003) Denver, United States Study period: Jul and Aug, 1993-1997, n = 310 days	Outcome(s) (ICD9): Acute MI 410.00-410.92; Atherosclerosis 14.00-414.05; Pulmonary Heart Failure 416.0-416.9; Dysrhythmia 427.0-427.9; CHF 428.0. Discharge data from Agency for Healthcare Research and Quality (AHRQ) database. Age group analyzed: 65+ yrs Study population: 60,000 Covariates : Seasonal adjustment not needed. Adjustment for temperature, dew point temperature made. Study design: Time series Statistical analysis: GLMs to analyze frequency of admissions as a function of exposure. GEEs to estimate parameters in Poisson regression models, adjusting for overdispersion. Lag(s): 0-4 day	SO_2 24-h avg (ppb) Mean (SD): 5.7 (2.94) Min: 0.4 25th: 3.8 50th: 5.3 75th: 7.2 Max: 18.9	O_3 (−0.10) CO (0.21) PM_{10} (0.36) NO_2 (0.46)	Effects were reported as percent change in hospitalizations based on an increment of 3.4 ppb. Single-pollutant model Dysrhythmia 8.9% (−0.34, 18.93) lag 0, adjusted for gender but not temperature SO_2 was found to be associated with cardiac dysrhythmia but not other outcomes. No association was observed for PM or NO_2 with the outcomes.
Low et al. (2006) New York City, NY Study period: 1995-2003, 3287 days	Outcome(s) (ICD): Ischemic stroke 433-434; Undetermined stroke 436; monitored intake in 11 hospitals (ER or clinic visits). Excluded stroke patients admitted for rehabilitation. Study design: Time series Statistical Analysis: Autoregressive integrated moving avg (ARIMA) models Software package: SAS	SO_2 24-h avg (ppm) Mean (SD): 0.009124 Min: 0 25th: 0.005 Median: 0.009 75th: 0.014 Max: 0.096	PM_{10} (0.042) NO_2 (0.33) CO (0.303) Pollen (0.085)	At the highest concentration of SO_2 (96 ppb) in New York city over the study period the expected increase in strokes would be 0.857 visits on the day of the event. Each 1000 ppb (1 ppm) SO_2 would produce an additional 8.878 visits (SE 4.471) (p = 0.0471) for stroke.

TABLE AX5.4 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR CARDIOVASCULAR DISEASES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean Levels & Monitoring Stations	Copollutants (Correlations)	Effects: Relative Risk or % Change & Confidence Intervals ([95% Lower, Upper])
UNITED STATES (cont'd)				
Metzger et al. (2004) Atlanta, GA Period of Study: Jan 1993-Aug 31 2000, 4 yrs	Outcome(s): IHD 410-414; AMI 410; Dysrhythmias 427; cardiac arrest 427.5; congestive heart failure 428; peripheral and cerebrovascular disease 433-437, 440, 443-444, 451-453; atherosclerosis 440; stroke 436. ED visits from billing records. N: 4,407,535 visits, 37 CVD visits/days # Hospitals: 31 Age groups analyzed: adults ≥19, elderly 56+ Statistical Analysis: Poisson regression, GLM. Sensitivity analyses using GEE and GAM (strict convergence criteria) Covariates: long-term trends, mean and dew point temp, relative humidity (cubic splines) Statistical Software: SAS Season: Warm, Apr 15-Oct 14, Cool, Oct 15-Apr 14. Lag(s): 0-3 days	SO_2 1-h max (ppb) Median: 11.0 10th-90th range: 2.0 to 39 ppb	PM_{10} (0.20) O_3 (0.19) NO_2 (0.34) CO (0.26) $PM_{2.5}$ (0.17) Course PM (0.21) Ultrafine (0.24) Multipollutant models used. All models specified a priori.	Results presented for RR of an incremental increase in SO_2 of 20 ppb (a priori lag 3 day moving avg). All CVD: 1.007 (0.993, 1.022) Dysrhythmia: 1.001 (0.975, 1.028) CHF: 0.992 (0.961, 1.025) IHD: 1.007 (0.981, 1.033) PERI: 1.028 (0.999, 1.059) Finger wounds 1.007 (0.998, 1.026) Single day lag models presented graphically. No multipollutant models run for SO_2 since association was not observed in single-pollutant models.
Michaud et al. (2004) Hilo, Hawaii Study period: 1997-2001, N = 1385 days	Outcome(s) (ICD9): Cardiac 410-414, 425-429, Emergency visits, primary diagnosis. Study design: Time series Statistical Analysis: Exponential regression, autocorrelation assessed by regressing square root of number of ED visits on covariates (Durbin-Watson statistic). Newey-West procedure also conducted for assessment of autocorrelation. Covariates: Temperature, humidity, interaction between SO_2 and PM Lag(s): 1-3 days	SO_2 (all hourly measurements) (ppb) Mean (SD): 1.92 (12.2) Min: 0 Max: 447 Daily SO_2 (12am-6am) (ppb) Mean (SD): 1.97 (7.12) Min: 0 Max: 108.5	PM	Effects were presented as relative risk based on an increment of 10 ppb and the 24-h avg SO_2 concentration. Cardiac 0.92 (0.85, 1.00) lag 3 No associations of cardiac ER visits with VOG (SO_2-acidic aerosols) observed.

TABLE AX5.4 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR CARDIOVASCULAR DISEASES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean Levels & Monitoring Stations	Copollutants (Correlations)	Effects: Relative Risk or % Change & Confidence Intervals ([95% Lower, Upper])
UNITED STATES (cont'd)				
Peel et al. (2007) Atlanta, GA Study period: Jan 1993-Aug 2000	Outcome(s) (ICD9): IHD 410-414; dysrhythmia 427; CHF 428; peripheral vascular and cerebrovascular disease 433-437, 440, 443, 444, 451-453. Computerized billing records for ED visits. Comorbid conditions: Hypertension 401-405; diabetes 250; dysrhythmia 427, CHF 428; atherosclerosis 440; COPD 491, 492, 496; pneumonia 480-486; upper respiratory infection 460-465, 466.0; asthma 493, 786.09. # Hospitals: 31 N: 4,407,535 visits Study design: Case-crossover. CVD outcomes among susceptible groups with comorbid conditions. Statistical analyses: Conditional logistic regression. Covariates: Cubic splines for temperature and humidity included in models. Time independent variables controlled through design. Statistical Software: SAS Lag(s): 3 day avg, lagged 0-2 day	SO_2 1-h max (ppb) Mean (SD): 16.5 (17.1) 10th: 2 90th: 39	PM_{10} 24-h avg O_3 8 h-max NO_2 1-h max CO 1-h max Correlations not reported	Results expressed as OR for association of CVD admissions with a 20 ppb incremental increase in SO_2. All CVD 1.009 (0.995,1.024), 3 day moving avg IHD 1.013 (0.988, 1.039), 3 day moving avg Dysrhythmia 1.003 (0.975, 1.031), 3 day moving avg Peripheral and Cerebrovascular 1.024 (0.993, 1.055), 3 day moving avg CHF 0.993 (0.961, 1.026), 3 day moving avg Effect modification by comorbid conditions was not observed.

TABLE AX5.4 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR CARDIOVASCULAR DISEASES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean Levels & Monitoring Stations	Copollutants (Correlations)	Effects: Relative Risk or % Change & Confidence Intervals ([95% Lower, Upper])
UNITED STATES (cont'd)				
Schwartz and Morris (1995)* Detroit, MI Study period: 1986-1989	Outcome(s) (ICD9): IHD 410-414; CHF 428; Dysrhythmia 427. Medicare data, diagnosis at discharge. Study design: Time series Statistical analysis: Poisson regression, GAM Age groups analyzed: 65+ yrs Covariates: Adjustments for long-term patterns, temperature, humidity, days of the wk, holidays, viral infections, etc. Lag(s): 0-3, cumulative up to 3 days	SO_2 24-h avg (ppb): Mean: 25.4 IQR: 18 ppb Q2: 15 Q3: 33 # Stations: 6	PM_{10} (0.42) CO (0.23) O_3 (0.15)	Effects were expressed as relative risk based on an increment of 18 ppb. IHD 1.014 (1.003, 1.026) lag 0, single pollutant 1.009 (0.994, 1.023), 2-pollutant model with PM_{10} CHF 1.002 (0.978, 1.017), single-pollutant model Risks for dysrhythmia were not reported for SO_2.
Schwartz (1997) * Tuscon, AZ Study period: Jan 1988-Dec 1990	Outcome(s) (ICD9): CVD 390-429. Ascertained from hospital discharge records. Study design: Time series Statistical analysis: Poisson regression, GAM Age groups analyzed: 65+ Covariates: Long-term and seasonal trends, day of the wk, temperature, dew point, Statistical software: S-PLUS	SO_2 24-h avg (ppb) Mean: 4.6 ppb IQR: 3.9 ppb 10th: 0.7 Q2: 2.0 Median: 3.4 Q3: 5.9 90th: 10.1	PM_{10} (0.095) NO_2 (0.482) CO (0.395) O_3 (−0.271)	Results were expressed as percent change based on an increment of 3.9 ppb. 0.14% (−1.3%, 1.6) No other statistically significant associations for cardiovascular outcomes were observed.

TABLE AX5.4 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR CARDIOVASCULAR DISEASES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean Levels & Monitoring Stations	Copollutants (Correlations)	Effects: Relative Risk or % Change & Confidence Intervals ([95% Lower, Upper])
UNITED STATES (cont'd)				
Wellenius et al. (2005b) Allegheny County, PA (near Pittsburgh) Study period: Jan 1987-Nov 1999	Outcome(s): CHF 428. Cases are Medicare patients admitted from ER with discharge of CHF Study design: Case-crossover, control exposures same mo and day of wk, controlling for season by design. Statistical analysis: Conditional logistic regression N: 55,019 admissions, including repeat admissions, 86% admitted ≤5 times Age groups analyzed: 65+ yrs (Medicare recipients) Covariates: Temperature and pressure. Effect modification by age, gender, secondary diagnosis arrhythmias, atrial fibrillation, COPD, hypertension, type 2 diabetes, AMI within 30 days, angina pectoris, IHD, acute respiratory infection. Statistical software: SAS Lag(s): 0-3	SO_2 24-h avg (ppb): Mean (SD): 14.78 (9.88) 5th: 3.98 25th: 7.70 Median: 12.24 75th: 18.98 95th: 33.93 # Stations: 10	PM_{10} (0.51) CO (0.54) NO_2 (0.52) O_3 (−0.19)	Effects were reported as percent change based on an increment of 11 ppb. CHF, single-pollutant models: 2.36 (1.05, 3.69) lag 0, or 2.14 (0.95, 3.35) lag 0 after adjusted to an increment of 10 ppb. CHF, 2-pollutant models: 1.35 (−0.27, 2.99), SO_2/PM_{10} 0.10 (−1.35, 1.57), SO_2/CO 0.68 (−0.82, 2.21), SO_2/NO_2 2.02 (0.68, 3.37), SO_2/O_3

TABLE AX5.4 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR CARDIOVASCULAR DISEASES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean Levels & Monitoring Stations	Copollutants (Correlations)	Effects: Relative Risk or % Change & Confidence Intervals ([95% Lower, Upper])
CANADA				
Burnett et al. (1997) * Metropolitan Toronto (Toronto, North York, East York, Etobicoke, Scarborough, York), Canada Study period: 1992-1994, 388 days, summers only	Outcome(s) (ICD9): IHD 410-414; Cardiac Dysrhythmias 427; Heart failure 428. All Cardiac 410-414, 427, 428. Obtained from hospital discharge data. Population: 2.6 Million residents Study design: Time series Age groups analyzed: All # Hospitals: NR Statistical analysis: Relative risk regression models, GAMs. Covariates: Adjusted for long- term trends, seasonal and subseasonal variation, day of the wk, temperature, dew point Seasons: Summer only Dose response: Figures presented Statistical package: NR Lag: 1-4 days	SO_2 daily 1-h max (ppb): Mean: 7.9 CV: 64 Min: 0 25th percentile: 4 50th percentile: 7 75th percentile: 11 Max: 26 # of Stations: 4-6 (Results are reported for additional metrics including 24-h avg and daytime avg (day)	H^+ (0.45) SO_4 (0.42) TP (0.55) FP (0.49) CP (0.44) COH (0.50) O_3 (0.18) NO_2 (0.46) CO (0.37)	Effects were expressed as relative risk based on an increment of 7.00 ppb (IQR). T ratio in parentheses. All cardiac disease Single-pollutant model 1.041 (2.66), daily max over 4 days, lag 0 Multipollutant model w/ SO_2, O_3, NO_2 Of 7.72 excess hospital admissions, 2.8% attributed to SO_2. Objective of study was to evaluate the role of particle size and chemistry on cardiac and respiratory diseases.

TABLE AX5.4 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR CARDIOVASCULAR DISEASES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean Levels & Monitoring Stations	Copollutants (Correlations)	Effects: Relative Risk or Percent Change & Confidence Intervals ([95% Lower, Upper])
CANADA (cont'd)				
Burnett et al. (1999) * Metropolitan Toronto (Toronto, North York, East York, Etobicoke, Scarborough, York), Canada Study period: 1980-1995, 15 yrs	Outcome(s) (ICD9): IHD 410-414; Cardiac Dysrhythmias 427; Heart failure 428; All cardiac 410-414, 427, 428; Cerebrovascular Disease obtained from hospital discharge data 430-438; Peripheral Circulation Disease 440-459. Population: 2.13-2.42 million residents Study design: Time series Statistical analysis: GAMs to estimate log RR per unit changes, stepwise regression used to select minimum number of air pollutants in multipollutant models. Covariates: Long-term trends, seasonal variation, day of wk, temperature, and humidity. Statistical package: S-PLUS Lag(s): 0-2 days	SO_2 daily avg (ppb) Mean: 5.35 5th percentile: 0 25th percentile: 1 50th percentile: 4 75th percentile: 8 95th percentile: 17 Max: 57 Multiple day avgs used in models	$PM_{2.5}$ (0.50) $PM_{10-2.5}$ (0.38) PM_{10} (0.52) CO (0.55) SO_2 (0.55) O_3 (−0.04)	Effects were reported as % change based on an increment of 5.35 ppb. Single-pollutant model Dysrhythmias 0.8% (−0.3, 1.9) Cerebrovascular 0.04% (−0.7, 0.8) CHF 1.93% (0.9, 2.9) IHD 2.32% (1.6, 3.1) Attributed percent increase in admissions for SO_2 were determined from multipollutant models. IHD Attributed percent increase: 0.95% Authors note SO_2 effects could be largely explained by other variables in the pollution mix as demonstrated by the multipollutant model.

TABLE AX5.4 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR CARDIOVASCULAR DISEASES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean Levels & Monitoring Stations	Copollutants (Correlations)	Effects: Relative Risk or % Change & Confidence Intervals ([95% Lower, Upper])
CANADA (cont'd)				
Fung et al. (2005) Windsor, Ontario, Canada Study period: Apr 1995-Jan 2000	Outcome(s) (ICD9): CHF 428; IHD 410-414; dysrhythmias 427 and all cardiac. Hospital admissions from Ontario Health Insurance Plan records. Study design: Time series Statistical analysis: GLM N: 11,632 cardiac admission, 4.4/day for 65+ age group Age groups analyzed: 65+, <65 yrs Statistical Software: SPLUS Lag(s): lag 0, 2, 3 day avg	SO_2 1-h max (ppb) Mean (SD): 27.5 (16.5) Min: 0 Max: 129 IQR: 19.3 ppb	CO (0.16) O_3 (−0.02) PM_{10} (0.22) NO_2 (0.22)	Effects were expressed as percent change of cardiac disease hospital admissions based on an increment of 19.3 ppb. Single-pollutant model: <65 yrs 2.3% (−1.8, 6.6) lag 0 3.9% (−1.5, 9.6) lag 0-1 3.4% (−3.0, 10.1) lag 0-2 ≥65 yrs 2.6% (0.0, 5.3) lag 0 4.0% (0.6, 1.6) lag 0-1 5.6% (1.5, 9.9) lag 0-2 Inclusion of particulate matter and adjustment for meteorological variables did not change the association between SO_2 and cardiac hospitalization.
Stieb et al. (2000) * Saint John, New Brunswick Canada Study period: Jul 1992-Mar 1996	Outcome(s): Angina pectoris; MI; dysrhythmia/conduction disturbance; CHF; All Cardiac. ED Visits collected prospectively. Study design: Time series Statistical analyses: Poisson regression, GAM N: 19,821 ER visits # Hospitals: 2 Lag(s): 1-8 days	SO_2 24-h avg (ppb) Mean (SD): 6.7 (5.6) 95th: 18 Max: 60 SO_2 max (ppb) Mean (SD): 23.8 (21.0) 95th: 62 Max: 161	CO, (0.31) H_2S (−0.01) O_3 (−0.02) NO_2 (0.41) PM_{10} (0.36) $PM_{2.5}$ (0.31) H^+ (−0.24) SO_4 (0.26) COH (0.31)	Results reported for percent change in admissions based on a single-pollutant model for incremental increase in NO_2 equivalent to one IQR (8.9 ppb) Cardiac visits (p-value in parentheses): 4.9 (0.002), 1 day avg, lag 8, all yr 2.8 (0.067), 5 day avg, lag 6, May-Sept Multi-pollutant models: 4.9, (1.7, 8.2), 1 day avg, lag 8, all yr (O_3) Lags 0-10 presented graphically. All but lag 8 in single-pollutant model approximately null.

TABLE AX5.4 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR CARDIOVASCULAR DISEASES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean Levels & Monitoring Stations	Copollutants (Correlations)	Effects: Relative Risk or % Change & Confidence Intervals ([95% Lower, Upper])
CANADA (cont'd)				
Villeneuve et al. (2006a) Edmonton, Canada Study period: Apr 1992-Mar 2002	Outcome(s) (ICD9): Acute ischemic stroke 434, 436; hemorrhagic stroke 430, 432; transient ischemic attach (TIA) 435; Other 433, 437, 438. ED visits supplied by Capital Health. N: 12,422 Stroke Visits Catchment area: 1.5 million people Study design: Case-crossover, exposure index time compared to referent time. Time independent variables controlled in the design. Index and referent day matched by day of wk. Statistical Analysis: Conditional logistic regression, stratified by season and gender. Covariates: Temperature and humidity Statistical software: SAS Season: Warm: Apr-Sept; Cool: Oct-Mar. Lag(s): 0, 1, 3 day avg	SO_2 24 h ppb: All yr Mean (SD): 2.6 (1.9) Median: 2.0 25th: 1.0 75th: 4.0 IQR: 3.0 Summer Mean (SD): 2.1 (1.6) Median: 2.0 25th: 1.0 75th: 3.0 IQR: 2 Winter Mean (SD): 3.1 (2.0) Median: 3.0 25th: 2.0 75th: 4.0 IQR: 2.0	Correlation between SO_2 and other pollutants (all yr): NO_2 (0.42) CO (0.41) O_3 (−0.25) $PM_{2.5}$ (0.22) PM_{10} (0.19)	Effects were reported as odds ratios based on an increment of 3 ppb. Acute Ischemic stroke, ≥65 yrs All yr OR 1.05 (0.99,1.11) lag 0 Warm OR 1.11 (1.01, 1.22) lag 0 Cold OR 1.00 (0.93, 1.09) lag 0 Effect stronger among males Hemorrhagic stroke, ≥65 yrs All yr: 0.98 (0.90, 1.06), lag 0 Cold: 0.94 (0.84, 1.05), lag 0 Warm: 1.03 (0.90, 1.17) Effect stronger among males Transient Cerebral Ischemic Attack, ≥65 yrs All yr: 1.06 (1.00, 1.12), lag 0 Cold: 1.03 (0.95, 1.11), lag 0 Warm OR 1.11 (1.02, 1.22) lag 0 2-pollutant models presented graphically. Association of SO_2 with Acute Ischemic stroke diminished with inclusion of CO and NO_2.

TABLE AX5.4 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR CARDIOVASCULAR DISEASES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean Levels & Monitoring Stations	Copollutants (Correlations)	Effects: Relative Risk or % Change & Confidence Intervals ([95% Lower, Upper])
EUROPE				
Ballester et al. (2006) Multi-city, Spain: Barcelona, Bilbao, Castellon, Gijon, Huelva, Madrid, Granada, Oviedo, Seville, Valencia, Zaragoza Period of Study: 1995/1996-1999, N = 1,096 days	Outcome(s) (ICD9): All CVD 390-459; Heart diseases 410-414,427,428. Emergency admission from hospital records. Discharge data used. Study design: Time series, meta-analysis to pool cities N: Daily mean admissions reported by city Statistical analyses: Poisson regression and GAM, with stringent convergence criteria, meta-analysis with random effect model. Tested linearity by modeling pollutant in linear and non-linear way (spline smoothing). Linear model provided best results 55% of time but used in all cases to facilitate comparability. Covariates: Temperature, humidity and influenza, day of wk unusual events, seasonal variation and trend of the series Seasons: Hot: May to Oct; Cold: Nov to Apr Statistical package: S-PLUS Lag: 0-3	SO_2 24-h avg (µg/m2) Mean, 10th, 90th Barcelona: 15.5, 6.6, 27.9 Bilbao: 18.6, 10.2, 29.3 Cartagena: 27.1, 14.6, 40.8 Castellon: 7.7, 3.8, 12.7 Gijon: 29.4, 10.3, 52.4 Granada: 19.1, 8.8, 31.5 Huelva: 11.9, 4.5, 22.6 Madrid: 21.8, 8.7, 41.8 Oviedo: 40.9, 16.3, 75.5 Pamplona: 7.6, 1.8, 17.0 Seville: 9.6, 5.6, 14.6 Valencia: 16.6, 9.4, 24.4 Vigo: 9.3, 2.6, 18.2 Zaragoza: 9.3, 2.0, 19.9 # of Stations: Depends on the city Correlation among stations: Correlations between SO_2 stations within cities poor.	CO 8-h max (0.58) O_3 8-h max (−0.03) NO_2 24 h (0.46) BS 24 h (0.24) TSP 24 h (0.31) PM_{10} 24 h (0.46) Correlations reported are the median for all cities. 2-pollutant models used to adjust for copollutants	Results reported for % change in admissions, increment 10 (µg/m^3). All cardiovascular 1.33% (0.21, 2.46) lag 0-1 Heart diseases 1.72% (0.50, 2.95) lag 0-1 Single day lags presented graphically. Effect size decreased with increasing lag. Multi-pollutant results presented graphically. Control for CO and particulates diminished SO_2 effects.

TABLE AX5.4 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR CARDIOVASCULAR DISEASES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean Levels & Monitoring Stations	Copollutants (Correlations)	Effects: Relative Risk or % Change & Confidence Intervals ([95% Lower, Upper])
EUROPE (cont'd)				
Anderson et al. (2001)* West Midlands conurbation, UK Study period: 1994-1996, n = 832 days	Outcome(s) (ICD9): All CVD 390-459; cardiac disease 390-429; IHD 410-414; stroke 430-438. Emergency admissions counted. Catchment area: 2.3 million Age groups analyzed: 0-14, 15-64, ≥65. Study design: Time series, APHEA 2 methods Statistical analyses: GAMs for modeling non-liner dependence of some variables. Covariates: Adjusted for effects of seasonal patterns, temperature and humidity, influenza episodes, day of wk and holidays. Software package: S-PLUS Seasons: Interaction by warm and cool season investigated. Lag(s): 0-3 days	SO_2 24-h avg (ppb) Mean (SD): 7.2 (4.7) Min: 1.9 10th: 3.3 Median: 5.8 90th: 12.3 Max: 59.8 # of Stations: 5 sites	PM_{10} (0.55) $PM_{2.5}$ (0.52) $PM_{2.5-10}$ (0.31) BS (0.50) SO_4 (0.19) NO_2 (0.52) O_3 (-0.22)	Results reported for % change in admissions, increment = 9 ppb (10th-90th). All CVD all ages −0.4 (−2.2, 1.5), mean lags 0 + 1 Cardiac all ages: 0.7 (−1.3, 2.8), mean lags 0 + 1 IHD ≥65 yrs 1.5 (−2.5, 5.6), mean lags 0 + 1 Stroke ≥65 yrs −5.1 (−9.6, −0.4), mean lags 0 + 1

TABLE AX5.4 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR CARDIOVASCULAR DISEASES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean Levels & Monitoring Stations	Copollutants (Correlations)	Effects: Relative Risk or % Change & Confidence Intervals ([95% Lower, Upper])
EUROPE (cont'd)				
Atkinson et al. (1999a) London, England Period of Study: 1992-1994, N = 1,096 days	Outcome(s) (ICD9): All CVD 390-459; IHD 410-414. Emergency admissions obtained from the Hospital Episode Statistics (HES) database (complaints). Ages groups analyzed: 0-14 yrs, 15-64 yrs, 0-64 yrs, 65+ yrs, 65-74 yrs, 75+ yrs Study design: Time series, hospital admission counts N: 189,109 CVD admissions Catchment area: 7 million residing in 1,600 Km^2 area of Thames basin. Statistical analyses: APHEA protocol, Poisson regression Covariates: adjusted long-term seasonal patterns, day of wk, influenza, temperature, humidity (compared alternative methods for modeling meteorological including linear, quadradic, piece-wise, spline) Seasons: Warm season Apr-Sept, cool season remaining mos, interactions between season investigated Dose response investigated: Yes, bubble charts presented Statistical package: SAS Lag: 0-3 Dose response: Bubble plots presented	SO_2 24 h avg (ppb): Mean: 21.2 SD: 7.8 Min: 7.4 10th: 13 Median: 19.8 90th: 31 Max: 82.2 10th-90th percentile: 11.2 # of Stations: 3, results averaged across stations	PM_{10} 24 h CO 24 h SO_2 24 h O_3 8 h BS 24 h Correlations of SO_2 with CO, NO_2, O_3, BS ranged from 0.5-0.6 Correlation of SO_2 with O_3 negative 2-pollutant models to used adjust for copollutants	Results reported for % change in admissions, increment 10th-90th percentile (11.2 ppb). All CVD, all ages 1.57 (0.22, 2.93), lag 0 All CVD, 0-64 yrs 2.44 (0.3, 4.63), lag 0 All CVD, 65+ 1.72 (0.15, 3.32), lag 0 IHD, 0-64 yrs −2.03 (−5.35, 0.91), lag 2 IHD, 65+ 3.10 (0.61, 5.65), lag 0 Effect size and significance diminished in models containing SO_2 and BS.

TABLE AX5.4 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR CARDIOVASCULAR DISEASES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean Levels & Monitoring Stations	Copollutants (Correlations)	Effects: Relative Risk or Percent Change & Confidence Intervals ([95% Lower, Upper])
EUROPE (cont'd)				
Ballester et al. (2001) * Valencia, Spain Period of Study: 1992-1996	Outcome(s) (ICD9): All CVD 390-459; heart diseases 410-414, 427, 428; cerebrovascular diseases 430-438. Admissions from city registry – discharge codes used. Study design: Time series N: 1080 CVD admissions # of Hospitals: 2 Catchment area: 376,681 inhabitants of Urban Valencia Statistical analyses: Poisson regression, GAM, APHEA/ Spanish EMECAM protocol. Both Linear and nonparametric model, including a loess term was fitted, departure from linearity assess by comparing deviance of both models. Covariates: Long-term trend and seasonality, temperature and humidity, weekdays, flu, special events, air pollution. Seasons: Hot season May to Oct; Cold season Nov to Apr Statistical package: SAS Lag: 0-4	24 h ($\mu g/m^3$): Mean: 25.6 SD: NR Min: 4.4 Max: 68.4 median: 25 # of Stations: 14 manual, 5 automatic Correlation among stations: 0.3-0.62 for BS, 0.46-0.78 for gaseous pollutants	CO 24 h, (0.74) NO_2 24 h, (0.22) O_3 8 h, (−0.35) BS, (0.63) 2-pollutant models used to adjust for copollutants	Results expressed as relative risk, increment of 10 $\mu g/m^3$. All CVD 1.0302 (1.0042, 1.0568), lag 2 Heart disease 1.0357 (1.0012, 1.0714), lag 2 Cerebrovascular disease 1.0378 (0.9844 to 1.0940), lag 5 Digestive diseases 1.0234 (0.9958, 1.0518), lag 1 All CVD, hottest semester 1.050 (1.010, 1.092), lag 2 Effect size for all CVD and cerebrovascular disease diminished in 2-pollutant models.

TABLE AX5.4 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR CARDIOVASCULAR DISEASES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean Levels & Monitoring Stations	Copollutants (Correlations)	Effects: Relative Risk or % Change & Confidence Intervals ([95% Lower, Upper])
EUROPE (cont'd)				
D'Ippoliti et al. (2003) Rome, Italy Study period: Jan 1995- June 1997	Outcome(s) (ICD): AMI 410 (first episode). Computerized hospital admission data. Study design: Case-crossover, time stratified, control days within same mo falling on the same day. Statistical analyses: Conditional logistic regression, examined homogeneity across co-morbidity categories N: 6531 cases Age groups analyzed: 18-64 yrs, 65-74 yrd, ≥75 Season: Cool: Oct-Mar; Warm: Apr-Sept. Lag(s): 0-4 day, 0-2 day cum avg Dose Response: OR for increasing quartiles presented and p-value for trend.	SO_2 24 h (µg/m^3) All yr: Mean (SD): 9.5 (6.0) 25th: 5.4 50th: 8.2 75th: 12.6 IQR: 7.2 Cold season: Mean (SD): 12.7 (6.5) Warm season: Mean (SD): 88.3 (15.4) # Stations: 5	TSP 24 h (0.29) NO_2 24 h (0.37) CO 24 h (0.56) No multipollutant models	Results reported as odds ratios for increment equal to one IQR (7.2 µg/m^3). AMI Quartile I (referent) Quartile II 0.987 (0.894, 1.089), lag 0-2 Quartile III 1.008 (0.892, 1.140), lag 0-2 Quartile IV 1.144 (0.991, 1.321), lag 0-2 Results at various lags not reported for SO_2.
Llorca et al. (2005) Torrelavega, Spain Study period: 1992-1995	Outcome(s) (ICD): CVD (called cardiac in paper) 390-459. Emergency admissions, excluding nonresidents. Obtained admissions records from hospital admin office. Study design: Time series Statistical analyses: Poisson regression, APHEA protocol Covariates: Rainfall, temperature, wind speed direction N: 18,137 admissions Statistical software: STATA Lag(s): not reported	SO_2 24 h µg/m^3: Mean (SD): 13.3 (16.7)	TSP (−0.40) NO_2 (0.588) SH_2 (0.957) NO (0.544) Multipollutant models	Results expressed as rate ratios. Increment = 100 µg/m^3. Cardiac admissions, single-pollutant model 0.94 (0.84, 1.05) Five-pollutant model 1.09 (0.83, 1.42) All cardiorespiratory admissions, single-pollutant model RR 0.98 (0.89, 1.07) Five-pollutant model 0.98 (0.80, 1.21)

TABLE AX5.4 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR CARDIOVASCULAR DISEASES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean Levels & Monitoring Stations	Copollutants (Correlations)	Effects: Relative Risk or % Change & Confidence Intervals ([95% Lower, Upper])
EUROPE (cont'd)				
Poloniecki et al. (1997)* London, UK Study period: Apr, 1987-Mar 1994, 7 yrs	Outcome(s): All CVD 390-459; MI 410; Angina pectoris 413; other IHD 414; ARR 427; congestive heart failure 428; cerebrovascular disease 430-438. Hospital Episode Statistics (HES) data on emergency hospital admissions. Study design: Time series N: 373, 556 CVD admissions Statistical analyses: Poisson regression with GAM, APHEA protocol Covariates: Long-term trends, seasonal variation, day of wk, influenza, temperature and humidity. Season: Warm, Apr-Sept; Cool, Oct-Mar. Lag: 0-1	SO_2 24 h ppb: Min: 0 10%: 2 Median: 6 90%: 21 Max: 114	Black Smoke CO 24 h NO_2 24 h O_3 8 h Correlations between pollutants high but not specified.	Effects were expressed as relative risk based on an increment of 19 ppb (10th-90th percentile). Single-pollutant models (lag 0-1) MI: 1.0326 (1.0133, 1.0511) Angina: 1.0133 (0.9907, 1.0383) IHD: 0.9944 (0.9651, 1.0239) ARR: 1.0181 (1.0000, 1.0448) CHF: 1.0057 (0.9846, 1.0258) Cerebrovascular: 1.0019 (0.9837, 1.0189) All circulatory: 1.0248 (1.0062, 1.0444) MI, 2-pollutant models, cool season 1.0399 (1.0171, 1.0628), SO_2 only 1.0285 (1.0019, 1.0571), SO_2/NO_2 1.0380 (1.0057, 1.0704), SO_2/CO 1.0285 (1.0019, 1.0552), SO_2/BS 1.0476 (1.0209, 1.0742), SO_2/O_3 In the warm season no significant associations were observed in 2-pollutant models.

TABLE AX5.4 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR CARDIOVASCULAR DISEASES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean Levels & Monitoring Stations	Copollutants (Correlations)	Effects: Relative Risk or % Change & Confidence Intervals ([95% Lower, Upper])
EUROPE (cont'd)				
Prescott et al. (1998)* Edinburgh, UK Study period: Oct 1992-Jun 1995	Outcome(s) (ICD9): Cardiac and cerebral ischemia 410-414, 426-429, 434-440. Extracted from Scottish record linkage system. Study design: Time series Statistical analysis: Poisson, log linear regression models Age groups analyzed: <65, 65+ yrs Covariates: Seasonal and weekday variation, temperature, and wind speed. Lag(s): 0, 1, 3 day moving avg	NO_2 24 h ppb Mean (SD): 8.3 (5.6) Range: 1-50 90th-10th Percentile = 12 ppb	O_3, 24 h PM, 24 h NO_2, 24 h CO, 24 h Correlations not reported.	Results reported as % increase in admissions, increment 10 ppb. All CVD, ≤65 yrs 4.9 (−1.0, 11.1), 3 day moving avg All CVD, ≥65 yrs −3.7 (−12.4, 5.9), 3 day moving avg
Yallop et al. (2007) London, England Study period: Jan. 1998-Oct. 2001, >1400 days	Outcome(s): Acute pain in Sickle Cell Disease (HbSS, HbSC, HbS/β0, thalassaemia, HbS/β+). Admitted to hospital for at least one night. Study design: Time series Statistical analyses: Cross-correlation function N: 1047 admissions Covariates: No adjustment made in analysis, discussion includes statement that the effects of weather variables and copollutants are inter-related. Statistical package: SPSS Lag(s): 0-2 days Dose response: quartile analysis, graphs presented, ANOVA comparing means across quartiles.	NR	O_3, CO, NO, NO_2, PM_{10}: daily avg used for all copollutants	No association for SO_2

TABLE AX5.4 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR CARDIOVASCULAR DISEASES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean Levels & Monitoring Stations	Copollutants (Correlations)	Effects: Relative Risk or % Change & Confidence Intervals ([95% Lower, Upper])
AUSTRALIA				
Jalaludin et al. (2006) Sydney, Australia Period of Study: Jan. 1997-Dec. 2001	Outcome(s) (ICD9): All CVD 390-459; cardiac disease 390-429; IHD 410-413; and cerebrovascular disease or stroke 430-438; Emergency room attendances obtained from health department data. Age groups included: 65+ Study design: Time series, multi-city APHEA2 Protocol. Statistical analysis: GAM (with appropriate convergence criteria) and GLM Models. Only GLM presented. Lag: 0-3 Covariates: Daily avg temperature and daily relative, humidity, long-term trends, seasonality, weather, day of wk, public school holidays, outliers and influenza epidemics. Dose response: quartile analysis Season: Separate analyses for warm (Nov-Apr) and cool periods (May-Oct).	SO_2 24 h avg (ppb) Mean (SD): 1.07 (0.58) Min: 0.09 25th: 0.64 Median: 1.01 75th: 1.39 Max: 3.94 IQR: 0.75 # of Stations: 14	BS (0.21) PM_{10} (0.37) O_3 (0.454) NO_2 (1 h) (0.52) CO (8 h) (0.46) 2-pollutant models to adjust for copollutants	Effects were presented as percent change based on an increment of 0.75 ppb. Single-pollutant model: All CVD, all yr 1.33% (0.24, 2.43) lag 0 Cardiac: 1.62% (0.33, 2.93) lag 0 IHD: 1.12% (−0.84, 3.12) lag 0 Stroke: −1.41% (−3.67, 0.90) lag 0 Cool Season All cardiovascular: 2.15% (0.84, 3.46) lag 0 Cardiac: 2.48% (0.94, 4.04) lag 0 IHD: 2.49% (0.13, 4.91) lag 0 Stroke: −0.19% (−2.90, 2.60) lag 0 Warm Season All cardiovascular: 0.06% (−1.48, 1.62) lag 0 Cardiac: 0.38% (−1.37, 2.16) lag 0 IHD: −0.47% (−3.08, 2.22) lag 0 Stroke: −2.74% (−5.92, 0.55) lag 0 Results for lags 0-3 presented. In general, effect size diminished with increasing lag. Effects of SO_2 on all CVD were diminished with inclusion of PM and CO (graphically presented.)

TABLE AX5.4 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR CARDIOVASCULAR DISEASES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean Levels & Monitoring Stations	Copollutants (Correlations)	Effects: Relative Risk or % Change & Confidence Intervals ([95% Lower, Upper])
AUSTRALIA (cont'd)				
Petroeschevsky et al. (2001) Brisbane, Australia Study period: Jan 1987-Dec 1994, 2,922 days	Outcome(s) (ICD9): CVD 390-459. Hospital admissions, non-residents excluded. Study design: Time series Statistical analyses: Poisson regression, APHEA protocol, linear regression and GEEs Age groups analyzed: 15-64, 65+ Covariates: Temperature, humidity, rainfall. Long-term trends, season, flu, day of wk, holidays. Dose response: Quintile analysis. Statistical software: SAS Lag(s): lag 0-4, 3 day avg, 5 day avg	SO_2 24-h avg (pphm) Summer: Mean, min, max 0.39, 0.0, 1.63 Fall: Mean, min, max 0.42, 0.01, 3.55 Winter: Mean, min, max 0.48, 0.0, 2.08 Spring: Mean, min, max 0.37, 0.0, 6.02 Overall: Mean, min, max 0.41, 0.0, 3.55 SO_2 1-h max (pphm) Summer: Mean, min, max 0.78, 0.0, 5.5 Fall: Mean, min, max 0.93, 0.05, 5.95 Winter: Mean, min, max 1.13, 0.0, 6.68 Spring: Mean, min, max 0.84, 0.0, 6.01 Overall: Mean, min, max 0.92, 0.0, 6.68	BSP O_3 NO_2 Correlation between pollutants not reported.	Effects were expressed as relative risk based on an increment of 10 ppb and the 24-h avg SO_2 concentrations. All CVD 15 to ≥65 yrs 1.028 (0.987, 1.070) lag 0 15 to 64 yrs 1.081 (1.010, 1.158) lag 0 ≥65 yrs 1.038 (0.988, 1.091) lag 1 Non-significant increasing risk for CVD in those 15-64 by quintile of SO_2 concentration observed.

TABLE AX5.4 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR CARDIOVASCULAR DISEASES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean Levels & Monitoring Stations	Copollutants (Correlations)	Effects: Relative Risk or % Change & Confidence Intervals ([95% Lower, Upper])
ASIA				
Chan et al. (2006) * Taipai, Taiwan Period of Study: Apr 1997-Dec 2002, 2090 days	Outcome(s) (ICD9): Cerebrovascular disease 430-437; stroke 430-434; hemorrhagic stroke 430-432; ischemic stroke 433-434. Emergency admission data collected from National Taiwan University Hospital. Ages groups analyzed: age >50 included in study Study design: Time series N: 7341 Cerebrovascular admissions among those >50 yrs old # of Hospitals: Catchment area: Statistical analyses: Poisson regression, GAMs used to adjust for non-linear relation between confounders and ER admissions. Covariates: Time trend variables: yr, mo, and day of wk, daily temperature difference, and dew point temperature. Linearity: Investigated graphically by using the LOESS smoother. Statistical package: NR Lag: 0-3, cumulative lag up to 3 days	SO_2 24-h avg (ppb): Mean: 4.3 SD: 2.4 Min: 0.4 Max: 17.1 IQR: 3.1 ppb # of Stations: 16 Correlation among stations: NR	PM_{10} 24 h (0.59) $PM_{2.5}$ 24 h (0.51) CO 8-h avg (0.63) NO_2 24 h (0.64) O_3 1-h max (0.51) 2-pollutant models to adjust for copollutants but not for SO_2, which was not associated with health outcomes.	Results reported for OR for association of emergency department admissions with an IQR increase in SO_2 (3.1 ppb) Cerebrovascular: 1.008 (0.969, 1.047), lag 0 Stroke: 0.991 (0.916, 1.066), lag 0 Ischemic stroke: 1.044 (0.966, 1.125), lag 0 Hemorrhagic stroke: 0.918 (0.815, 1.021), lag 0 No significant associations for SO_2 reported. Lag 0 shown but similar null results were obtained for lags 0-3.

TABLE AX5.4 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR CARDIOVASCULAR DISEASES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean Levels & Monitoring Stations	Copollutants (Correlations)	Effects: Relative Risk or % Change & Confidence Intervals ([95% Lower, Upper])
ASIA (cont'd)				
Chang et al. (2005) Taipei, Taiwan Study period: 1997-2001, 5 yrs	Outcome(s) (ICD9): CVD 410-429. Daily clinic visits or hospital admission from computerized records of National Health Insurance. Discharge data. Source population: 2.64 Million N: 40.8 admissions/day, 74,509/5 yrs # Hospitals: 41 Study design: Case-crossover, referent day 1 wk before or after index day Statistical analyses: Conditional logistic regression. Covariates: Same day temperature and humidity. Season: warm/cool (stratified by temperature cutpoint of 20 ºC) Lag(s): 0-2 days	SO_2 24-h avg (ppb) Mean: 4.32 Min: 0.15 25th: 2.74 Median: 3.95 75th: 5.49 Max: 14.57 IQR: 2.75 # of Stations: 6	CO 24-h avg O_3 24-h avg NO_2 24-h avg PM_{10} 24-h avg Correlations not reported. 2-pollutant models to adjust for copollutants	Effects were expressed as odds ratios based on an increment of 2.75 ppb. Warm (≥20 ºC) 0.967 (0.940, 0.995) Cool (<20 ºC) 1.015 (0.965, 1.069) In 2-pollutant models with (PM_{10}, NO_2, CO, or O_3) the effect of SO_2 was attenuated for both temperature ranges such that it was negatively associated with CVD. ≥20 ºC: 0.874 (0.77, 0.880), w/ PM_{10} <20 ºC: 0.986 (0.928, 1.048), w/ PM_{10} ≥20 ºC: 0.826 (0.798, 0.854), w/ NO_2 <20 ºC: 0.922 (0.865, 0.984), w/ NO_2 ≥20 ºC: 0.903 (0.876, 0.931), w/ CO <20 ºC: 0.960 (0.901, 1.022), w/ CO ≥20 ºC: 0.953 (0.926, 0.981), w/ O_3 <20 ºC: 1.014 (0.963, 1.067), w/ O_3
Lee et al. (2003) Seoul, Korea Study period: Dec 1997-Dec 1999, 822-days, 184 days in summer	Outcome(s) (ICD10): IHD: Angina pectoris 120; Acute or subsequent MI 121-123; other acute IHD 124. Electronic medical insurance data used. Study design: Time series Statistical methods: Poisson regression, GAM with strict convergence criteria. Age groups analyzed: all ages, 64+ Covariates: Long-term trends LOESS smooth, temperature, humidity, day of wk. Season: Presented results for summer (Jun, Jul, Aug) and entire period. Lag(s): 0-6	SO_2 24 h (ppb): 5th: 3.7 10th: 5.1 Median: 7.0 75th: 9.5 95th: 14.3 Mean (SD): 7.7 (3.3) IQR: 4.4	All yr NO_2 (0.72) O_3 (−0.30) CO (0.81) PM_{10} (0.59) Warm season NO_2 (0.79) O_3 (−0.56) CO (0.41) PM_{10} (0.61) 2-pollutant models	Results reported for RR of IHD hospital admission for an incremental increase in SO_2 equivalent to one IQR (4.4 ppb). Single-pollutant model: Entire season- IHD All ages 0.96 (0.92, 0.99) lag 3 ≥64 yrs 0.95 (0.90, 1.01) lag 3 Summer- IHD All ages 1.09 (0.96, 1.24) lag 3 ≥64 yrs 1.32 (1.08, 1.62) lag 3 2-pollutant model: Entire season; SO_2 and PM_{10} ≥64 yrs 0.98 (0.94, 1.03) lag 3

TABLE AX5.4 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR CARDIOVASCULAR DISEASES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean Levels & Monitoring Stations	Copollutants (Correlations)	Effects: Relative Risk or % Change & Confidence Intervals ([95% Lower, Upper])
ASIA (cont'd)				
Tsai et al. (2003a) Kaohsiung, Taiwan Study period: 1997-2000	Outcome(s) (ICD9): All cerebrovascular 430-438; SHS 430; PIH 431-432; IS 433-435; Other 436-438. Ascertained from National Health Insurance Program computerized admissions records. Study design: Case-crossover Statistical analysis: Conditional logistic regression. N: 23,179 stroke admissions # Hospitals: 63 Statistical software: SAS Seasons: Warm (≥20 ºC); Cool (<20 ºC). Lag(s): 0-2, cumulative lag up to 2 previous days	SO_2 (ppb) Min: 1.25 25th: 6.83 Median: 9.76 75th: 13.00 Max: 26.80 Mean: 10.08 # Station: 6	PM_{10} SO_2 CO O_3	Results reported as OR for the association of admissions with an incremental increase of SO_2 equivalent to the IQR of 6.2 ppb PIH admissions Warm: 1.06 (0.95, 1.18), lag 0-2 Cool: 0.85 (0.58, 1.26), lag 0-2 IS admissions: Warm: 1.06 (1.00, 1.13), lag 0-2 Cool: 1.11 (0.83, 1.48), lag 0-2 2-pollutant models: PIH 0.91 (0.80, 1.03) w/ NO_2 IS 0.93 (0.87, 1.00) w/ NO_2 PIH 0.94 (0.83, 1.06), w/ CO IS 0.94 (0.88, 1.02), w/ CO PIH 1.08 (0.96, 1.20) w/ O_3 IS 1.08 (1.01, 1.15) w/ O_3 PIH 0.99 (0.88, 1.11) w/ PM IS 1.01 (0.95-1.08) w/ PM
Wong et al. (1999) Hong Kong, China Study period: 1994-1995	Outcome(s) (ICD9): CVD: 410-417, 420-438, 440-444; CHF 428; IHD 410-414; Cerebrovascular Disease 430-438. Hospital admissions through ER departments via Hospital Authority (discharge data). Study design: Time series Statistical analyses: Poisson regression, APHEA protocol # Hospitals: 12 Covariates: Daily temperature, relative humidity day of wk, holidays, influenza, long-term trends (yr and seasonality variables). Interaction of pollutants with cold season examined. Season: Cold (Dec-March) Lag(s): 0-3 days	SO_2 24-h avg (μg/m^3) Mean: 20.2 IQR: 10	PM_{10} SO_2 O_3	Results reported for RR associated with incremental increase in NO_2 equal to 10 μg/m^3. All CVD, All ages 1.016 (1.006, 1.026) lag 0-1 All CVD, 5-65 yrs 1.004 (0.989, 1.020) lag 0-1 All CVD, >65 yrs 1.021 (1.010, 1.032) lag 0-1 CHF 1.036 (1.013, 1.059) lag 0 IHD 1.010 (0.995, 1.025) lag 0-1 Cerebrovascular 0.990 (0.978, 1.002) lag 3 2-pollutant model results not presented for SO_2

TABLE AX5.4 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR CARDIOVASCULAR DISEASES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean Levels & Monitoring Stations	Copollutants (Correlations)	Effects: Relative Risk or % Change & Confidence Intervals ([95% Lower, Upper])
ASIA (cont'd)				
Wong et al. 2002a* Hong Kong, London Study period: 1995-1997 (Hong Kong), 1992-1994 (London)	Outcome(s) (ICD9): Cardiac disease 390-429; IHD 410-414. Patients admitted to hospitals from emergency departments, out patient departments or directly to inpatient wards. Statistical analysis: Poisson regression, GAMs Covariates: Smooth functions of time, temperature, humidity (up to 3 days before admission) day of wk, holidays and unusual events. Statistical software: S-PLUS Seasons: Warm/cold Lag(s): 0-3, cumulative 0-1	SO_2 24-h avg ($\mu g/m^3$) Hong Kong Mean, all yr: 17.7 (12.3) Mean, warm: 18.3 Mean, cold: 17.2 Min: 1.1 10th: 6.2 50th: 14.5 90th: 32.8 Max: 90 London Mean, all yr: 23.7 (12.3) Mean, warm: 22.2 Mean, cold: 25.3 Min 6.2 10th: 13.2 50th: 20.6 90th: 38.1 Max: 113.6	Hong Kong NO_2 (0.37) PM_{10} (0.30) O_3 (−0.18) London NO_2 (0.71) PM_{10} (0.64) O_3 (−0.25)	Effects expressed as % change, increment was 10 $\mu g/m^3$ Cardiac (all ages) Hong Kong All yr: 2.1% (1.3, 2.8) lag 0-1 Warm: 1.0% (0.0, 2.0) lag 0-1 Cold: 1.9% (1.2, 2.7) lag 0-1 London All yr: 1.6% (1.0, 2.2) lag 0-1 Warm: 0.6% (−0.6, 1.7) lag 0-1 Cold: 1.9% (1.2, 2.7) lag 0-1 IHD (all ages) Hong Kong All yr: 0.1% (−1.1, 1.2) lag 0-1 Warm: −0.6% (−2.0, 0.8) lag 0-1 Cold: 1.0% (−0.8, 2.8) lag 0-1 London All yr: 1.7% (0.8, 2.6) lag 0-1 Warm: 1.0% (−0.6, 2.6) lag 0-1 Cold: 2.0% (0.9, 3.1) lag 0-1 Multipollutant model Cardiac (all ages) Hong Kong SO_2 alone 2.1% (1.3, 2.8) SO_2/NO_2 1.4% (0.4, 2.3) SO_2/O_3 2.1% (1.4, 2.9) SO_2/PM_{10} 2.0% (1.1, 2.8) London SO_2 1.6% (1.0, 2.2) SO_2/NO_2 1.4% (0.6, 2.3) SO_2/O_3 1.6% (0.9, 2.2) SO_2/PM_{10} 2.2% (1.2, 3.2)

TABLE AX5.4 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR CARDIOVASCULAR DISEASES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean Levels & Monitoring Stations	Copollutants (Correlations)	Effects: Relative Risk or % Change & Confidence Intervals ([95% Lower, Upper])
ASIA (cont'd)				
Yang et al. (2004a) Kaohsiung, Taiwan Period of Study: 1997-2000	Outcome(s) (ICD9): All CVD: 410-429 * (All CVD typically defined to include ICD9 codes 390-459) N: 29,661 Study design: Case-crossover Statistical analysis: Poisson Time series regression models, APHEA protocol # of Hospitals: 63 Seasons: Authors indicate not considered because the Taiwanese climate is tropical with no apparent seasonal cycle Covariates: Stratified by warm (≥25º) and cold (<25º) days, temperature, and humidity measurements included in the model Statistical package: SAS Lag: 0-2 days	SO_2 24-h avg (ppb) Min: 1.25 25%: 6.83 50%: 9.76 75%: 13.00 Max: 26.80 Mean: 10.08 # of Stations: 6 Correlation among stations: NR	PM_{10} CO SO_2 O_3 8 2-pollutant models used to adjust for copollutants Correlations NR	OR's for the association of one IQR (17.08 ppb) increase in SO_2 with daily counts of CVD hospital admissions are reported All CVD (ICD9: 410-429), one-pollutant model ≥25º: 0.999 (0.954, 1.047) <25º: 1.187 (1.092, 1.291) All CVD (ICD9: 410-429), 2-pollutant models Adjusted for PM_{10}: ≥25º: 0.961 (0.917, 1.008) <25º: 1.048 (0.960, 1.145) Adjusted for NO_2: ≥25º: 0.921 (0.875, 0.969) <25º: 0.711 (0.641, 0.789) Adjusted for CO: ≥25º: 0.831 (0.785, 0.879) <25º: 0.996 (0.910, 1.089) Adjusted for: O_3 ≥25º: 1.034 (0.987, 1.084) <25º: 1.194 (1.098, 1.299)

TABLE AX5.4 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE WITH EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR CARDIOVASCULAR DISEASES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean Levels & Monitoring Stations	Copollutants (Correlations)	Effects: Relative Risk or % Change & Confidence Intervals ([95% Lower, Upper])
MIDDLE EAST				
Hosseinpoor et al. (2005) Tehran, Iran Study period: Mar 1996-Mar 2001, 5 yrs	Outcome(s) (ICD9): Angina pectoris 413. Primary discharge diagnosis from registry databases or records. Study design: Time series Statistical methods: Poisson regression # Hospitals: 25 Covariates: Long-term trends, seasonality, temperature, humidity, holiday, post-holiday, day of wk. Lag(s): 0-3	SO_2 24-h avg (µg/m^3) Mean (SD): 73.74 (33.30) Min: 0.30 25th: 48.23 Median: 74.05 75th: 98.64 Max: 499.26	NO_2 CO O_3 PM_{10} Correlations not reported	Results reported for relative risk in hospital admissions per increment of 10 µg/m^3 SO_2. Angina 0.99995 (0.99397, 1.00507), lag 1 In a multipollutant model only CO (lag 1) was significantly associated with angina pectoris related hospital admissions.

*Default GAM

AMI Acute Myocardial Infarction
ARR Arrhythmia
BC Black Carbon
COH coefficient of haze
CP Course Particulate
CVD Cardiovascular Disease
EC Elemental Carbon
FP Fine Particulate
HS Hemorrhagic Stroke
ICD9 International Classification of Disease, 9th Revision
IHD Ischemic Heart Disease
IS ischemic stroke
MI Myocardial Infarction
OC Organic Carbon
OHC Oxygenated Hydrocarbons
PERI Peripheral Vascular and Cerebrovascular Disease
PM Particulate Matter
PIH primary intracerebral hemorrhage
PNC Particle Number Concentration
SHS Subarachnoid hemorrhagic stroke
TP Total Particulate
UBRE Unbiased Risk Estimator

TABLE AX5.5. ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE ON MORTALITY

Reference, Study Location, and Period	Outcome Measure	Mean SO_2 Levels	Copollutants Considered	Lag Structure Reported	Method/Design	Effect Estimates* % Increase in Risk (95% CI)
META ANALYSIS						
Stieb et al. (2002; reanalysis 2003) meta-analysis of estimates from various countries.	All cause	24-h avg ranged from 0.7 ppb (San Bernardino) to 75 ppb (Shenyang) "Representative" concentration: 9.4 ppb	PM_{10}, O_3, NO_2, CO	The lags and multiday averaging used varied	Meta-analysis of time-series study results.	Single-pollutant model (29 estimates): 1.0% (0.6, 1.3) Multipollutant model estimates (10 estimates): 0.9% (0.3, 1.4)
UNITED STATES						
Dockery et al. (1992) St. Louis, MO and Eastern Tennessee 1985-1986	All cause	24-h avg: St. Louis: 9 ppb Eastern Tennessee: 5 ppb	PM_{10}, $PM_{2.5}$, SO_4^{2-}, H^+, O_3, NO_2,	1	Poisson with GEE. Time-series study.	All cause: St. Louis, MO: 0.8% (−1.7, 3.2) Eastern Tennessee: 0.4% (−0.4, 1.1)
Moolgavkar (2000; reanalysis 2003a). Cook County, IL; Los Angeles County, CA; and Maricopa County, AZ 1987-1995	Cardiovascular; cerebrovascular; COPD	24-h avg median: Cook County: 6 ppb Los Angeles: 2 ppb Maricopa County: 2 ppb	$PM_{2.5}$, PM_{10}, O_3, NO_2, CO; 2- and 3-pollutant models	0, 1, 2, 3, 4, 5	Poisson GAM with default convergence criteria in the original Moolgavkar (2000); GAM with stringent convergence criteria and GLM with natural splines in the 2003 re-analysis. The 2000 analysis presented total death risk estimates only in figures.	GLM (re-analysis): Cook County: All-cause: Lag 1: 2.6% (1.4, 3.8) Cardiovascular: Lag 1: 2.9% (1.0, 4.8) Los Angeles: Cardiovascular: Lag 1: 5.9% (3.0, 9.0)

TABLE AX5.5 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE ON MORTALITY

Reference, Study Location, and Period	Outcome Measure	Mean SO_2 Levels	Copollutants Considered	Lag Structure Reported	Method/Design	Effect Estimates* % increase in risk (95% CI)
UNITED STATES (cont'd)						
Moolgavkar (2003b) Cook County, IL and Los Angeles County, CA 1987-1995	All cause; cardiovascular	24-h avg median: Cook County: 6 ppb Los Angeles: 2 ppb	$PM_{2.5}$, PM_{10}, O_3, NO_2, CO; 2-pollutant models	0, 1, 2, 3, 4, 5	Poisson GAM with default convergence criteria. Time-series study.	All cause: Cook County: Single pollutant: Lag 1: 2.6% (1.5, 3.7) With PM_{10}: Lag 1: 1.9% (0.6, 3.2) Los Angeles: Single pollutant: Lag 1: 6.9% (5.4, 8.4) With $PM_{2.5}$: Lag 1: 7.6% (3.4, 12.0)
Samet et al. (2000a,b; reanalysis Dominici et al., 2003) 90 U.S. cities (58 U.S.cities with SO_2 data) 1987-1994	All cause; cardiopulmonary	24-h avg ranged from 0.4 ppb (Riverside) to 14.2 ppb (Pittsburgh)	PM_{10}, O_3, NO_2, CO; multipollutant models	0, 1, 2	Poisson GAM, reanalyzed with stringent convergence criteria; Poisson GLM. Time-series study.	Posterior means: All cause: Single pollutant: Lag 1: 0.6% (0.3, 1.0) With PM_{10} and NO_2: Lag 1: 0.4% (−0.6, 1.4)
Schwartz (2004) 14 U.S. cities that had daily PM_{10} data	All cause	24-h avg median ranged from 2.2 ppb (Spokane, WA) to 39.4 ppb (Pittsburgh, PA)	PM_{10} risk estimates computed, matched by the levels of SO_2, CO, NO_2, and O_3	1	Case-crossover design, estimating PM_{10} risks by matching by the levels of gaseous pollutants.	SO_2 risk estimates not computed. PM_{10} risk estimates showed the largest risk estimate when matched for SO_2.

TABLE AX5.5 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE ON MORTALITY

Reference, Study Location, and Period	Outcome Measure	Mean SO_2 Levels	Copollutants Considered	Lag Structure Reported	Method/Design	Effect Estimates* % increase in risk (95% CI)
UNITED STATES (cont'd)						
Chock et al. (2000) Pittsburgh, PA 1989-1991	All cause; age <74 yrs; age 75+ yrs	Not reported.	PM_{10}, O_3, NO_2, CO; 2-, 5-, and 6-pollutant models	0, 1, 2, 3	Poisson GLM. Time-series study. Numerous results	All cause: Age 0-74 yrs: Lag 1: 0.7% (−0.7, 2.2) Age 75+ yrs: Lag 1: −0.2% (−1.6, 1.3)
De Leon et al. (2003) New York City 1985-1994	Circulatory and cancer with and without contributing respiratory causes	24-h avg: 15 ppb	PM_{10}, O_3, NO_2, CO; 2-pollutant models	0 or 1	Poisson GAM with stringent convergence criteria; Poisson GLM. Time-series study.	Gaseous pollutants results were given only in figures. Circulatory: Age <75 yrs: ~2% Age 75+ yrs: ~2%
Gamble (1998) Dallas, TX 1990-1994	All cause; respiratory; cardiovascular	24-h avg: 3 ppb	PM_{10}, O_3, NO_2, CO; 2-pollutant models	0	Poisson GLM. Time-series study.	All cause: −0.8% (−3.8, 2.4) Respiratory: −1.0% (−5.8, 4.1) Cardiovascular: −0.5% (−11.4, 11.8)
Gwynn et al. (2000) Buffalo, NY	All cause; respiratory; circulatory	24-h avg: 12 ppb	PM_{10}, CoH, SO_4^{2-}, O_3, NO_2, CO, H^+	0, 1, 2, 3	Poisson GAM with Default convergence criteria. Time-series study.	All cause: Lag 0: −0.1% (−1.8, 1.7) Circulatory: Lag 3: 1.3% (−2.9, 5.6) Respiratory: Lag 0: 6.4% (−2.5, 16.2)

TABLE AX5.5 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE ON MORTALITY

Reference, Study Location, and Period	Outcome Measure	Mean SO_2 Levels	Copollutants Considered	Lag Structure Reported	Method/Design	Effect Estimates* % increase in risk (95% CI)
UNITED STATES (cont'd)						
Kelsall et al. (1997) Philadelphia, PA 1974-1988	All cause; respiratory; cardiovascular	24-h avg: 17 ppb	TSP, CO, NO_2, O_3	0 (AIC presented for 0 through 5)	Poisson GAM.	All cause: Single-pollutant: 0.8% (0.3, 1.4) With all other pollutants: 0.8% (0.1, 1.6)
Kinney and Özkaynak (1991) Los Angeles County, CA 1970-1979	All cause; respiratory; circulatory	24-h avg: 15 ppb	KM (particle optical reflectance), O_x, NO_2, CO; multipollutant models	1	OLS (ordinary least squares) on high-pass filtered variables. Time-series study.	All cause: Exhaustive multipollutant model: 0.0% (−1.1, 1.2)
Klemm and Mason (2000); Klemm et al. (2004) Atlanta, GA Aug 1998-Jul 2000	All cause; respiratory; cardiovascular; cancer; other; age <65 yrs; age 65+ yrs	1-h max: 19 ppb	$PM_{2.5}$, $PM_{10-2.5}$, EC, OC, SO_4^{2-}, NO_3^-, O_3, NO_2, CO	0-1	Poisson GLM using quarterly, monthly, or biweekly knots for temporal smoothing. Time-series study.	All cause Age 65+ yrs: Quarterly knots: 4.7% (−2.6, 12.5) Monthly knots: 3.4% (−4.1, 11.5) Bi-weekly knots: 1.0% (−6.7, 9.3)
Lipfert et al. (2000a) Seven counties in Philadelphia, PA area 1991-1995	All cause; respiratory; cardiovascular; all ages; age 65+ yrs; age <65 yrs; various subregional boundaries	24-h avg: 8 ppb 1-h max: 18 ppb	PM_{10}, $PM_{2.5}$, $PM_{10-2.5}$, SO_4^{2-}, other PM indices, O_3, NO_2, CO; 2-pollutant models	0-1	Linear with 19-day weighted avg Shumway filters. Time-series study. Numerous results.	All-cause: Philadelphia: 0.7% ($p > 0.05$)

TABLE AX5.5 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE ON MORTALITY

Reference, Study Location, and Period	Outcome Measure	Mean SO_2 Levels	Copollutants Considered	Lag Structure Reported	Method/Design	Effect Estimates* % increase in risk (95% CI)
UNITED STATES (cont'd)						
Lippmann et al. (2000; reanalysis Ito, 2003, 2004) Detroit, MI 1985-1990 1992-1994	All cause; respiratory; circulatory; cause-specific	24-h avg: 1985-1990: 10 ppb 1992-1994: 7 ppb	PM_{10}, $PM_{2.5}$, $PM_{10-2.5}$, SO_4^{2-}, H^+, O_3, NO_2, CO; 2-pollutant models	0, 1, 2, 3, 0-1, 0-2, 0-3	Poisson GAM, reanalyzed with stringent convergence criteria; Poisson GLM. Numerical SO_2 risk estimates were not presented in the re-analysis. Time-series study.	Poisson GAM: All cause: 1985-1990: Lag 1: 0.5% (−1.5, 2.4) 1992-1994: Lag 1: 1.1% (−1.4, 3.6)
Mar et al. (2000; re-analysis in 2003) Phoenix, AZ. 1995-1997.	All cause, cardiovascular	24-h avg: 3.1 ppb	$PM_{2.5}$, PM_{10}, $PM_{10-2.5}$, CO, NO_2, O_3, and selected trace elements, ions, EC, OC, TOC, and factor analysis components	0 for all cause; 0, 1, 2, 3, 4 for cardiovascular	Poisson GAM with default convergence criteria (only cardiovascular deaths were reanalyzed in 2003). Time-series study.	Poisson GAM: All cause: Lag 0: 11.2% (−1.5, 25.6) Poisson GLM: Cardiovascular: Lag 1: 7.4% (−13.1, 32.6)
Moolgavkar et al. (1995) Philadelphia, PA 1973-1988.	All cause	24-h avg: Spring: 17 ppb Summer: 16 ppb Fall: 18 ppb Winter: 25 ppb	TSP, O_3; 2-pollutant models	1	Poisson GLM. Time-series study.	All yr: 1.3% (0.8, 1.8) Spring: 1.7% (0.6, 2.9) Summer: 0.9% (−0.7, 2.5) Fall: 1.3% (0.0, 2.6) Winter: 2.0% (0.9, 3.0)

TABLE AX5.5 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE ON MORTALITY

Reference, Study Location, and Period	Outcome Measure	Mean SO_2 Levels	Copollutants Considered	Lag Structure Reported	Method/Design	Effect Estimates* % increase in risk (95% CI)
UNITED STATES (cont'd)						
Schwartz (1991) Detroit, MI 1973-1982	All cause	24-h avg: 12 ppb	TSP (predicted from extinction coefficient); 2-pollutant models	0, 1, 0-1	Poisson GEE. Time-series study.	Poisson regression coefficient Single pollutant: Lag 1: 0.863 (SE = 0.323) With TSP: Lag 1: 0.230 (SE = 0.489) (Though SO_2 levels were reported in ppb, these coefficients must have been for SO_2 in ppm.)
Schwartz (2000) Philadelphia, PA 1974-1988	All cause	24-h avg summer mean declined from 20 ppb in 1974 to 9 ppb in 1988; winter mean declined from 35 ppb in 1974 to 17 in 1988	TSP, extinction coefficient	0	Poisson GAM model in 15 winter and 15 summer periods. The second stage regressed the TSP and SO_2 risk estimates on SO_2/TSP relationships.	Single pollutant: 2.3% (1.6, 3.0) With TSP: 0.4% (−2.2, 3.1)

TABLE AX5.5 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE ON MORTALITY

Reference, Study Location, and Period	Outcome Measure	Mean SO_2 Levels	Copollutants Considered	Lag Structure Reported	Method/Design	Effect Estimates* % increase in risk (95% CI)
CANADA						
Burnett et al. (2004) 12 Canadian cities 1981-1999	All cause	24-h avg ranged from 1 ppb (Winnipeg) to 10 ppb (Halifax)	$PM_{2.5}$, $PM_{10-2.5}$, O_3, NO_2, CO	1	Poisson GLM. Time-series study.	Single pollutant: 0.7% (0.3, 1.2) With NO_2: 0.4% (0.0, 0.8)
Burnett et al. (1998a) 11 Canadian cities 1980-1991	All cause	24-h avg ranged from 1 ppb (Winnipeg) to 11 ppb (Hamilton)	O_3, NO_2, CO	0, 1, 2, 0-1, 0-2 examined but the best lag/averaging for each city chosen	Poisson GAM with default convergence criteria. Time-series study.	Single pollutant: 3.4% (2.0, 4.7) With all gaseous pollutants: 2.6% (1.3, 3.9)
Burnett et al. (1998b) Toronto 1980-1994	All cause	24-h avg: 5 ppb	O_3, NO_2, CO, TSP, COH, estimated PM_{10}, estimated $PM_{2.5}$	0, 1, 0-1	Poisson GAM with default convergence criteria. Time-series study.	Single pollutant: Lag 0: 1.0% (0.3, 1.8) With CO: Lag 0: 0.6% (−0.4, 1.5)
Goldberg et al. (2003) Montreal, Quebec 1984-1993	Congestive heart failure (CHF) as underlying cause of death versus those classified as having CHF 1 yr prior to death	24-h avg: 6 ppb	$PM_{2.5}$, coefficient of haze, SO_4^{2-}, O_3, NO_2, CO	0, 1, 0-2	Poisson GLM with natural splines. Time-series study.	CHF as underlying cause of death: Lag 1: −0.1% (−8.9, 9.6) Having CHF 1 yr prior to death: Lag 1: 5.4% (1.3, 9.5)

TABLE AX5.5 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE ON MORTALITY

Reference, Study Location, and Period	Outcome Measure	Mean SO_2 Levels	Copollutants Considered	Lag Structure Reported	Method/Design	Effect Estimates* % increase in risk (95% CI)
CANADA (cont'd)						
Vedal et al. (2003) Vancouver, British Columbia 1994-1996	All cause; respiratory; cardiovascular	24-h avg: 3 ppb	PM_{10}, O_3, NO_2, CO	0, 1, 2	Poisson GAM with stringent convergence criteria. Time-series study. By season.	Results presented in figures only. All cause: Summer: Lag 0: ~3% Winter: Lag 1: ~1%
Villeneuve et al. (2003) Vancouver, British Columbia 1986-1999	All cause; respiratory; cardiovascular; cancer; socioeconomic status	24-h avg: 5 ppb	$PM_{2.5}$, PM_{10}, $PM_{10-2.5}$, TSP, coefficient of haze, SO_4^{2-}, O_3, NO_2, CO	0, 1, 0-2	Poisson GLM with natural splines. Time-series study.	All yr: All cause: Lag 1: 1.7% (−1.1, 4.5) Cardiovascular: Lag 1: 1.1% (−3.1, 5.4) Respiratory: Lag 1: 8.3% (0.6, 16.6)
EUROPE						
Ballester et al. (2002) 13 Spanish cities 1990-1996	All cause, cardiovascular, respiratory	24-h avg SO_2 ranged from 2.8 ppb (Sevilla) to 15.6 ppb (Oviedo)	TSP, BS, PM_{10}	0-1 for 24-h avg SO_2; 0 for 1-h max SO_2	Poisson GAM with default convergence criteria. Time-series study.	All cause: Lag 0-1: 1.4% (0.2, 2.7) Cardiovascular: Lag 0-1: 1.4% (−0.4, 3.3) Respiratory: Lag 0-1: 3.5% (1.0, 6.0)
Biggeri et al. (2005) 8 Italian cities Period variable between 1990-1999	All cause; respiratory; cardiovascular	24-h avg ranged from 2 ppb (Verona) to 14 ppb (Milan)	O_3, NO_2, CO, PM_{10}	0-1	Poisson GLM. Time-series study.	All cause: 4.1% (1.1, 7.3) Respiratory: 7.4% (−3.6, 19.6) Cardiovascular: 4.9% (0.4, 9.7)

TABLE AX5.5 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE ON MORTALITY

Reference, Study Location, and Period	Outcome Measure	Mean SO_2 Levels	Copollutants Considered	Lag Structure Reported	Method/Design	Effect Estimates* % increase in risk (95% CI)
EUROPE (cont'd)						
Hoek et al. (2000; reanalysis Hoek, 2003) The Netherlands: Entire country, four urban areas 1986-1994	All cause; COPD; pneumonia; cardiovascular	24-h avg median: 3.5 ppb in the Netherlands; 5.6 ppb in the four major cities	PM_{10}, BS, SO_4^{2-}, NO_3^-, O_3, NO_2, CO; 2-pollutant models	1, 0-6	Poisson GAM, reanalyzed with stringent convergence criteria; Poisson GLM. Time-series study.	Poisson GLM: All cause: Lag 1: 1.3% (0.7, 1.9) Lag 0-6: 1.8% (0.9, 2.7) With BS: 1.1% (−0.3, 2.4) Cardiovascular: Lag 0-6: 2.7% (1.3, 4.1) COPD: Lag 0-6: 3.6% (−0.3, 7.7) Pneumonia: Lag 0-6: 6.6% (1.2, 12.2)
Katsouyanni et al. (1997) 12 European cities Study periods vary by city, ranging from 1977 to 1992	All cause	24-h avg median of the median across the cities was 14 ppb, ranging from 5 ppb (Bratislava) to 26 ppb (Cracow)	BS, PM_{10}	"Best" lag variable across cities from 0 to 3	Poisson autoregressive. Time-series study.	All cities: 1.1% (0.9, 1.4) Western cities: 2.0% (1.2, 2.8) Central eastern cities: 0.5% (−0.4, 1.4)
Le Tertre et al. (2002) Bordeaux , Le Havre, Lille, Lyon, Marseille, Paris, Rouen, Strasbourg, France Study periods vary by city, ranging from 1990-1995	All cause; respiratory; cardiovascular	24-h avg ranged from 3 ppb (Bordeaux) to 9 ppb (Rouen)	BS, O_3, NO_2	0-1	Poisson GAM with default convergence criteria. Time-series study.	8-city pooled estimates: All cause: 2.0% (1.2, 2.9) Respiratory: 3.2% (0.1, 6.3) Cardiovascular: 3.0% (1.5, 4.5)

TABLE AX5.5 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE ON MORTALITY

Reference, Study Location, and Period	Outcome Measure	Mean SO_2 Levels	Copollutants Considered	Lag Structure Reported	Method/Design	Effect Estimates* % increase in risk (95% CI)
EUROPE (cont'd)						
Peters et al. (2000b) NE Bavaria, Germany 1982-1994 Coal basin in Czech Republic 1993-1994	All cause; respiratory; cardiovascular; cancer	24-h avg: Czech Republic: 35 ppb Bavaria, Germany: 14 ppb	TSP, PM_{10}, O_3, NO_2, CO	0, 1, 2, 3	Poisson GLM. Time-series study.	Czech Republic: All cause: Lag 1: 0.8% (−0.2, 1.8) Bavaria, Germany: All cause: Lag 1: 0.3% (−0.3, 0.9)
Saez et al. (2002) Seven Spanish cities Variable study periods between 1991 and 1996	All cause; respiratory; cardiovascular	Values for SO_2 not reported.	O_3, PM, NO_2, CO	0-3	Poisson GAM with default convergence criteria. Time-series study.	Risk estimates for SO_2 was not reported. Including SO_2 in regression model did not appear to reduce NO_2 risk estimates.
Zmirou et al. (1998) 10 European cities Study periods vary by city, ranging from 1985-1992	Respiratory; cardiovascular	24-h avg: Cold season: Ranged from 12 ppb (London) to 87 ppb (Milan) ppb Warm season: Ranged from 5 ppb (Bratislava) to 21 ppb (Cracow) in warm season	BS, TSP, NO_2, O_3	0, 1, 2, 3, 0-1, 0-2, 0-3 (best lag selected for each city)	Poisson GLM. Time-series study.	Western cities: Respiratory: 2.8% (1.7, 4.0) Cardiovascular: 2.3% (0.9, 3.7) Central eastern cities: Respiratory: 0.6% (−1.1, 2.3) Cardiovascular: 0.6% (0.0, 1.1)
Zeghnoun et al. (2001) Rouen and Le Havre, France 1990-1995	All cause; respiratory; cardiovascular	24-h avg: Rouen: 10 ppb Le Havre: 12 ppb	NO_2, BS, PM_{13}, O_3	0, 1, 2, 3, 0-3,	Poisson GAM with default convergence criteria. Time-series study.	All cause: Rouen: Lag 1: 2.3% (−1.1, 5.9) Le Havre: Lag 1: 1.1% (−0.3, 2.5)

TABLE AX5.5 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE ON MORTALITY

Reference, Study Location, and Period	Outcome Measure	Mean SO_2 Levels	Copollutants Considered	Lag Structure Reported	Method/Design	Effect Estimates* % increase in risk (95% CI)
EUROPE (cont'd)						
Anderson et al. (1996) London, England 1987-1992	All cause; respiratory; cardiovascular	24-h avg: 11 ppb	BS, O_3, NO_2; 2-pollutant models	1	Poisson GLM. Time-series study.	All cause: 1.0% (0.0, 2.0) Respiratory: 1.7% (−1.3, 4.9) Cardiovascular: 0.2% (−1.4, 1.8)
Anderson et al. (2001) West Midlands region, England 1994-1996	All cause; respiratory; cardiovascular	24-h avg: 7 ppb	PM_{10}, $PM_{2.5}$, $PM_{10-2.5}$, BS, SO_4^{2-}, O_3, NO_2, CO	0-1	Poisson GAM with default convergence criteria. Time-series study.	All cause: −0.2% (−2.5, 2.1) Respiratory: −2.2% (−7.4, 3.2) Cardiovascular: −0.2% (−3.5, 3.1)
Bremner et al. (1999) London, England 1992-1994	All cause; respiratory; cardiovascular; all cancer; all others; all ages; age specific (0-64, 65+, 65-74, 75+ yrs)	24-h avg: 7 ppb	BS, PM_{10}, O_3, NO_2, CO; 2-pollutant models	Selected best from 0, 1, 2, 3, (all cause); 0, 1, 2, 3, 0-1, 0-2, 0-3 (respiratory, cardiovascular)	Poisson GLM. Time-series study.	All cause: Lag 1: 1.6% (−0.5, 3.7) Respiratory: Lag 2: 4.8% (−0.2, 10.0) Cardiovascular Lag 1: 1.3% (−1.7, 4.3)
Clancy et al. (2002) Dublin, Ireland 1984-1996	All cause, cardiovascular, and respiratory	24-h avg: 1984-1990: 11.7 ppb 1990-1996: 7.7 ppb	BS	NA	Comparing standardized mortality rates for 72 mos before and after the ban on coal sales in Sept 1990.	BS mean declined by a larger percentage (70%) than SO_2 (34%) between the two periods. All cause death rates reduced by 5.7% (4, 7); respiratory deaths by 15.5% (12, 19); cardiovascular deaths by 10.3% (8, 13).

TABLE AX5.5 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE ON MORTALITY

Reference, Study Location, and Period	Outcome Measure	Mean SO_2 Levels	Copollutants Considered	Lag Structure Reported	Method/Design	Effect Estimates* % increase in risk (95% CI)
EUROPE (cont'd)						
Dab et al. (1996) Paris, France 1987-1992	Respiratory	24-h avg: 10 ppb 1-h max: 21 ppb	BS, PM_{13}, O_3, NO_2, CO	1	Poisson autoregressive. Time-series study.	Lag 1: 2.3% (−0.9, 5.5)
Díaz et al. (1999) Madrid, Spain 1990-1992	All cause; respiratory; cardiovascular	24-h avg Levels not reported.	TSP, O_3, NO_2, CO	1	Autoregressive OLS regression. Time-series study.	Only significant regression coefficients were shown, but description of the table was not clear enough to derive risk estimates.
Fischer et al. (2003) The Netherlands, 1986-1994	All-cause, cardiovascular, COPD, and pneumonia in age groups <45, 45-64, 65-74, 75+	24-h avg median: 3.5 ppb	PM_{10}, BS, O_3, NO_2, CO	0-6	Poisson GAM with default convergence criteria. Time-series study.	Cardiovascular: Age <45 yrs: 4.3% (−4.6, 13.9) Age 45-64 yrs: −0.5% (−3.6, 2.7) Age 65-74 yrs: 1.6% (−0.8, 4.2); Age 75+ yrs: 2.8% (1.3, 4.3)

TABLE AX5.5 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE ON MORTALITY

Reference, Study Location, and Period	Outcome Measure	Mean SO_2 Levels	Copollutants Considered	Lag Structure Reported	Method/Design	Effect Estimates* % increase in risk (95% CI)
EUROPE (cont'd)						
Garcia-Aymerich et al. (2000) Barcelona, Spain 1985-1989	All cause; respiratory; cardiovascular; general population; patients with COPD	Levels not reported.	BS, O_3, NO_2	Selected best averaged lag	Poisson GLM. Time-series study.	All cause: General population: Lag 0-3: 4.4% (2.3, 6.5) COPD patients: Lag 0-2: 2.6% (−5.0, 10.7) Respiratory: General population: Lag 0-1: 3.5% (−0.6, 7.8) COPD patients: Lag 0-2: 2.3% (−8.9, 15.0) Cardiovascular: General population: Lag 0-3: 5.1% (2.3, 8.0) COPD patients: Lag 0-2: 2.0% (−11.5, 17.5)
Hoek et al. (2002) Rotterdam, the Netherlands 1983-1991	All cause	24-h avg median: 7.7 ppb	TSP, BS, Fe, O_3, CO	1	Poisson GAM with default convergence criteria. Time-series study.	Single pollutant: \1.5% (0.0, 3.0) With TSP and O_3: 0.5% (−1.2, 2.3)

TABLE AX5.5 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE ON MORTALITY

Reference, Study Location, and Period	Outcome Measure	Mean SO_2 Levels	Copollutants Considered	Lag Structure Reported	Method/Design	Effect Estimates* % increase in risk (95% CI)
EUROPE (cont'd)						
Hoek et al. (2001; reanalysis Hoek, 2003) The Netherlands 1986-1994	Total cardiovascular; myocardial infarction; arrhythmia; heart failure; cerebrovascular; thrombosis-related	24-h avg median: 3.5 ppb in the Netherlands; 5.6 ppb in the four major cities	PM_{10}, O_3, NO_2, CO	0-6	Poisson GAM, reanalyzed with stringent convergence criteria; Poisson GLM. Time-series study.	Poisson GLM: Total cardiovascular: 2.7% (1.3, 4.1) Myocardial infarction: 0.8% (−1.2, 2.8) Arrhythmia: 2.3% (−3.9, 8.8) Heart failure: 7.1% (2.6, 11.7) Cerebrovascular: 4.4% (1.4, 7.5) Thrombosis-related: 9.6% (3.1, 16.6)
Kotesovec et al. (2000) Northern Bohemia, Czech Republic 1982-1994	All cause, cardiovascular (only age = <65 presented), cancer	24-h avg: 34.9 ppb	TSP	0, 1, 2, 3, 4, 5, 6, 0-6	Poisson GLM, time-series study	All cause: Lag 1: 0.1% (−0.1, 0.4)
Michelozzi et al. (1998) Rome, Italy 1992-1995	All-cause	24-h avg: 5.7 ppb	PM_{13}, NO_2, O_3, CO	0, 1, 2, 3, 4	Poisson GAM with default convergence criteria. Time-series study.	Lag 1: −2.0% (−4.4, 0.5); (negative estimates at all lags examined)

TABLE AX5.5 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE ON MORTALITY

Reference, Study Location, and Period	Outcome Measure	Mean SO_2 Levels	Copollutants Considered	Lag Structure Reported	Method/Design	Effect Estimates* % increase in risk (95% CI)
EUROPE (cont'd)						
Pönkä et al. (1998) Helsinki, Finland 1987-1993	All cause; cardiovascular; age <65 yrs, age 65+ yrs	24-h avg median: 3.5 ppb	TSP, PM_{10}, O_3, NO_2	0, 1, 2, 3, 4, 5, 6, 7	Poisson GLM. Time-series study.	No risk estimate presented for SO_2. PM_{10} and O_3 were reported to have stronger associations.
Prescott et al. (1998) Edinburgh, Scotland 1992-1995	All cause; respiratory; cardiovascular; all ages; age <65 yrs; age 65+ yrs	24-h avg: 1981-1995: 15 ppb 1992-1995: 8 ppb	BS, PM_{10}, O_3, NO_2, CO; 2-pollutant models	0	Poisson GLM. Time-series study.	Results presented as figures only. Essentially no associations in all categories. Very wide confidence intervals.
Rahlenbeck and Kahl (1996) East Berlin, Germany 1981-1989	All cause	24-h avg: 61.9 ppb	"SP" (beta absorption)	0, 1, 2, 3, 4, 5	OLS, with log of SO_2, Time-series study.	Single pollutant: Lag 1: 4.4% (0, 8.7); With SP: Lag 1: 2.9% (−2.7, 8.5)
Roemer and van Wijinen (2001) Amsterdam, the Netherlands 1987-1998	All cause	24-h avg: Background sites: 3.1 ppb Traffic sites: 4.2 ppb	BS, PM_{10}, O_3, NO_2, CO	1, 2, 0-6	Poisson GAM with default convergence criteria (only one smoother). Time-series study.	Total population using background sites: Lag 1: 2.6% (−0.6, 5.8) Traffic population using background sites: Lag 1: 0.6% (−6.9, 8.6) Total population using traffic sites: Lag 1: 2.4% (−0.3, 5.1)
Saez et al. (1999) Barcelona, Spain 1986-1989	Asthma mortality; age 2-45 yrs	Levels not reported.	BS, O_3, NO_2,	0-1	Poisson with GEE. Time-series study.	RR = 1.9 (0.7, 4.4)

TABLE AX5.5 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE ON MORTALITY

Reference, Study Location, and Period	Outcome Measure	Mean SO_2 Levels	Copollutants Considered	Lag Structure Reported	Method/Design	Effect Estimates* % increase in risk (95% CI)
EUROPE (cont'd)						
Spix and Wichman (1996) Koln, Germany 1977-1985	All-cause	24-h avg: 15 ppb 1-h max: 32 ppb	TSP, PM_7, NO_2	0, 1, 0-3	Poisson GLM. Time-series study.	Lag 1: 0.8% (0.2, 1.4)
Sunyer et al. (2002) Barcelona, Spain 1986-1995	All cause, respiratory, and cardiovascular mortality in a cohort of patients with severe asthma	24-h avg median: 6.6 ppb	PM_{10}, BS, NO_2, O_3, CO, pollen	0-2	Conditional logistic (case-crossover)	Odds ratio: Patients with 1 asthma admission: All cause: 14.8% (−19.8, 64.4) Patients with more than 1 asthma adm: All cause: 50.4% (−48.6, 340.4) Patients with more than 1 asthma or COPDadm: All cause: 20.2% (−17.5, 75.0) NO_2 and O_3 were more strongly associated with outcomes than SO_2.

TABLE AX5.5 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE ON MORTALITY

Reference, Study Location, and Period	Outcome Measure	Mean SO_2 Levels	Copollutants Considered	Lag Structure Reported	Method/Design	Effect Estimates* % increase in risk (95% CI)
EUROPE (cont'd)						
Sunyer et al. (1996) Barcelona, Spain 1985-1991	All cause; respiratory; cardiovascular; all ages; age 70+ yrs	24-h avg median: Summer: 13 ppb Winter: 16 ppb	BS, NO_2, O_3	Selected best single-day lag	Autoregressive Poisson. Time-series study.	All yr, all ages: All cause: Lag 1: 3.5% (1.9, 5.1) Respiratory: Lag 0: 3.5% (−0.2, 5.0) Cardiovascular: Lag 1: 2.2% (0.5, 3.9)
Verhoeff et al. (1996) Amsterdam, the Netherlands 1986-1992	All cause; all ages; age 65+ yrs	24-h avg: 4.5 ppb	BS, PM_{10}, O_3, CO; multipollutant models	0, 1, 2	Poisson GLM. Time-series study.	Single pollutant: Lag 1: 1.4% (−1.4, 4.2) With BS: −3.7% (−8.1, 0.9)
Zmirou et al. (1996) Lyon, France 1985-1990	All cause; respiratory; cardiovascular; digestive	24-h avg: 16 ppb	PM_{13}, NO_2, O_3	Selected best from 0, 1, 2, 3	Poisson GLM. Time-series study.	All cause: Lag 0: 3.4% (1.4, 5.4) Respiratory: Lag 3: 2.8% (0.9, 4.8) Cardiovascular: Lag 0-3: 4.5% (2.0, 7.0)

TABLE AX5.5 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE ON MORTALITY

Reference, Study Location, and Period	Outcome Measure	Mean SO_2 Levels	Copollutants Considered	Lag Structure Reported	Method/Design	Effect Estimates* % increase in risk (95% CI)
LATIN AMERICA						
Borja-Aburto et al. (1998) SW Mexico City 1993-1995	All cause; respiratory; cardiovascular; other; all ages; age >65 yrs	24-h avg: 5.6 ppb	$PM_{2.5}$, O_3, NO_2; 2-pollutant models	0, 1, 2, 3, 4, 5, and multiday avg.	Poisson GAM with default convergence criteria (only one smoother). Time-series study.	SO_2 risk estimates not reported. $PM_{2.5}$ and O_3 were associated with mortality.
Borja-Aburto et al. (1997) Mexico City 1990-1992	All cause; respiratory; cardiovascular; all ages; age <5 yrs; age >65 yrs	24-h avg median: 5.3 ppb	TSP, O_3 CO; 2-pollutant models	0, 1, 2	Poisson iteratively weighted and filtered least-squares method. Time-series study.	All-cause: Lag 0: 0.2% (−1.1, 1.5) Cardiovascular: Lag 0: 0.7% (−1.6, 3.0) Respiratory: Lag 0: −1.0% (−5.0, 3.2)

TABLE AX5.5 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE ON MORTALITY

Reference, Study Location, and Period	Outcome Measure	Mean SO_2 Levels	Copollutants Considered	Lag Structure Reported	Method/Design	Effect Estimates* % increase in risk (95% CI)
LATIN AMERICA (cont'd)						
Cakmak et al. (2007) 7 Chilean urban centers 1997-2003	All cause; respiratory; cardiovascular; all ages; age <65 yrs; age 65-74 yrs; age 75-84 yrs; age 85+ yrs	24-h avg ranged from 9.12 ppb (Las Condes) to 64.06 ppb (Independencia) Population-weighted avg concentration: 14.08 ppb	PM_{10}, O_3, CO	0, 1, 2, 3, 4, 5, 0-5	Poisson GLM with random effects between cities. Time-series study.	All cause: All ages: Single pollutant: Lag 1: 4.0% (2.4, 5.6) Lag 0-5: 6.5% (4.5, 8.5) Multipollutant: Lag 1: 3.2% (1.3, 5.1) <65 yrs: Lag 0-5: 3.0% (0.6, 5.5) 65-74 yrs: Lag 0-5: 5.1% (1.2, 9.1) 75-84 yrs: Lag 0-5: 7.8% (4.1, 11.6) 85+ yrs: 7.8% (4.2, 11.5) Warm season: Lag 0-5: 7.2% (4.1, 10.3) Cool season: Lag 0-5: 3.0% (-0.4, 6.5)
Cifuentes et al. (2000) Santiago, Chile 1988-1966	All cause	24-h avg: 18.1 ppb	$PM_{2.5}$, $PM_{10-2.5}$, CO, NO_2, O_3	1-2	Poisson GAM with default convergence criteria; Poisson GLM. Time-series study.	Poisson GLM: Single pollutant: Lag 1-2: 0.2% (−0.9, 1.3) With other pollutants: Lag 1-2: −0.6% (−1.7, 0.5)

TABLE AX5.5 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE ON MORTALITY

Reference, Study Location, and Period	Outcome Measure	Mean SO_2 Levels	Copollutants Considered	Lag Structure Reported	Method/Design	Effect Estimates* % increase in risk (95% CI)
LATIN AMERICA (cont'd)						
Conceição et al. (2001) São Paulo, Brazil 1994-1997	Child mortality (age under 5 yrs)	24-h avg: 7.4 ppb	PM_{10}, CO, O_3	2	Poisson GAM with default convergence criteria. Time-series study.	Single pollutant: Lag 2: 17.0% (7.0, 28.0); With all other pollutants: Lag 2: 13.7% (−1.1, 30.8)
Loomis et al. (1999) Mexico City 1993-1995	Infant mortality	24-h avg: 5.6 ppb	$PM_{2.5}$, O_3	0, 1, 2, 3, 4, 5, 3-5	Poisson GAM with default convergence criteria. Time-series study.	SO_2 risk estimates not reported. $PM_{2.5}$ and O_3 were associated with mortality.
Ostro et al. (1996) Santiago, Chile 1989-1991	All cause	1-h max: 60 ppb	PM_{10}, O_3, NO_2; 2-pollutant models	0	OLS, Poisson. Time-series study.	Lag 0: 0.7% (−0.3, 1.7)
Pereira et al. (1998) São Paulo, Brazil 1991-1992	Intrauterine mortality	24-h avg: 6.6 ppb	PM_{10}, O_3, NO_2, CO	0	Poisson GLM. Time-series study.	Single-pollutant model: 11.5% (−0.3, 24.7) With other pollutants: 8.6% (−8.7, 29.3)
Saldiva et al. (1994) São Paulo, Brazil 1990-1991	Respiratory; age <5 yrs	24-h avg: 6.0 ppb	PM_{10}, O_3, NO_2, CO; multipollutant models	0-2	OLS of raw or transformed data. Time-series study.	−1.0% (−47.1, 45.1)
Saldiva et al. (1995) São Paulo, Brazil 1990-1991	All cause; age 65+ yrs	24-h avg: 6.5 ppb	PM_{10}, O_3, NO_2, CO; 2-pollutant models	0-1	OLS; Poisson with GEE. Time-series study.	Single pollutant: 8.5% (1.3, 15.6) With other pollutants: −3.1% (−13.0, 6.9)

TABLE AX5.5 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE ON MORTALITY

Reference, Study Location, and Period	Outcome Measure	Mean SO_2 Levels	Copollutants Considered	Lag Structure Reported	Method/Design	Effect Estimates* % increase in risk (95% CI)
ASIA						
Lee et al. (2000) 7 Korean cities 1991-1997	All cause	24-h avg SO_2 ranged from 12.1 ppb (Kwangju) to 31.4 ppb (Taegu)	TSP, NO_2, O_3, CO	0-1	Poisson GAM with default convergence criteria. Time-series study.	Single pollutant: Lag 0-1: 0.6% (0.3, 0.8) Multipollutant: Lag 0-1: 0.6% (0.2, 0.9)
Lee et al. (1999) Seoul and Ulsan, Korea 1991-1995	All cause	1-h max: Seoul: 26 ppb Ulsan: 31 ppb	TSP, O_3	0-2	Poisson with GEE. Time-series study.	Seoul: 1.5% (1.1, 1.9) Ulsan: 1.0% (−0.2, 2.2)
Ha et al. (2003) Seoul, Korea 1995-1999	All cause; respiratory; postneonatal (1 mo to 1 yr); age 2-64 yrs; age 65+	24-h avg: 11.1 ppb	PM_{10}, O_3, NO_2, CO	0	Poisson GAM with default convergence criteria. Time-series study.	All cause: Postneonates: 11.3% (4.0, 19.1) Age 65+ yrs: 3.2% (3.1, 3.3)
Hong et al. (2002) Seoul, Korea 1995-1998	Acute stroke mortality	24-h avg: 12.1 ppb	PM_{10}, O_3, NO_2, CO	2	Poisson GAM with default convergence criteria. Time-series study.	5.2% (1.4, 9.0)
Kwon et al. (2001) Seoul, Korea 1994-1998	Mortality in a cohort of patients with congestive heart failure	24-h avg: 13.4 ppb	PM_{10}, O_3, NO_2, CO	0	Poisson GAM with default convergence criteria; case-crossover analysis using conditional logistic regression.	Odds ratio in general population: 1.0% (−0.1, 2.1) Congestive heart failure cohort: 6.9% (−3.4, 18.3)

TABLE AX5.5 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE ON MORTALITY

Reference, Study Location, and Period	Outcome Measure	Mean SO_2 Levels	Copollutants Considered	Lag Structure Reported	Method/Design	Effect Estimates* % increase in risk (95% CI)
ASIA (cont'd)						
Lee and Schwartz (1999) Seoul, Korea 1991-1995	All cause	1-h max: 26 ppb	TSP, O_3	0-2	Conditional logistic regression. Case-crossover with bidirectional control sampling.	Two controls, ± 1 wk: 0.3% (−0.5, 1.0) Four controls, ± 2 wks: 1.0% (0.3, 1.6)
Tsai et al. (2003b) Kaohsiung, Taiwan 1994-2000	All cause; respiratory; cardiovascular; tropical area	24-h avg: 11.2 ppb	PM_{10}, NO_2, O_3, CO	0-2	Conditional logistic regression. Case-crossover analysis.	Odds ratios: All cause: 1.1% (−4.4, 6.8) Respiratory: 3.5% (−17.6, 29.9) Cardiovascular: 2.4% (−9.1, 15.4)
Venners et al. (2003) Chonqing, China 1995	All cause, cardiovascular, respiratory, cancer, and other	24-h avg: 74.5 ppb	$PM_{2.5}$	0, 1, 2, 3, 4, 5	Poisson GLM, time-series study	All cause: Lag 2: 1.1% (−0.1, 2.4) Cardiovascular: Lag 2: 2.8% (0.4, 5.2) Respiratory: Lag 2: 3.0% (0.4, 5.7)
Wong et al. (2002b) Hong Kong 1995-1998	Respiratory; cardiovascular; COPD; pneumonia and influenza; ischemic heart dis.; cerebrovascular	24-h avg: 29 ppb	PM_{10}, O_3, NO_2; 2-pollutant models	0, 1, 2, 0-1, 0-2	Poisson GLM. Time-series study.	Respiratory: Lag 0-1: 2.6% (0.2, 5.1) Cardiovascular: Lag 0-1: 1.2% (−1.0, 3.5)

TABLE AX5.5 (cont'd). ASSOCIATIONS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE ON MORTALITY

Reference, Study Location, and Period	Outcome Measure	Mean SO_2 Levels	Copollutants Considered	Lag Structure Reported	Method/Design	Effect Estimates* % increase in risk (95% CI)
ASIA (cont'd)						
Wong et al. (2001b) Hong Kong 1995-1997	All cause; respiratory; cardiovascular	24-h avg: Warm season: 6.4 ppb Cool season: 6.0 ppb	PM_{10}, O_3, NO_2; 2-pollutant models	0, 1, 2	Poisson GAM with default convergence criteria. Time-series study.	All cause: Lag 1: 3.2% (1.1, 5.3) Respiratory: Lag 0: 5.3% (2.2, 8.6) Cardiovascular: Lag 1: 4.3% (1.1, 7.5)
Yang et al. (2004b) Taipei, Taiwan 1994-1998	All cause; respiratory; cardiovascular; subtropical area	24-h avg: 5.5 ppb	PM_{10}, NO_2, O_3, CO	0-2	Conditional logistic regression. Case-crossover analysis.	Odds ratios: All cause: −0.5% (−7.0, 6.6); Respiratory: −1.8% (−23.1, 25.3); Cardiovascular: −3.4% (−15.2, 10.0)
AUSTRALIA						
Simpson et al. (1997) Brisbane, Australia 1987-1993	All cause; respiratory; cardiovascular	24-h avg: 4.2 ppb 1-h max: 9.6 ppb	PM_{10}, bsp, O_3, NO_2, CO	0	Autoregressive Poisson with GEE. Time-series study.	All cause: All yr: Lag 0: −2.8% (−2.7, 8.6) Summer: Lag 0: 2.8% (−8.3, 15.2) Winter: Lag 0: 2.8% (−3.9, 9.8)

* Effect estimates standardized to 10 ppb incremental change in 24-h avg SO_2 or 40 ppb incremental change in 1-h max SO_2.

TABLE AX5.6. ASSOCIATIONS OF LONG-TERM EXPOSURE TO SULFUR DIOXIDE WITH RESPIRATORY MORBIDITY

Reference, Study Location, and Period	Mean SO_2 Levels	Study Description	Results and Comments
UNITED STATES and CANADA			
Dockery et al. (1996) 18 sites in U.S. 6 sites in Canada	Sulfur Dioxide mean 4.8 ppm SD 3.5 Range 0.2, 12.9	Study of the respiratory health effects of acid aerosols in 13,369 white children aged 8 to 12 yrs old from 24 communities in the United States and Canada between 1988 and 1991. Information was gathered by questionnaire and a pulmonary function.	With the exception of the gaseous acids (nitrous and nitric acid), none of the particulate or gaseous pollutants, including SO_2, were associated with increased asthma or any asthmatic symptoms. Stronger associations with particulate pollutants were observed for bronchitis and bronchitic symptoms. Odds Ratio (95% CI) for 12.7 ppb range of SO_2 pollution Asthma 1.05 (057, 1.93) Attacks of Wheeze 1.07 (0.75, 1.55) Persistent Wheeze 1.19 (0.80, 1.79) Any asthmatic symptoms 1.16 (0.80, 1.68) Bronchitis 1.56 (0.95, 2.56) Chronic cough 1.02 (0.66, 1.58) Chronic phlegm 1.55 (1.01, 2.37) Any Bronchitic symptoms 1.29 (0.98, 1.71)

TABLE AX5.6 (cont'd). ASSOCIATIONS OF LONG-TERM EXPOSURE TO SULFUR DIOXIDE WITH RESPIRATORY MORBIDITY

Reference, Study Location, and Period	Mean SO_2 Levels	Study Description	Results and Comments
UNITED STATES and CANADA (cont'd)			
Dockery et al. (1989) Watertown, MA; St. Louis, MO; Portage, WI; Kingston-Harriman, TN; Steubenville, OH; Topeka, KS 1980-1981 school yr	Daily mean concentrations, averaging hourly concentrations for each day with at least 18 hourly values Portage: 4.2 ppb Topeka: 3.5 Watertown: 10.5 Kingston: 6.5 St. Louis: 13.5 Steubenville: 27.8	Cross-sectional assessment of the association between air pollution and chronic respiratory health of 5,422 (10-12 yrs) white children examined in the 1980-1981 school yr. Children were part of the cohort of children in the Six Cities Study of Air pollution and Health. Symptoms were analyzed using logistic regression that included sex, age, indicators of parental education, maternal smoking, indicator for gas stove, and an indicator for city. Respiratory symptoms investigated were bronchitis, chronic cough, chest illness, persistent wheeze, asthma. The logarithm of pulmonary function was fitted to a multiple linear regression model that included sex, sex-specific log of height, age, indicators of parental education, maternal smoking, a gas stove indicator, and city indicator. Annual means of the 24 h avg air pollutant concentration for the 12 mos preceding the examination of each child was calculated for each city.	No significant associations between SO_2 and any pulmonary function measurements. No significant association between SO_2 and symptoms. Relative odds and 95% CI between most/least polluted cities: Bronchitis: 1.5 (0.4, 5.8) Chronic cough: 1.8 (0.3, 12.5) Chest illness: 1.5 (0.4, 5.9) Persistent wheeze: 0.9 (0.4, 1.9) Asthma: 0.6 (0.3, 1.2) Reference symptoms: Hay fever: 0.6 (0.2, 1.7) Ear ache: 1.2 (0.3, 5.3) Nonrespiratory illness: 1.0 (0.6, 1.5) Analysis stratified by asthma or persistent wheeze bronchitis No wheeze or asthma 1.5 (0.5, 4.3) Yes wheeze or asthma 2.0 (0.3, 14.3) Chronic cough No wheeze or asthma 2.4 (0.5, 11.7) Yes wheeze or asthma 1.9 (0.1, 44.1) Chest illness No wheeze or asthma 1.5 (0.4, 5.6) Yes wheeze or asthma 1.9 (0.3, 13.0)

TABLE AX5.6 (cont'd). ASSOCIATIONS OF LONG-TERM EXPOSURE TO SULFUR DIOXIDE WITH RESPIRATORY MORBIDITY

Reference, Study Location, and Period	Mean SO_2 Levels	Study Description	Results and Comments
UNITED STATES and CANADA (cont'd)			
Euler et al. (1987) California, USA	None provided	Cross-sectional study of 7,445 (25 yrs or older) Seventh-Day Adventists who lived in their 1977 residential areas (Los Angeles and it border counties, San Francisco, and San Diego) for at least 10 yrs to determine the effect of long-term cumulative exposure to ambient levels of TSP and SO_2 on COPD symptoms. Study population is subgroup of NCI-funded ASHMOG study that enrolled 36,805 Seventh-Day Adventists in 1974. Each participant's cumulative exposure to the pollutant exceeding 4 different threshold levels were estimated using moly residence ZIP code histories and interpolated dosages from state monitoring stations. Participants completed a questionnaire on respiratory symptoms, smoking history, occupational history, and residence history.	Study reported that SO_2 exposure was not associated with symptoms of COPD until concentrations exceeded 4 ppm. The correlation coefficient of SO_2 (above 4 ppm) with TSP (above 200 $\mu g/m^3$) the highest exposure levels for these two pollutants was 0.30; thus, the authors believed that it was possible to separate the effects of SO_2 from TSP. Multiple regressions used in the analysis. No significant effect at exposures levels below 4 ppm or above 8 ppm. Relative risk estimate (based on 1,003 cases) SO_2 exposure above 2 ppm during 11 yrs of study 2000 h/yr: 1.09 1000 h/yr : 1.04 500 h/yr: 1.03 SO_2 exposure above 4 ppm 500 h/yr : 1.18 250 h/yr: 1.09 100 h/yr: 1.03 SO_2 above 8 ppm 60 h/yr: 1.07 30 h/yr: 1.03 15 h/yr: 1.02 SO_2 above 14 ppm 10 h/yr: 1.03 5 h/yr: 1.01 1 h/yr: 1.00

TABLE AX5.6 (cont'd). ASSOCIATIONS OF LONG-TERM EXPOSURE TO SULFUR DIOXIDE WITH RESPIRATORY MORBIDITY

Reference, Study Location, and Period	Mean SO_2 Levels	Study Description	Results and Comments
UNITED STATES and CANADA (cont'd)			
Goss et al. (2004) U.S. nationwide 1999-2000	Mean (SD): 4.91 (2.6) ppb Median: 4.3 ppb IQR: 2.7-5.9 ppb	Cohort study of 18,491 cystic fibrosis patients over 6 yrs of age who were enrolled in the Cystic Fibrosis Foundation National Patient Registry in 1999 and 2000. Mean age of patients was 18.4 yrs; 92% had pancreatic insufficiency. Air pollution from the Aerometric Information Retrieval System linked with patient's home ZIP code. Air pollutants studied included O_3, NO_2, SO_2, CO, PM_{10}, and $PM_{2.5}$. Health endpoints of interest were pulmonary exacerbations, lung function, and mortality. However, study did not have enough power to assess the outcome of mortality. Logistic regression and polytomous regression models that adjusted for sex, age, weight, race, airway colonization, pancreatic function, and insurance status were used.	With the single-pollutant model, no significant association between SO_2 and pulmonary exacerbations. Odds ratio per 10 ppb increase in SO_2: 0.83 (95% CI: 0.71, 1.01), p = 0.068 No clear association between pulmonary function and SO_2. No effect estimates provided.
McDonnell et al. (1999) California, U.S. 1973-1992	Mean: SO_2 6.8 µg/m^3 Range: 0.0-10.2 µg/m^3 Correlation coefficient r = 0.25 with O_3	Prospective study (over 15 yrs) of 3,091 nonsmokers aged 27-87 yrs that evaluated the association between long-term ambient O_3 exposure and the development of adult-onset asthma. Cohort consisted of nonsmoking, non-Hispanic white, California Seventh Day Adventists who were enrolled in 1977 in the AHSMOG study. Logistic regression used to assess the association between the 1973-1992 mean 8-h avg ambient O_3 concentration and the 1977-1992 incidence of doctor-told asthma. Levels of PM_{10}, NO_2, and SO_4 were measured but no effect estimates were given.	No significant positive association between SO_2 and asthma for males or females. Addition of a second pollutant to the O_3 model for the male subjects, did not result in a decrease of more than 10% in the magnitude of the regression coefficient for O_3, and for the females addition did not cause the coefficient for O_3 to become significantly positive

TABLE AX5.6 (cont'd). ASSOCIATIONS OF LONG-TERM EXPOSURE TO SULFUR DIOXIDE WITH RESPIRATORY MORBIDITY

Reference, Study Location, and Period	Mean SO_2 Levels	Study Description	Results and Comments
EUROPE			
Ackermann-Liebrich et al. (1997) 8 communities in Switzerland Aarau, Basel, Davos, Geneva, Lugano, Montana, Payerne, and Wald 1991-1993	Mean SO_2 in 1991 (µg/m^3) Mean: 11.7 SD = 7.1 Range: 2.5, 25.5	Cross-sectional population based study of 9,651 adults (18-60 yrs) in 8 areas in Switzerland (SAPALDIA), to evaluate the effect of long-term exposure of air pollutants on lung function. Examined the effects of SO_2, NO_2, O_3, TSP, and PM_{10}. Participants were given a medical exam that included questionnaire data, lung function tests, skin prick testing, and end-expiratory CO concentration. Subjects had to reside in the area for at least 3 yrs to be in the study.	Mean values of SO_2, PM_{10}, and NO_2 were significantly associated with reduction in pulmonary function. SO_2 was correlated with PM_{30} (r = 0.78), PM_{10} (r = 0.93) and NO_2 (r = 0.86). Authors stated that the association with SO_2 disappeared after controlling for PM_{10} but no data was shown. Regression coefficients and 95% CI in healthy never smokers (per10 µg/m^3 increase in annual avg SO_2) FVC: −0.0325 (−0.0390, −0.0260) FEV_1: −0.0125 (−0.0192,−0.0058)
Braun-Fahrlander et al. (1997) 10 communities in Switzerland Anieres, Bern, Biel, Geneva, Langnau, Lugano, Montana, Payerne, Rheintal, Zurich 1992-1993	Annual mean SO_2 (µg/m^3) Lugano: 23 Geneva: 13 Zurich: 16 Bern: 11 Anieres: 4 Biel: 15 Rheintal: 8 Langnau: NA Payerne: 3 Montan: 2	Cross-sectional study of 4,470 children (6-15 yrs) living in 10 different communities in Switzerland to determine the effects of long term exposure to PM_{10}, NO_2, SO_2, and O_3 on respiratory and allergic symptoms and illnesses. Part of the Swiss Study on Childhood Allergy and Respiratory Symptoms with Respect to Air Pollution (SCARPOL).	This study reported that the annual mean SO_2, PM_{10}, and NO_2 were positively and significantly associated with prevalence rates of chronic cough, nocturnal dry cough, and bronchitis and conjunctivitis symptoms. Strongest association found with PM_{10}. However, there was no significant association between SO_2 and asthma or allergic rhinitis. Adjusted relative odds between the most/least polluted community 2-23 µg/m^2 (0.8, 8.8 ppb) Chronic cough: 1.57 (1.02, 2.42) Nocturnal dry cough: 1.66 (1.16, 2.38) Bronchitis: 1.48 (0.98, 2.24) Wheeze: 0.88 (0.54, 1.44) Asthma (ever): 0.74 (0.45, 1.21) Sneezing during pollen season: 1.07 (0.67, 1.70) Hay fever: 0.84 (0.55, 1.29) Conjunctivitis symptoms: 1.74 (1.22, 2.46) Diarrhea: 1.02 (0.75, 1.39)

TABLE AX5.6 (cont'd). ASSOCIATIONS OF LONG-TERM EXPOSURE TO SULFUR DIOXIDE WITH RESPIRATORY MORBIDITY

Reference, Study Location, and Period	Mean SO_2 Levels	Study Description	Results and Comments
EUROPE (cont'd)			
Charpin et al. (1999) Etang de Berre area of France: Arles, Istres, Port de Bouc, Rognac-Velaux, Salon de Provence, Sausset, Vitrolles Jan-Feb 1993	24-h mean (SD) SO_2 ($\mu g/m^3$) Arles: 29.7 (15.5) Istres: 23.8 (12.7) Port de Bouc: 32.3 (24.5) Rognanc-Velaux: 39.5 (21.8) Salon de Provence: 17.3 (11.6) Sausset: 29.0 (28.7) Vitrolles : 57.4 (32.0)	Cross-sectional cohort study of 2,073 children (10-11 yrs) from 7 communities in France (some with the highest photochemical exposures in France) to test the hypothesis that atopy is greater in towns with higher photochemical pollution levels. Mean levels of SO_2, NO_2, and O_3 were measured for 2 mos in 1993. Children tested for atopy based on skin prick test (house dust mite, cat dander, grass pollen, cypress pollen, and Alternaria). To be eligible for the study, subjects must have resided in current town for at least 3 yrs. Questionnaire filled out by parents that included questions on socioeconomic status and passive smoking at home. Two-mo mean level of air pollutants used in logistic regression analysis.	Study did not demonstrate any association between air pollution and atopic status of the children living in the seven communities, some with high photochemical exposures. A limitation of study is that authors did not consider short-term variation in air pollution and did not have any indoor air pollution measurements.
Frischer et al. (2001) Nine communities in Austria Sep-Oct 1997	½-hour avg SO_2: 30-day mean 2.70 ppb IQR 2.1 ppb	Cross-sectional cohort study of 877 children (mean age 11.2 yrs) living in 9 sites with different O_3 exposures. Urinary eosinophil protein U-EPX) measured as a marker of eosinophil activation. U-EPX determined from a single spot urine sample analyzed with linear regression models.	No significant association between SO_2 and U-EPX Regression coefficient and SE –10.57 (0.25) per ppb SO_2

TABLE AX5.6 (cont'd). ASSOCIATIONS OF LONG-TERM EXPOSURE TO SULFUR DIOXIDE WITH RESPIRATORY MORBIDITY

Reference, Study Location, and Period	Mean SO_2 Levels	Study Description	Results and Comments
EUROPE (cont'd)			
Frischer et al. (1999) Nine communities in Austria 1994-1996	Annual mean SO_2 (ppb) in 1994 Amstetten: 3.75 St. Valentin: 3.00 Krems: 3.75 Heidenreichstein: 4.13 Ganserndorf: 5.63 Mistelbach: 5.25 Wiesmath: 6.00 Bruck: 4.88 Pollau: 2.25	Longitudinal cohort study of 1150 children (mean age 7.8 yrs) to investigate the long-term effects of O_3 on lung growth. Children were followed for 3 yrs and lung function was recorded biannually, before and after summertime. The dependant variables were change in FVC, FEV_1, and MEF_{50}. The 9 sites were selected to represent a broad range of O_3 exposures. GEE models adjusted for baseline function, atopy, gender, site, environmental tobacco smoke exposure, season, and change in height. Other pollutants studied included PM_{10}, SO_2, and NO_2.	No consistent association observed between lung function and SO_2, NO_2 and PM_{10}. A negative effect estimate was observed during the summer and a positive estimate during the winter. Change in lung function (per ppb SO_2): FEV_1 (mL/day): Summer: −0.018 (0.004), $p < 0.001$ Winter : 0.003 (0.001), $p < 0.001$ FVC (mL/day): Summer: −0.009 (0.004), $p = 0.02$ Winter: 0.002 (0.001), $p = 0.03$ MEF50 (mL/s/day): Summer: −0.059 (0.010), $p < 0.001$ Winter: 0.003 (0.003), $p = 0.26$
Frye et al. (2003) Zerbst, Hettstedt, Bitterfeld,East Germany, 1992-93, 1995-1996, 1998-1999	Used avg of annual means of pollutants 2 yrs preceding health measurement High of 113 µg/m^3 (in Bitterfeld) to a low of 6 µg/m^3. (Pollution values only described in figure)	Three consecutive cross-sectional surveys of children (11-14 yrs) from three communities in East Germany. Parents of 3,155 children completed a questionnaire on symptoms. Lung function tests performed on 2,493 children. Study excluded children if they lived for less than 2 yrs in current home and if their previous home was more than 2 km away. The log-transformed lung function parameters were used as the response variables in a linear regression analysis that controlled for sex, height, season of examination, lung function equipment, parental education, parental atopy, and environmental tobacco smoke. Used avg of annual means of pollutants 2 yrs preceding each survey.	The annual mean TSP declined from 79 to 25 µg/m^3 and SO_2 from 113 to 6 µg/m^3 and the mean FVC and FEV_1 increased from 1992-1993 to 1998-1999. Study concluded that reduction of air pollution in a short time period may improve children's lung function. Percent change of lung function for a 100-µg/m^3 decrease in SO_2 2 yrs before the investigation (n = 1,911) FVC: 4.9 (0.7, 9.3) FEV_1: 3.0 (−1.1, 7.2) FEV_1/FVC: −1.5 (−3.0, 0.1)

TABLE AX5.6 (cont'd). ASSOCIATIONS OF LONG-TERM EXPOSURE TO SULFUR DIOXIDE WITH RESPIRATORY MORBIDITY

Reference, Study Location, and Period	Mean SO_2 Levels	Study Description	Results and Comments
EUROPE (cont'd)			
Heinrich et al. (2002) Reunified Germany Bitterfeld, Hettstedt, Zerbst 1992-1993, 1995-1996, 1998-1999	SO_2 concentration in µg/m^3 Yr Zerbst Bitterf. Hettst. 1991 78 113 84 1992 58 75 46 1993 42 60 49 1994 29 35 38 1995 21 30 26 1996 25 24 25 1997 13 13 13 1998 8 9 6	Three cross-sectional surveys of children (5-14 yrs) from 3 areas that were formerly part of East Germany to investigate the impact of declines in TSP and SO_2 on prevalence of nonallergic respiratory disorders in children. Study excluded children if they lived for less than 2 yrs in current home and if their previous home was more than 2 km away. GEE used for analysis.	Study found that SO_2 exposure was significantly associated with prevalence of bronchitis, frequent colds, and febrile infections. While results are reported as risk for an increase in air pollutant, the respiratory health of children improved with declines in TSP and SO_2. Authors concluded that exposure to combustion-derived air pollution is causally related to nonallergic respiratory health in children. Odds ratio and 95% CI: (per 100 µg/m^3 in 2 yr mean SO_2) All children: Bronchitis: 2.72 (1.74, 4.23) Otitis media: 1.42 (0.94, 2.15) Sinusitis: 2.26 (0.85, 6.04) Frequent colds: 1.81 (1.23, 2.68) Febrile infections: 1.76 (1.02, 3.03) Cough in morning: 1.10 (0.73, 1.64) Shortness of breath: 1.31 (0.84, 2.03) Children without indoor exposures (living in damp houses with visible molds, ETS in the home, gas cooking emissions, and contact with cats) Bronchitis: 4.26 (2.15, 8.46) Otitis media: 1.43 (0.73, 2.81) Sinusitis: 2.95 (0.52, 16.6) Frequent colds: 2.29 (1.15, 4.54) Febrile infections: 1.75 (0.78, 3.91) Cough in morning: 1.00 (0.38, 2.64) Shortness of breath: 2.07 (0.90, 4.75)

TABLE AX5.6 (cont'd). ASSOCIATIONS OF LONG-TERM EXPOSURE TO SULFUR DIOXIDE WITH RESPIRATORY MORBIDITY

Reference, Study Location, and Period	Mean SO_2 Levels	Study Description	Results and Comments
EUROPE (cont'd)			
Herbarth et al. (2001) East Germany 1993-1997	Avg lifetime exposure burden of SO_2 ($\mu g/m^3$) KIGA: 142 LISS: 48 LIISS: R 47 KIGA-IND: 59	Meta-analysis of three cross-sectional studies: (1) Study on Airway Diseases and Allergies among Kindergarten Children (KIGA), (2) the Leipzig Infection, Airway Disease and Allergy Study on School starters (LISS), and (3) KIGA-IND, which was based on the KIGA design but conducted in 3 differentially polluted industrial areas. A total of 3,816 children participated in the three studies. Analysis of data from parent-completed questionnaires to determine the effect of life time exposure to SO_2 and TSP on the occurrence of acute bronchitis. Total lifetime exposure burden corresponds to the exposure duration from birth to time of the study. The LISS study was divided in to LISS-U for the urban area and LISS-R for the rural area. Logistic regression analysis used that adjusted for predisposition in the family (mother or father with bronchitis), ETS, smoking during pregnancy or in the presence of the pregnant women.	This study found the highest bronchitis prevalence in the KIGA cohort and the lowest in the LISS cohort, which is consistent with the SO_2 concentrations in these cohorts. Study found a correlative link between SO_2 and bronchitis ($R = 0.96$, $p < 0.001$) but not TSP ($R = 0.59$). Results of study suggest that SO_2 may be a more important factor than TSP in the occurrence of bronchitis in these study areas. Odds ratio for bronchitis adjusted for parental predisposition, smoking, and lifetime exposure to SO_2 and TSP (2-pollutant model). SO_2: 3.51 (2.56, 4.82) TSP: 0.72 (0.49, 1.04)

TABLE AX5.6 (cont'd). ASSOCIATIONS OF LONG-TERM EXPOSURE TO SULFUR DIOXIDE WITH RESPIRATORY MORBIDITY

Reference, Study Location, and Period	Mean SO_2 Levels	Study Description	Results and Comments
EUROPE (cont'd)			
Horak et al. (2002) Eight communities in Austria 1994-1997	Seasonal mean SO_2 µg/m^3: Winter: Mean: 16.8 Range: 7.5, 37.4 Summer: Mean : 6.9 µg/m^3 Range: 3.1, 11.7	Longitudinal cohort study that continued the work of Frischer et al. (1999) by adding one more yr of data and analyzing the effects of PM_{10} in addition to SO_2, NO_2, and O_3. At the beginning of the study 975 children (mean age 8.11 yrs) were recruited for the study, but only 80.6% of the children performed all 6 lung function tests (twice a yr). The difference for each lung function parameter between two subsequent measures was divided by the days between measurements and presents as difference per day (dpd) for that parameter. 860 children were included in the GEE analysis that controlled for sex, atopy, passive smoking, initial height, height difference, site, and initial lung function.	Moderate correlation between PM_{10} and SO_2 in the winter (r = 0.52). In a one-pollutant model for SO_2, long term seasonal mean concentration of SO_2 was had a positive association with FVC dpd and FEV_1 dpd in the winter, but no effect on MEF_{25-75} dpd. In a two-pollutant model with PM_{10}, wintertime SO_2 had a positive association with FEV_1 dpd. Single-pollutant model FVC dpd: Summer: 0.009, p = .336 Winter: 0.006, p = .009 FEV_1 dpd: Summer : 0.005, p = 0.576 Winter: 0.005, p = 0.013 MEF_{25-75}: Summer: 0.015, p = 0.483 Winter: 0.003, p = 0.637 Two-pollutant model: SO_2 + PM_{10} FVC dpd: Summer: 0.008, p = 0.395 Winter: 0.004, p = 0.225 FEV_1 dpd: Summer : 0.010 (0.271) Winter: 0.007 (0.025) MEF_{25-75} dpd: Summer : 0.037, p = 0.086 Winter: 0.007, p = 0.429

TABLE AX5.6 (cont'd). ASSOCIATIONS OF LONG-TERM EXPOSURE TO SULFUR DIOXIDE WITH RESPIRATORY MORBIDITY

Reference, Study Location, and Period	Mean SO_2 Levels	Study Description	Results and Comments
EUROPE (cont'd)			
Kopp et al. (2000) Ten communities in Austria and SW Germany	Mean SO_2 (95% CI) ppb Apr-Sep 1994 Amstetten: 3.7 (0.7, 3.9) St Valentin: 2.6 (1.5, 5.2) Krems: 3.7 (0.7, 7.5) Villingen: 0.7 (0 , 3.0) Heindenreichstein: 3.7, (0.7, 7.5) Ganserndorf: 3.7 (0.7, 11.2) Mistelbach: 3.7 (0.7, 7.5) Wiesmath: 6.3 (3.4, 9.4) Bruck: 1.5 (0.7, 4.1) Freudenstadt: 0.7 (0, 3.0) Oct 1994-Mar 1995 Amstetten: 3.7 (0.7, 7.5) St Valentin: 3.0 (1.1, 9.4) Krems: 3.7 (0.7, 11.0) Villingen: 1.9 (0 , 3.0) Heindenreichstein: 3.7 (0.7, 15.0) Ganserndorf: 3.7 (0.7, 22.5) Mistelbach: 3.7 (0.7, 22.5) Wiesmath: 2.23 (0.7, 10.1) Bruck: 15 (1.1, 7.9) Freudenstadt: 1.57 (0.4, 5.3) Apr-Sep 1995 Amstetten: 3.7 (0.7, 3.8) St Valentin: 2.6 (1.1, 6.8) Krems: 3.7 (0.5, 3.8) Villingen: 0.7 (0 , 2.6) Heindenreichstein: 0.7 (0.5, 0.9) Ganserndorf: 3.7 (0.7, 7.5) Mistelbach: 3.7 (0.7, 7.5) Wiesmath: 7.5 (0.7, 14.9) Bruck: 3.7 (0.4, 4.9) Freudenstadt: 0.7 (0, 3.4)	Longitudinal cohort study of 797 children (mean age 8.2 yrs) from 2nd and 3rd grades of 10 schools in Austria and SW Germany to assess the effects of ambient O_3 on lung function in children over a 2-summer period. Study also examined the association between avg daily lung growth and SO_2, NO_2, and PM_{10}. Each child performed 4 lung function tests during spring 1994 and summer 1995. ISAAC questionnaire used for respiratory history. Linear regression models used to assess effect of air pollutants on FVC and FEV_1, which were surrogates of lung growth.	Lower FVC and FEV_1 increases observed in children exposed to high ambient O_3 levels vs. those exposed to lower levels in the summer. This study found no effect of SO_2 and PM_{10} on FVC increase during the summer of 1995 and winter 1994/1995, however, SO_2 was negatively associated with FVC during the summer of 1994. Change in FVC (per ppb SO_2) Summer 1994: −0.044, p = 0.006 Winter 1994/95: 0.007, p = 0.243 Summer 1995: 0.045, p = 0.028

TABLE AX5.6 (cont'd). ASSOCIATIONS OF LONG-TERM EXPOSURE TO SULFUR DIOXIDE WITH RESPIRATORY MORBIDITY

Reference, Study Location, and Period	Mean SO_2 Levels	Study Description	Results and Comments
EUROPE (cont'd)			
Kramer et al. (1999) East and West Germany, 1991 to 1995	East Germany 2-yr avg concentration ranged from 45 to 240 µg/m^3 West Germany 2-yr avg concentration ranged from 18-33	Repeated cross-sectional studies between 1991 and 1995 on 7-yr-old children in East Germany and between 1991 and 1994 in West Germany. Comparison of prevalence of airway diseases and allergies in East and West Germany during the first five yrs after reunification. A total of 19,090 children participated in the study. Logistic regression used to assess the effect of SO_2 and TSP on airway diseases and allergies. Analysis performed on 14,144 children with information on all covariates of interest.	All infectious airway diseases and irritation of the airways was associated with either SO_2 or TSP in East Germany in 1991. The decrease of pollution between 1991 and 1995 had a favorable effect on the prevalence of these illnesses. SO_2 was significantly associated with more than 5 colds in the last 12 mos, tonsillitis, dry cough in the last 12 mos, and frequent cough in 1991-1995. Odds ratio and 95% CI: (per 200 µg/m^3 SO_2) in East Germany areas, 1991-1995 for children living at least 2 yrs in the areas, adjusted for time trend: Infectious airway diseases Pneumonia ever diagnosed: 1.17 (0.85, 1.62) Bronchitis ever diagnosed: 0.85 (0.68, 1.05) ≥5 colds in last 12 mos: 1.55 (1.18, 2.04) Tonsillitis in the last 12 mos: 1.89 (1.49, 2.39) Dry cough in the last 12 mos: 1.46 (1.12, 1.91) Frequent cough ever: 2.51 (1.79. 3.53) Allergic diseases and symptoms: Irritated eyes in the last 12 mos: 1.06 (0.66, 1.70) Irritated nose in the last 12 mos: 1.26 (0.96, 1.66) Wheezing ever diagnosed: 0.68 (0.46, 1.01) Bronchial asthma ever diagnosed: 2.73 (1.24, 6.04) Hay fever ever diagnosed: 0.60 (0.24, 1.52) Eczema ever diagnosed: 0.87 (0.65, 1.18) Allergy ever diagnosed: 0.93 (0.67, 1.29)

TABLE AX5.6 (cont'd). ASSOCIATIONS OF LONG-TERM EXPOSURE TO SULFUR DIOXIDE WITH RESPIRATORY MORBIDITY

Reference, Study Location, and Period	Mean SO_2 Levels	Study Description	Results and Comments
EUROPE (cont'd)			
Penard-Morand et al. (2005) Six communities in France: Bordeaux, Clermont-Ferrand, Creteil, Marseille, Strasbourg and Reims Mar 1999-Oct 2000	Estimated 3-yr avg concentrations at 108 schools Low conc: 4.6 µg/m^3 (range: 1.3, 7.4), High conc: 9.6 µg/m^3 (range 7.7, 13.7)	Cross-sectional study of 4,901 children (9-11 yrs) form 108 randomly selected schools in 6 cities to assess the association between long-term exposure to background air pollution (NO_2, SO_2, PM_{10}, O_3) and atopy and respiratory outcomes. Analysis restricted to children who had lived at least the last 3 yrs in their house at the time of the examination. Analysis used three yr avgd air pollutant concentrations at the children's schools. Parents completed questionnaire on respiratory and allergic disorders (asthma, allergic rhinitis [AR], and atopic dermatitis) and children underwent examination that included a skin prick test to assess allergic sensitization, evidence of visible flexural dermatitis and measure of exercise-induced bronchial reactivity (EIB).	Increased concentrations of SO_2 were significantly associated with an increased risk of EIB, lifetime asthma and lifetime AR. Past yr wheeze and asthma were also associated with SO_2. In a two-pollutant model with PM_{10}, significant associations were observed between SO_2 and EIB and past yr wheeze. Odds ratio and 95% CI (per 5 µg/m^3 SO_2) EIB: 1.39 (1.15, 1.66), $p < 0.001$ Flexural dermatitis: 0.86 (0.73, 1.02), $p < 0.10$ Past yr wheeze: 1.23 (1.0, 1.51), $p < 0.05$ Past yr asthma: 1.28 (1.00, 1.65), $p < 0.01$ Past yr rhinoconjunctivitis: 1.05 (0.89, 1.24) Past yr atopic dermatitis: 1.01 (0.86, 1.18) Lifetime asthma: 1.19 (1.00, 1.41), $p < 0.10$ Lifetime allergic rhinitis: 1.16 (1.01, 1.32), $p < 0.05$ Lifetime atopic dermatitis: 0.93 (0.82, 1.05) Two-pollutant model with PM_{10} EIB: 1.46 (1.12, 1.90) Past yr wheeze: 1.45 (1.09, 1.93)
Ramadour et al. (2000) Seven towns in SE France Jan-Feb 1993	Mean (SD) µg/m^3 of SO_2 during 2-mo period Port de Bouc: 32.3 (24.5) Istres: 23.8 (12.7) Sausset: 29.0 (28.7) Rognanc-Velaux: 39.5 (21.8) Vitrolles: 57.4 (32.0) Arles: 29.7 (15.5) Salon: 17.3 (11.6)	Cross-sectional cohort study of 2,445 children (age 13-14 yrs) who had lived for at least 3 yrs in their current residence to compare the levels of O_3, SO_2, and NO_2 to the prevalence rates of rhinitis, asthma, and asthmatic symptoms. Some of the communities had the heaviest photochemical exposure in France. Subjects completed ISAAC survey of asthma and respiratory symptoms. Analysis conducted with logistic regression models that controlled for family history of asthma, personal history of early -life respiratory diseases, and SES. Also performed simple univariate linear regressions.	Study found no relationship between mean levels of SO_2, NO_3, or O_3 and rhinitis ever, 12-mo rhinitis, rhinoconjunctivitis, and hay fever or asthmatic symptoms. Simple regression analyses of respiratory outcomes vs. mean SO_2 levels in the 7 towns indicated that nocturnal dry cough was associated with mean SO_2 levels ($r = 0.891$). Potential confounding across towns.

TABLE AX5.6 (cont'd). ASSOCIATIONS OF LONG-TERM EXPOSURE TO SULFUR DIOXIDE WITH RESPIRATORY MORBIDITY

Reference, Study Location, and Period	Mean SO_2 Levels	Study Description	Results and Comments
EUROPE (cont'd)			
Soyseth et al. (1995) Ardal and Laerdal, Norway winter seasons 1989-92	Median SO_2 37.1 µg/m^3 at ages 0-12 mos 37.9 µg/m^3 at ages 13-36 mos	Cross-sectional study of 529 children (aged 7-13 yrs) to determine whether exposure to SO_2 during infancy is related to the prevalence of bronchial hyperresponsiveness (BHR). A sulfur dioxide emitting aluminum smelter is present in Ardal, but there is no air polluting industry in Laerdal. Parents filled out questionnaire regarding family history of asthma, type of housing, respiratory symptoms and parent's smoking habits. Spirometry was performed on each child and bronchial hyperactivity was determined by methacholine challenge or reversibility test. Skin prick test done to assess atopy. Also examined, the effects of fluoride.	This study found that the risk of BHR was associated with SO_2 exposure at 0-12 mos Odds ratio for BHR (per 10 µg/m^3 SO_2) for various ages at exposure 0-12 mos: 1.62 (1.11, 2.35) 13-36 mos: 1.40 (0.90, 2.21) 37-72 mos: 1.19 (0.77, 1.82) 73-108 mos: 1.19 (0.63, 2.22)
Garcia-Marcos et al. (1999) Cartagena, Spain winter 1992	Annual mean SO_2 (µg/m^3) Polluted areas 75 µg/m^3 Nonpolluted areas: 20 µg/m^3	A total of 340 children (10-11 yrs) living in and attending schools within a polluted and a relatively nonpolluted area were included in this study which aimed to establish the relative contribution socioeconomic status, parental smoking, and air pollution on asthma symptoms, spirometry, and bronchodilator response. Parents completed questionnaire on respiratory symptoms and risk factors including, living in polluted area, maternal smoking, paternal smoking, number of people living in the house, proximity to heavy traffic roads. Spirometry was performed before and after an inhaled 0.2 mg fenoterol was delivered to determine bronchodilator response. Bronchodilator response was considered positive if the FVC after fenoterol was increased by at least 10% or PEF by 12%. Logistic regression included as independent variables all the risk factors.	This study found that living in the polluted areas reduced the risk of a positive bronchodilator response (RR = 0.61, p = 004).

TABLE AX5.6 (cont'd). ASSOCIATIONS OF LONG-TERM EXPOSURE TO SULFUR DIOXIDE WITH RESPIRATORY MORBIDITY

Reference, Study Location, and Period	Mean SO_2 Levels	Study Description	Results and Comments
EUROPE (cont'd)			
Gokirmak et al. (2003) Malatya, Turkey	SO_2 conc ranged from 106.6 to 639.2 ppm in 9 apricot farms. Mean conc around sulfurization chamber: 324.1 (35.1) ppm	Study on occupational exposure to SO_2 in apricot sulfurization workers that investigated the role of oxidative stress resulting exposure to high concentrations of SO_2 on bronchoconstriction. Forty workers (mean age: 28 yrs, range 16-60 yrs) who have been working in apricot sulfurization for 20-25 days each yr and 20 controls (mean age: 29 yrs, range 17-42) who had no SO_2 exposure participated in the study. Activities of antioxidant enzymes (glutathione peroxidase [GSH-Px], superoxide dismutase [SOD] and catalase) malondialdehyde (MDA) concentrations (marker of lipid peroxidation), and pulmonary function test measured in subjects.	SOD, GSH-Px, and catalase activities were lower and malondialdehyde concentrations were higher in the apricot sulfurization workers compared to controls. Pulmonary function decreased after SO_2 exposure among the apricot sulfurization workers. Authors concluded that occupational exposure to high concentrations of SO_2 enhances oxidative stress and that lipid peroxidation may be a mechanism of SO_2 induced bronchoconstriction. Apricot sulfurization workers vs. controls Mean (SD) SOD (U/mL): 2.2 (0.6) vs. 3.2 (0.7) U/m , $p < 0.0001$ Glutathione peroxidase (U/mL): 0.6 (0.3) vs. 1.1 (0.3), $p < 0.0001$ Catalase (L/L): 107.6 (27.4) vs. 152.6 (14.3), $p < 0.0001$ MDA (nmol/L): 4.1 (0.9) vs. 1.9 (5.3) , $p < 0.0001$ Before vs. after SO_2 exposure among apricot sulfurization workers Mean (SD) FVC (% predicted) 88 (17) vs. 84 (16) , $p < 0.001$ FEV_1 (% predicted) 98 (14) vs. 87 (14), $p < 0.001$ FEVV1/FVC: 92 (7) vs. 86 (9), $p < 0.001$ FEF25-75% (% predicted) 108 (19) vs. 87 (23) , $p < 0.001$

TABLE AX5.6 (cont'd). ASSOCIATIONS OF LONG-TERM EXPOSURE TO SULFUR DIOXIDE WITH RESPIRATORY MORBIDITY

Reference, Study Location, and Period	Mean SO_2 Levels	Study Description	Results and Comments
EUROPE (cont'd)			
Hirsch et al. (1999) Dresden, Germany	Mean (µg/m^3): 48.3 Range: 29.0-69.3 25-75 percentile 42.7-54.3	Cross sectional study to relate the prevalence of respiratory and allergic diseases in childhood to measurements of outdoor air pollutants. 5,421 children ages 5-7 yrs and 9-11 yrs were evaluated by questionnaires, skin-prick testing, venipuncture for (Ig)E, lung function, and bronchial challenge test.	Sox was positively associated with current morning cough but not with bronchitis. Prevalence odds ratio (95% CI) for symptoms within past 12 mos, +10 µg/m^3: Wheeze: Atopic 103 (0.79, 1.35) µg/m^3 Nonatopic 1.36 (1.01, 1.84) Morning Cough: Atopic 1.22 (0.92, 1.61) Nonatopic 1.32 (1.07, 1.63) Prevalence odds ratio (95% CI) for doctor's diagnosis, +10 µg/m^3: Asthma Atopic 1.07 (0.79, 1.45) Nonatopic 1.35 (1.00, 1.82) Bronchitis Atopic 1.04 (0.87, 1.25) Nonatopic 0.99 (0.88, 1.12)
Koksal et al. (2003) Malatya, Turkey	SO_2 conc ranged from 106.6 to 721.0 ppm	Study on occupational exposure to high concentrations of SO_2 on respiratory symptoms and pulmonary function on apricot sulfurization workers. Apricot sulfurization workers (n = 69) from 15 apricot farms who have been working in sulfurization of apricots for 20-25 days a yr during each summer were recruited for the study. Subjects rated symptoms (itchy eyes, runny nose, stuffy nose, itchy or scratchy throat, cough, shortness of breath, phlegm, chest pain, and fever) before during and 1 h after each exposure.	SO_2 exposure at high concentrations increased symptoms of itchy eyes, shortness of breath, cough, running and/or stuffy nose, and itchy or scratchy throat during exposure ($p < 0.05$). Inhalation of high concentrations of SO_2 for 1 h caused significant decreases in pulmonary function. Difference in pulmonary function measured before and after exposure: FVC (L) 0.16 (0.42), $p < 0.05$ FEV_1 (L) 0.39 (0.36), $p < 0.001$ FEV_1/FVC: 5.22 (6.75), $p < 0.001$ PEF (L/s) 1.39 (1.06), $p < 0.001$ $FEF_{25-75\%}$ (L/s) 0.82 (0.70), $p < 0.001$

TABLE AX5.6 (cont'd). ASSOCIATIONS OF LONG-TERM EXPOSURE TO SULFUR DIOXIDE WITH RESPIRATORY MORBIDITY

Reference, Study Location, and Period	Mean SO_2 Levels	Study Description	Results and Comments
EUROPE (cont'd)			
Pikhart et al. (2001) Czech Republic, Poland, 1993-1994	Mean SO_2 ($\mu g/m^3$) Prague: 83.9 , Range: 65.8-96.6 Poznan: 79.7 , Range: 44.2-140.2	Part of the small-area variation in air pollution and health (SAVIAH) study to assess long-term effects of air pollution on respiratory outcomes. Analysis on data from two centers of the multicenter study: Prague, Czech Republic, and Poznan, Poland. Both cities had wide variation in air pollution levels. Parents/guardians of 6,959 children (7-10 yrs) completed a questionnaire about the socioeconomic situation of the family, type of housing, family history of atopy, parental smoking, family composition, and health of the child. SO_2 was measured at 80 sites in Poznan and 50 sites in Prague during 2-wk campaigns. From these data GIS was used to estimate pollutant concentrations at a small area level. Logistic regression used to assess effect of air pollution on the prevalence of respiratory outcomes.	SO_2 levels (mean of home and school) were associated with the prevalence of wheezing/whistling in the past 12 mos. There was a marginal association between SO_2 and lifetime prevalence of wheezing and physician diagnosed asthma. Fully adjusted model controlled for age, gender, maternal education, number of siblings, dampness at home, heating and cooking on gas, maternal smoking, and family history of atopy and center. Authors noted SO_2 is strongly spatially correlated with particles in the Czech Republic and probably Poland, so SO_2 may be proxy for exposure to other pollutants. Not other pollutants measured in study. Odds ratio (per 50 $\mu g/m^3$) SO_2 Wheezing/whistling in past 12 mos: 1.32 (1.10, 1.57) Wheezing/whistling ever: 1.13 (0.99, 1.30) Asthma ever diagnosed by doctor: 1.39 (1.01, 1.92) Dry cough at night: 1.06 (0.89, 1.27)
von Mutius et al. (1995) Leipzig, East Germany, Oct 1991-Jul 1992	During winter mos, SO_2 daily max concentrations ranged from 40-1283 $\mu g/m^3$. During high pollution period, mean concentration of SO_2 was 188 $\mu g/m^3$ and during low pollution mean was 57 $\mu g/m^3$.	The effects of high to moderate levels of air pollution (SO_2, NO_x, and PM) on the incidence of upper respiratory were investigated in 1,500 schoolchildren (9-11 yrs) in Leipzig, East Germany. Logistic regression models controlled for paternal education, passive smoke exposure, number of siblings, temperature, and humidity.	The daily mean values of SO_2 and NO_x were significantly associated with increased risk of developing upper respiratory illnesses during the high concentration period. In the low concentration period, only NO_x daily mean values were associated with increased risks. In a two-pollutant model with PM, similar estimates to the single-pollutant model were obtained, thus collinearity of data may not account for the effects of high mean concentrations of SO_2. Odds ratio and 95% CI: (did not indicate per what level of SO_2 increase) Daily mean SO_2 High period: 1.72 (1.19, 2.49) Low period: 1.40 (0.95, 2.07) Daily maximum SO_2 High period: 1.26 (0.80, 1.96) Low period: 0.99 (0.66, 1.47)

TABLE AX5.7. ASSOCIATIONS OF LONG-TERM EXPOSURE TO SULFUR DIOXIDE WITH INCIDENCE OF CANCER

Reference, Study Location, & Period	Design & Methods	Mean SO_2 Levels	Copollutants Considered	Conclusions
EUROPE				
Nafstad et al. (2003) Oslo, Norway 1972-1998	Retrospective study associating cardiovascular risk factors to a national cancer register among 16,209 men ages 10-49 yrs. Survival analyses and Cox proportional hazards regression were used to estimate associations.	Estimated for each person each year from 1974 to 1998 Five-year median average levels SO_2 participants home address, 1974-1978: 9.4 µg/m^3 (range 0.2 to 55.8) Median levels within the quartiles: 2.5 µg/m^3 6.2 µg/m^3 14.7 µg/m^3 31.3 µg/m^3	NO_x	Adjusted risk ratios (95% CI) of developing lung cancer: Model 1: 0-9.99 µg/m^3: Ref 10-19.99 µg/m^3: 1.05 (0.81, 1.35) 20-29.99 µg/m^3: 0.95 (0.72, 1.27) 30+ µg/m^3: 1.06 (0.79, 1.43) Model 2: Per 10 µg/m^3: 1.01 (0.94, 1.08) Adjusted risk ratios (95% CI) of developing non-lung cancer Model 1: 0-9.99 µg/m^3: Ref. 10-19.99 µg/m^3: 1.07 (0.96, 1.19) 20-29.99 µg/m^3: 0.90 (0.80, 1.02) 30+ µg/m^3: 0.98 (0.86, 1.10) Model 2: Per 10 µg/m^3: 0.99 (0.96, 1.02)

TABLE AX5.7 (cont'd). ASSOCIATIONS OF LONG-TERM EXPOSURE TO SULFUR DIOXIDE WITH INCIDENCE OF CANCER

Reference, Study Location, & Period	Design & Methods	Mean SO_2 Levels	Copollutants Considered	Conclusions
EUROPE (cont'd)				
Nyberg et al. (2000) Stockholm County, Sweden Jan 1, 1985-Dec 31, 1990	Case-control study of men 40-70 yrs, with 1,042 cases of lung cancer and 1,274 controls, to evaluate the suitability of an indicator of air pollution from heating.	Annual levels computed for each year between 1950 and 1990, but not provided herein	NO_x/NO_2	Little effect of SO_x in any time window, but highest correlations in early years. SO_x RR (CI 95%) from heating (per 10 µg/m^3) for 30-yr avg <41.30 µg/m^3: 1 ≥41.30 to <52.75: 1.06 (0.83, 1.35) ≥52.75 to <67.14: 0.98 (0.77, 1.24) ≥67.14 to <78.20: 0.90 (0.68, 1.19) ≥78.20: 1.00 (0.73, 1.37) SO_x RR (CI 95%) from heating (per 10 µg/m^3) for 10-yr avg <66.20 µg/m^3: 1 ≥66.20 to <87.60: 1.16 (0.91, 1.47) ≥87.60 to <110.30: 1.00 (0.79, 1.27) ≥110.30 to <129.10: 0.92 (0.70, 1.21) ≥129.10: 1.21 (0.89, 1.66)

TABLE AX5.8. ASSOCIATIONS OF LONG-TERM EXPOSURE TO SULFUR DIOXIDE WITH PRENATAL AND NEONATAL OUTCOMES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean Levels & Monitoring Stations	Copollutants & Correlations	Method, Findings, Interpretation	Effects: Relative Risk or % Change & Confidence Intervals (95%)
UNITED STATES					
Bell et al. (2007) Connecticut and Massachusetts Period of Study: 1999-2002	Outcome: LBW Study design: Case-control N: 358,504 live singleton births Statistical analysis: Linear models and logistic regression Covariates: Gestational length, prenatal care, type of delivery, child's sex, birth order, weather, yr, and mother's race, education, marital status, age, and tobacco use.	Gestational exposure (ppb) Mean: 4.7 SD = 1.2 IQR: 1.6	NO_2 CO PM_{10} $PM_{2.5}$	No relationship between gestational exposure to SO_2 and birth weight. First trimester exposure to SO_2 was associated with low birth weight. No statistical difference n the effect estimates of SO_2 for infants of black and white mothers.	Increment: 1.6 ppb (IQR) Change in birth weight: Entire pregnancy: −0.9 g (−4.4, 2.6) Black mother: 1.2 (−6.5, 8.8) White mother: −1.4 (−5.1, 2.3) 1st trimester: −3.7 to −3.3 grams LBW: OR 1.003 (0.961, 1.046)
Gilboa et al. (2005) Seven Texas Counties Period of Study: 1997-2000	Outcome: Selected birth defects Study design: Case-control N: 4,570 cases and 3,667 controls Statistical analysis: Logistic regression Covariates: Maternal education, maternal race/ethnicity, season of conception, plurality, maternal age, maternal illness Statistical package: SAS vs. 8.2	NR	PM_{10} O_3 NO_2 CO	When the fourth quartile of exposure was compared with the first, SO_2 was associated with increased risk of isolated ventricular septal defects. Inverse associations were noted for SO_2 and risk of isolated atrial septal defects and multiple endocardial cushion defects.	Aortic artery and valve defects <1.3 ppb: 1.00 1.3 to <1.9: NA 1.9 to <2.7: 1.06 [0.34, 3.29] ≥2.7: 0.83 [0.26, 2.68] Atrial septal defects <1.3 ppb: 1.00 1.3 to <1.9: 1.22 [0.79, 1.88] 1.9 to <2.7: 0.76 [0.47, 1.23] ≥2.7: 0.42 [0.22, 0.78] Pulmonary artery and valve defects <1.3 ppb: 1.00 1.3 to <1.9: 0.63 [0.23, 1.74] 1.9 to <2.7: 0.93 [0.36, 2.38] ≥2.7: 1.07 [0.43, 2.69]

TABLE AX5.8 (cont'd). ASSOCIATIONS OF LONG-TERM EXPOSURE TO SULFUR DIOXIDE WITH PRENATAL AND NEONATAL OUTCOMES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean Levels & Monitoring Stations	Copollutants & Correlations	Method, Findings, Interpretation	Effects: Relative Risk or % Change & Confidence Intervals (95%)
UNITED STATES (cont'd)					
Gilboa et al. (2005) (cont'd)					Ventricular septal defects <1.3 ppb: 1.00 1.3 to <1.9: 1.02 [0.68, 1.53] 1.9 to <2.7: 1.13 [0.76, 1.68] ≥2.7: 2.16 [1.51, 3.09] Conotruncal defects <1.3 ppb: 1.00 1.3 to <1.9: 0.71 [0.46, 1.09] 1.9 to <2.7: 0.71 [0.46, 1.09] ≥2.7: 0.58 [0.37, 0.91] Endocardial cushion and mitral valve defects <1.3 ppb: 1.00 1.3 to <1.9: 0.89 [0.50, 1.61] 1.9 to <2.7: 0.89 [0.49, 1.62] ≥2.7: 1.18 [0.68, 2.06] Cleft lip with or without cleft palate <1.3 ppb: 1.00 1.3 to <1.9: 0.79 [0.52, 1.20] 1.9 to <2.7: 0.95 [0.64, 1.43] ≥2.7: 0.75 [0.49, 1.15] Cleft palate <1.3 ppb: 1.00 1.3 to <1.9: 0.89 [0.40, 1.97] 1.9 to <2.7: 1.49 [0.72, 3.06] ≥2.7: 1.22 [0.56, 2.66]

TABLE AX5.8 (cont'd). ASSOCIATIONS OF LONG-TERM EXPOSURE TO SULFUR DIOXIDE WITH PRENATAL AND NEONATAL OUTCOMES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean Levels & Monitoring Stations	Copollutants & Correlations	Method, Findings, Interpretation	Effects: Relative Risk or % Change & Confidence Intervals (95%)
UNITED STATES (cont'd)					
Maisonet et al. (2001) 6 Northeastern cities of U.S. Period of Study: 1994-1996	Outcome: Term LBW Study design: Case-control N: 89,557 live singleton births Statistical analysis: Logistic regression models linear regression models Covariates: Maternal age, race, season of the yr, smoking and alcohol use during pregnancy, firstborn, gender, marital status, and previous terminations, prenatal care (ordinal variable), weight gain, and gestational age Stratified by race/ethnicity Statistical package: STATA	Exposure distribution (<25th, 25th to <50th, 50th to <75th, 75th to <95th, ≥95th) First trimester: <7.09, 7.090 to 8.906, 8.907 to 11.969, 11.970 to 18.447, ≥18.448 Second trimester: <6.596, 6.596 to 8.896, 8.897 to 11.959, 11.960 to 18.275, ≥18.276 Third trimester: <5.810, 5.810 to 8.453, 8.454 to 11.777, 11.778 to 18.134, ≥18.135	CO PM_{10}	This study provides evidence of an increased risk for term LBW in relation to increased ambient air levels of SO_2 at concentrations well below the established standards. Higher risk estimates among whites when stratified by race/ethnicity	First trimester: <25th: Referent 25th-50th: 1.04 [0.88, 1.23] 50th-75th: 1.04 [0.94, 1.15] 75th-95th: 0.98 [0.81, 1.17] >95th: 0.88 [0.73, 1.07] Increment (10 ppm): 0.98 [0.93, 1.03] Second trimester: 25th-50th: 1.18 [1.12, 1.25] 50th-75th: 1.12 [1.07, 1.17] 75th-95th: 1.13 [1.05, 1.22] >95th: 0.87 [0.80, 0.95] Increment (10 ppm): 1.01 [0.93, 1.10] Third trimester: 25th-50th: 1.04 [0.92, 1.18] 50th-75th: 1.02 [0.87, 1.18] 75th-95th: 1.04 [0.84, 1.28] >95th: 1.06 [0.76, 1.47] Increment (10 ppm): 1.01 [0.86, 1.20]

TABLE AX5.8 (cont'd). ASSOCIATIONS OF LONG-TERM EXPOSURE TO SULFUR DIOXIDE WITH PRENATAL AND NEONATAL OUTCOMES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean Levels & Monitoring Stations	Copollutants & Correlations	Method, Findings, Interpretation	Effects: Relative Risk or % Change & Confidence Intervals (95%)
UNITED STATES (cont'd)					
Sagiv et al. (2005) 4 Pennsylvania counties Period of Study: 1997-2001	Outcome: Pre-term birth Study design: Time-series N: 187,997 births Study design: Poisson-regression models Covariates: Long-term trends, copollutants, temperature, dew point temperature, and day of wk. Lag: Daily lags ranging from 1-7 days	6-wk mean: 7.9 ± 3.5 ppb (Range: 0.8, 17), Median: 8.1 Daily mean: 7.9 ± 6.2 (Range: 0, 54.1), Median: 6.4	PM_{10}; r = 0.46 CO NO_2	This study found an increased risk for preterm delivery during the last 6 wks of pregnancy with exposure to SO_2.	Increment: 15 ppb Mean: 6-wk SO_2: RR = 1.15 [1.00, 1.32] <4.9 ppb: Referent 4.9 to 8.1 ppb: 1.02 [0.97, 1.06] 8.1 to 10.6 ppb: 1.04 [0.98, 1.10] 10.6 to 17.0 ppb: 1.06 [0.99, 1.14] Mean: Daily SO_2: RR = 1.07 [0.99, 1.15] lag 3
CANADA					
Dales et al. (2004) 12 Canadian cities Period of Study: 1984-1999	Outcome: SIDS Study design: Time series N: 1556 SIDS deaths Statistical analysis: Random effects regression model Covariates: Temperature, humidity, barometric pressure, season Lag: 0-5 days	24-h avg: 5.51 ppb IQR: 4.92	CO NO_2 O_3 PM_{10} $PM_{2.5}$ PM_{10}-2.5	SIDS was associated with air pollution, with the effects of SO_2 seeming to be independent of sociodemographic factors, temporal trends, and weather.	Increment: 4.92 ppb (IQR) Increase in SIDS incidence: 8.49%; p = 0.0079 lag 1

TABLE AX5.8 (cont'd). ASSOCIATIONS OF LONG-TERM EXPOSURE TO SULFUR DIOXIDE WITH PRENATAL AND NEONATAL OUTCOMES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean Levels & Monitoring Stations	Copollutants & Correlations	Method, Findings, Interpretation	Effects: Relative Risk or % Change & Confidence Intervals (95%)
CANADA (cont'd)					
Dales et al. (2006) 11 Canadian cities Period of Study: 1986-2000	Outcome: Hospitalization for respiratory disease in the neonatal period Study design: Time series N: 9,542 Statistical analysis: Random effects regression model; Poisson using fixed- or random-effects model Covariates: Fay of wk, temperature, humidity, pressure Lag: 0-5 days Statistical package: S-PLUS vs. 6.2	24-h avg: 4.3 ppb IQR: 3.8	NO_2; r = 0.20, 0.67 CO; r = 0.19, 0.66 O_3; r = −0.41, 0.13 PM_{10}; r = −0.09, 0.61 SO_4	This study detected a significant association for respiratory disease among neonates and gaseous air pollutants.	Increment: 3.8 ppb (IQR) Increase in neonatal respiratory hospital admissions: SO_2 alone: 2.06% [1.04, 3.08] Multipollutant model: 1.66% [0.63, 2.69] Multipollutant model restricted to days with PM_{10} measures: 1.41% [0.35, 2.47]
Liu et al. (2006) Calgary, Edmonton and Montreal, Canada Period of Study: 1986-2000	Outcome: IUGR Study design: Case-control N: 386,202 singleton live births Statistical analysis: Multiple logistic regression Covariates: Maternal age, parity, infant sex, season of birth, city of residence	24-h avg: 3.9 ppb, 25% 2.0 ppb 50% 3.0 ppb 75% 5.0 ppb 95% 10.0 ppb 1-h max: 10.8 ppb, 25% 5.0 ppb 50% 8.6 ppb 75% 14.0 ppb 95% 28.0 ppb	NO_2; r = 0.34 CO; r = 0.21 O_3; r = −0.30 $PM_{2.5}$; r = 0.44	IUGR did not increase with maternal exposure to SO_2. Risk decreased during first 3 mos.	Increment: 3.0 ppb ORs estimated from graph: 1st mo: OR~0.966 (0.94, 0.99) 2nd mo: OR~0.97 (0.95, 0.995) 3rd mo: OR~0.97 (0.95, 0.995) 1st trimester: OR~0 .96 (0.93, 0.99)

TABLE AX5.8 (cont'd). ASSOCIATIONS OF LONG-TERM EXPOSURE TO SULFUR DIOXIDE WITH PRENATAL AND NEONATAL OUTCOMES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean Levels & Monitoring Stations	Copollutants & Correlations	Method, Findings, Interpretation	Effects: Relative Risk or % Change & Confidence Intervals (95%)
CANADA (cont'd)					
Dugandzic et al. (2006) Nova Scotia, Canada Period of Study: 1988-2000	Outcome: Term LBW Study design: Retrospective cohort study N: 74,284 term, singleton births Statistical analysis: Logistic regression models Covariates: Maternal age, parity, prior fetal death, prior neonatal death, and prior low birth weight infant, smoking during pregnancy, neighborhood family income, infant gender, gestational age, weight change, and yr of birth. Statistical package: SAS vs. 8.0	Mean: SO_2 10 ppb Median: 10 25th%: 7 75th%: 14 Max: 38	O_3 PM_{10}	In the analyses unadjusted for birth yr, first trimester exposures in the highest quartile for SO_2 associated with increased risk of LBW. After adjusting for birth yr, RR attenuated and not statistically significant. There was a linear concentration-response effect with increasing levels of SO_2 during the first trimester.	First Trimester 25th-50th: 0.96 [0.73, 1.28] 51st-75th: 1.18 [0.88, 1.58] >75th: 1.36 [1.04, 1.78] Increment (7 ppb): 1.20 [1.05, 1.38] Second Trimester 25th-50th: 1.12 [0.86, 1.46] 51st-75th: 1.13 [0.85, 1.50] >75th: 1.04 [0.79, 1.37] Increment (7 ppb): 0.99 [0.87, 1.13] Third Trimester 25th-50th: 1.04 [0.80, 1.34] 51st-75th: 0.85 [0.63, 1.15] >75th: 0.88 [0.67, 1.15] Increment (7 ppb): 0.93 [0.81, 1.06]
Liu et al. (2003) Vancouver, Canada Period of Study: 1986-1998	Outcomes: Preterm birth, LBW, IUGR Study design: Case-control N: 229,085 singleton live births Statistical analysis: Multiple logistic regressions Covariates: Maternal age, parity, infant sex, gestational age or birth weight and season of birth	24-h avg: 4.9 ppb, 5th: 1.5 25th: 2.8 50th: 4.3 75th: 6.3 95th: 10.5 100th: 30.5 1-h max: 13.4 ppb, 5th: 4.3 25th: 7.8 50th: 11.7 75th: 16.8 95th: 28.3 100th: 128.5	NO_2; r = 0.61 CO; r = 0.64 O_3; r = −0.35	LBW and IUGR were associated with maternal exposure to SO_2 during the first mo of pregnancy and preterm birth was associated with SO_2 during the last mo. These results were robust to adjustment for copollutants.	Increment: 5 ppb Low birth weight First mo: OR 1.11 [1.01, 1.22] Last mo: OR 0.98 [0.89, 1.08] Preterm birth First mo: OR 0.95 [0.88, 1.03] Last mo: OR 1.09 [1.01, 1.19] IUGR First mo: OR 1.07 [1.01, 1.13] Last mo: OR 1.00 [0.94, 1.06] First trimester: OR 1.07 (1.00, 1.14) Second trimester: 0.98 [0.91, 1.04] Third trimester: 1.03 [0.96, 1.10]

TABLE AX5.8 (cont'd). ASSOCIATIONS OF LONG-TERM EXPOSURE TO SULFUR DIOXIDE WITH PRENATAL AND NEONATAL OUTCOMES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean Levels & Monitoring Stations	Copollutants & Correlations	Method, Findings, Interpretation	Effects: Relative Risk or % Change & Confidence Intervals (95%)
EUROPE					
Mohorovic (2004) Labin, Istra, Croatia Period of Study: 1987-1989	Outcomes: LBW and preterm delivery Study design: Cross-sectional N: 704 births Statistical analysis: Multiple correlation analyses, factor analyses, chi-square Statistical package: DBASE IV, SPSS	Monthly ground levels of SO_2: Range: 34.1, 252.9 ug/m^3		The results show an association between SO_2 exposure at the end of the first and second mo of pregnancy and a negative correlation between length of gestations and lower birth weight of newborns.	Correlation coefficients: 1st mo: Gestation length: −0.09, p = 0.008 Birthweight: −0.08, p = 0.016 2nd mo: Gestation length: −0.08, p = 0.016 Birthweight: −0.07, p = 0.026 3rd mo: Gestation length: −0.04, p = 0.147 Birthweight: −0.04, p = 0.135 6th mo: Gestation length: −0.02, p = 0.266 Birthweight: −0.04, p = 0.151 Whole pregnancy: Gestation length: −0.09, p = 0.007 Birthweight: −0.04, p = 0.153 Weekly avg during whole pregnancy: Gestation length: −0.05, p = 0.086 Birthweight: −0.06, p = 0.069

TABLE AX5.8 (cont'd). ASSOCIATIONS OF LONG-TERM EXPOSURE TO SULFUR DIOXIDE WITH PRENATAL AND NEONATAL OUTCOMES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean Levels & Monitoring Stations	Copollutants & Correlations	Method, Findings, Interpretation	Effects: Relative Risk or % Change & Confidence Intervals (95%)
EUROPE (cont'd)					
Bobak et al. (2000) Czech Republic Period of Study: 1990-1991	Outcomes: LBW, preterm birth Study design: Case-control N: 108,173 live singleton births Statistical analysis: Logistic regression Covariates: Temperature, humidity, day of wk, season, residential area, maternal age, gender Statistical package: STATA	Mean trimester exposures 25th: 17.5 µg/m^3 50th: 32.0 µg/m^3 75th: 55.5 µg/m^3	TSP; r = 0.68, 0.73 NO_x; r = 0.53, 0.63	LBW and preterm birth were associated with maternal exposure to SO_2, though the association between SO_2 and LBW was explained to a large extent by low gestational age.	Increment: 50 µg/m^3 LBW (adjusted for sex, parity, maternal age group, education, marital status, and nationality, and mo of birth) 1st trimester: 1.20 (1.11, 1.30) 2nd trimester: 1.14 (1.06, 1.22) 3rd trimester: 1.14 (1.06, 1.23) LBW (also adjusted for gestational age) 1st trimester: 1.01 (0.88, 1.17) 2nd trimester: 0.95 (0.82, 1.10) 3rd trimester: 0.97 (0.85, 1.10) Preterm birth (AOR) 1st trimester: 1.27 (1.16, 1.39) 2nd trimester: 1.25 (1.14, 1.38) 3rd trimester: 1.24 (1.13, 1.36) Reduction in mean birth weight: 1st trimester: 1.4 g (5.9, 16.9)

TABLE AX5.8 (cont'd). ASSOCIATIONS OF LONG-TERM EXPOSURE TO SULFUR DIOXIDE WITH PRENATAL AND NEONATAL OUTCOMES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean Levels & Monitoring Stations	Copollutants & Correlations	Method, Findings, Interpretation	Effects: Relative Risk or % Change & Confidence Intervals (95%)
LATIN AMERICA					
Gouveia et al. (2004) São Paulo, Brazil Period of Study: 1997	Outcome: LBW Study design: Case-control N: 179,460 live singleton births Statistical analysis: Logistic regression with GAM Covariates: Gender, gestational age, maternal age, maternal education, antenatal care, parity, delivery method Statistical package: S-Plus 2000	Annual mean: SO_2 ($\mu g/m^3$) Mean: 19.6 SD = 10.3 Range: 3.4, 56.9 Jan-Mar: 22.3 (7.7) Apr-June: 28.1 (10.1) Jul-Aug: 17.9 (8.7) Oct-Dec: 10.3 (3.9)	PM_{10} CO NO_2 O_3	First and second trimester exposures to SO_2 had a significant association with birth weight, though in different directions. When air pollutants were divided into quartiles and the lowest quartile was used as the referent exposure category, SO_2 during the second trimester was marginally associated with low birth weight.	Increment: 10 $\mu g/m^3$ Reduction in birth weight First trimester: −24.2 g (−55.5, 7.1) Second trimester: 33.7 g (1.6, 65.8) Third trimester: 9.7 g (−25.6, 44.9) First trimester: 2nd: 0.902 (0.843, 0.966) 3rd: 0.911 (0.819, 1.013) 4th: 0.906 (0.793, 1.036) Second trimester: 2nd: 0.986 (0.922, 1.053) 3rd: 1.005 (0.904, 1.117) 4th: 1.017 (0.883, 1.173) Third trimester: 2nd: 1.203 (0.861, 1.68) 3rd: 1.225 (0.872, 1.722) 4th: 1.145 (0.749, 1.752)
Pereira et al. (1998) São Paulo, Brazil Period of Study: 1991-1992	Outcome: Intrauterine mortality Study design: Time series N: Statistical analysis: Poisson regression models Covariates: Mo, day of wk, minimum daily temperature, relative humidity Lag: 2 to 14 days	24-h avg SO_2: 18.90 (8.53) mg/m^3 Range: 3.80, 59.70	PM_{10}; r = 0.45 NO_2; r = 0.41 O_3; r = 0.17 CO; r = 0.24	SO_2 exhibited a marginal association with intrauterine mortality, but only when Poisson regression was employed. A concentration-response relationship was found.	Estimated regression coefficients and standard errors: SO_2 alone: 0.0038 (0.0020) $SO_2 + NO_2 + CO + PM_{10} + O_3$: 0.0029 (0.0031)

TABLE AX5.8 (cont'd). ASSOCIATIONS OF LONG-TERM EXPOSURE TO SULFUR DIOXIDE WITH PRENATAL AND NEONATAL OUTCOMES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean Levels & Monitoring Stations	Copollutants & Correlations	Method, Findings, Interpretation	Effects: Relative Risk or % Change & Confidence Intervals (95%)
ASIA					
Lin et al. (2004c) Kaohsiung and Taipei, Taiwan Period of Study: 1995-1997 Kaohsiung and Taipei, Taiwan Period of Study: 1995-1997	Outcome: LBW Study design: Case-control N: 92,288 live births Statistical analysis: Multiple logisistic regression Covariates: Gestational period, gender, birth order, maternal age, maternal education, season of birth	24-h avg: Kaohsiung Range: 10.07, 25.36 ppb Taipei: Range: 5.65, 9.33 ppb	CO NO_2 O_3 PM_{10}	Few women living in Taipei were exposed to high levels of SO_2. In Kaohsiung, almost all women were exposed to high levels of SO_2. Women living in Kaohsiung had significantly higher risk of term LBW compared with women living in Taipei.	OR for Kaoshiung births (compared to Taipei births) All births: OR: 1.13 [1.03, 1.24] Female births only: OR: 1.14 [1.01, 1.28]
Lin et al. (2004d) Kaohsiung and Taipei, Taiwan Period of Study: 1995-1997	Outcome: Term LBW Study design: Cohort N: 92,288 live births Statistical analysis: Multiple logisistic regression Covariates: Gestational period, gender, birth order, maternal age, maternal education, season of birth	24-h avg: Kaohsiung Range: 10.07, 25.36 ppb Taipei: Range: 5.65, 9.33 ppb	CO NO_2 O_3 PM_{10}	This study found a 26% higher risk of term LBW delivery for mothers exposed to mean SO_2 concentrations exceeding 11.4 ppb during the entire pregnancy, as compared with mothers exposed to mean concentrations less than 7.1 ppb. Trimester specific analysis showed a significant association only for the third trimester.	Lowest quartile of exposure = referent Entire pregnancy: 25th-75th: 1.16 [1.02, 1.33] >75th: 1.26 [1.04, 1.53] 1st trimester: 25th-75th: 1.02 [0.90, 1.16] >75th: 1.11 [0.94, 1.33] 2nd trimester: 25th-75th: 1.09 [0.96, 1.24] >75th: 1.17 [0.99, 1.37] 3rd trimester: 25th-75th: 1.13 [0.99, 1.28] >75th: 1.20 [1.01, 1.41]

TABLE AX5.8 (cont'd). ASSOCIATIONS OF LONG-TERM EXPOSURE TO SULFUR DIOXIDE WITH PRENATAL AND NEONATAL OUTCOMES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean Levels & Monitoring Stations	Copollutants & Correlations	Method, Findings, Interpretation	Effects: Relative Risk or % Change & Confidence Intervals (95%)
ASIA (cont'd)					
Wang et al. (1997) Four residential areas: Dongcheng, Xicheng, Congwen, Xuanwu Beijing, China Period of Study: 1988-1991	Outcome: Term LBW Study design: Cohort study N: 74,671 first parity live births Statistical analysis: Multiple linear regression and logistic regression with GAM Covariates: Gestational age, residence, yr of birth, maternal age, and infant gender.	Mean pollution concentrations provided in graph	TSP; r = 0.92	Exposure-response relationship between SO_2 during the third trimester of pregnancy and low birth weight.	3rd trimester: 9 to 18 µg/m^3 (reference) 18 to 55: 1.09 (0.94, 1.26) 55 to 146: 1.12 (0.97, 1.29) 146 to 239: 1.16 (1.01, 1.34) 239 to 308: 1.39 (1.22, 1.60) SO_2 as continuous variable: Odds ratio per 100 µg/m^3 1.11 (1.06, 1.16)
Xu et al. (1995) Four residential areas: Dongchen, Xichen, Congwen, Xuanwu Beijing, China Period of Study: 1988	Outcome: Preterm delivery Study design: Prospective cohort study N: 25,370 singleton first live births Statistical analysis: Multiple linear and logistic regression Covariates: Temperature, humidity, day of wk, season, residential area, maternal age, and gender of child.	2 monitors for SO_2: Dongcheng and Xicheng Dongcheng Annual mean: 108 µg/m^3 SD = 141 µg/m^3) Xicheng annual mean: 93 µg/m^3 (SD = 122 µg/m^3)	TSP	Exposure response relationship between quartiles of SO_2 and crude incidence rates of preterm birth. Dose dependent relationship between SO_2 and gestational age. The estimated reduced length of gestation was 0.075 wks or 12.6 h per 100/m^3 increase in SO_2. When TSP and SO_2 included in a multipollutant model, the effect of SO_2 was reduced by 32%.	Effect on gestational age (wk) per 100 µg/m^3 regression coef and SE for lagged moving avg of SO_2. lag 0: −0.016 (0.021) lag 1: −0.022 (0.021) lag 6: −0.067 (0.024), $p < 0.01$ lag 7: −0.075 (0.024) , $p < 0.01$ lag 8: −0.075 (0.025), $p < 0.01$ OR for each quartile of SO_2 1st: 1.00 2nd: 1.70 (1.15, 2.52) 3rd: 1.74 (1.03, 2.92) 4th: 1.58 (0.87, 2.86) Adjusted OR for preterm delivery: 1.21 (1.01, 1.46) per Ln µg/m^3 increase in SO_2

TABLE AX5.8 (cont'd). ASSOCIATIONS OF LONG-TERM EXPOSURE TO SULFUR DIOXIDE WITH PRENATAL AND NEONATAL OUTCOMES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean Levels & Monitoring Stations	Copollutants & Correlations	Method, Findings, Interpretation	Effects: Relative Risk or % Change & Confidence Intervals (95%)
ASIA (cont'd)					
Ha et al. (2001) Seoul, Korea Period of Study: 1996-1997	Outcome: LBW Study design: Case-control N: 276,763 Statistical analysis: Logistic regression, GAM Covariates: Gestational age, maternal age, parental education level, infant's birth order, gender	24-h avg: 1st trimester: 25th: 10.0 ppb 50th: 13.2 ppb 75th: 16.2 ppb 3rd trimester: 25th: 8.4 ppb 50th: 12.2 ppb 75th: 16.3 ppb	CO; r = 0.83 NO_2; r = 0.70 TSP; r = 0.67 O_3; r = −0.29	Ambient SO_2 concentrations during the first trimester of pregnancy were associated with LBW	Increment: 1st trimester: 6.2 ppb; 3rd trimester: 7.9 ppb 1st trimester: RR 1.06 [1.02, 1.10] 3rd trimester: RR 0.93 [0.88, 0.98] Reduction in birth weight: 8.06 g [5.59, 10.53]
Lee et al. (2003) Seoul, Korea Period of Study: 1996-1998	Outcome: Term LBW Study design: N: 388,105 full-term singleton births Statistical analysis: GAM Covariates: Infant sex, birth order, maternal age, parental education level, time trend, and gestational age.	Avg concentration (ppb) Mean: 12.1 SD = 7.4 Range: 3, 46 25th: 6.8 50th: 9.8 75th: 15.6	PM_{10}; r = 0.78, 0.85 CO; r = 0.79, 0.86 NO_2; r = 0.75, 0.76	Second trimester exposures to SO_2 as well as during the entire pregnancy were associated with LBW. Reduction in birth weight was 14.6 g for IQR increase in SO_2 in the second trimester. When the exposure for each mo of pregnancy was evaluated separately, SO_2 exposure during 3 to 5 mos of pregnancy associated with LBW.	Increment: 8.8 ppb (IQR) First trimester: 1.02 (0.99, 1.06) Second trimester: 1.06 (1.02, 1.11) Third trimester: 0.96 (0.91, 1.00) All trimesters: 1.14 (1.04, 1.24)

TABLE AX5.8 (cont'd). ASSOCIATIONS OF LONG-TERM EXPOSURE TO SULFUR DIOXIDE WITH PRENATAL AND NEONATAL OUTCOMES

Reference, Study Location, & Period	Outcomes, Design, & Methods	Mean Levels & Monitoring Stations	Copollutants & Correlations	Method, Findings, Interpretation	Effects: Relative Risk or % Change & Confidence Intervals (95%)
ASIA (cont'd)					
Leem et al. (2006) Incheon, Korea Period of Study: 2001-2002	Outcome: Preterm delivery Study design: N: 52,113 singleton births Statistical analysis: Log-binomial regression Covariates: Maternal age, parity, sex, season, maternal education, paternal education	Mean: SO_2 Concentrations by trimester: 1st trimester: Min: 7.86 ug/m^3 25th: 17.61 50th: 22.74 75th: 45.85 Max: 103.96 3rd trimester: Min: 6.55 ug/m^3 25th: 17.03 50th: 25.62 75th: 46.53 Max: 103.15	NO_2; r = 0.54 CO; r = 0.31 PM_{10}; r = 0.13	This study found the highest SO_2 concentrations during the first trimester to be significantly associated with elevated risks of preterm delivery.	1st trimester: 7.86 to 17.61 ug/m^3: referent 17.62 to 22.74: 1.13 [0.99, 1.28] 22.75 to 45.85: 1.13 [0.98, 1.30] 45.86 to 103.96: 1.21 [1.04, 1.42] 3rd trimester: 6.55 to 17.03 ug/m^3: referent 17.04 to 25.62: 0.87 [0.76, 1.01] 25.63 to 46.53: 0.97 [0.83, 1.13] 46.54 to 103.15: 1.11 [0.94, 1.31]
Yang et al. (2003b) Kaohsiung, Taiwan Period of Study: 1995-1997	Outcome: Term LBW Study design: Case-control N: 13,396 first parity singleton live births Statistical Analysis: Multiple linear regression Covariates: Maternal age, season, marital status, maternal education, gender Statistical package: SAS	Mean: trimester exposure (ug/m^3) 1st trimester 33rd: 26.02 67th: 36.07 2nd trimester 33rd: 25.76 67th: 35.63 3rd trimester 33rd: 25.39 67th: 36.96	PM_{10}; r = 0.45, 0.46	A significant exposure-response relationship between maternal exposures to SO_2 and birth weight was found during the first trimester of pregnancy.	Reduction in birth weight: 1st trimester: 33rd-67th: 3.68 g [−12.45, 19.21] >67th: 18.11 g [1.88, 34.34] Continuous: 0.52 g [0.09, 2.63] 2nd trimester: 33rd-67th: 1.78 g [−17.91, 14.35] >67th: 13.53 g [−2.62, 29.68] Continuous: 0.19 g [−0.78, 1.8] 3rd trimester: 33rd-67th: 0.43 g [−16.56, 15.70] >67th: 1.97 g [−18.24, 14.30] Continuous: 0.03 g [−1.21, 1.37]

TABLE AX5.9. ASSOCIATIONS OF LONG-TERM EXPOSURE TO SULFUR DIOXIDE WITH MORTALITY

Reference, Location, Study Period	Mean SO_x Levels	Study Description	Results and Comments
UNITED STATES			
Abbey et al. (1999) Three California air basins: San Francisco, South Coast (Los Angeles and eastward), San Diego 1977-1992	24-h avg SO_2: 5.6 ppb	Prospective cohort study of 6,338 nonsmoking non-Hispanic white adult members of the Adventist Health Study followed for all cause, cardiopulmonary, nonmalignant respiratory, and lung cancer mortality. Participants were aged 27-95 yrs at enrollment in 1977. 1,628 (989 females, 639 males) mortality events followed through 1992. All results were stratified by gender. Used Cox proportional hazards analysis, adjusting for age at enrollment, past smoking, environmental tobacco smoke exposure, alcohol use, education, occupation, and body mass index. Analyzed mortality from all natural causes, cardiopulmonary, nonmalignant respiratory, and lung cancer.	SO_2 was not associated with total (RR = 1.07 [95% CI: 0.92, 1.24] for male and 1.00 [95% CI: 0.88, 1.14] for female per 5-ppb increase in multiyear average SO_2), cardiopulmonary, or respiratory mortality for either sex. Lung cancer mortality showed large risk estimates for most of the pollutants in either or both sexes, but the number of lung cancer deaths in this cohort was very small (12 for female and 18 for male) Generally wide confidence intervals (relative to other U.S. cohort studies).
Beeson et al. (1998) Three California air basins: San Francisco, South Coast (Los Angeles and eastward), San Diego 1977-1992	24-h avg SO_2: 5.6 ppb	Prospective cohort study of 6,338 nonsmoking non-Hispanic white adult members of the Adventist Health Study aged 27-95 yrs at time of enrollment. 36 (20 females, 16 males) histologically confirmed lung cancers were diagnosed through 1992. Extensive exposure assessment, with assignment of individual long-term exposures to O_3, PM_{10}, SO_4^{2-}, and SO_2, was a unique strength of this study. All results were stratified by gender. Used Cox proportional hazards analysis, adjusting for age at enrollment, past smoking, education, and alcohol use.	Lung cancer incidence relative risk: Male: RR = 3.72 (95%CI: 1.91, 7.28); Female: RR = 2.78 (95%CI: 1.51, 5.12) per 5-ppb increase in SO_2. Case number very small (16 for male, 20 for female).

TABLE AX5.9 (cont'd). ASSOCIATIONS OF LONG-TERM EXPOSURE TO SULFUR DIOXIDE WITH MORTALITY

Reference, Location, Study Period	Mean SO_x Levels	Study Description	Results and Comments
UNITED STATES (cont'd)			
Dockery et al. (1993) Portage, WI; Topeka, KS; Watertown, MA; Harriman, TN; St. Louis, MO; Steubenville, OH 1974-1991.	24-h avg NO_2 ranged from 1.6 (Topeka) to 24.0 (Steubenville) ppb.	A prospective cohort study to study the effects of air pollution with main focus on PM components in six U.S. cities, which were chosen based on the levels of air pollution (Portage, WI, the least polluted to Steubenville, OH, the most polluted). Cox proportional hazards regression was conducted with data from a 14-to-16-yr follow-up of 8,111 adults in the six cities, adjusting for smoking, sex, BMI, occupational exposures, etc. $PM_{2.5}$ and sulfate were associated with these causes of deaths.	SO_2 result presented only graphically. Fine particles and sulfate showed better fit than SO_2.
Krewski et al. (2000) Re-analysis and sensitivity analysis of Dockery et al. (1993) study.	24-h avg NO_2 ranged from 1.6 (Topeka) to 24.0 (Steubenville) ppb	Gaseous pollutants risk estimates were presented.	SO_2 showed positive associations with total (RR = 1.05 [95% CI: 1.02, 1.09] per 5-ppb increase in the average SO_2 over the study period), cardiopulmonary (1.05 [95% CI: 1.00, 1.10]), and lung cancer deaths (1.03 [95% CI: 0.91, 1.16]), but in this dataset, SO_2 was highly correlated with $PM_{2.5}$ (r = 0.85), sulfate (r = 0.85), and NO_2 (r = 0.84)
Krewski et al. (2000); Jerrett et al. (2003) Re-analysis/sensitivity analysis of Pope et al. (1995) study.	Multiyear avg of 24-h avg 9.3 ppb.	Re-analysis of Pope et al. (1995) study. Extensive sensitivity analysis with ecological covariates and spatial models to account of spatial pattern in the ACS data.	The relative risk estimates for total mortality was 1.06 (95% CI: 1.05, 1.07) per 5-ppb increase in the annual average SO_2. In the spatial filtering model (this was the model that resulted in the largest reduction of SO_2 risk estimate when sulfate was included), the SO_2 total mortality risk estimate was 1.07 (95% CI: 1.03, 1.11) in the single-pollutant model and 1.04 (95% CI: 1.02, 1.06) with sulfate in the model. The risk estimates for $PM_{2.5}$ and sulfate were diminished when SO_2 was included in the models.

TABLE AX5.9 (cont'd). ASSOCIATIONS OF LONG-TERM EXPOSURE TO SULFUR DIOXIDE WITH MORTALITY

Reference, Location, Study Period	Mean SO_x Levels	Study Description	Results and Comments
UNITED STATES (cont'd)			
Lipfert et al. (2000b; 2003) 32 Veterans Administration hospitals nationwide in the U.S. 1976-1996	SO_2 mean levels not reported.	Cohort study of approximately 50,000 U.S. veterans (all males) diagnosed with hypertension. Mean age at recruitment was 51 yrs. Exposure to O_3 during four periods (1960-1974, 1975-1981, 1982-1988, 1989-1996) associated with mortality over three periods (1976-1981, 1982-1988, 1989-1996). Long-term exposures to TSP, PM_{15}, PM_{10}, $PM_{2.5}$, $PM_{15-2.5}$, SO_4^{2-}, NO_2, and CO also analyzed. Used Cox proportional hazards regression, adjusting for race, smoking, age, systolic and diastolic blood pressure, body mass index, and socioeconomic factors.	"SO_2 and Pb were considered less thoroughly". The authors presented only qualitative results for SO_2 from the "Screening regressions" which indicated negatively significant risk estimate in the univariate model and non-significant positive estimate in the multivariate model.
Lipfert et al. (2006a) 32 Veterans Administration hospitals nationwide in the U.S. 1976-2001	Mean of the 95th percentile of the 24-h avg SO_2 for 1997-2001 period: 15.8 ppb.	Update of the Lipfert et al. (2000) study, with follow-up period extended to 2001. Study focused on the traffic density data. The county-level traffic density was derived by dividing vehicle-km traveled by the county land area. Because of the wide range of the traffic density variable, log-transformed traffic density was used in their analysis. They 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 weakly correlated with SO_2 ($r = 0.32$) in this data set.	RR using the 1997-2001 air quality data period: 0.99 (95% CI: 0.97, 1.01) per 5-ppb increase; in a single-pollutant model. The 2-pollutant model with the traffic density variable: 0.99 [95% CI: 0.96, 1.01] per 5 ppb.
Lipfert et al. (2006b) 32 Veterans Administration hospitals nationwide in the U.S. 1997-2001	Mean of the 95th percentile of the 24-h avg SO_2 for 1999-2001 period: 16.3 ppb.	Update of the Lipfert et al. (2000) study, examined $PM_{2.5}$ chemical constituents data. The analysis used county-level air pollution data for the period 1999-2001 and cohort mortality data for 1997-2001.	Traffic density was the most important predictor of mortality, but associations were also seen for elemental carbon, V, nitrate, and Ni. NO_2, ozone, and PM_{10} also showed positive but weaker associations. The risk estimate for SO_2 was essentially the same as that reported in the 2006a Lipfert et al. analysis (0.99 [95% CI: 0.96, 1.01] per 5 ppb) in a single-pollutant model. Multipollutant model results were not presented for SO_2.

TABLE AX5.9 (cont'd). ASSOCIATIONS OF LONG-TERM EXPOSURE TO SULFUR DIOXIDE WITH MORTALITY

Reference, Location, Study Period	Mean SO_x Levels	Study Description	Results and Comments
UNITED STATES (cont'd)			
Miller et al. (2007). 36 U.S. metropolitan areas from 1994 to 1998	Not reported.	Cohort study of 65,893 postmenopausal women between the ages of 50 and 79 yrs without previous cardiovascular disease in 36 U.S. metropolitan areas from 1994 to 1998. They examined the association between one or more fatal or nonfatal cardiovascular events and the women's exposure to air pollutants. Subject's exposures to air pollution were estimated by assigning the annual mean levels of air pollutants measured at the nearest monitor to the location of residence on the basis of its five-digit ZIP Code centroid. A total of 1,816 women had one or more fatal or nonfatal cardiovascular events, including 261 deaths from cardiovascular causes. Hazard ratios were estimated for the first cardiovascular event using Cox proportional hazards model, adjusting for age, race or ethnic group, smoking status, educational level, household income, BMI, and presence or absence of diabetes, hypertension, or hypercholesterolemia	In the single-pollutant model results, $PM_{2.5}$ showed the strongest associations with the CVD events by far among the pollutants, followed by SO_2 (HR of 1.07 [95% CI: 0.95, 1.20] per 5 ppb increase in the annual avg). In the multipollutant model (apparently, all the pollutants were included in the model), the $PM_{2.5}$'s association with the overall CVD events was even stronger and the estimate larger, and the association with SO_2 also became stronger and the estimate larger (1.13 [95% CI: 0.98, 1.30]). Correlations among these pollutants were not described, and therefore it is not possible to estimate the extent of confounding among these pollutants in these associations, but it is clear that $PM_{2.5}$ was the best predictor of the CVD events.
Pope et al. (1995) U.S. nationwide 1982-1989	Not analyzed/ reported.	Investigated associations between long-term exposure to PM and the mortality outcomes in the American Cancer Society cohort. 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. Cox proportional hazards model adjusted for smoking, education, BMI, and occupational exposures. $PM_{2.5}$ and sulfate were associated with total, cardiopulmonary, and lung cancer mortality, but not with mortality for all other causes.	Gaseous pollutants not analyzed.

TABLE AX5.9 (cont'd). ASSOCIATIONS OF LONG-TERM EXPOSURE TO SULFUR DIOXIDE WITH MORTALITY

Reference, Location, Study Period	Mean SO_x Levels	Study Description	Results and Comments
UNITED STATES (cont'd)			
Pope et al. (2002) U.S. nationwide 1982-1998	24-h avg mean of 118 MSA's in1980: 9.7 ppb; mean of 126 MSA's during 1982-1998: 6.7 ppb.	Prospective cohort study of approximately 500,000 members of American Cancer Society cohort enrolled in 1982 and followed through 1998 for all cause, cardiopulmonary, lung cancer, and all other cause mortality. Age at enrollment was 30+ yrs. Air pollution concentrations in urban area of residence at time of enrollment assessed from 1982 through 1998. Other pollutants considered include TSP, PM_{15}, PM_{10}, $PM_{2.5}$, $PM_{15-2.5}$, SO_4^{2-}, SO_2, NO_2, and CO.	$PM_{2.5}$ was associated with total, cardiopulmonary, lung cancer mortality, but not with deaths for all other causes. SO_2 was associated with all the mortality outcomes, including all other causes of deaths. SO_2's risk estimate for total mortality was 1.03 (95% CI: 1.02, 1.05) per 5 ppb increase (1982-1998 average). Residential location was known only at enrollment to study in 1982. Thus, exposure misclassification possible.
Willis et al. (2003) Re-analysis/sensitivity analysis of Pope et al. (1995) study.	Multiyear average of 24-h avg using MSA scales: 9.3 ppb; using county scales: 10.7 ppb.	Investigation of the effects of geographic scale over which the air pollution exposures are averaged. Exposure estimates were averaged over the county scale, and compared the original ACS results in which MSA scale average exposures were used. Less than half of the cohort used in the MSA-based study were used in the county scale based analysis because of the limited availability of sulfate monitors and because of the loss of subjects from the use of five-digit zip codes	In the analysis comparing the 2-pollutant model with sulfate and SO_2, they found that, in the MSA-scale model, the inclusion of SO_2 reduced sulfate risk estimates substantially (>25%), but not substantially (<25%) in the county-scale model. In the MSA-level anlaysis (with 113 MSA's), SO_2 relative risk estimate was 1.04 (95% CI: 1.02, 1.06) per 5 ppb increase, with sulfate in the model. In the county-level anaysis (91 counties) with sulfate in the model, the corresponding estimate was smaller (RR = 1.02 [95% CI: 1.00, 1.05]). The correlation between covariates are different between the MSA-level data and county-level data.

TABLE AX5.9 (cont'd). ASSOCIATIONS OF LONG-TERM EXPOSURE TO SULFUR DIOXIDE WITH MORTALITY

Reference, Location, Study Period	Mean SO_x Levels	Study Description	Results and Comments
EUROPE			
Elliott et al. (2007) Great Britain; 1966-1994 air pollution; 1982-1998 mortality in four periods.	24-h avg SO_2 levels declined from 41.4 ppb in 1966-1970 to 12.2 ppb in 1990-1994	A small area analysis of mortality rates in electoral ward, with the mean area of 7.4 km^2 and the mean population of 5,301 per electoral ward. Deaths rates were computed for four successive 4-yr periods from 1982 to 1994. The number of wards in these four periods ranged from 118 in the 1994-1998 period to 393 in the 1982-1986 period. Poisson model was fit to model observed deaths for each ward with a linear function for pollutant and random intercept, with and without adjustment for social deprivation.	They observed 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 periods and most recent mortality period (pollution levels were lower). The adjustment for social deprivation reduced the risk estimates for both pollutants. The adjusted risk estimates for SO_2 for the pooled mortality periods using the most recent exposure windows were: 1.021 (95% CI: 1.018, 1.024) for all-cause; 1.015 (95% CI: 1.011, 1.019) for cardiovascular; and 1.064% (95% CI: 1.056, 1.072) for respiratory causes per 5 ppb increase in SO_2. The risk estimates for the most recent mortality period using the most recent exposure windows were larger.
Filleul et al. (2005) Seven French cities 1975-2001	24-h avg SO_2 ranged from 5.9 ppb ("Area 3" in Lille) to 29.7 ppb ("Area 3" in Marseille) in the 24 areas in seven cities during 1974-1976. Median levels during 1990-1997 ranged from 3.0 ppb (Bordeaux) to 8.2 ppb (Rouen) in the five cities where data were available.	Cohort study of 14,284 adults who resided in 24 areas from seven French cities when enrolled in the PAARC survey (air pollution and chronic respiratory diseases) in 1974. Daily measurements of SO_2, TSP, black smoke, NO_2, and NO were made in 24 areas for three yrs (1974–76). Cox proportional hazards models adjusted for smoking, educational level, BMI, and occupational exposure. Models were run before and after exclusion of six area monitors influenced by local traffic as determined by the NO/NO_2 ratio >3.	Before exclusion of the six areas, none of the air pollutants were 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 (1.01 [95% CI: 0.97, 1.06] per 5 ppb multi-yr average). From these results, the authors noted that inclusion of air monitoring data from stations directly influenced by local traffic could overestimate the mean population exposure and bias the results. It should be noted that the table describing air pollution levels in Filleul et al.'s report indicates that the SO_2 levels in these French cities declined markedly between 1974-76 and 1990-1997 period, by a factor of 2 to 3, depending on the city, whereas NO_2 levels between the two periods were variable, increased in some cities, and decreased in others. These changes in air pollution levels over the study period complicates interpretation of reported risk estimates.

TABLE AX5.9 (cont'd). ASSOCIATIONS OF LONG-TERM EXPOSURE TO SULFUR DIOXIDE WITH MORTALITY

Reference, Location, Study Period	Mean SO_x Levels	Study Description	Results and Comments
EUROPE (cont'd)			
Nafstad et al. (2004) Oslo, Norway 1972-1998.	The yearly averages of 24-h avg SO_2 were reduced with a factor of 7 during the study period from 5.6 ppb in 1974 to 0.8 ppb in 1995.	Cohort study of 16,209 Norwegian men 40-49 yrs of age living in Oslo, Norway, in 1972-1973. Data from the Norwegian Death Register were linked with estimates of average yrly air pollution levels at the participants' home addresses from 1974 to 1998. NO_x, rather than NO_2 was used. Exposure estimates for NO_x and SO_2 were constructed using models based on the subject's address, emission data for industry, heating, and traffic, and measured concentrations. Addresses linked to 50 of the busiest streets were given an additional exposure based on estimates of annual average daily traffic. Cox proportional-hazards regression was used to estimate associations between exposure and total and cause-specific mortality, adjusting for age strata, education, occupation, smoking, physical activity level, and risk groups for cardiovascular diseases.	NO_x was associated with total, respiratory, lung cancer, and ischemic heart disease deaths. SO_2 did not show any associations with mortality (e.g., 0.97 [95% CI: 0.94, 1.01] per 5 ppb multi-yr average). The risk estimates presented for categorical levels of these pollutants showed mostly monotonic exposure-response relationships for NO_x, but not for SO_2. Note the very low levels of SO_2.
Nafstad et al. (2003) Oslo, Norway 1972-1998	The yrly averages of 24-h avg. SO_2 were reduced with a factor of 7 during the study period from 5.6 ppb in 1974 to 0.8 ppb in 1995.	Lang cancer incidence was examined in the above cohort. During the follow-up period, 418 men developed lung cancer.	NO_x was associated with lung cancer incidence. SO_2 showed no association (1.01; [95% CI: 0.92, 1.12] per 5 ppb multi-yr average).

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