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Integrated Science Assessment for Sulfur Oxides – Health Criteria

(First External Review Draft)

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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 (1981). 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.

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Abbreviations and Acronyms

α	alpha
ACS	American Cancer Society
ADS	annular denuder system
AHR	airways hyperreactiveness
AM	alveolar macrophages
APHEA	Air Pollution on Health: a European Approach (study)
APEX	Air Pollution Exposure (model)
APIMS	atmospheric pressure ionization mass spectrometer
ARIC	Atherosclerosis Risk in Communities (study)
ARP	Acid Rain Program
AQCD	Air Quality Criteria Document
asl	above sea level
atm	atmosphere
β	beta; the calculated Health Effect Parameter
B[*a*]P	benzo[*a*]pyrene
BHR	bronchial hyperresponsiveness
BS	black smoke
CAA	Clean Air Act
CAMP	Childhood Asthma Management Program
CASAC	Clean Air Scientific Advisory Committee
CASTNet	Clean Air Status and Trends Network
CDC	Centers for Disease Control and Prevention
CHAD	Consolidated Human Activities Database
CHF	congestive heart failure
CHS	Children's Health Study
CH_3-S-H	methyl mercaptan
CH_3-S-S-CH_3	dimethyl disulfide
CI	confidence interval
CMSA	consolidated metropolitan statistical area
CO	carbon monoxide
CoH	coefficient of haze
CONUS	continental United States
COPD	chronic obstructive pulmonary disease
CS_2	carbon disulfide
CVD	cardiovascular disease
DEN	diethylnitrosamine
DEP	diesel exhaust particle
DL	detection limit
DMS	dimethyl sulfide

ED	emergency department
ECG	electrocardiography; electrocardiogram
EIB	exercise-induced bronchial reactivity
ELF	epithelial lining fluid
EMECAM	Spanish Multicentre Study on Air Pollution and Mortality
EPA	U.S. Environmental Protection Agency
eNO	exhaled nitric oxide
ET	extrathoracic
FEMs	Federal Equivalent Methods
$FEV_{0.75}$	forced expiratory volume in 0.75 second
FEV_1	forced expiratory volume in 1 second
FPD	flame photometric detection
FPD-TA	flame photometric detection-thermal analysis
FRM	Federal Reference Method
FVC	forced vital capacity
GAM	Generalized Additive Model(s)
GIS	Geographic Information System
GLM	Generalized Linear Model(s)
GSH	glutathione; reduced glutathione
GST	glutathione *S*-transferase (e.g., GSTM1, GSTP1, GSTT1)
H^+	hydrogen ion
HEADS	Harvard-EPA Annular Denuder System
HEI	Health Effects Institute
HF	high frequency
HNO_2	nitrous acid
HNO_3	nitric acid
HO_2	hydroperoxyl; hydroperoxy radical
H_2O_2	hydrogen peroxide
HR	hazard ratio
HRV	heart rate variability
H_2S	hydrogen sulfide
HSO_3^-	hydrogen sulfite, bisulfite
HSO_4^-	bisulfate ion
H_2SO_4	sulfuric acid
hν	solar ultraviolet photon
ICD9	International Classification of Diseases, Ninth Revision
ICDs	implanted cardioverter defibrillators
Ig	immunoglobulin (e.g., IgA, IgE, IgG)
IHD	ischemic heart disease
IL	interleukin (e.g., IL-4, IL-6, IL-8)

IQR	interquartile range
ISA	Integrated Science Assessment
IUGR	intrauterine growth retardation
K	mass transfer coefficient
LF	low frequency
LOD	limit of detection
LRD	lower respiratory disease
MCh	methacholine
MENTOR	Modeling Environment for Total Risk for One-Atmosphere studies
MI	myocardial infarction
$MEF_{50\%}$	maximal midexpiratory flow at 50% of forced vital capacity
MMEF	maximal midexpiratory flow
MONICA	Monitoring Trend and Determinants in Cardiovascular Disease (registry)
MOZART-2	Model for Ozone and Related Chemical Tracers, version 2
MSA	metropolitan statistical area
N, n	number of observations
NAAQS	National Ambient Air Quality Standards
NaCl	sodium chloride
$NaCO_3$	sodium carbonate
NADP	National Atmospheric Deposition Program
NAMS	National Air Monitoring Stations
NAS	Normative Aging Study
NCICAS	National Cooperative Inner-City Asthma Study
NCore	National Core Monitoring Network
NERL	National Exposure Research Laboratory
NH_4^+	ammonium ion
NHAPS	National Human Activity Pattern Survey
NHANES	National Health and Nutrition Examination Survey
NMMAPS	National Morbidity, Mortality, and Air Pollution Study
NO	nitric oxide
NO_2	nitrogen dioxide
NO_3	nitrate radical
NO_3^-	nitrate ion
NO_x	oxides of nitrogen
NR	not reported
NTN	National Trends Network
O_2	molecular oxygen, diatomic oxygen
O_3	ozone
OCS	carbonyl sulfide
OH	hydroxyl radical

OR	odds ratio
P, p	probability value
PAARC	Air Pollution and Chronic Respiratory Diseases (study)
PAH	polycyclic aromatic hydrocarbon
PC(SO_2)	provocative concentration of SO_2 that produces a 100% increase in specific airways resistance
PD20FEV_1	20% decrease in forced expiratory volume in 1 second
PD20	provocative dose that produces a 20% decrease in FEV_1
PD100	provocative dose that produces a 100% increase in sRAW
PEACE	Pollution Effects on Asthmatic Children in Europe (study)
PEC	pulmonary endocrine cell
PEF	peak expiratory flow
PEMs	personal exposure monitors
PF	pulsed fluorescence
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
PMT	photomultiplier tube
ppb	parts per billion
ppbv	parts per billion by volume
ppm	parts per million
pptv	parts per trillion by volume
PRB	policy relevant background
PS	passive sample
r	correlation coefficient
R^2	multiple correlation coefficient
RAS	roll-around system
Raw	airways resistance
RH	relative humidity
r-MSSD	root mean square of successive differences in R-R intervals.
RR	rate ratio; relative risk
S^{2-}	sulfur radical
SAPALDIA	Study of Air Pollution and Lung Diseases in Adults
SAVIAH	Small-Area Variation in Air Pollution and Health (study)

SD	standard deviation
SDNN	standard deviation of normal R-R intervals
SES	socioeconomic status
SHEDS	Simulation of Human Exposure and Dose System
SIDS	sudden infant death syndrome
SNP	single nucleotide polymorphism
^{35}S	sulfur-35 radionuclide
SLAMS	State and Local Air Monitoring Stations
SO	sulfur monoxide
SO_2	sulfur dioxide
SO_3	sulfur trioxide
SO_3^{2-}	sulfite ion
SO_4^{2-}	sulfate ion
SO_x	sulfur oxides
S_2O	disulfur monoxide
SPM	suspended particulate matter
sRaw	specific airways resistance
STN	Speciation Trends Network
τ	tau; atmospheric lifetime
TBARS	thiobarbituric acid reactive substances
TEA	triethanolamine
TNF	tumor necrosis factor (e.g., TNF-α)
TSP	total suspended particles
URI	upper respiratory infections
UV	ultraviolet
$\dot{V}_E$	minute ventilation

1. INTRODUCTION

The draft 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).[1] The draft ISA is intended to "accurately reflect the latest scientific knowledge useful in indicating the kind and extent of identifiable effects on public health which may be expected from the presence of [a] pollutant in ambient air" (Clean Air Act, Section 108 (42 U.S.C. 7408)).[2] The draft ISA contains the key information and judgments formerly found in the Air Quality Criteria Document (AQCD) for Sulfur Oxides (SO_x), and a series of Annexes to the draft ISA provide more extensive and detailed summaries of the most pertinent scientific literature. The draft ISA thus serves to update and revise the information included in the AQCD published by the U.S. Environmental Protection Agency (EPA) in 1982 (U.S. Environmental Protection Agency, 1982).

The draft ISA for this review of the SO_2 NAAQS critically evaluates and integrates scientific information on the health effects associated with exposure to sulfur oxides in the ambient air. It focuses on scientific information that has become available since the last review and reflects the current state of knowledge on the most relevant issues pertinent to the review of the primary SO_2 NAAQS. The ISA is supported by a more detailed and comprehensive assessment of the scientific literature, which will be compiled into a series of annexes. Together, the ISA and annexes replace the AQCD that was prepared in previous NAAQS reviews.

SO_2 is one of a group of substances known as sulfur oxides, which include multiple gaseous (e.g., SO_2, sulfur trioxide [SO_3], particulate (e.g., sulfate [SO_4^{2-}], or sulfuric acid [H_2SO_4]) species. For the current review, multiple species of sulfur oxides are considered as appropriate and as allowed by the available data. For example, descriptions of the atmospheric chemistry of sulfur oxides include both gaseous and particulate species, because a meaningful analysis would not be possible otherwise. In addition, the health effects of gaseous sulfur oxides other than SO_2 are considered when information on these other species is available. Finally, the

[1] Information on legislative requirements and history of SO_2 NAAQS reviews are presented in the Preface.

[2] The secondary NAAQS for SO_2 is being reviewed independently, in conjunction with the review of the secondary NAAQS for nitrogen dioxide (NO_2). A review of the primary NAAQS for NO_2 is also underway.

possible influence of other atmospheric pollutants on the interpretation of the role of SO_2 in health effects studies is considered, including interactions of SO_2 with other pollutants that co-occur in the environment (e.g., nitrogen oxides, carbon monoxide [CO], ozone [O_3], particulate matter [PM]).

As discussed in the Draft Integrated Plan for the Review of the Primary NAAQS for Sulfur Dioxide (U.S. Environmental Protection Agency, 2007), a series of policy-relevant questions frames this review of the scientific evidence to provide a scientific basis for a decision on whether the current primary NAAQS for SO_2 (0.030 parts per million [ppm], annual average; 0.14 ppm, 24-h average) should be retained or revised. The draft ISA focuses on evaluation of the newly available scientific evidence to best inform consideration of these framing questions, including the following:

- Has new information altered/substantiated the scientific support for the occurrence of health effects following short- and/or long-term exposure to levels of SO_x found in the ambient air?
- Does new information impact conclusions from the previous review regarding the effects of SO_x on susceptible populations?
- At what levels of SO_x exposure do health effects of concern occur?
- Has new information altered conclusions from previous reviews regarding the plausibility of adverse health effects caused by SO_x exposure?
- To what extent have important uncertainties identified in the last review been reduced and/or have new uncertainties emerged?
- What are the air quality relationships between short-term and longer-term exposures to SO_x?

1.1 DOCUMENT DEVELOPMENT

EPA formally initiated the current review of the SO_2 NAAQS by announcing the commencement of the review in the Federal Register with a call for information in May 2006 (Federal Register, 2006). In addition to the call for information, publications are identified through an ongoing literature search process that includes searching MEDLINE and other databases using as key words the terms: sulfur oxides, sulfur dioxide, SO_x, SO_2, and reduced

sulfur gases. This search strategy is periodically reexamined and modified to enhance identification of pertinent published papers. Additional papers are identified for inclusion in the publication base in several ways. First, EPA staff reviews pre-publication tables of contents for journals in which relevant papers may be published. Second, expert chapter authors are charged with independently identifying relevant literature. Finally, additional publications that may be pertinent are identified by both the public and the Clean Air Scientific Advisory Committee (CASAC) during the external review process. The studies identified include research published or accepted for publication by a date determined to be as inclusive as possible given the relevant target dates in the NAAQS review schedule. Some additional studies, published after that date, may also be included if they provide new information that impacts one or more key scientific issues. The combination of these approaches should produce a comprehensive collection of pertinent studies to form the basis of the ISA and to appear summarized in the next ISA annexes.

The following sections briefly summarize criteria for selection of studies for this draft ISA. Consideration of these issues informs our judgments on the relative quality of individual studies and allows us to focus the assessment on the most pertinent studies.

Criteria for Selecting Epidemiological Studies

In selecting epidemiological studies for the present assessment, EPA considers whether a given study contains information on (1) short- or long-term exposures at or near ambient levels of SO_x; (2) health effects of specific SO_x species or indicators related to SO_2 sources; (3) health endpoints that repeat or extend findings from earlier assessments as well as those not previously researched; (4) susceptible and vulnerable populations to SO_x exposure; (5) multiple pollutant analyses and other approaches to address issues related to potential interactions (e.g., synergistic effects of SO_x with other pollutants), confounding (e.g., SO_x associations with health endpoints independent of copollutants), and effect modification (e.g., copollutant modification of SO_x effects on health endpoints); and/or (6) important methodological issues (e.g., lag of effects, model specifications, thresholds, mortality displacement). Among the epidemiological studies, particular emphasis is focused on those relevant to standard setting in the United States. Specifically, studies conducted in the United States or Canada will be generally accorded more text discussion than those from other geographic regions, as the potential impacts of different health care systems and the underlying health status of populations need to be accounted for in the assessment. In addition, emphasis in the text is placed on discussion of (1) new, multicity

studies that employ standardized methodological analyses for evaluating SO_x effects, provide overall estimates for effects based on combined analyses of information pooled across cities, and examine results for consistency across cities; (2) new studies that provide quantitative effect estimates for populations of interest; and (3) studies that regard SO_x as a component of a complex mixture of air pollutants and, thus, give consideration to the levels of other copollutants, correlations of SO_x with these copollutants, and conduct multipollutant analyses.

Criteria for Selecting Experimental Studies

A set of explicit criteria is also used to select experimental studies for discussion. The selection of research evaluating controlled exposures of laboratory animals focuses primarily on those studies conducted at or near ambient SO_x concentrations and those studies that approximate expected human exposure conditions in terms of concentration and duration which will depend on the toxicokinetics and biological sensitivity of the particular laboratory animal examined. In discussing the mechanisms of SO_x toxicity, studies conducted under atmospherically relevant conditions are emphasized whenever possible. However, studies at higher levels are also considered to allow for species-to-species differences and potential differences in sensitivity between study subjects and especially susceptible human populations. For research evaluating controlled human exposures to SO_x, emphasis is placed on studies that (1) investigate effects on potentially susceptible populations such as asthmatics, particularly studies where subjects serve as their own control to compare responses following SO_x exposure and sham exposure and where responses in susceptible individuals are compared with those in age-matched healthy controls; (2) address issues such as dose-response or time-course of responses; (3) investigate exposure to SO_x separately and in combination with other pollutants; (4) include controlled exposures to filtered air; and (5) have sufficient sample size to adequately assess findings.

In assessing the scientific quality and relevance of epidemiological, animal toxicological, and human controlled exposure studies, the following considerations are taken into account: (1) where ambient air measurements are used, to what extent are the data of adequate quality and sufficiently representative to serve as credible exposure indicators; (2) were the study populations adequately selected and are they sufficiently well-defined to allow for meaningful comparisons between study groups; (3) are the health endpoint measurements meaningful and reliable; (4) are the statistical analyses appropriate, properly performed, and properly interpreted;

(5) are likely covariates (i.e., potential confounders or effect modifiers) adequately controlled or taken into account in the study design and statistical analyses; and (6) are the reported findings internally consistent. Consideration of these issues informs our judgments on the relative quality of individual studies and will allow us to focus the assessment on the most pertinent studies.

1.2 ORGANIZATION OF THE DOCUMENT

This draft ISA includes five chapters. This introductory chapter (Chapter 1) presents background information on the purpose of the document and characterizes how policy-relevant scientific studies are identified. Chapter 2 highlights key concepts or issues relevant to understanding the atmospheric chemistry, sources, exposure, and dosimetry of sulfur oxides, following a "source-to-dose" paradigm. Chapter 3 evaluates and integrates health information relevant to the review of the primary NAAQS for SO_2. In this chapter, findings from epidemiological, toxicological, and human clinical studies are integrated in an assessment of the relationships between exposure to ambient SO_x and health outcomes. The focus of this chapter is on the strength of underlying epidemiological or toxicological evidence and the coherence and plausibility of the body of evidence for effects on the respiratory, cardiovascular, or other system. Chapter 4 provides information relevant to the public health impact of exposure to ambient SO_x, including potential susceptible population groups. Finally, Chapter 5 summarizes key findings and conclusions from the atmospheric sciences, ambient air data analyses, exposure assessment, dosimetry, and health effects in consideration of the review of the NAAQS for SO_2.

The draft ISA is supplemented by a series of annexes, which are focused on accomplishing two goals. The first goal is to identify scientific research that is relevant to informing key policy issues. The second goal is to produce a base of evidence containing all of the publications relevant to the SO_2 NAAQS review. The annexes provide information on (1) the atmospheric chemistry of SO_x as well as the sampling/analytic methods for measurement of SO_x[3], (2) environmental concentrations and human exposure to SO_x, (3) dosimetry; (4) toxicological studies of SO_x health effects in laboratory animals, and (5) epidemiological

[3] This section will also provide information on NO_2 in order to support the reviews of the primary and secondary NAAQS for both SO_2 and NO_2. The atmospheric chemistry of NO_x and SO_x are intricately linked. Therefore, discussion of their combined chemistry is more effective and more efficient than a separate discussion of each pollutant.

studies of health effects from short- and long-term exposure to SO_x. More detailed information on various methods and results for the health studies is summarized in tabular form in the annex. These tables are generally organized to include information about (1) concentrations of SO_x and averaging times, (2) description of study methods employed, (3) results and comments, and (4) quantitative outcomes for SO_x effect estimates.

2. SOURCE-TO-TISSUE DOSE

This chapter provides basic information about concepts and findings that relate to considerations in atmospheric science, human exposure assessment, and human dosimetry. It is meant to serve as a prologue for detailed discussions of evidence on health effects that will follow in Chapters 3 and 4. Section 2.1 provides an overview of the atmospheric chemistry processes involved in the oxidation of SO_2 and those involved in the production of SO_2 from reduced sulfur gases in the atmosphere. Sources of SO_2 are presented in Section 2.2. A description of the methods for measuring SO_2 and issues associated with its measurement are presented in Section 2.3. Data for ambient SO_2 concentrations are characterized in Section 2.4. Policy Relevant Background concentrations of SO_2, i.e., those concentrations that basically define uncontrollable levels are also presented in Section 2.4. Factors governing personal exposures to SO_2 and associated issues are discussed in Section 2.5. Finally, the dosimetry of SO_2 in the respiratory tract is discussed in Section 2.6. The order of topics in this chapter follows in large measure that given in the National Research Council paradigm for integrating air pollutant research (National Research Council, 1998).

2.1 ATMOSPHERIC CHEMISTRY

The only forms of monomeric sulfur oxides of interest in tropospheric chemistry are sulfur dioxide (SO_2) and sulfur trioxide (SO_3). 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 sulfuric acid (H_2SO_4) which then partitions into the aqueous phase of particles. Thus, only SO_2 is present in the tropospheric boundary layer at concentrations significant for atmospheric chemistry and human exposures.

SO_2 is oxidized either in the gas phase or in the aqueous phase in cloud drops because it is highly water-soluble. The gas phase oxidation of SO_2 proceeds through the reaction:

$$SO_2 + OH + M \rightarrow HSO_3 + M \qquad (2\text{-}1)$$

followed by:

$$HSO_3 + O_2 \rightarrow SO_3 + HO_2 \quad (2\text{-}2)$$

$$SO_3 + H_2O \rightarrow H_2SO_4 \quad (2\text{-}3)$$

Because 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 the reactions of SO_2 with either the hydroperoxyl (HO_2) or nitrate radical (NO_3) are too low to be significant (JPL, 2003).

The major sulfur species in clouds are hydrogen sulfite (HSO_3^-) and the sulfite ion (SO_3^{2-}) (both of which are derived from the dissolution of SO_2 in water and are referred to as S(IV)), and bisulfate ion (HSO_4^-) and sulfate (SO_4^{2-}) (which are referred to as S(VI)). The chief species capable of oxidizing S(IV) to S(VI) in cloud water are ozone (O_3), peroxides (either hydrogen peroxide [H_2O_2] or organic peroxides), hydroxyl (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 (1999), and Jacobson (2002). Following Jacobson (2002), the steps involved in the aqueous phase oxidation of SO_2 can be summarized as follows:

Dissolution of SO_2

$$SO_2(g) \Leftrightarrow SO_2(aq) \quad (2\text{-}4)$$

The formation and dissociation of H_2SO_3

$$SO_2(aq) + H_2O(aq) \Leftrightarrow H_2SO_3 \Leftrightarrow H^+ + HSO_3^- \Leftrightarrow 2H^+ + SO_3^{2-} \quad (2\text{-}5)$$

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

$$HSO_3^- + H_2O_2 + H^+ \Leftrightarrow SO_4^{2-} + H_2O + 2H^+ \quad (2\text{-}6)$$

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

For pH up to about 5.3, H_2O_2 is the dominant oxidant, while at pH > 5.3, O_3 followed by Fe(III) become dominant. Higher pH levels 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 the ammonium ion (NH_4^+) is so effective in neutralizing acidity, when present, 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.

A comparison of the relative rates of oxidation by gas and aqueous phase reactions by Warneck (1999) indicates that only about 20% of SO_2 is oxidized by gas phase reactions. Thus, SO_2 is oxidized mainly by aqueous phase reactions. SO_2 is also removed from the atmosphere by dry deposition to moist surfaces, resulting in an atmospheric lifetime (τ) with respect to deposition on the order of 1 week, depending on humidity. The rate of oxidation of SO_2 to SO_4^{2-} ranges from 0.5 to ~2% h^{-1} as measured in power plant plumes (Pueschel and van Valin, 1978), resulting in an atmospheric lifetime ranging from about 2 days to about a week, with respect to this process. These two processes, oxidation and deposition, lead to an overall lifetime of SO_2 in the atmosphere of a few days.

2.2 SOURCES OF SULFUR OXIDES

Anthropogenic emissions of SO_2 are mainly from combustion of fossil fuels by electrical utilities (~66 %) and industry (~29%), with transportation-related sources making only a minor contribution (~5%) in 2002 (U.S. Environmental Protection Agency, 2006a). Thus, most SO_2 emissions originate from point sources. Since sulfur is a volatile component of fuels, it is almost quantitatively released during combustion. Hence, sulfur emissions can be calculated on the basis of sulfur content in fuel stocks to greater accuracy than can be done for other pollutants like nitrogen oxides or primary particulate matter (PM). However, the estimates given above are nationwide averages and may not accurately reflect the contribution of specific local sources determining a person's exposures to SO_2 at any given location and time. For example, shipping and associated in-port activities may be a significant source of SO_2 in some coastal cities (Wang et al., 2007).

The largest natural sources of SO_2 are volcanoes and biomass burning. Even so, SO_2 constitutes a relatively minor fraction (0.005% by volume) of total volcanic emissions (Holland, 1978). Volcanic sources of SO_2 in the United States are limited to the Pacific Northwest, Alaska, and Hawaii. Emissions of SO_2 from burning vegetation are generally in the range of 1 to 2% of the biomass burned (see e.g., Levine and Pinto, 1998). Sulfur is bound in amino acids in

vegetation and is released during combustion. Gaseous sulfur emissions from this source are mainly in the form of SO_2.

In addition to its role as an emitted primary pollutant, SO_2 is also produced by the photochemical oxidation of reduced sulfur compounds such as dimethyl sulfide, or DMS, (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). The sources for these compounds are mainly biogenic and are discussed in Annex Section 2.5. 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. 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). Except for OCS, which is lost mainly by photolysis ($\tau \sim 6$ months), all the other species are lost mainly by reaction with OH and NO_3 radicals and are relatively short-lived, having lifetimes of the order of a few hours to a few days (see Annex Section 2.3). Reaction with NO_3 radicals at night most likely represents the major loss process for DMS and methyl mercaptan. Although the mechanisms for the oxidation of DMS are still not completely understood, excess sulfate in marine aerosol appears related mainly to the production of SO_2 from the oxidation of DMS. Emissions of sulfur from natural sources are small compared to anthropogenic emissions within the United States. However, important exceptions occur locally as the result of volcanic activity, wildfires and in certain coastal zones as described here.

Because OCS is relatively long lived, it can survive oxidation in the troposphere and be transported upwards into the stratosphere. Crutzen (1976) proposed that its oxidation to sulfate in the stratosphere serves as the major source of mass in the stratospheric aerosol layer. However, Myhre et al. (2004) proposed that SO_2 transported upwards from the troposphere by deep convection is the most likely source, as the flux of OCS is too small. In addition, in-situ measurements of the isotopic composition of sulfur in stratospheric sulfate do not match those of OCS (Leung et al., 2002). Thus, anthropogenic SO_2 emissions could be important precursors to the formation of the stratospheric aerosol layer.

2.3 MEASUREMENT METHODS AND ASSOCIATED ISSUES

Currently, ambient SO_2 is measured using instruments based on pulsed ultraviolet (UV) fluorescence. The UV fluorescence monitoring method for atmospheric SO_2 was developed to improve upon the flame photometric detection (FPD) method, which in turn had displaced the pararosaniline wet chemical method. The pararosaniline method is still the EPA Federal Reference Method (FRM) for atmospheric SO_2, but it 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 Federal Equivalent Methods (FEMs) by EPA, but UV fluorescence has largely supplanted the FPD approach because of the UV method's inherent linearity, sensitivity, and the need for consumable hydrogen gas for the FPD method.

In the UV fluorescence method, SO_2 molecules absorb UV light at one wavelength and emit UV light at longer wavelengths in the process known as fluorescence through excitation of the SO_2 molecule to a higher energy (singlet) electronic state. Once excited, the molecule decays nonradiatively 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., a lower-energy photon) than the original, incident photon. The intensity of the emitted light is thus 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 at 330 nm is different from its excitation wavelength, an optical bandwidth filter is placed in front of the PMT to filter out any stray light from the UV lamp. A lens is located between the filter and the PMT to focus the fluorescence onto the active area of the detector and optimize the fluorescence signal. The limit of detection (LOD) for a non-trace level SO_2 analyzer is 10 ppb (CFR, 2006). However, most commercial analyzers have detection limits of about 3 ppb. The EPA through its NCore initiative (U.S. Environmental Protection Agency, 2005) is engaged in a program to install and operate newer trace-level SO_2 instruments that will increase the accuracy and precision of measurements at much lower levels.

Sources of Positive Interference

The most common source of interference to the UV fluorescence method for SO_2 is from other gases that fluoresce in a similar fashion to SO_2 when exposed to UV radiation of that wavelength. The most significant of these are polycyclic aromatic hydrocarbons (PAHs), of which naphthalene is a prominent example. Xylene is another common hydrocarbon that can cause fluorescent interference. Consequently, any such aromatic hydrocarbons that are in the optical chamber can act as a positive interference. To remove this source of interference, high-sensitivity SO_2 analyzers like 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.

Luke (1997) reported the positive artifacts of a modified pulsed fluorescence detector generated by the coexistence of nitric oxide (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 membrane, the interference from ppm levels of many aromatic hydrocarbons was eliminated entirely. NO fluoresces in a spectral region close to that of SO_2. However, in high-sensitivity SO_2 analyzers, the bandpass filter in front of the PMT is designed to prevent NO fluorescence from being detected at the PMT. Care must be exercised when using multicomponent calibration gases containing both NO and SO_2 so that the NO rejection ratio of the SO_2 analyzer is sufficient to prevent NO interference.

The most common source of positive bias (as contrasted 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.

Nicks and Benner (2001) reported a sensitive SO_2 chemiluminescence detector 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 when both air samples contain other detectable sulfur species. Assuming monotonic efficiency of the sulfur scrubber, all positive artifacts should also be reduced with this technique.

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, hence, an underestimation of SO_2 concentration in the air sample. Of particular concern is the variable water vapor content of air. Luke (1997) reported that the response of the detector could be reduced by about 7 and 15% at water vapor mixing ratios of 1 and 1.5 mole percent (relative humidity [RH] = 35 to 50% at 20 to 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 water on the inlet surfaces 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 dewpoint and to 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 might occur, forming SO_3 and SO (Calvert et al., 1978). However, the possibility that this artifact might be affecting measurements at very high SO_2 levels has not been examined.

Other Techniques for Measuring SO_2

More sensitive techniques for measuring SO_2 are available, but most of these systems are too complex and expensive for routine monitoring applications. However, techniques such as those described by Luke (1997) can be used to improve the sensitivity of ambient SO_2 monitors by eliminating sources of common interference.

2.4 ENVIRONMENTAL CONCENTRATIONS OF SULFUR OXIDES

2.4.1 Ambient Air Quality Data for Sulfur Dioxide and Other Sulfur Oxides

SO_2 data collected from the State and Local Air Monitoring Stations (SLAMS) and National Air Monitoring Stations (NAMS) networks show that the decline in SO_2 emissions from electric generating utilities has improved air quality. There has not been a single monitored exceedance of the SO_2 annual ambient air quality standard in the United States since 2000, according to the U.S. Environmental Protection Agency Acid Rain Program (ARP) 2005 Progress Report (U.S. Environmental Protection Agency, 2006b). EPA's trends data (www.epa.gov/airtrends) reveal that the national composite average SO_2 annual mean ambient concentration decreased by 48% from 1990 to 2005, with the largest single-year reduction coming in 1994-1995, the ARP's first operating year (U.S. Environmental Protection Agency, 2006b). Figure 2.4-1 depicts data for SO_2 emissions in the continental United States (CONUS) in these years that reflect this reduction with individual state-level totals.

These emissions data trends are consistent with the trends in the observed ambient concentrations from the Clean Air Status and Trends Network (CASTNet). Following implementation of the Phase I controls on ARP sources between 1995 and 2000, significant reductions in SO_2 and ambient SO_4^{2-} concentrations were observed at CASTNet sites throughout the eastern United States. The mean annual concentrations of SO_2 and SO_4^{2-} from CASTNet's long-term monitoring sites can be compared using two 3-year periods (1989 through 1991 and 2003 through 2005) in Figures 2.4-2a and 2.4-2b for SO_2, and Figures 2.4-3a and 2.4-3b for SO_4^{2-}.

From 1989 through 1991, that is, in the years prior to implementation of the ARP Phase I, the highest ambient mean concentrations of SO_2 and SO_4^{2-} were observed in western Pennsylvania and along the Ohio River Valley: >20 $\mu g\ m^{-3}$ (~8 ppb) SO_2 and >15 $\mu g\ m^{-3}$ SO_4^{2-}. As with SO_2, in the years since the ARP controls were enacted, both the magnitude of SO_4^{2-} concentrations and their areal extent have been significantly reduced, with the largest decreases again coming along the Ohio River Valley.

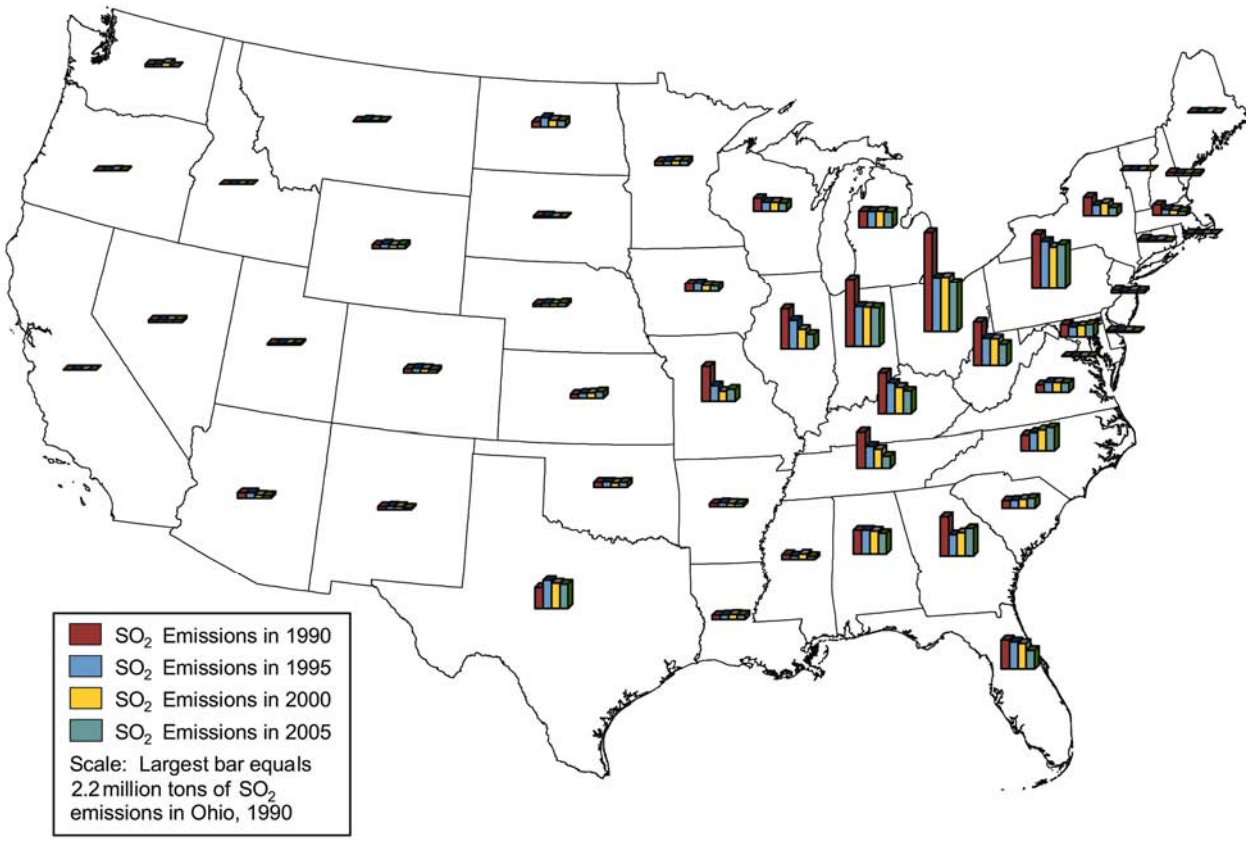

Figure 2.4-1. State-level SO_2 emissions, 1990-2005.

Source: Environmental Protection Agency Clean Air Markets Division (www.epa.gov/airmarkets/index.html).

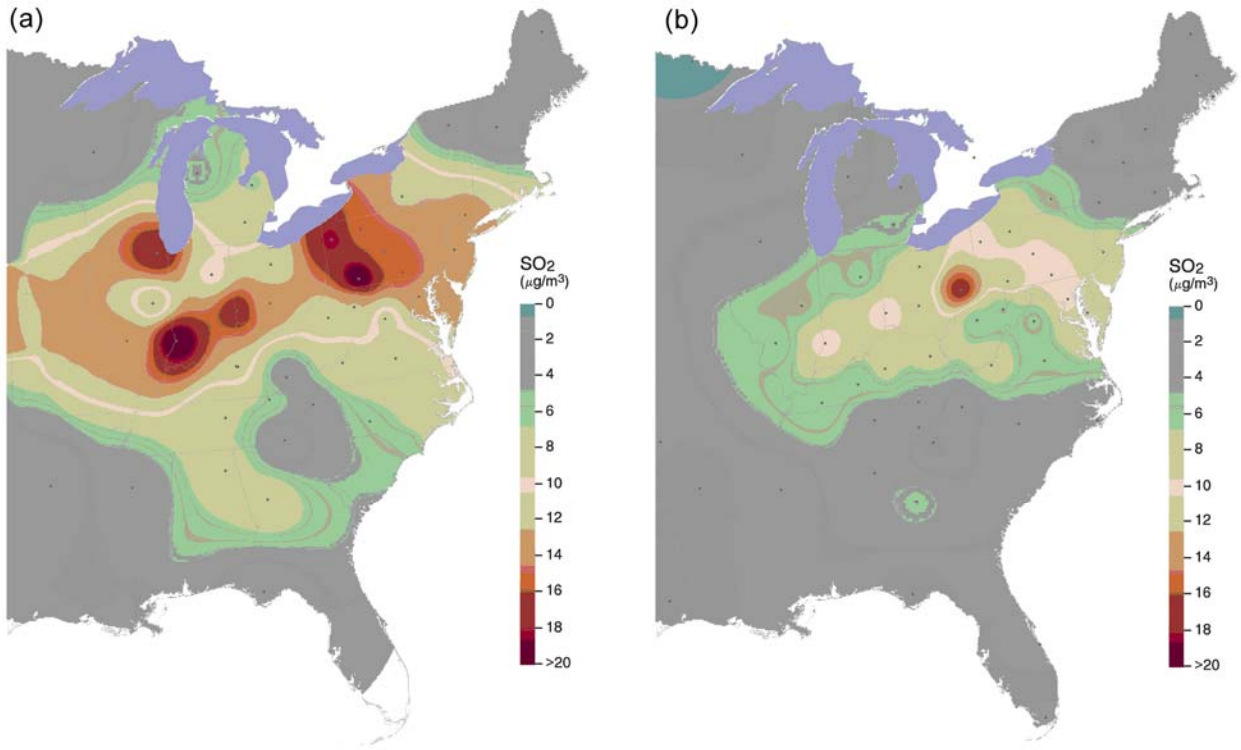

Figure 2.4-2. Annual mean ambient SO_2 concentration, (a) 1989 through 1991, and (b) 2003 through 2005.

* Dots on all maps represent monitoring sites. Lack of shading for Southern Florida indicates lack of monitoring coverage.

Source: Environmental Protection Agency, CASTNet (www.epa.gov/castnet/).

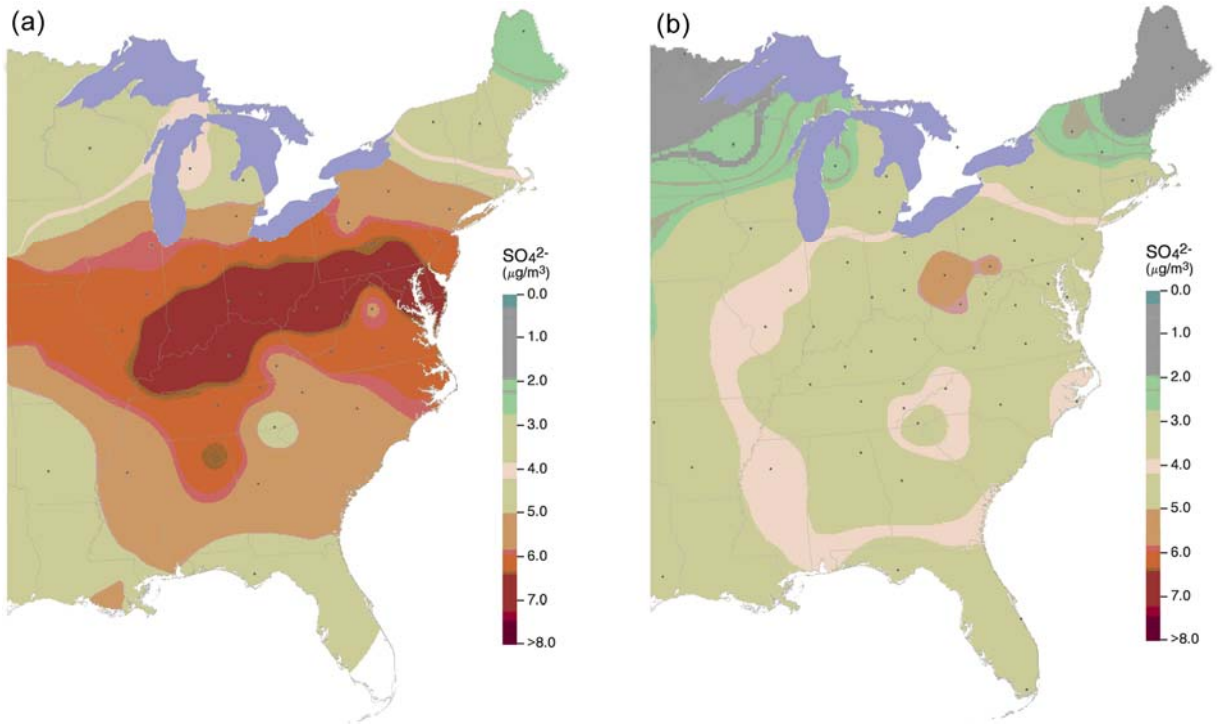

Figure 2.4-3. Annual mean ambient SO_4^{2-} Concentration, (a) 1989 through 1991, and (b) 2003 through 2005.

* Dots on all maps represent monitoring sites. Lack of shading for Southern Florida indicates lack of monitoring coverage.

Source: Environmental Protection Agency, CASTNet (www.epa.gov/castnet/).

Figure 2.4-4 depicts for the CONUS the magnitude and spatial distribution of SO_2 emissions in 2006 from sources in the ARP. This depiction shows clearly the continuing overrepresentation of SO_2 sources in the United States east of the Mississippi River as compared to west of it, a trend even stronger in the central Ohio River Valley and which was evident in the smoothed concentration plots in Figures 2.4-2a and 2.4-2b. As shown in Table 2.4-1, regional distributions of SO_2 and SO_4^{2-} concentrations averaged for the 3 years 2003 through 2005 reflect this geospatial emissions source difference as well.

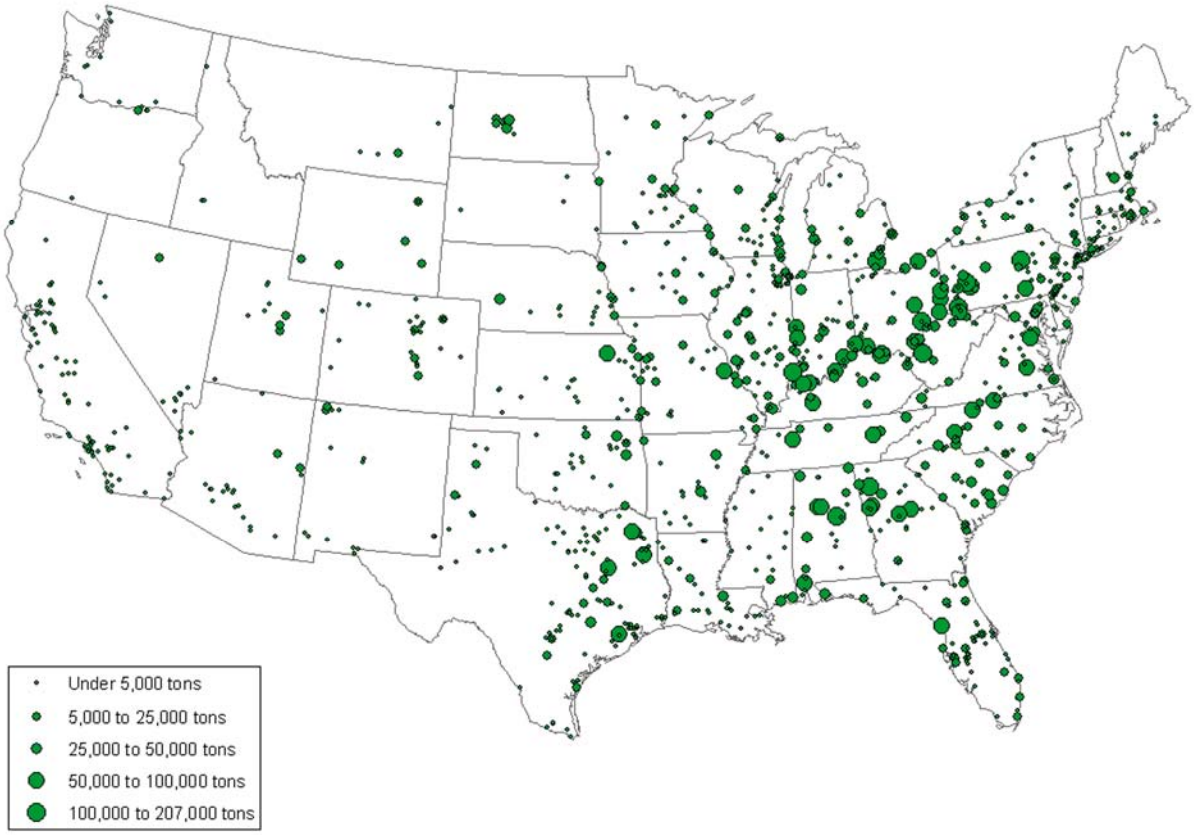

Figure 2.4-4. Annual SO_2 Emissions in 2006 for Acid Rain Program Cooperating Facilities.

Source: Environmental Protection Agency, Clean Air Markets Division (www.epa.gov/airmarkets/index.html).

2.4.2 Spatial and Temporal Variability of Ambient Sulfur Dioxide Concentrations

SO_2 concentrations have been falling throughout all regions of the United States as demonstrated by the CASTNet data reviewed above. In and around most individual Consolidated Metropolitan Statistical Areas (CMSAs), the trends are also toward lower SO_2 levels. Table 2.4-2 shows that many annual and even 1-h mean concentrations for the years 2003 through 2005 were consistently at or below the operating LOD of ~3 ppb for the standard SO_2 monitor deployed in the regulatory networks, while the aggregate mean value over all 3 years and all sites in and around the CMSAs was just above the LOD at ~4 ppb, and identical to the

1-h and 24-h means. Hence, it appears reasonable to aggregate up in time from available 1-h samples to daily and even annual exposure estimates.

Figure 2.4-5 shows the composite diurnal variation in hourly SO_2 concentrations in boxplot form from all monitors reporting SO_2 data into the Air Quality System (AQS) database. The AQS contains measurements of air pollutant concentrations in the 50 states, plus the District of Columbia, Puerto Rico, and the Virgin Islands for the six criteria air pollutants (SO_2, NO_2, PM, CO, Pb, O_3) and hazardous air pollutants. The same data were used to construct Table 2.4-2 and to configure Figure 2.4-5. As can be seen from Figure 2.4-5, concentrations beneath the 95th percentile level are indistinguishable from each other, but are typically in the range of only a few ppb. However, the peaks in the distribution at any hour of the day can be a factor of 10 or more higher than values in the bulk of the concentration distribution. Overall, there is some indication that the highest values are reached either at midday or during the middle of the night. Daytime peaks could result from down-mixing of air aloft due to convective activity, as SO_2 is emitted mainly by elevated sources. Nighttime peaks are more likely due to trapping of local emissions beneath a shallow nocturnal boundary layer.

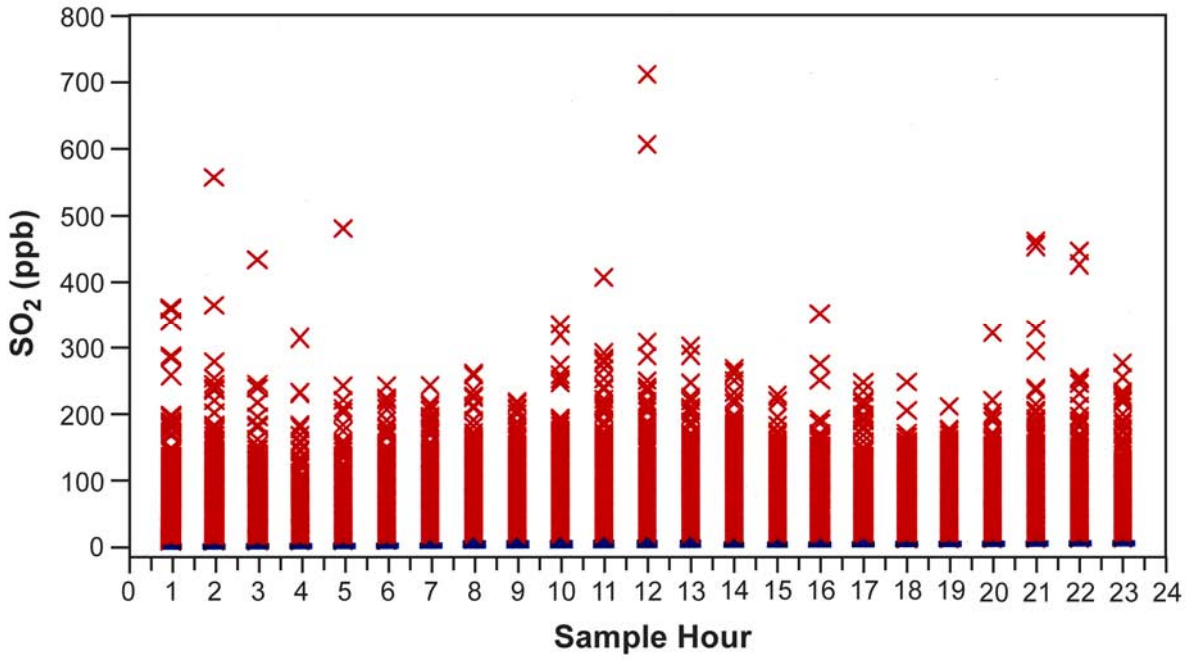

Figure 2.4-5. Boxplot of hourly SO_2 concentrations across all cities in focus.

To be sure, the maximum 1-h concentration observed at some sites in and around some CMSAs did still exceed the mean by a large margin, with maximum 1-h values in Table 2.4-2 of >600 ppb. However, the 50th percentile maximum value outside CMSAs, 5 ppb, was only slightly greater than the 1-h, 24-h, and annual mean value, 4 ppb. The 50th percentile maximum value inside CMSAs, 7 ppb, was 75% greater than these longer-term averages, reflecting heterogeneity in source strength and location. In addition, even with 1-h maximum values of >600 ppb, the maximum annualized mean value for all CMSAs was still <16 ppb, and, hence, below the current annual primary SO_2 NAAQS.

The strong east-to-west gradient in SO_2 emissions described above is well replicated in the observed concentrations in individual CMSAs. Thus, for example, values in Table 2.4-3 represent the mean annual concentrations in the years 2003 through 2005 for the 12 CMSAs with four or more SO_2 regulatory monitors, ranging from a reported low of ~1 ppb in Riverside, CA and San Francisco, CA to a high of ~12 ppb in Pittsburgh, PA and Steubenville, OH in the highest SO_2 source region.

The Pearson correlation coefficients (r) for multiple monitors in these CMSAs (see also Table 2.4-3) were generally very low for all cities, especially at the lower end of the observed concentration ranges, and are even negative at the very lowest levels on the West Coast. This reflects strong heterogeneity in SO_2 ambient concentrations even within any one CMSA and, therefore, indicates possibly different exposures of spatially distinct subgroups of humans in these CMSAs to these very low concentrations of SO_2. At higher concentrations, the r values were also higher. In some CMSAs, this heterogenerity may result from meteorological effects whereby a generally well-mixed subsiding air mass containing one or more relatively high concentration SO_2 plumes would be spread more nearly uniformly across an area than would faster-moving plumes with lower SO_2 concentrations. However, because the highest r values, i.e., those >0.7, correspond to the highest SO_2 concentrations, i.e., >6 and >10 ppb, instrument error may also play a role. Since the lowest SO_2 concentrations are at or below the operating LOD and demonstrate the lowest correlation across monitors that share at least some air mass characteristics most of the year, the unbiased instrument error in this range may be confounding interpretation of any possible correlation. This could be because the same actual ambient value would be reported by different monitors (with different error profiles) in the CMSA as different values in this lowest concentration range.

To better characterize the extent and spatiotemporal variance of SO_2 concentrations within each of the CMSAs having more than four SO_2 monitors (listed in Table 2.4-3), the means, minima, and maxima were computed from daily mean data across all available monitors for each month for the years 2003 through 2005. Because many of these CMSAs with SO_2 monitors also reported SO_4^{2-}, it is possible to compute the degree of correlation between SO_2, the emitted species, and SO_4^{2-}, the most prominent oxidized product from SO_2. SO_4^{2-} values, however, while averaged over all available data, are generally available at their monitoring sites on a schedule of only 1 in 3 days or 1 in 6 days. Furthermore, SO_2 and SO_4^{2-} monitors are not collocated throughout the CMSAs. For each of five example CMSAs, Figures 2.4-6 through 2.4-10 depict monthly values aggregated from daily means of (a) the monthly mean, minimum, and maximum SO_2 concentrations; (b) the monthly mean, minimum and maximum SO_4^{2-} concentrations; and (c) a scatterplot of SO_2 versus SO_4^{2-} concentrations.

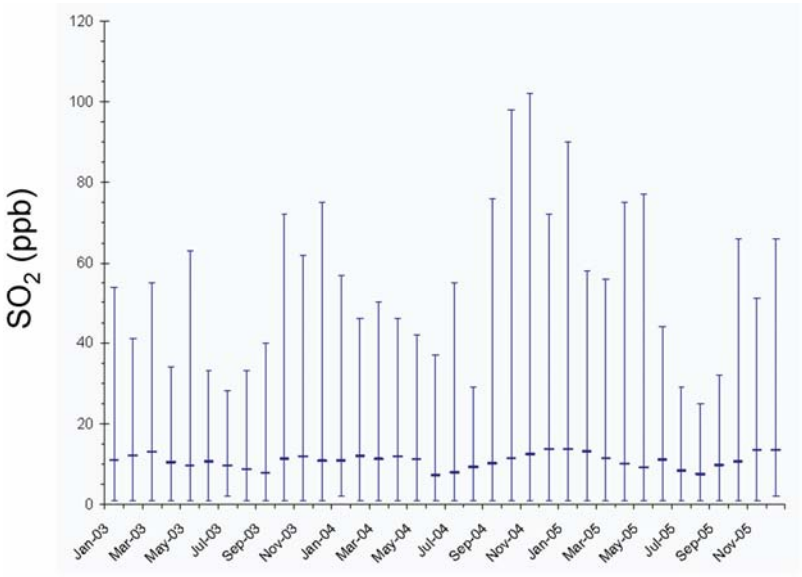

Figure 2.4-6(a). Monthly mean, minimum, and maximum SO_2 concentrations at Steubenville, OH for the years 2003 through 2005.

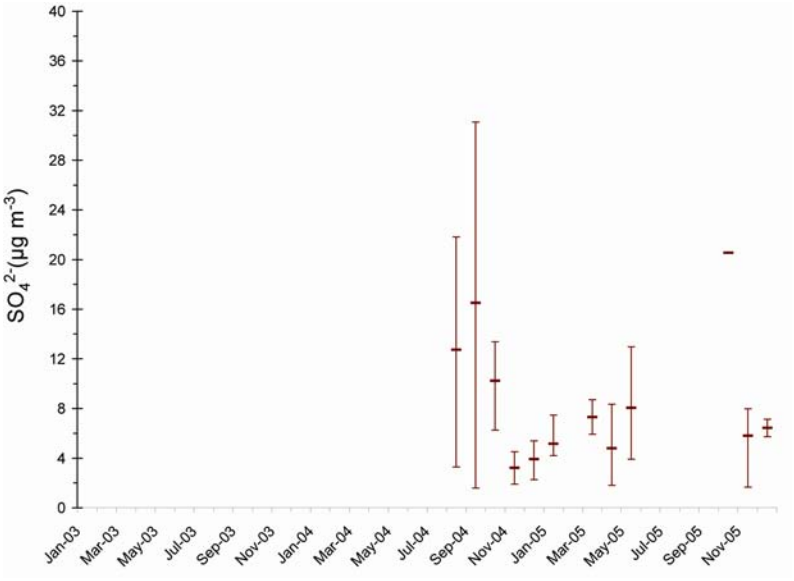

Figure 2.4-6(b). Monthly mean, minimum, and maximum SO_4^{2-} concentrations at Steubenville, OH for the years 2003 through 2005.

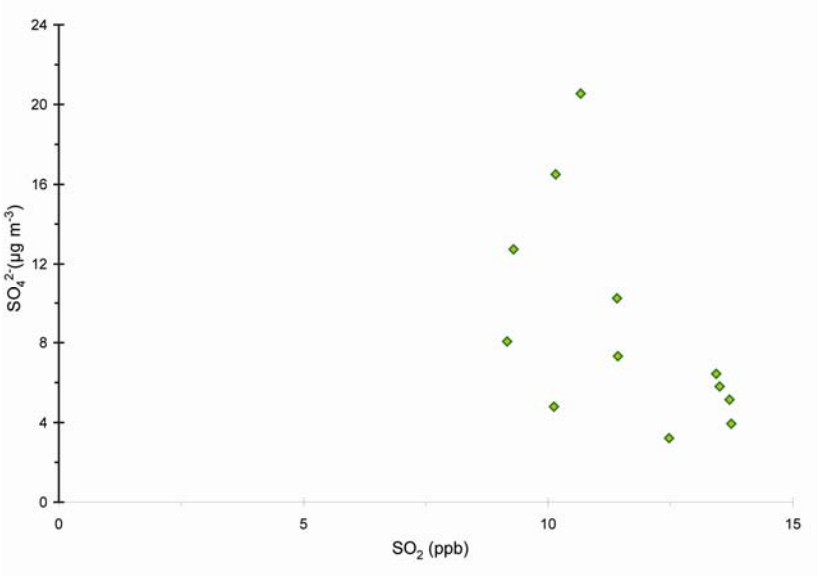

Figure 2.4-6(c). Monthly mean SO_4^{2-} concentrations as a function of SO_2 concentrations at Steubenville, OH for the years 2003 through 2005.

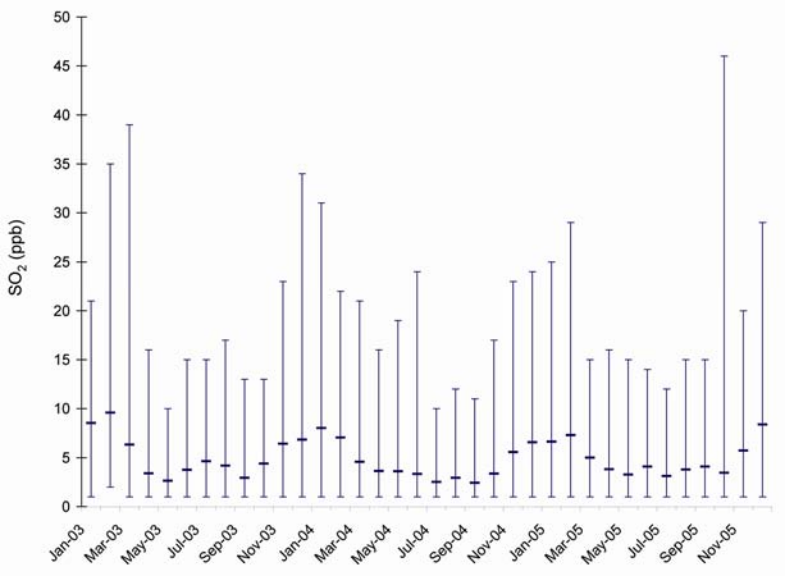

Figure 2.4-7(a). Monthly mean, minimum, and maximum SO_2 concentrations at Philadelphia, PA for the years 2003 through 2005.

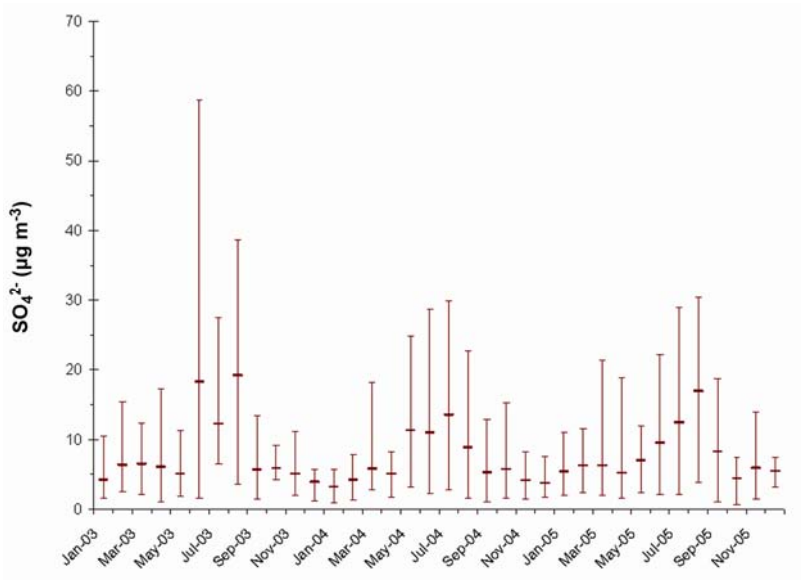

Figure 2.4-7(b). Monthly mean, minimum, and maximum SO_4^{2-} concentrations at Philadelphia, PA for the years 2003 through 2005.

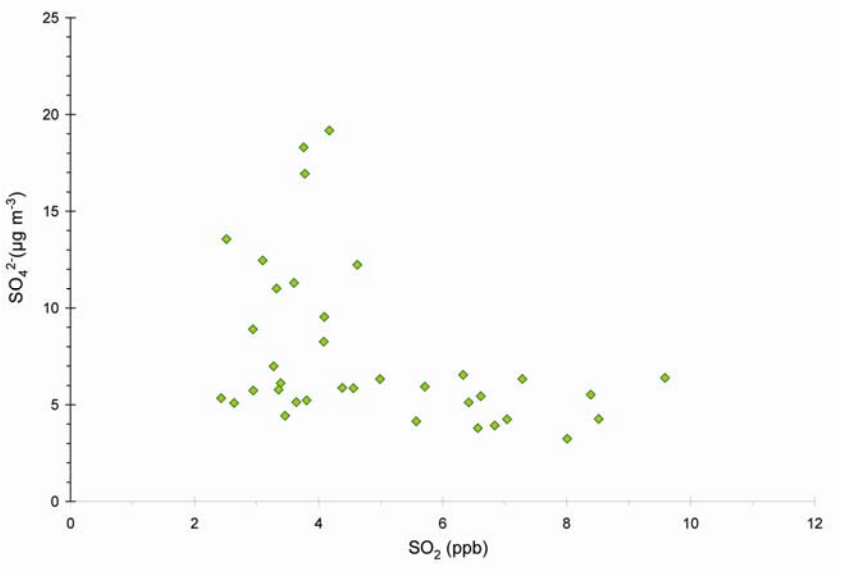

Figure 2.4-7(c). Monthly mean SO_4^{2-} concentrations as a function of SO_2 concentrations at Philadelphia, PA for the years 2003 through 2005.

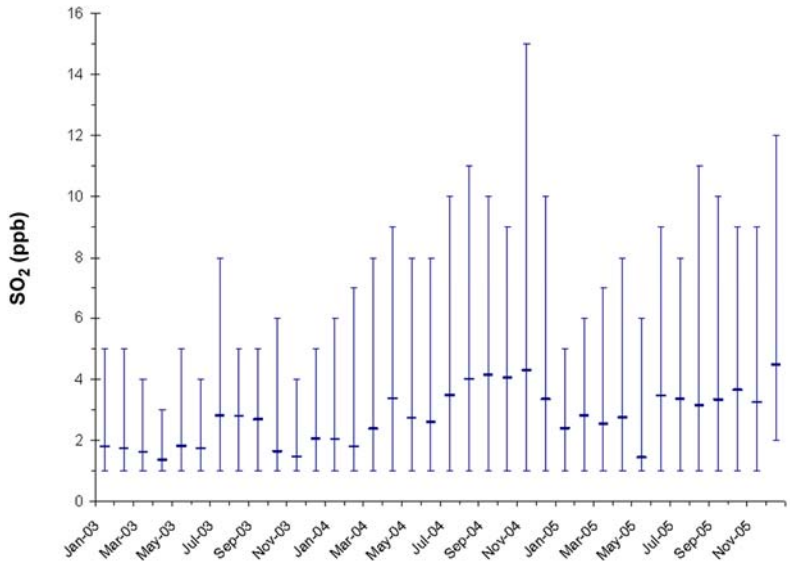

Figure 2.4-8(a). Monthly mean, minimum, and maximum SO_2 concentrations at Los Angeles, CA for the years 2003 through 2005.

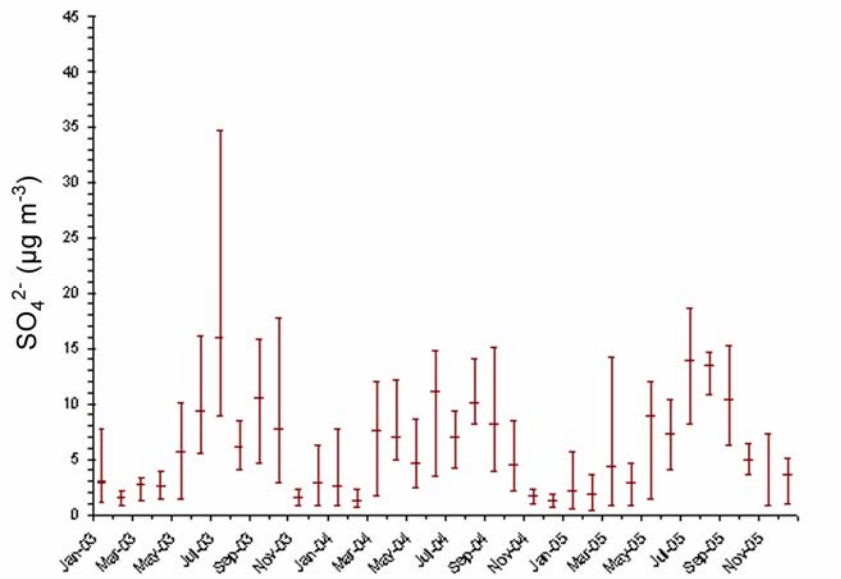

Figure 2.4-8(b). Monthly mean, minimum, and maximum SO_4^{2-} concentrations at Los Angeles, CA for the years 2003 through 2005.

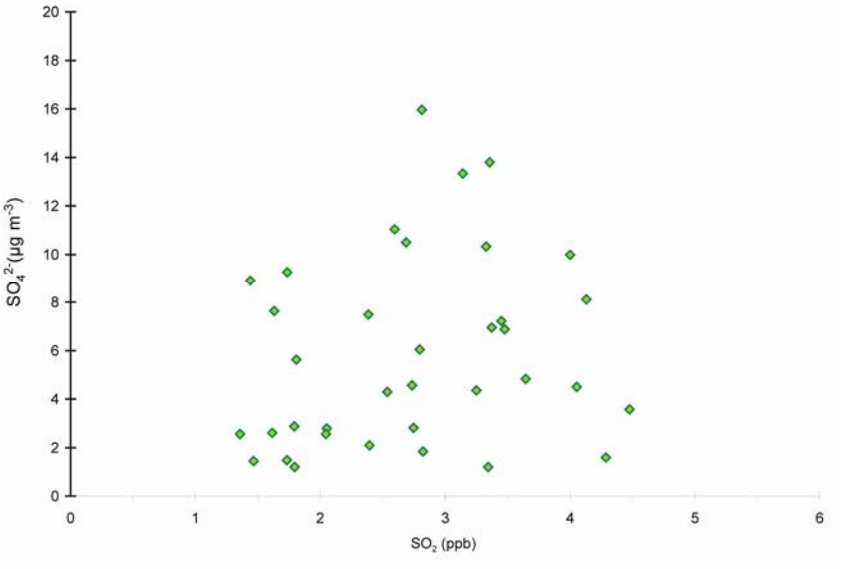

Figure 2.4-8(c). Monthly mean SO_4^{2-} concentrations as a function of SO_2 concentrations at Los Angeles, CA for the years 2003 through 2005.

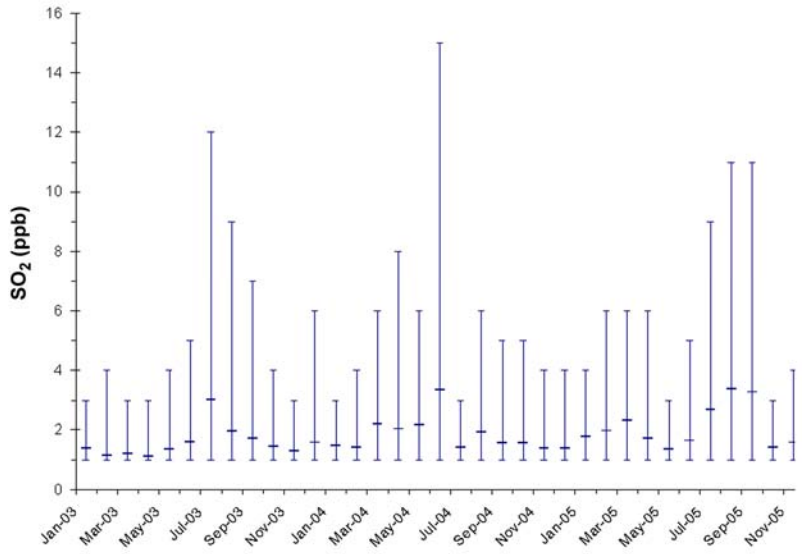

Figure 2.4-9(a). Monthly mean, minimum, and maximum SO_2 concentrations at Riverside, CA for the years 2003 through 2005.

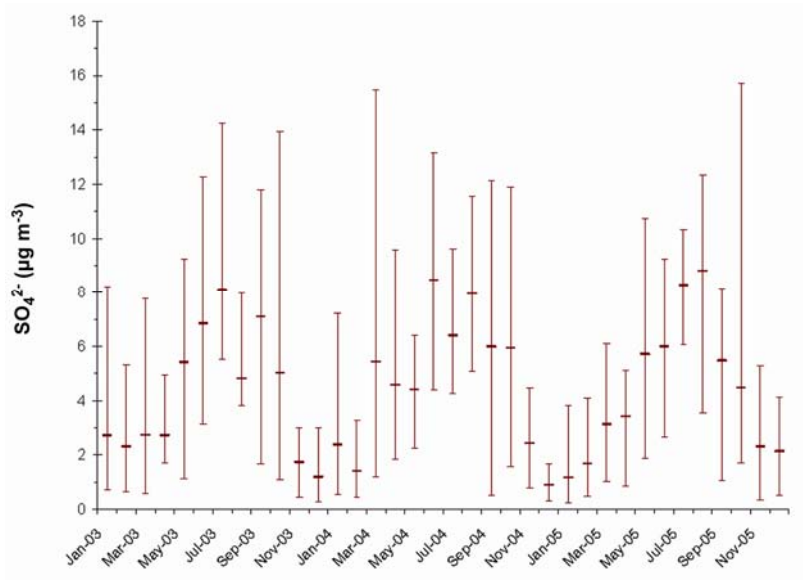

Figure 2.4-9(b). Monthly mean, minimum, and maximum SO_4^{2-} concentrations at Riverside, CA for the years 2003 through 2005.

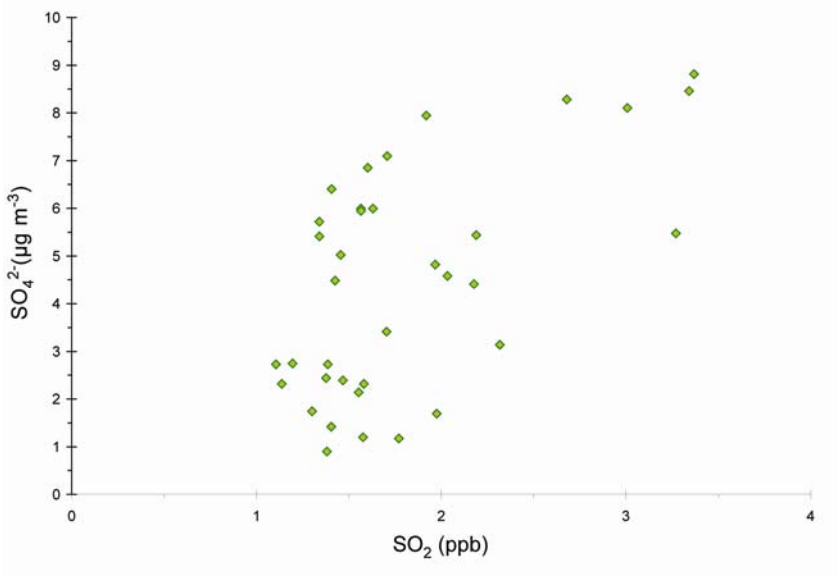

Figure 2.4-9(c). Monthly mean SO_4^{2-} concentrations as a function of SO_2 concentrations at Riverside, CA for the years 2003 through 2005.

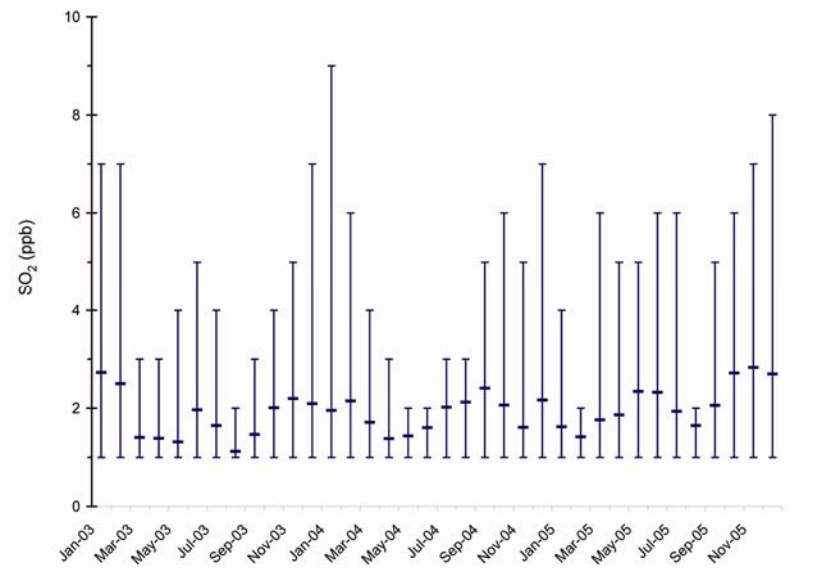

Figure 2.4-10(a). Monthly mean, minimum, and maximum SO_2 concentrations at Phoenix, AZ for the years 2003 through 2005.

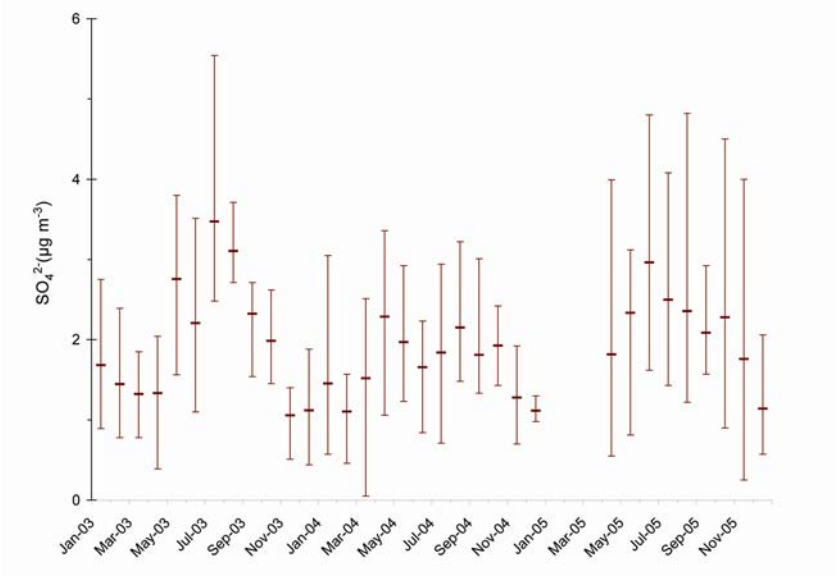

Figure 2.4-10(b). Monthly mean, minimum, and maximum SO_4^{2-} concentrations at Phoenix, AZ for the years 2003 through 2005.

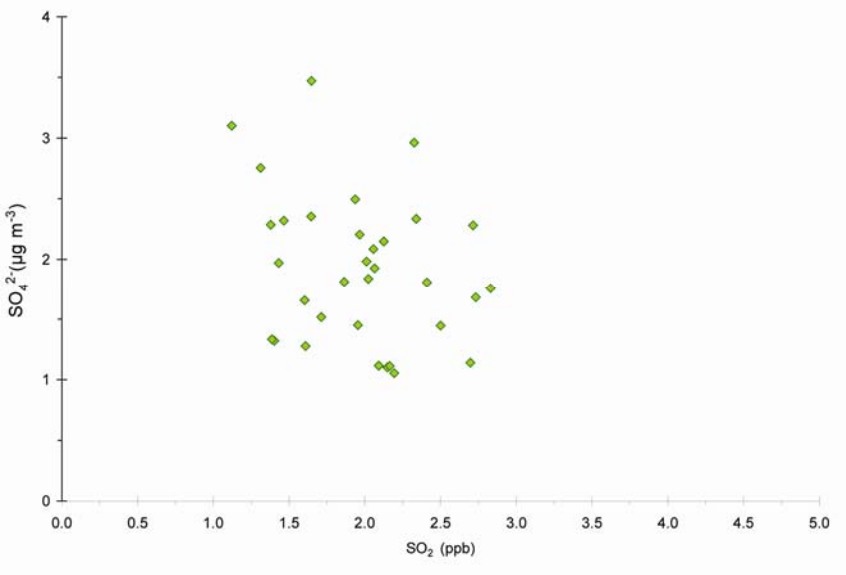

Figure 2.4-10(c). Monthly mean SO_4^{2-} concentrations as a function of SO_2 concentrations at Phoenix, AZ for the years 2003 through 2005.

Moving in order from the region of highest to lowest SO_2 concentrations, consider Steubenville, OH (Figure 2.4-6), where the SO_2 concentrations were highest of all 12 CMSAs with more than four monitors. Even here, however, all monthly mean SO_2 concentrations (Figure 2.4-6a) were substantially <30 ppb, though maximum daily means in some months were often >60 ppb, or even >90 ppb. Sulfate data at Steubenville (Figure 2.4-6b) were insufficient to make meaningful comparisons, though the 12 months of available SO_4^{2-} data suggest no correlation with SO_2 (see Figure 2.4-6c).

Next, consider Philadelphia, PA. SO_2 in Philadelphia, PA (Figure 2.4-7a) is present at roughly one-half the monthly mean concentrations in Steubenville, OH (compare Figures 2.4-6a and 2.4-7a), and demonstrates a strong seasonality with SO_2 concentrations peaking in winter. By contrast, SO_4^{2-} concentrations (Figure 2.4-7b) in Philadelphia peak in the three summer seasons, with pronounced wintertime minima. This seasonal anticorrelation still contains considerable monthly scatter, however, as Figure 2.4-7c makes clear.

Los Angeles, CA (see Figure 2.4-8a-c) presents a special case since its size and power requirements place a larger number of SO_2 emitters near it than would otherwise be expected on the West Coast. Concentrations of SO_2 (Figure 2.4-8a) demonstrate weak seasonality in these 3 years, with summertime means of ~3 to 4 ppb, and maxima generally higher than wintertime ones, though the highest means and maxima occur during the winter of 2004-2005. SO_4^{2-} at Los Angeles (Figure 2.4-8b) shows stronger seasonality, most likely because the longer summer days of sunny weather allow for additional oxidation of SO_2 to SO_4^{2-} than would be available in winter. Weak seasonal effects in SO_2 likely explain the complete lack of correlation between SO_2 and SO_4^{2-} here, as Figure 2.4-8c shows.

The Riverside, CA CMSA (see Figure 2.4-9a-c) presents the strongest example among the 12 examined for this study of correlation between SO_2 and SO_4^{2-} (Figure 2.4-9c), though even here the R^2 value is merely 0.3. Seasonal peaks are obvious in summertime for SO_2 and SO_4^{2-}, both at roughly half the ambient concentrations seen in Los Angeles (compare Figures 2.4-8a and 2.4-8b to Figures 2.4-9a and 2.4-9b). This is very likely due to Riverside's geographic location just downwind of the regionally large sources near Los Angeles and the prevailing westerly winds in summer. Again, as with Los Angeles, the summertime peaks in SO_4^{2-} are most likely due to the combination of peaking SO_2 and favorable meteorological conditions allowing more complete oxidation.

Phoenix, AZ was the CMSA with the lowest monthly mean SO_2 and SO_4^{2-} concentrations examined here (see Figures 2.4-10a and b). In Phoenix, nearly all monthly mean SO_2 values were at or below the regulatory monitors' operating LOD of ~3 ppb. SO_4^{2-} concentrations were equivalently low, roughly one-half the concentrations seen in Riverside, CA, for example. The monthly mean data in Figures 2.4-10a and 2.4-10b show strong summertime peaks for even these very low-level SO_4^{2-} observations, which, at ~1 to 3 μg m^{-3}, were generally one-half those in Philadelphia (compare Figure 2.4-7b). Figure 2.4-10a suggests some seasonality in SO_2, though anticorrelated with SO_4^{2-}; however, the trend is very weak, as the correlation scatterplot (Figure 2.4-10c) shows.

2.4.3 Policy Relevant Background Concentrations of Sulfur Dioxide

Background concentrations of SO_2 used for purposes of informing decisions about NAAQS are referred to as Policy Relevant Background (PRB) concentrations. PRB 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). PRB 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 cases where pollution levels can be controlled by U.S. regulations (or through international agreements with neighboring countries) from cases where pollution is generally uncontrollable by the United States. EPA assesses risks to human health and environmental effects from SO_2 levels in excess of PRB concentrations.

Contributions to PRB concentrations include natural emissions of SO_2 and photochemical reactions involving reduced sulfur compounds of natural origin as well as their long-range transport from outside of North America from whatever source. As an example, transport of SO_2 from Eurasia across the Pacific Ocean or the Arctic Ocean would carry PRB SO_2 into the U.S. A schematic diagram showing the major photochemical processes involved in the sulfur cycle including natural sources of reduced sulfur species from anaerobic microbial activity in wetlands and volcanic activity appears in Annex 2. Volcanoes 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 Annex Section 2.6.2.

Analysis of PRB Contributions to Sulfur Oxide Concentrations and Deposition over the United States

The MOZART-2 global model of tropospheric chemistry (Horowitz et al., 2003) is used to estimate 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, i.e., including all sources in the U.S. Canada and Mexico, was 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 the National Oceanic and Atmospheric Administration's National Center for Environmental Prediction (NOAA/NCEP) meteorological fields and the International Institute for Applied Systems Analysis (IIASA) 2000 emissions at a resolution of $1.9° \times 1.9°$ with 28 σ (sigma) levels in the vertical, and includes gas- and aerosol-phase chemistry. Results shown in Figure 2.4-11 are for the meteorological year 2001. An additional PRB simulation was conducted in which continental North American anthropogenic emissions were set to zero.

The role of PRB in contributing to SO_2 concentrations in surface air is examined first. Figure 2.4-11 shows the annual mean predicted SO_2 concentrations in surface air in the simulation including all sources, or the "base case" (top panel); the PRB simulation (middle panel); and the percentage contribution of the background to the total base case SO_2 (bottom panel). Maximum concentrations in the base case simulation, >5 ppb, occur along the Ohio River Valley (upper panel Figure 2.4-11). Background SO_2 concentrations are orders of magnitude smaller, below 10 parts per trillion (ppt) over much of the United States (middle panel; of Figure 2.4-11). 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 Coast where volcanic SO_2 emissions cause high PRB concentrations, the PRB contributes <1% to present-day SO_2 concentrations in surface air (bottom panel Figure 2.4-11).

When estimating background concentrations it is instructive to consider also measurements of SO_2 at relatively remote monitoring sites, i.e., sites located in sparsely populated areas not subject to obvious local sources of pollution. Berresheim et al. (1993) used a type of atmospheric pressure ionization mass spectrometer (APIMS) at Cheeka Peak, WA (48.30°N 124.62°W, 480 m asl), in April 1991 during a field study for dimethyl sulfide (DMS)

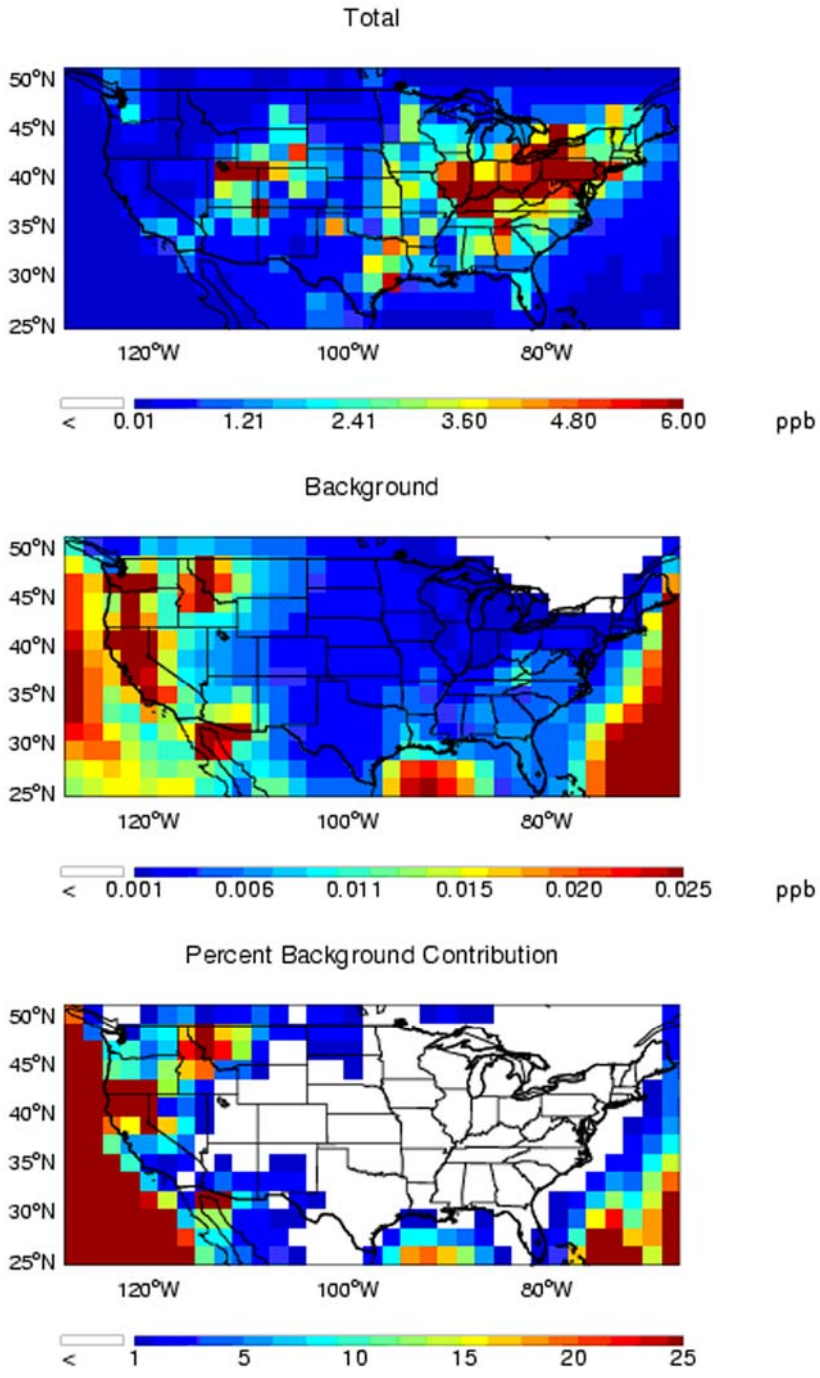

Figure 2.4-11. **Annual mean model-predicted concentrations of SO_2 (ppb) in surface air over the United States in the present-day (upper panel) and policy relevant background (middle panel) MOZART-2 simulations. The bottom panel shows the percentage contribution of the background to the present-day concentrations.**

oxidation products. SO_2 concentrations ranged between 20 and 40 ppt. Thornton et al. (2002) have also used an APIMS with an isotopically labeled internal standard to determine background SO_2 levels. SO_2 concentrations of 25 to 40 ppt were observed in northwestern Nebraska in October 1999 at 150 m above ground using the National Center for Atmospheric Research (NCAR)'s C-130 research aircraft. These data are comparable to remote central South Pacific convective boundary layer SO_2 data (Thornton et al., 1999).

As noted earlier in Section 2.4.2, volcanic sources of SO_2 in the United States are found in the Pacific Northwest, Alaska, and Hawaii. 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 produces SO_2 in such large amounts that as far as >100 km downwind of the island SO_2 concentrations can exceed 30 ppb (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 SO_4^{2-} aerosols for the past decade. Indeed, SO_2 levels in Volcanoes National Park, HI exceeded both the secondary 3-h and the primary 24-h average (24-h avg) NAAQS in 2004-2005. Since 1980, the Mount 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 effects 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 emitted variable quantities of SO_2 since its last major eruptions in 1986. Volcanoes in the Kamchatka peninsula in far eastern Siberia do not particularly affect the surface concentrations in northwestern North America.

Overall, the background contribution to SO_x over the United States is relatively small, with a maximum PRB of 0.030 ppb SO_2, except for areas with volcanic activity.

2.5 ISSUES ASSOCIATED WITH EVALUATING EXPOSURES TO SULFUR OXIDES

2.5.1 General Considerations for Personal Exposures

Human exposure to an airborne pollutant consists of contact between the human and the pollutant at a specific concentration for a specified period of time. People spend various

amounts of time in different microenvironments (Figure 2.5-1) characterized by different pollutant concentrations. The figure represents a composite average across the United States across all age groups. Different cohorts, e.g., the elderly, might be expected to exhibit different activity patterns. The integrated exposure of a person to a given pollutant is the sum of the exposures over all time intervals for all microenvironments in which the individual spent time.

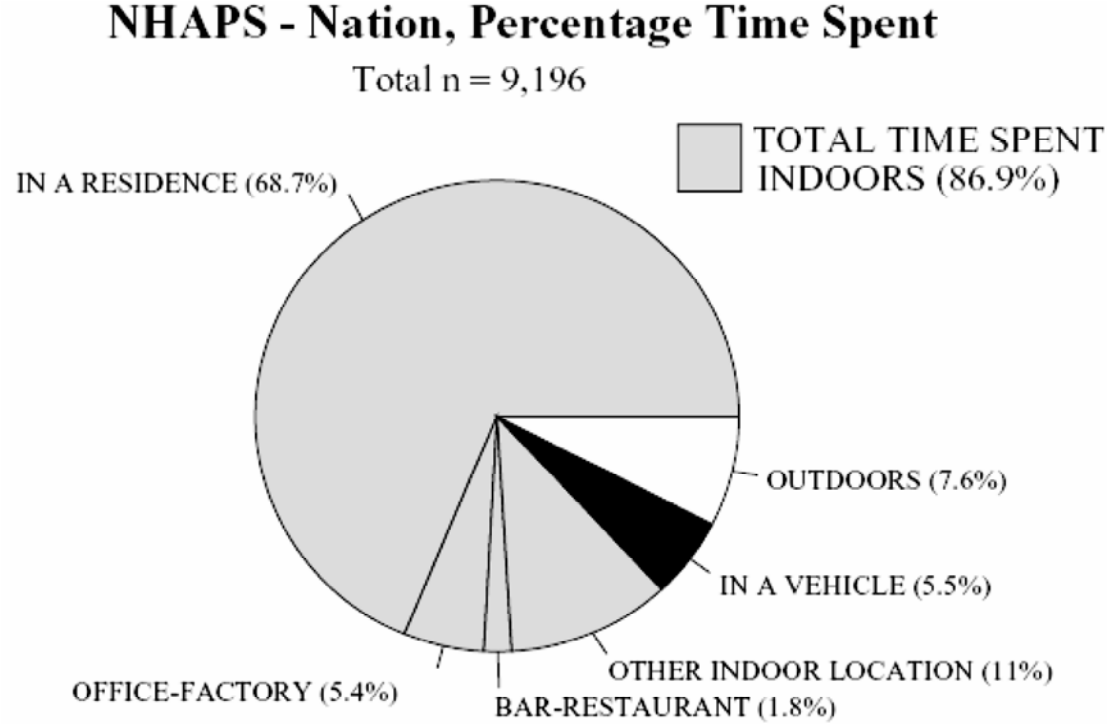

Figure 2.5-1. Percentage of time people spend in different environments in the United States as determined by the National Human Activity Pattern Survey (NHAPS).

Source: Klepeis et al. (2001).

Therefore, the total personal exposure to a pollutant, such as SO_2, can be represented by the following equation:

$$E_t = \sum_{i=1}^{n} C_i f_i \qquad (2\text{-}7)$$

where E_t is the time-weighted personal exposure concentration over a certain period of time, n is the total number of microenvironments that a person encounters, f_i is the fraction of time spent in the ith microenvironment, and C_i is the average concentration in the ith microenvironment during the time fraction, f_i. The types of exposure a person experiences can be characterized as an instantaneous exposure, a peak exposure, an average exposure, or an integrated exposure over all the environments a person encounters. These distinctions are important because health effects caused by long-term, low-level exposures may differ from those caused by short-term, peak exposures.

An individual's total exposure (E_t) can also be represented by the following equation:

$$E_T = E_a + E_{na} = \{y_o + \sum_i y_i \, [P_i a_i/(a_i + k_i)] \, \} C_a + E_{na} = \{y_o + \sum_i y_i F_{inf_i}\} C_a + E_{na} \quad (2\text{-}8)$$

subject to the constraint

$$y_o + \sum_i y_i = 1 \quad (2\text{-}9)$$

where E_a is the person's exposure to pollutants of ambient origin; E_{na} is the person's exposure to pollutants that are not of ambient origin; y_o is the fraction of time people spend outdoors and y_i is the fraction of time they spend in the ith microenvironment; F_{infi}, P_i, a_i, and k_i are the infiltration factor, penetration coefficient, air exchange rate, and decay rate for a pollutant in the ith microenvironment. In this equation, it is assumed that each microenvironment is well mixed (i.e., concentrations are homogeneous) and that air exchange occurs with ambient air only, not between microenvironments.

In the case where microenvironmental exposures occur mainly in one microenvironment, Equation 2-8 may be approximated by

$$E_T = E_a + E_{na} = \{y + (1-y)[Pa/(a + k)]\} C_a + E_{na} = \alpha C_a + E_{na} \quad (2\text{-}10)$$

where y is the fraction of time people spend outdoors, α is the ratio of a person's exposure to a pollutant of ambient origin to the pollutant's ambient concentration. Other symbols have the same definitions in Equation 2-8 and 2-9. If microenvironmental concentrations are considered, then Equation 2-10 can be recast as

$$C_{me} = C_a + C_{na} = [Pa/(a+k)]C_a + S/[V(a+k)] \quad (2\text{-}11)$$

where C_{me} is the concentration in a microenvironment; C_a and C_{na} are the contributions to C_{me} from ambient and nonambient sources; S is the microenvironmental source strength; V is the volume of the microenvironment, and the symbols in brackets have the same meaning as in Equation 2-10.

Microenvironments in which people are exposed to air pollutants typically include residential indoor environments, other indoor locations, outdoor environments, and in vehicles, as shown in Figure 2.5-1. Indoor combustion sources such as kerosene space heaters need to be considered when evaluating exposures to SO_2. Exposure misclassification may result when total human exposure is not disaggregated between various microenvironments, and this may obscure the true relationship between ambient air pollutant exposures and health outcomes.

In a given microenvironment, the ambient component of a person's microenvironmental exposure to a pollutant is determined by the following physical factors:

- Ambient concentration,
- The air exchange rate,
- The pollutant specific penetration coefficient,
- The pollutant specific decay rate, and
- The fraction of time an individual spends in the microenvironment.

These factors are in turn determined by the following potential exposure factors:

- Environmental conditions, such as weather and season;
- Dwelling conditions, such as the location of the house which determines proximity to sources and geographical features that can modify transport from sources; the amount of natural ventilation (e.g., open windows and doors, and the "draftiness" of the dwelling) and ventilation system (e.g., filtration efficiency and operation cycle);
- Personal activities (e.g., time spent cooking or commuting);
- Socioeconomic status (e.g., level of education and the income level);
- Demographic factors (e.g., age and gender);
- Indoor sources and sinks of a pollutant; and
- Microenvironmental line and point sources (e.g., lawn equipment).

In general, the relationship between personal exposures and ambient concentrations can be modified by microenvironments in the following ways. (1) Ambient pollutants can be lost through chemical and physical loss processes during infiltration, and therefore, the ambient component of a pollutant's concentration in a microenvironment is not the same as its ambient concentration. Instead it is the product of the ambient concentration and the infiltration factor (F_{inf} or α if people spend 100% of their time indoors) and (2) exposure to nonambient, microenvironmental sources.

Time activity diaries, completed by study participants, are often used in exposure models and assessments. The EPA's National Exposure Research Laboratory (NERL) has consolidated the majority of the most significant human activity databases into one comprehensive database called the Consolidated Human Research Laboratory Database (CHAD). Eleven different human activity pattern studies were united to obtain over 22,000 person-days of 24-h human activities in CHAD (McCurdy et al., 2000). These data can be useful in assembling population cohorts for exposure modeling and analysis and determining inhalation rates for dosimetry calculations.

In practice, it is extremely difficult to characterize community exposures by measurements of each individual's personal exposures. Instead, the distribution of personal exposures in a community, or the population exposure can be characterized by extrapolating measurements of personal exposure using various techniques or by stochastic, deterministic, or hybrid exposure modeling approaches such as APEX, SHEDS, and MENTOR (see Annex AX3 for a description of these modeling methods). Variations in community-level personal exposures are determined by cross-community variations in ambient pollutant concentrations and the physical and exposure factors mentioned above. These factors also determine the strength of the association between population exposure to SO_2 of ambient origin and ambient SO_2 concentrations.

2.5.2 Methods Used for Monitoring Personal Exposure to SO_2

Three basic methods of analysis have been used as personal exposure monitors (PEMs) to measure personal exposure to SO_2. The Harvard-EPA annular denuder system (HEADS) was initially developed to measure particles and acid gases simultaneously (Koutrakis et al, 1988). The aerosol is initially sampled at 10 L/min through an impactor that is attached to an annular

denuder to remove particles. Subsequently, the aerosol is sampled through an annular denuder coated with sodium carbonate (Na_2CO_3). This denuder is used to trap SO_2, nitric acid (HNO_3), and nitrous acid (HNO_2). Following sampling, the denuder is extracted with ultrapure water and analyzed by ion chromatography. Collection efficiencies of SO_2 in the denuder are typically around 0.993, which compares well with predicted values. Because the HEADS system is not easily converted for use as a PEM, other personal monitoring systems have been employed more recently in exposure monitoring studies.

For a study conducted in Baltimore, MD, Chang et al., (2000) developed and employed a personal roll-around system (RAS, an active sampling system designed to measure short-term exposure) to measure personal exposure concentrations of several atmospherically relevant species, including SO_2. For the measurement of SO_2, the RAS employed an NO_2/SO_2 sorbent denuder worn on a vest by the study participant. The hollow glass denuder, incased in an aluminum jacket, is coated with triethanolamine (TEA) for the collection of SO_2 and NO_2, and aerosol is sampled through the denuder at 100 cc/min. Following sampling, the denuder can be extracted and analyzed for SO_2 concentrations by ion chromatography. The detection limit for 1-h sampling of SO_2 was reported to be 66 ppb.

The most commonly employed SO_2 PEM method for personal exposure studies is the passive badge sampler. A personal multipollutant sampler has been developed to measure particulate and gaseous pollutants simultaneously (Demokritou et al, 2001). A single elutriator, operating at 5.2 L/min, is employed to sample particulate pollutants. A passive SO_2 badge is attached diametrically to the elutriator, which has been coated with Teflon to minimize reactive gas losses. The passive badge sample is coated with TEA for the collection of SO_2 and NO_2. Because wind speed can affect the collection rate of the passive badge sampler, this system employs a constant face velocity across the passive badge sampler. For 24-h sampling times, the estimated limit of detection (LOD) for SO_2 is 5 ppb.

Currently, limits exist in using PEM systems to measure personal exposure to SO_2. Because SO_2 concentrations have been declining annually in the United States, little focus has been placed on improving methods of analysis for SO_2. LODs for SO_2 PEMs (~5 ppb) are often greater than the concentrations of SO_2 that are typically observed in urban ambient environments. Personal exposure monitoring studies often suffer from many of the SO_2 samples (30 to 70%) being collected being below the sampler's LOD.

2.5.3 Relationships between Personal Exposures and Ambient Concentrations

Relationships between personal, indoor, outdoor, and ambient concentrations are examined in this section. Because SO_2 concentrations have declined markedly over the past few decades, relatively few studies have focused on SO_2 since the last AQCD for SO_2 was published. Another consideration is that currently, indoor and outdoor levels in many areas are often beneath detection personal monitor limits for SO_2.

2.5.3.1 Indoor versus Outdoor SO_2 Concentrations

Several studies in the United States, Canada, Europe, and Asia have examined the relationships of indoor, outdoor, and personal concentrations of SO_2 to ambient SO_2 concentrations. Perhaps the most comprehensive set of indoor-outdoor data was obtained by Spengler et al. (1979) during the Harvard Six Cities Study. These data are shown in Figure 2.5-2. Twenty-four-hour ambient and indoor SO_2 concentrations were measured every sixth day for 1 year in a minimum of 10 homes or public facilities for each of the cities studied. One-year average concentrations for indoor and outdoor concentrations of SO_2 for each city studied are shown in Figure 2.5-2.

A summary of ratios of indoor to outdoor concentrations found in this and other studies is given in Table 2.5-1. As can be seen from Table 2.5-1, a wide range is found in the ratio of indoor to outdoor concentrations among the different studies. These differences among studies could be due in part to differences in building characteristics (e.g., residences versus schools or other public buildings), in activities affecting air exchange rates, and in analytical capabilities. In several studies, high values for R^2 were found, suggesting that indoor levels were largely driven by outdoor levels. A few studies found higher levels of SO_2 indoors than outdoors in some samples. This situation could have arisen if there were indoor sources or because of analytical measurement issues. One would expect to find lower concentrations indoors than outdoors, because SO_2 is consumed by reactions on indoor surfaces, especially those that are moist. Chao (2001) acknowledged this point but could not account for the findings of this study. It was noted that two samples had unusually high indoor to outdoor ratios and that the mean ratios would have been much lower otherwise. Winter-summer differences in the indoor:outdoor ratio are consistent with seasonal differences in air exchange rates, as noted by Brauer et al. (1991).

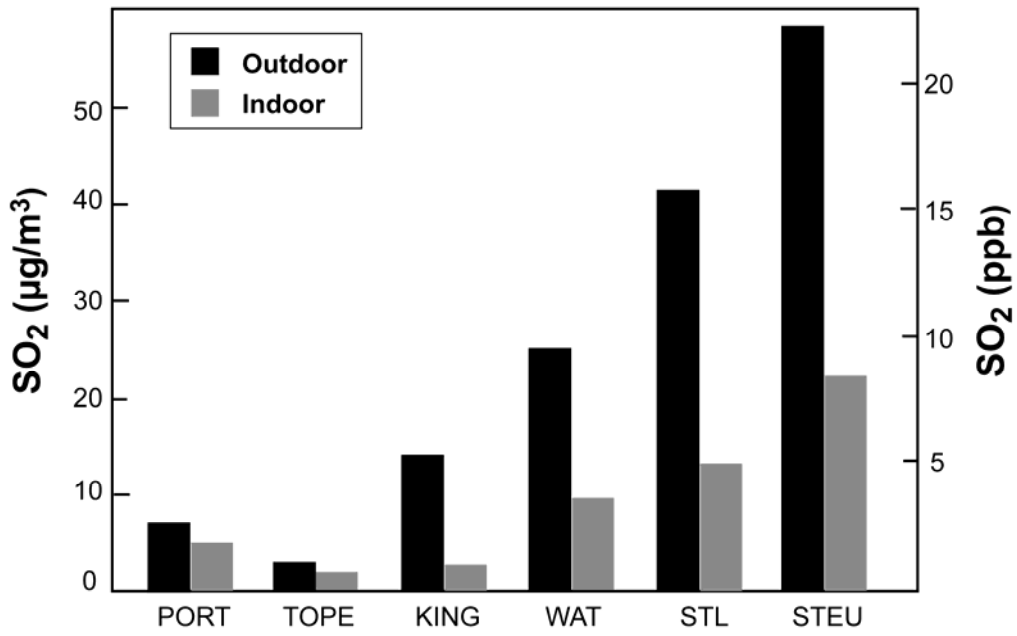

Figure 2.5-2. Average annual indoor and outdoor SO_2 concentrations for each of the six cities included in the analysis. PORT = Portage, WI; TOPE = Topeka, KS; KING = Kingston, TN; WAT = Watertown, MA; STL = St. Louis, MO; STEU = Steubenville, OH.

Source: Adapted from Spengler et al. (1979).

Indoor, or nonambient, sources of SO_2 could complicate associations between personal exposure to ambient SO_2 and ambient SO_2. Possible sources of indoor SO_2 are associated with the use of sulfur-containing fuels, with higher levels expected when emissions are poorly vented. Brauer et al. (2002) noted that only one study (Biersteker et al., 1965) conducted inferential analyses of potential determinants of exposure to indoor SO_2 levels. In the Biersteker et al. study, conducted in the Netherlands, indoor levels increased with oil, coal, and gas heating and smoking in homes and with increased outdoor levels.

Triche et al. (2005) measured SO_2 levels in homes in which secondary heating sources (fireplaces, kerosene heaters, gas space heaters, and wood stoves) were used. They found elevated indoor levels of SO_2 when kerosene heaters were in use. Median levels of SO_2 when kerosene heaters were used (6.4 ppb) were much higher than when they were not in use (0.22 ppb). The maximum SO_2 level associated with kerosene heater use was 90.5 ppb. They did not find elevated SO_2 levels when the other secondary heating sources were in use.

2.5.3.2 Relationship of Personal Exposure to Ambient Concentrations

A few studies evaluated the association of personal exposure to SO_2 to ambient concentrations (Brauer et al., 1989; Chang et al., 2000; Sarnat et al., 2000, 2001, 2005, 2006). Some of these studies fall under the umbrella of the Health Effects Institute's Characterization of Particulate and Gas Exposures of Sensitive Subpopulations Living in Baltimore and Boston research plan (Koutrakis et al., 2005). However, the focus of many of these studies has been exposure to particles, with acid gases included to evaluate confounder or surrogate issues.

Brauer et al. (1989) determined the slope of the regression line between personal and ambient concentrations to be 0.13 ± 0.02, $R^2 = 0.43$, based on 44 measurements made in Boston, MA during the summer of 1988. Most if not all of the data points obtained using the HEADS appeared to be above analytical detection limits based on the use of laboratory blanks and ion chromatography instrument sensitivity instead of field blanks, which are used in most other studies to calculate the overall method detection limit. Note that calculating detection limits in this way could result in lower detection limits than if field blanks are used. The authors reported significance at the $p<0.001$ level, but the intercept was not significant at the $p<0.001$ level. Since the stationary monitoring site was located at an elevation of 250 m above street level, the use of data from this ambient monitoring site will overestimate personal exposure, as the concentration of SO_2 increases with height because it is emitted mainly by elevated point sources. Indeed, the ambient concentrations are about a factor of two higher than the outdoor concentrations.

A few personal exposure studies were conducted in Baltimore, MD (Chang et al., 2000; Sarnat et al., 2000, 2001). Chang et al. (2000) tested a new personal active sampling device (a RAS with a TEA-based denuder) on volunteer participants to measure hourly personal exposure to SO_2. However, the method detection limit was too high for SO_2 (62 ppb for 1-h sampling) to generate a robust SO_2 exposure dataset to perform further analysis, and so the authors did not use the SO_2 data for this purpose. Sarnat et al. (2000) reported a longitudinal exposure study with older adults as participants. Twenty-four-hour averaged personal SO_2 exposures were measured with TEA-based passive sampler badges. The authors reported that 70% of the personal exposure concentrations of SO_2 were below the method detection limit (6.5 ppb for 24-h sampling). The mean ambient and personal exposure concentrations were reported as 8.9 and 0.0 ppb, respectively, during February and March of 1999. The maximum,

minimum, and median Spearman rank correlation coefficients between personal exposure and ambient concentrations over 12 days for 14 participants were 0.65, −0.75, and 0.02, respectively. Sarnat et al. (2001) reported another (8- to 12-day) longitudinal exposure study with a cohort that was similar to that used in Sarnat et al. (2000) except for including children and patients with chronic obstructive pulmonary disease (COPD). Data quality was not specifically discussed in Sarnat et al., (2001), but the readers were referred to Sarnat (2000) and Chang et al. (2000) for information about precision, accuracy, and method-detection limits. During the study, the median ambient and personal exposures were 8 and 1 ppb, respectively (estimated from Figure 1 in Sarnat et al., 2001). The authors reported that during the winter of 1999, ambient SO_2 was a significant predictor (at 5% significance level) of personal exposure to SO_2 (slope = −0.05), personal exposure to fine particulate matter ($PM_{2.5}$) (slope = −0.24), personal exposure to SO_4^{2-} (slope = −0.03), and personal exposure to $PM_{2.5}$ of ambient origin (slope = −0.16). However, it should be noted that all the slopes are negative.

Sarnat et al. (2005) conducted a longitudinal 12-day exposure study on 43 children and older adults in Boston, MA during the summer of 1999 and the following winter (1999-2000). They reported that 95.4 and 96.5% of the SO_2 concentrations were below detection limits (3.2 and 2.3 ppb, respectively, for winter and summer 24-h sampling). The absolute and relative sampling precisions for SO_2 were 0.8 ppb and 69.5%, respectively. The authors reported that the mean ambient concentrations ranged from 2.8 to 10.7 ppb during the study, while the mean personal exposure concentrations were <1.9 ppb. Associations between ambient SO_2 and either personal exposures or ambient concentrations of other pollutants were found for personal SO_4^{2-} (winter, slope = 0.06), personal SO_4^{2-} (summer, slope = 0.39), personal $PM_{2.5}$ (summer, slope = 1.68), ambient SO_4^{2-} (winter, slope = 0.19), and ambient $PM_{2.5}$ (winter, slope = 0.80).

Sarnat et al. (2006) reported the results of a personal exposure study in Steubenville, OH. The authors reported that 36.5 and 33.8% of ambient SO_2 were below the detection limit during the summer (5.5 ppb) and fall (3.8 ppb), and 53.5 and 36.1% of personal concentrations of SO_2 were below the detection limit during the summer (5.5 ppb) and fall (3.8 ppb), respectively. On average, personal exposures were lower than the ambient concentrations (1.5 ppb for personal and 2.7 for ambient during the summer; 0.7 ppb for personal and 5.4 ppb for ambient during the fall); however, the maximum personal exposure could be higher than the ambient concentration (30.4 ppb for personal and 21.9 ppb for ambient during the summer). Ambient SO_2 was

observed to be significantly associated with personal SO_2 exposures during the fall (slope = 0.08 for overall population, 0.07 for subjects in buildings with low ventilation rates, and 0.13 for subjects in buildings with high ventilation rates).

Of significant concern is the ability of currently available techniques for monitoring either personal exposures or ambient concentrations to measure SO_2 concentrations that are typically found in most urban environments. In some studies, most data, especially data for monitoring personal exposure and indoor concentrations, might be beneath detection limits. Indeed, in one study (Chang et al., 2000), the investigators had to discard data for SO_2, because the values were mostly beneath detection limits. In the study of Kindzierski and Ranganathan (2006), all indoor concentration data were beneath detection limits. In Sarnat et al. (2000), ~70% of personal measurements were beneath detection limits, and ~33% of personal measurements returned apparent negative concentration values. In such situations, associations between ambient concentrations and personal exposure are inadequately characterized. When personal exposure concentrations are above detection limits, a reasonably strong association is observed between personal exposures and ambient concentrations.

2.5.4 Exposure Measurement Errors in Epidemiological Studies

For the purposes of the draft Integrated Science Assessment (ISA), the effects of exposure error on epidemiological study results refers to changes in the point estimate and in the standard error of the calculated health effect estimate, β, that result from using the concentration of an air pollutant as an exposure indicator rather than using the actual personal exposure to the causal factor in the epidemiological statistical analysis. There are many assumptions made in going from the available experimental measurement of a pollution indicator to an estimate of the personal exposure to the causal factor. The importance of these assumptions and their effect on β depend on the type of epidemiological study.

The considerations of exposure error for SO_2 are simplified compared to those for NO_2 and PM. The only experimental measure available is the ambient concentration of SO_2. In addition, indoor and other nonambient sources of SO_2 are not thought to be important in population studies, lessening concerns about the possible influence of exposures other than to ambient SO_2. The only known significant indoor source of SO_2 in the United States is the use of kerosene heaters, which is not thought to be widespread enough to influence population studies.

In addition, as is the case with other air pollutants, exposure to nonambient SO_2 would not affect β in time-series studies using ambient concentrations as the exposure surrogate unless the nonambient exposures were correlated with the ambient concentrations.

2.5.4.1 Community Time-Series Studies

This section applies primarily to studies of the association of daily average SO_2 concentrations with daily measures of mortality or morbidity. With SO_2 time-series epidemiological analysis, the following four exposure issues are of primary concern: (1) the relationship of the experimental measurement of SO_2 to the true concentration of SO_2; (2) the relationship of day-to-day variations of the concentration of the indicator, as measured at a central monitoring site, with the corresponding variations in the average concentration of the indicator over the geographic area from which the health measurements are drawn; (3) the relationship of the community average concentration of SO_2 to the average personal exposure to ambient SO_2; and (4) the relationship of SO_2 to the true causal factor. These four issues are described below.

2.5.4.1.1 Relationship of Experimental Measurement of SO_2 to the True Concentration

Since there is always some instrumental measurement error, the correlation of the measured SO_2 with the true SO_2, on either a 24-h or 1-h basis, will be less than 1. Sheppard et al. (2005) indicate that instrument error in the individual or daily average concentrations have "the effect of attenuating the estimate of α." However, Zeger et al. (2000) state that the "instrument error in the ambient levels is close to the Berkson type" and in order for this error to cause substantial bias in β_C, the error term (the difference between the true concentrations and the measured concentrations) must be strongly correlated with the measured concentrations. Zeger et al. (2000) suggest that, "Further investigations of this correlation in cities with many monitors are warranted." Averaging across multiple unbiased ambient monitors in a region should reduce the instrument measurement error (Sheppard et al., 2005; Wilson and Brauer, 2006; Zeger et al., 2000). There are concerns about the precision and accuracy of the ambient concentration measurements, because SO_2 concentrations are much lower now than when the SO_2 standards were first promulgated. Current ambient concentrations of SO_2 in the United States are nearly all at or very near the detection limit of the monitors currently used in the regulatory network. Thus, greater uncertainty is most often observed at the lower ambient

concentrations as compared with the less frequent higher concentration exposures because of the plume downwash near local sources or entrainment of plumes downwind from large power plants or smelters. It is unclear how uncertainties in the true concentrations of SO_2, i.e., instrument measurement error, will change β. Zeger et al. (2000) suggest that instrument error has both Berkson and non-Berkson error components.

2.5.4.1.2 Relationship of Day-to-day Variations of the Concentration of the Indicator

There has been little analysis of the spatial variation of SO_2 across communities. SO_2 is thought to come primarily from power plants or smelters. New power plants and smelters in the United States generally have SO_2 emission controls and are no longer located within urban areas. However, older sources may still be located within urban areas and may not have as effective SO_2 emission controls. Therefore, it is not clear whether SO_2 will act as a regional or local pollutant and whether its spatial behavior might differ in different cities. Site-to-site correlations of SO_2 concentrations, as shown for several cities in Table 2.4-3 include some very low values. This suggests the concentration of SO_2, measured at any given monitoring site, may not be highly correlated with the average community concentration. This could be due to local sources that cause the SO_2 to be unevenly distributed spatially, to a monitoring site being chosen to represent a nearby source, or to terrain features, source, or sink locations that divide the community into several subcommunities that differ in the temporal pattern of pollution. It is also possible that errors in the measurement of the low concentrations of SO_2 present at most sites contribute to the lack of high correlations between monitors. To the extent that the correlation of the ambient concentration with the community average concentration is <1, β will be reduced if the single pollutant model is the true model. Similarly, β will be reduced if there are subareas of the community where the correlation of the subarea average concentrations with the concentrations measured at the ambient monitoring site is <1. Concentrations in an area of a community impacted by plumes from local SO_2 sources or a large power plant or smelter might be higher than, and not well-correlated with, the concentrations measured at the community measurement site. If such high concentrations affected a sizable portion of the population, that community might not be suitable for time-series epidemiological analyses.

2.5.4.1.3 Relationship of Community Average Concentration of SO_2 to Average Personal Exposure to Ambient SO_2

People spend much of their time indoors and, in the absence of indoor sources, indoor concentrations are lower than outdoor concentrations. It is necessary to consider how this difference between the ambient concentration, which is used in epidemiological analyses, and the personal exposure to the ambient concentration (which includes exposure to the full outdoor concentration while outdoors and exposure of only a fraction of the outdoor concentrations while indoors) will affect the calculated β. The contribution of the ambient concentration of SO_2 to the personal exposure to ambient SO_2 is given by $E^A = \alpha \bullet C$ where E^A is exposure to ambient SO_2, α is the exposure factor (or more correctly the ambient exposure factor) with value between 0 and 1 as defined in Equation 2-10, and C is the ambient SO_2 concentration as measured at a community monitoring site. Zeger et al. (2000) made a major contribution to our understanding of exposure error by pointing out that for community time-series epidemiology, which analyzes the association between health effects and potential causal factors at the community scale rather than the individual scale, it is the correlation of the daily community average personal exposure to the ambient concentration, X_t^A, with daily community average concentration, C_t, that is important, not the correlation of each individual's exposure X_{it}^A with C_t. Thus, the low correlation of X_{it}^A with C_t, as frequently found in pooled panel exposure studies, is not relevant to error in community time-series epidemiological analysis. Unfortunately, few experimental studies provide adequate information to calculate the community average exposure. Most exposure panel studies measure one or a few subjects on 1 day, and another one or a few subjects on the next day, etc. (i.e., a pooled study design). A few studies have measured one subject for several days and another subject for a different several days (i.e., a longitudinal study design). However, in order to use experimental data to calculate a community average ambient exposure, it is necessary to measure the personal exposure of every subject on every day and to have sufficient information to estimate the ambient exposure from the measured total personal exposure. Such information is available from one study of combined coarse and fine PM (PM_{10}) and shows that the correlation of X_t^A with C_t is much greater than the correlation of X_{it}^A with C_t (U.S. Environmental Protection Agency, 2004). The Research Triangle Park PM Panel Study found similar effects in the relationship of outdoor and personal $PM_{2.5}$ concentrations (Williams et al., 2003). Ott et al. (2000) have provided a statistical argument that such an increase in the correlation of the daily average over the individual values should be expected.

There has also been concern with the variation of α. Zeger et al. (2000) have stated (for PM) and Sheppard et al. (2005) have used simulations (for PM or other nonreactive pollutant such as CO) to show that the variations in individual daily values of α_{it} around the daily average α_t is a Berkson error and will not change the point estimate of β, although it may increase the standard error. Sheppard et al. (2005) have shown that day-to-day variations in the average α will not change the point estimate unless α_t is correlated with C_t. (Since most time-series epidemiology uses 24-h concentrations, no anaylsis is available for shorter time periods.)

Both Zeger et al. (2000) and Sheppard et al. (2005) show that if β_A is the health effect parameter that would be obtained with an epidemiological analysis using the ambient exposure and β_C is the health effect parameter that would be obtained with an epidemiological analysis using the ambient concentration, C_t, then $\beta_C = \alpha \bullet \beta_A$. Thus, an epidemiological analysis using the ambient concentration, C_t, yields not β_A, but $\alpha \bullet \beta_A$. Overestimation of exposure by substitution of the ambient concentration for the ambient exposure leads to underestimation of the effect estimate, or bias toward the null.

2.5.4.1.4 Relationship of SO_2 to the True Causal Factor

The remaining and most critical assumption is whether SO_2 is the causal factor (pollutant that causes the examined health effect) or whether SO_2 is a surrogate for some other pollutant, mixture of other pollutants, or mixture of pollutants including SO_2 that is the true causal factor. For example, depending on the source of SO_2, SO_2 might be a surrogate for vanadium and nickel from oil-fired power plants; selenium, arsenic, and mercury from coal-fired power plants; and/or nickel and copper from smelters. The current data do not permit a quantitative assessment of the relative contribution of SO_2 and correlated pollutants to the observed β value.

2.5.4.2 Long-Term Cohort Studies

For long-term exposure epidemiologic studies, concentrations are integrated over time periods of a year or more, and usually for spatial areas the size of a city, county, or metropolitan statistical area (MSA), although integration over smaller areas may be feasible. Health effects are then regressed, in a statistical model, against the average concentrations in the series of cities (or other areas). In time-series studies, a constant difference between the measured and the true concentration (instrument offset) will not affect β, nor will variations in the daily average α or the daily average nonambient exposure, unless the variations are correlated with the daily

variations in concentrations. However, in long-term exposure epidemiologic studies, if instrument measurement errors, long-term average values of α, or long-term averages of nonambient exposure differ for different cities (or other areas used in the analysis), the city-to-city long-term ambient SO_2 concentrations will not be perfectly correlated with the long-term average exposure to either ambient or total SO_2. This lack of correlation would be expected to lead to a lowering of the point estimate of β.

In summary, the use of ambient concentrations of SO_2 as a surrogate for exposure to ambient SO_2 is not generally expected to change the principal conclusions from SO_2 epidemiological studies, because the errors and uncertainties would be expected to reduce rather to increase β. However, SO_2 may not be the causal agent, or the sole causal agent, but may be serving as a surrogate for some other pollutant, or mix of pollutants, whose concentration is correlated with that of SO_2. This may be particularly relevant for SO_2 because of atmospheric chemistry linking it to its oxidation products SO_4^{2-} and to fine particulate matter. Therefore, while population health risk estimates derived using ambient SO_2 levels are useful, evidence from clinical and animal toxicological studies also needs to be considered in attempting to understand the potential effects of SO_2 on human health.

2.6 DOSIMETRY OF INHALED SO_2

This section is intended to present an overview of general concepts related to the dosimetry of SO_2 in the respiratory tract. Dosimetry of SO_2 refers to the measurement or estimation of the amount of SO_2 or its reaction products reaching and persisting at specific respiratory tract sites after exposure. One of the principal effects of inhaled SO_2 is that it stimulates bronchial epithelial receptors and initiates a reflexive contraction of smooth muscles in the bronchial airways. The compound most directly responsible for health effects may be the inhaled SO_2 or perhaps its chemical reaction products. Complete identification of the causative agents and their integration into SO_2 dosimetry is a complex issue that has not been thoroughly evaluated. Few studies have investigated SO_2 dosimetry since the 1982 AQCD and the 1986 Second Addendum.

The major factors affecting the transport and fate of aerosols and gases in the respiratory tract are the morphology of the respiratory tract; the physiochemical properties of the mucous and surfactant layers; tidal volume, flow rate, and route of breathing; physicochemical properties

of the gas; and the physical processes that govern gas transport. When SO_2 contacts the fluids lining the airways, it dissolves into the aqueous fluid and forms hydrogen (H^+) ions and bisulfite (HSO_3^-) and sulfite (SO_3^{2-}) anions (Bascom et al., 1996). The majority of anions are expected to be present as HSO_3^- at a concentration proportional to the gas phase concentration of SO_2 (Ben-Jebria et al., 1990). Because of the chemical reactivity of these anions, various reactions are possible, leading to the oxidation of SO_3^{2-} to SO_4^{2-} (see Section 12.2.1, U.S. Environmental Protection Agency, 1982). Clearance of SO_3^{2-} from the respiratory tract may involve several intermediate chemical reactions and transformations (see Section 12.2.1.2, U.S. Environmental Protection Agency, 1982). Gunnison and Benton (1971) identified *S*-sulfonate in blood as a reaction product of inhaled SO_2.

Physicochemical properties of SO_2 relevant to respiratory tract uptake include its solubility and diffusivity in epithelial lining fluid (ELF), as well as its reaction-rate with ELF constituents. Henry's law relates the gas phase and liquid phase interfacial concentrations at equilibrium and is a function of temperature and pressure. Henry's law shows that the amount of SO_2 in the aqueous phase is directly proportion to the partial pressure or concentration of SO_2 in the gas phase. Although the solubility of most gases in mucus and surfactant is not known, the Henry's law constant is known for many gases in water. The Henry's law constant for SO_2 is 0.048 (mole/liter)air / (mole/liter)water at 37 °C and 1 atm; for comparison, the value for O_3 is 6.4 under the same conditions (Kimbell and Miller, 1999). In general, the more soluble a gas is in biological fluids, the sooner, and more proximally, it is absorbed in the respiratory tract. When the partial pressure of SO_2 on mucosal surfaces exceeds that of the gas phase, such as during expiration, some desorption of SO_2 from the ELF may be expected.

Because SO_2 is highly soluble in water, it is expected to be almost completely absorbed in the nasal passages of subjects at rest. The dosimetry of SO_2 can be contrasted with the lower solubility gas, O_3, for which the predicted tissue doses (O_3 flux to liquid-tissue interface) are very low in the trachea and increase to a maximum in the terminal bronchioles or first airway generation in the pulmonary region (see Chapter 4, U.S. Environmental Protection Agency, 2006b). Similar to O_3, the nasal passages remove SO_2 more efficiently than the oral pathway (Brain, 1970; Melville, 1970; Nodelman and Ultman, 1999). With exercise, the pattern of SO_2 absorption shifts from the upper airways to the tracheobronchial airways in conjunction with a shift from nasal to oronasal breathing and increased ventilatory rates. Due to its effect on

delivery and uptake, mode of breathing is also recognized as an important determinant of the severity of SO_2-induced bronchoconstriction, with the greatest responses occurring during oral breathing followed by oronasal breathing and the smallest responses observed during nasal breathing.

Melville (1970) measured the absorption of SO_2 (1.5 to 3.4 ppm) during nasal and oral breathing in 12 healthy volunteers. Total respiratory tract absorption of SO_2 was significantly greater ($p < 0.01$) during nasal than oral breathing (85 versus 70%, respectively) and was independent of the inspired concentration. Respired flows were not reported. Andersen et al. (1974) measured the nasal absorption of SO_2 (25 ppm) in 7 volunteers at an average inspired flow of 23 L/min (i.e., eucapnic hyperpnea [presumably] to simulate light exertion). These investigators reported that the oropharyngeal SO_2 concentration was below their limit of detection (0.25 ppm), implying that at least 99% of SO_2 was absorbed in the nose of subjects during inspiration. Speizer and Frank (1966) also measured the absorption of SO_2 (16.1 ppm) in 7 healthy subjects at an average ventilation of 8.5 L/min (i.e., at rest). They reported that 14% of the inhaled SO_2 was absorbed within the first 2 cm into nose. The concentration of SO_2 reaching the pharynx was below the limit of detection, suggesting that at least 99% was absorbed during inspiration. On expiration, 12% of the SO_2 absorbed during inspiration was desorbed into the expired air. During the first 15 min after the 25- to 30-min SO_2 exposure, another 3% was desorbed. In total, 15% of the amount originally inspired and absorbed SO_2 was desorbed from the nasal mucosa.

Frank et al. (1969) and Brain (1970) investigated the oral and nasal absorption of SO_2 in the surgically isolated upper respiratory tract of anesthetized dogs. Radiolabeled SO_2 ($^{35}SO_2$) at the concentrations of 1, 10, and 50 ppm was passed separately through the nose and mouth at the steady flows of 3.5 and 35 L/min for 5 min. The nasal absorption of SO_2 (1 ppm) was 99.9% at 3.5 L/min and 96.8% at 35 L/min. The oral absorption of SO_2 (1 ppm) was 99.56% at 3.5 L/min, but only 34% at 35 L/min. The nasal absorption of SO_2 at 3.5 L/min increased with concentration at 1, 10, and 50 ppm and was reported to be 99.9, 99.99, and 99.999%, respectively. This increase in absorption with concentration was hypothesized to be due to increased mucous secretion and increased nasal resistance at the higher SO_2 concentrations. The increased mucus was thought to provide a larger reservoir for SO_2 uptake. The increased nasal resistance may increase turbulence in the airflow and, thereby, decrease the boundary layer

between the gas and liquid phases. Dissimilar to the nose, SO_2 absorption in the mouth decreased from 99.56 to 96.3% when the concentration was increased from 1 to 10 ppm at 3.5 L/min. Frank et al. (1969) reported that up to 18% of the SO_2 was desorbed within ~10 min after exposure. The authors noted that the aperture of the mouth may vary considerably, and that this variation may affect SO_2 uptake in the mouth. Although SO_2 absorption was dependent on inhaled concentration, the rate and route of flow had a greater effect on the magnitude of SO_2 absorption in the upper airways.

Strandberg (1964) studied the uptake of SO_2 in the respiratory tract of rabbits. A tracheal cannula with two outlets was utilized to allow sampling of inspired and expired air, and SO_2 absorption was observed to depend on inhaled concentration. The absorption during maximal inspiration was 95% at high concentrations (100 to 700 ppm), reflecting an increased SO_2 removal in the extrathoracic (ET) airways, whereas it was only 40% at low concentrations (0.05 to 0.1 ppm). On expiration, the total SO_2 absorbed (i.e., inspiratory removal in the ET airways plus removal in the lower airways) was 98% at high concentrations and only 80% at the lower concentrations.

Amdur (1966) examined changes in airways resistance in guinea pigs due to SO_2 exposure. Guinea pigs were exposed for 1 h to 0.1- to 800-ppm SO_2 during natural unencumbered breathing or to 0.4 to 100 ppm while breathing through a tracheal cannula. At concentrations of 0.4- to 0.5-ppm SO_2, route of administration did not affect the airway resistance response, whereas at concentrations of >2 ppm, the responses were greater in animals exposed by tracheal cannula. Based on the concentration-dependent absorption of SO_2 in the ET airways observed by Strandberg (1964), Amdur (1966) concluded that the airway resistance responses at low-exposure concentrations were independent of method of administration, because the lung received nearly the same concentration with or without the cannula as evidenced by minimal ET absorption.

More recently, Ben-Jebria et al. (1990) investigated the absorption of SO_2 in excised porcine tracheae. Absorption was monitored over a 30-min period following the introduction of SO_2 (0.1 to 0.6 ppm, inlet concentration) at a constant flow (2.7 to 11 L/min). The data were analyzed using diffusion-reactor theory. An overall mass transfer coefficient (K_{SO2}) was determined and separated into its contributions due to gas (convection and diffusion) and tissue phase (diffusivity, solubility, and reaction rates) resistances. SO_2 in the liquid phase was

assumed to form HSO_3^- rapidly, in proportion with the gas phase SO_2 concentration, HSO_3^- then diffused down the concentration gradient into the tissues where it reacted irreversibly with biochemical substrates. Initially, K_{SO2} was limited only by gas phase resistance, but decreased exponentially over the first 5 to 10 min of SO_2 exposure to a smaller steady-state value because of tissue resistance to SO_2 absorption. The initial and steady-state K_{SO2} values were found to be independent of inlet SO_2 concentration, i.e., for a given flow, the fractional absorption of SO_2 did not depend on SO_2 concentration. An increased K_{SO2} (initial and steady-state) was observed with an increasing flow that was thought to be due to a decrease in the boundary layer near the walls of the trachea for radial SO_2 transport. This is in agreement with Aharonson et al. (1974), who also reported that the transfer rate coefficient for SO_2 increases with increasing flow. However, the initial molar flux of SO_2 across the gas-tissue interface appears to increase purely as a function of the increase in mass transport occurring with increasing flow (see Figure 5 in Ben-Jebria, 1990). Given that the steady-state K_{SO2} remained stable during the 10 to 30 min of exposure and that no SO_2 leakage through the tissue was identified, the authors concluded that there was an irreversible sink for SO_2 within the tissue.

In summary, inhaled SO_2 is readily absorbed in the upper airways. During nasal breathing, the majority of available data suggests 95% or greater SO_2 absorption occurs in the nasal passages, even under ventilation levels comparable to exercise. One study, however, reported only 85% nasal absorption of SO_2 in humans. Somewhat less SO_2 is absorbed in the oral passage than in the nasal passages. The difference in SO_2 absorption between the mouth and the nose is highly dependent on respired flow rates. In one study, for example, with an increase in flow from 3.5 to 35 L/min, nasal absorption was reduced from 100 to 97%; whereas, oral absorption was reduced from 100 to 34%. Several in vivo studies have reported greater respiratory tract absorption of SO_2 at high versus low SO_2 concentrations. However, the ex vivo uptake of SO_2 is not related to SO_2 concentration. It has been postulated that increased mucous secretion and/or increased nasal resistance at high SO_2 concentrations may account for the increased absorption efficiency observed in vivo. Although SO_2 absorption may depend on inhaled SO_2 concentration, the rate and route of breathing have a greater effect on the magnitude of SO_2 absorption in the upper airways. In exercising humans, the pattern of SO_2 absorption should be expected to shift from the upper airways to the tracheobronchial airways in

conjunction with a shift from nasal to oronasal breathing and associated increased ventilatory rates.

TABLE 2.4-1. REGIONAL DISTRIBUTION OF SO_2 AND SO_4^{2-} AMBIENT CONCENTRATIONS, AVERAGED FOR 2003-2005

Region	Concentration	
	SO_2 (ppb)	SO_4^{2-} (μg m^{-3})
Mid-Atlantic	3.3	4.5
Midwest	2.3	3.8
Northeast	1.2	2.5
Southeast	1.3	4.1

TABLE 2.4-2. DISTRIBUTIONS OF TEMPORAL AVERAGING INSIDE AND OUTSIDE CMSAS

Averaging Time Monitor Locations	n	Mean	Percentiles											
			1	5	10	25	30	50	70	75	90	95	99	Max
1-h Maximum Concentration														
Inside CMSAs	332405	13	1	1	1	3	4	7	13	16	30	45	92	714
Outside CMSAs	53417	13	1	1	1	1	2	5	10	13	31	51	116	636
1-h Average Concentration														
Inside CMSAs	7408145	4	1	1	1	1	1	2	4	5	10	15	34	714
Outside CMSAs	1197179	4	1	1	1	1	1	2	3	3	7	13	36	636
24-h Average Concentration														
Inside CMSAs	327918	4	1	1	1	1	2	3	5	6	10	13	23	148
Outside CMSAs	52871	4	1	1	1	1	1	2	3	4	8	12	25	123
Annual Average Concentration														
Inside CMSAs	898	4	1	1	1	1	2	4	5	6	8	10	12	15
Outside CMSAs	143	4	1	1	1	1	2	3	4	5	8	9	13	14
Aggregate 3-yr Average Concentration, 2003-2005														
Inside CMSAs	283	4	1	1	1	2	3	3	5	5	8	10	12	14
Outside CMSAs	42	4	1	1	1	2	2	3	4	5	8	9	13	13

* Values are ppb

** CMSA = Consolidated Metropolitan Statistical Area

TABLE 2.4-3. RANGE OF MEAN SO_2 CONCENTRATIONS AND PEARSON CORRELATION COEFFICIENTS IN URBAN AREAS HAVING AT LEAST FOUR MONITORS

Metropolitan Area (Number of Monitors)	Mean SO_2 Concentration (ppb)	Pearson Correlation Coefficient
Philadelphia, PA (10)	3.6 – 5.9	0.37 – 0.84
Washington, DC (5)	3.2 – 6.5	0.30 – 0.68
Jacksonville, FL (5)	1.7 – 3.4	−0.03 – 0.51
Tampa, FL (8)	2.0 – 4.6	−0.02 – 0.18
Pittsburgh, PA (10)	6.8 – 12	0.07 – 0.77
Steubenville, OH (13)	8.6 – 14	0.11 – 0.88
Chicago, IL (9)	2.4 – 6.7	0.04 – 0.45
Salt Lake City, UT (5)	2.2 – 4.1	0.01 – 0.25
Phoenix, AZ (4)	1.6 – 2.8	−0.01 – 0.48
San Francisco, CA (7)	1.4 – 2.8	−0.03 – 0.60
Riverside, CA (4)	1.3 – 3.2	−0.06 – 0.15
Los Angeles, CA (5)	1.4 – 4.9	−0.16 – 0.31

TABLE 2.5-1. RELATIONSHIPS OF INDOOR TO OUTDOOR SO_2 CONCENTRATIONS

Reference	Location	Indoor to Outdoor Ratio (number of samples)	Notes
Spengler et al. (1979)	Portage, WI	0.67 (349)	One year during Harvard Six Cities study. West-Gaeke method.
	Topeka, KS	0.50 (389)	
	Kingston, TN	0.08 (425)	
	Watertown, MA	0.33 (486)	
	St. Louis. MO	0.31 (543)	
	Steubenville, OH	0.39 (499)	
Stock et al. (1985)	Houston, TX	0.54 (2425)	May to October, continuous FRM for indoor and outdoor.
Meranger and Brule (1987)	Antigonish, NS, Canada	0.84 (8)	Early spring, 1 wk avg in 1 house with oil furnace, FPD-TA
Brauer et al. (1989)	Boston, MA	0.23 (24)	Summer, HEADS
Li and Harrison (1990)	Essex, UK	0.22	Summer
Brauer et al. (1991)	Boston, MA	0.39 (geom. mean) (29), $R^2 = 0.89$	Summer, HEADS
		0.05 (geom. mean) (23), $R^2 = 0.73$	Winter, HEADS
Chan et al. (1994)	Taipei, Taiwan	0.24 (15)	Summer, PS
		0.23 (37)	Winter, PS
Lee et al. (1999)	Hong Kong	0.92, $R^2 = 0.56$	Winter, PF
Patterson and Eatough (2000)	Lindon, UT	0.027 ± 0.0023, $R^2 = 0.73$	Winter, ADS, all samples
Kindzierski and Sembaluk (2001)	Boyle, Alberta, Canada	0.12 (12)	Late Fall, PS
	Sherwood Park, Alberta, Canada	0.14 (13)	Late Fall, PS
Chao (2001)	Hong Kong	1.01 ± 0.78 (10)	Summer. Windows mainly kept closed, PS
Kindzierski and Ranganathan (2006)	Fort McKay, Alberta, Canada	0.35 (30)	Fall. All indoor levels < LOD and set =1/2 LOD, PS

FPD-TA = Flame Photometric Detection-Thermal Analysis
HEADS = Harvard-EPA Annular Denuder System
PS= passive sampler
PF = pulsed fluorescence
ADS = Annular Denuder System

3. INTEGRATED HEALTH EFFECTS OF EXPOSURE TO SULFUR DIOXIDE

This integrated discussion is structured to provide a coherent framework for the assessment of health risks associated with human exposure to ambient sulfur dioxide (SO_2) in the United States. The main goal of this chapter is to integrate newly available epidemiological, human clinical, and animal toxicological evidence with consideration of key findings and conclusions from the 1982 Air Quality Criteria Document (AQCD) for Sulfur Oxides (U.S. Environmental Protection Agency, 1982), 1986 Second Addendum (U.S. Environmental Protection Agency, 1986b), and 1994 Supplement to the Second Addendum, (U.S. Environmental Protection Agency, 1994a), so as to address issues central to the U.S. Environmental Protection Agency (EPA)'s assessment of evidence needed to support the current review of the primary SO_2 National Ambient Air Quality Standards (NAAQS).

This chapter is organized to present morbidity and mortality associated with short-term exposures to SO_2, followed by morbidity and mortality associated with long-term exposures. These sections describe the findings of epidemiological studies that have examined the association between short-term (generally 24-h average) and long-term (generally months to years) ambient SO_2 exposure and heath outcomes such as increases in respiratory symptoms in asthmatics; increases in emergency department (ED) visits and hospital admissions for respiratory and cardiovascular diseases (CVDs); and increased risk of premature mortality. Human clinical studies examining the effect of peak (1 h or less, generally 5-15 min) exposures of SO_2 on respiratory symptoms and lung function are also discussed in this chapter. These outcomes are presented with relevant animal toxicological data to assess coherence, biological plausibility, and potential mechanistic evidence.

The epidemiological studies constitute important information on associations between health effects and exposures of human populations to ambient levels of SO_2 and also help to identify susceptible subgroups and associated risk factors. However, associations observed between specific air pollutants and health outcomes in epidemiological studies may be confounded by copollutants and/or meteorological conditions and influenced by model specifications in the analytical methods. Extensive discussion of issues related to confounding effects among air pollutants in epidemiological studies are provided in the 2004 AQCD for

Particulate Matter (PM) and therefore not reported here. Briefly, the use of multipollutant regression models has been the prevailing approach for controlling potential confounding by copollutants in air pollution health effects studies. A specific concern is that a given pollutant may act as a surrogate for other unmeasured or poorly measured pollutants. In the event that one or more pollutants act as surrogates for an unmeasured component of a mixture actually responsible for the observed association, the strongest predictor in a multipollutant model could simply indicate which measured pollutant is the best surrogate for the unmeasured pollutant of interest. Particularly in the case of SO_2, atmospheric chemistry links SO_2 to SO_2-derived fine sulfate (SO_4^{2-}) particles. Since SO_2 and SO_4^{2-} particles coexist in most ambient situations, observational epidemiologic studies have little ability to distinguish between the adverse health effects of pure gaseous SO_2 with SO_4^{2-} or other particulate matter (PM) indices. Attempts to distinguish the gaseous and particle effects related to SO_2 using multipollutant epidemiologic models must be interpreted with caution. Despite the limitations, the use of multipollutant models is still the prevailing approach employed in most studies of SO_2 health effects and serves as an important tool in addressing the issue of confounding by copollutants.

Model specification and model selection also are factors to consider in the interpretation of the epidemiological evidence. Epidemiological studies investigated the association between various measures of SO_2 (e.g., multiple lags, different exposure metrics) and various health outcomes using different model specifications (for further discussion, see 2006 AQCD for Ozone [O_3] and Related Photochemical Oxidants). The summary of health effects in this chapter is vulnerable to the errors of publication bias and multiple testing. Efforts have been made to reduce the impact of multiple testing errors on the conclusions in this document. For example, although many studies examined multiple single-day lag models, priority was given to effects observed at 0- or 1-day lags rather than at longer lags. Both single- and multiple-pollutant models that include SO_2 were considered and examined for robustness of results. Analyses of multiple model specifications for adjustment of temporal or meteorological trends will be considered sensitivity analyses.

In addition to evaluating available evidence from epidemiologic studies, this chapter also examined human clinical studies. Human clinical studies conducted in controlled exposure chambers use fixed concentrations of air pollutants under carefully regulated environmental conditions and subject activity levels to minimize possible confounding of the health associations

by other factors. While human clinical studies do in fact provide a direct quantitative assessment of the SO_2 exposure-health response relationship, such studies have a number of limitations. First, study subjects must be either healthy individuals or individuals whose level of illness does not preclude them from participating in the study. Subjects with a recent history of upper respiratory tract infections are typically excluded from clinical studies of exposure to SO_2, as are asthmatics who are unable to withhold the use of brochodilators for at least 6 hours prior to exposure. Therefore, the results of human clinical studies may underestimate the health effects of exposure to certain sensitive subpopulations. In addition, studies of controlled exposure to SO_2 have typically used peak concentrations for shorter durations (5-15 min). While these studies provide important information on the biological plausibility of associations observed between SO_2 exposure and health outcomes in epidemiological studies, the concentration-response relationships cannot be directly extrapolated to concentrations below those administered in the laboratory. Finally, human clinical studies are normally conducted on a relatively small number of subjects, which reduces the power of the study to detect significant differences in the health outcomes of interest between exposure to varying concentrations of SO_2 and clean air.

The chapter discussion focuses on the important new scientific studies, with emphasis on those conducted at or near current ambient concentrations. The attached annexes include a broad survey of the epidemiology and toxicology literature to supplement the information presented here.

3.1 MORBIDITY ASSOCIATED WITH SHORT-TERM SO_2 EXPOSURE

3.1.1 Respiratory Effects Associated with Short-Term Exposure to SO_2

In the 1982 AQCD for Sulfur Oxides, only a few epidemiological studies were useful in determining the concentration-response relationship of respiratory health effects from short-term exposure to SO_2. The most notable study was by Lawther et al. (1970), which examined the association between air pollution and worsening health status in bronchitic patients. It was concluded in the 1982 AQCD that worsening of health status among chronic bronchitic patients was associated with daily black smoke (BS) levels of 250 to 500 $\mu g/m^3$ in the presence of SO_2

levels in the range of 500 to 600 μg/m^3 (191 to 229 ppb). In the 1986 Second Addendum, additional studies investigated morbidity associated with short-term exposure to SO_2. The most relevant study was by Dockery et al. (1982), which examined pulmonary function in school children in Steubenville, OH as part of the Harvard Six Cities Study. This study found that small but statistically significant reversible decrements in forced vital capacity (FVC) and forced expiratory volume in 0.75 s ($FEV_{0.75}$) were associated with increases in 24-h average concentrations of total suspended particles (TSP) at levels ranging up to 220 to 420 μg/m^3 and SO_2 at levels ranging up to 280 to 460 μg/m^3 (107 to 176 ppb). However, it was impossible to separate the relative contributions of TSP and SO_2, and no threshold level for the observed effects could be discerned from the wide range of exposure levels.

Epidemiological evidence for an association between SO_2 and morbidity as indicated by increased use of ED facilities or increased hospital admissions for respiratory disease outcomes were also reported in the 1982 AQCD. Overall, these results suggested increased upper respiratory tract morbidity, especially among older adults, during episodic marked elevations of PM or SO_2 (0.4 to 0.5 ppm). The 1982 AQCD further concluded that the reviewed studies provided essentially no evidence for an association between asthma attacks and acute exposures at typical ambient 24-h average PM or SO_2 levels in the United States.

The majority of the SO_2 human clinical studies reviewed in the 1982 AQCD evaluated respiratory effects of SO_2 exposure in healthy adults, with some limited data from clinical studies of adults with asthma. Respiratory effects from SO_2 exposure such as increased airway resistance and decreased forced expiratory volume in 1 s (FEV_1) were well documented. The 1986 Second Addendum and 1994 Supplement to the Second Addendum reviewed several additional controlled studies involving both healthy and asthmatic individuals. In general, these studies found no pulmonary effects of SO_2 exposure in healthy subjects exposed to concentrations of <1.0 ppm (Bedi et al., 1984; Folinsbee et al., 1985; Kulle et al., 1984; Stacy et al., 1983). However, in exposures of asthmatic adults, respiratory effects have been observed following short-term exposures (<5 min) to levels of <1.0 ppm (Balmes et al., 1987; Horstman et al., 1988). Decreases in lung function have consistently been demonstrated in relatively healthy, exercising asthmatic adults following 5-15 minute exposures to 0.5-1.0 ppm SO_2.

The 1982 AQCD also noted that numerous effects on the respiratory system were observed in animals exposed to SO_2. Effects were generally observed at levels exceeding

ambient exposure levels and included morphological changes, altered pulmonary function, lipid peroxidation, and changes in host lung defenses. The immediate effect of acute SO_2 exposure in animals was observed to be increased pulmonary resistance to airflow, a measure of bronchoconstriction. It was postulated that increased pulmonary resistance is mediated through bronchial epithelial receptors that activate an autonomic reflex arc through the vagus nerve, a process that is also believed to occur in humans. Because the reflex was blocked by atropine, it was determined to be cholinergic. SO_2-induced bronchoconstriction was hypothesized to involve smooth muscle contraction, because it was reversed by β-adrenergic agonists such as isoproterenol. Acetylcholine and histamine were also thought to be involved in SO_2-induced bronchoconstriction. The 1982 AQCD reported some effects of SO_2 on lung defenses that usually occurred at concentrations exceeding ambient exposure concentrations. Alterations in the antiviral defense system and pulmonary immune system and slowed mucociliary clearance were reported in mice exposed to 2- to 10-ppm SO_2.

Collectively, the epidemiological, human clinical, and animal toxicological studies provided biological plausibility and coherent evidence of an adverse effect of ambient SO_2 on respiratory health. Since the 1982 AQCD, 1986 Second Addendum, and 1994 Supplement to the Second Addendum, additional studies have been conducted on the relationship between short-term exposures to ambient SO_2 and adverse respiratory health effects, including respiratory symptoms, lung function, airways inflammation, airways hyperresponsiveness, lung host defenses, and ED visits and hospitalizations for respiratory causes. The epidemiological, human clinical, and animal toxicological evidence on the effects of SO_2 on these various endpoints are discussed below.

3.1.1.1 Respiratory Symptoms

Respiratory symptoms in air pollution field studies are usually measured using questionnaire forms (or "daily diaries") that are filled out by study subjects. Questions address the daily experience of coughing, wheezing, shortness of breath (or difficulty breathing), production of phlegm, and others. In this section, the effects of short-term exposure to SO_2 on respiratory symptoms in children and adults will be discussed separately. Epidemiological studies on respiratory symptoms published since the last review are summarized in Annex Table AX5-1 with key studies discussed in further detail below.

Children

The strongest epidemiological evidence for an association between respiratory symptoms and exposure to ambient SO_2 comes from two large U.S. multicity studies (Mortimer et al., 2002; Schildcrout et al., 2006). Mortimer et al. (2002) examined 846 asthmatic children from eight U.S. urban areas in the National Cooperative Inner-City Asthma Study (NCICAS) for summertime air pollution-related respiratory symptoms. Median 3-h average SO_2 (8 to 11 a.m.) levels ranged from 17 ppb in Detroit to 37 ppb in East Harlem. Morning symptoms were found to be most strongly associated with an average of a 1- to 2-day lag of SO_2 concentrations. In two-pollutant models with O_3 and nitrogen dioxide (NO_2) (measured in seven cities), the SO_2 association remained robust. When particulate matter with an aerodynamic diameter of $\leq 10\mu$ (PM_{10}) was also included in the multipollutant models using data from three cities, the effect estimate remained similar, but became nonsignificant likely due to reduced statistical power.

In the Childhood Asthma Management Program (CAMP) study, the association between ambient air pollution and asthma exacerbations in children (n = 990) from eight North American cities was investigated (Schildcrout et al., 2006). SO_2 measurements were available in seven of the eight cities. The median 24-h average SO_2 concentrations ranged from 2.2 ppb (interquartile range [IQR]: 1.7, 3.1) in San Diego to 7.4 ppb (IQR: 5.3, 10.7) in St. Louis. Results for the associations between asthma symptoms and all pollutants are shown in Figure 3.1-1. Analyses indicated that, although SO_2 lags were positively related to increased risk of asthma symptoms, only the 3-day moving average was statistically significant. Stronger associations were observed for carbon monoxide (CO) and NO_2. In two-pollutant models with CO, NO_2, and PM_{10}, the effect estimate and 95% confidence interval (CI) remained consistent (Figure 3.1-1).

A longitudinal study of 1,844 schoolchildren during the summer from the Harvard Six Cities Study suggested that the association between SO_2 and respiratory symptoms could be confounded by PM_{10} (Schwartz et al., 1994). The median 24-h average SO_2 concentration during this period was 4.1 ppb (10th–90th percentile: 0.8, 17.9; maximum 81.9). SO_2 concentrations were found to be associated with cough incidence and lower respiratory symptoms. Of the pollutants examined, PM_{10} had the strongest associations with respiratory symptoms. In two-pollutant models, the effect of PM_{10} was found to be robust to adjustment for other copollutants, while the effect of SO_2 was substantially reduced after adjustment for PM_{10}.

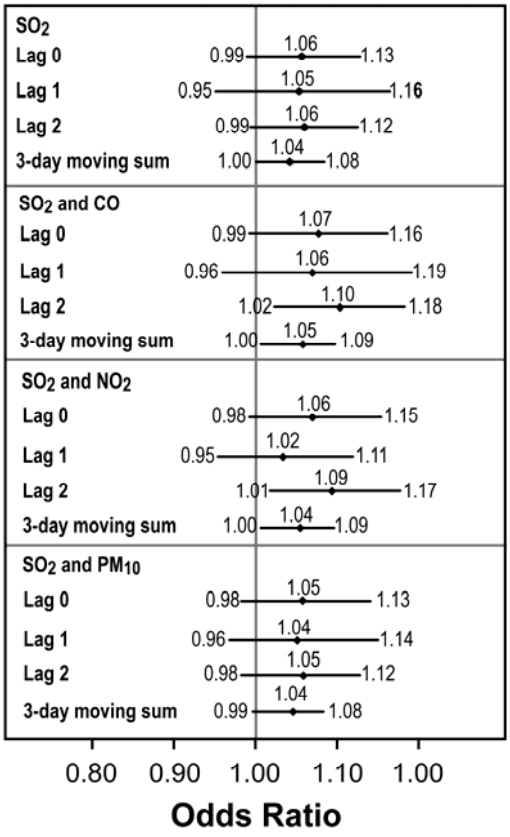

Figure 3.1-1. Odds ratios for daily asthma symptoms associated with a 10-ppb increase in within-subject concentrations of 24-h average SO_2, using data collected from November 1993 to September 1995. All city-specific estimates of pollutant effects were included in calculations of study-wide effects except SO_2 in Albuquerque, NM and NO_2 in Seattle, WA.

Source: Schildcrout et al. (2006).

As the PM_{10} concentrations were correlated strongly to SO_2-derived SO_4^{2-} particles (r = 0.80), the diminution of the SO_2 effect estimate may indicate that for PM_{10} dominated by fine SO_4^{2-} particles, PM_{10} has a slightly stronger association than SO_2. This study further investigated the concentration-response function and observed a nonlinear relationship between SO_2 concentrations and respiratory symptoms. A figure plotting the relative odds of incidence of lower respiratory symptoms against SO_2 concentrations lagged 1 day indicated that no statistically significant increase in the incidence of lower respiratory symptoms was seen until

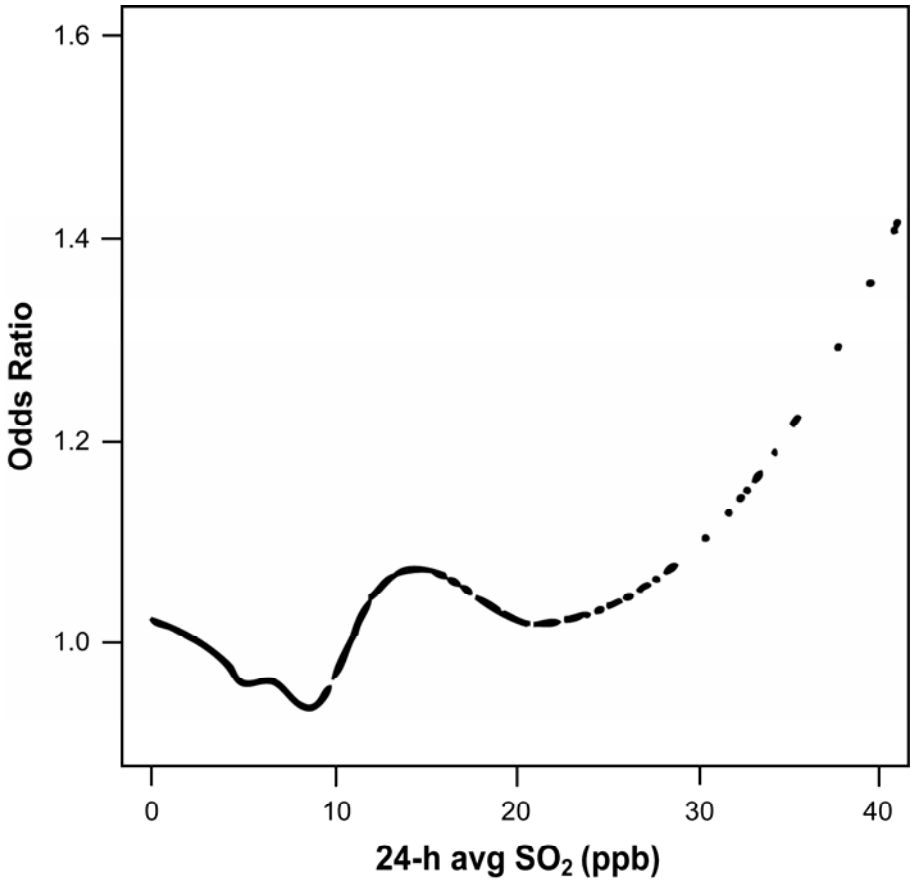

Figure 3.1-2. Relative odds ratio of incidence of lower respiratory symptoms smoothed against 24-h average SO_2 concentrations on the previous day, controlling for temperature, city, and day of week.

Source: Schwartz et al. (1994).

concentrations exceeded a 24-h average SO_2 of 22 ppb though an increasing trend was observed at concentrations as low as 10 ppb (Figure 3.1-2).

In the Pollution Effects on Asthmatic Children in Europe (PEACE) study, a multicenter study of 14 cities across Europe, the effects of acute exposure to various pollutants including SO_2 on the respiratory health of children with chronic respiratory symptoms (n = 2,010) was examined during the winter of 1993-1994 (Roemer et al., 1998). Mean 24-h average SO_2 concentrations ranged from 2 $\mu g/m^3$ (1 ppb) in the urban area of Umeå, Sweden, to 113.9 $\mu g/m^3$ (43 ppb) in the urban area of Prague, Czech Republic. No associations were observed between SO_2 and daily prevalence of respiratory symptoms or bronchodilator use at any of the single- and

multiday lags considered. In addition, no associations were observed for any of the other pollutants examined. It should be noted that during the study period, there were only two major air pollution episodes, one at the beginning and one at the end of the study period. In the epidemiologic model, the control for time trend was accomplished through the use of linear and quadratic terms. Given the timing of the air pollution episodes, the quadratic trend term would have removed most of the air pollution effect. Other studies that participated in the PEACE study and analyzed results for longer periods of times have observed statistically significant associations between SO_2 and respiratory symptoms in children (for example, see van der Zee et al., 1999, presented below).

Other studies have examined the relationship between respiratory symptoms and ambient SO_2 concentrations. These studies generally indicated positive associations, including two U.S. studies (Delfino et al., 2003; Neas et al., 1995) and several European studies (Hoek and Brunekreef, 1994; Peters et al., 1996; Roemer et al., 1993; Segala et al., 1998; Timonen and Pekkanen, 1997; van der Zee et al., 1999). However, some studies found no consistent association (e.g., Hoek and Brunekreef, 1993, 1995; Romieu et al., 1996) between respiratory symptoms and SO_2 concentrations. Given the high correlations among the air pollutants, particularly with PM indices or sulfate (SO_4^{2-}), it is possible that SO_2 might be an indicator for particulate air pollution characterized by PM_{10} or SO_4^{2-} or it might also be a surrogate for other unmeasured combustion products. Only one of these studies examined possible confounding of the SO_2 effect by copollutants. Van der Zee et al. (1999) studied the association between respiratory symptoms and SO_2 in 7- to 11-year-old children (n = 633) with and without chronic respiratory symptoms in the Netherlands. Significant associations with lower respiratory symptoms and increased bronchodilator use were observed for SO_2, as well as PM_{10}, BS, and SO_4^{2-}, in symptomatic children living in urban areas (n = 142). In a two-pollutant model with PM_{10}, the results were robust for bronchodilator use, but slightly reduced for lower respiratory symptoms.

Figures 3.1-3 and 3.1-4 present the odds ratios for SO_2-related cough and lower respiratory or asthma symptoms, respectively, from several epidemiological studies with relevant data. The results for cough are somewhat variable with wide confidence intervals, as shown in Figure 3.1-3. The studies conducted in the summer generally indicate increased risk of cough from exposure to SO_2. A more consistent effect of SO_2 is observed on lower respiratory or

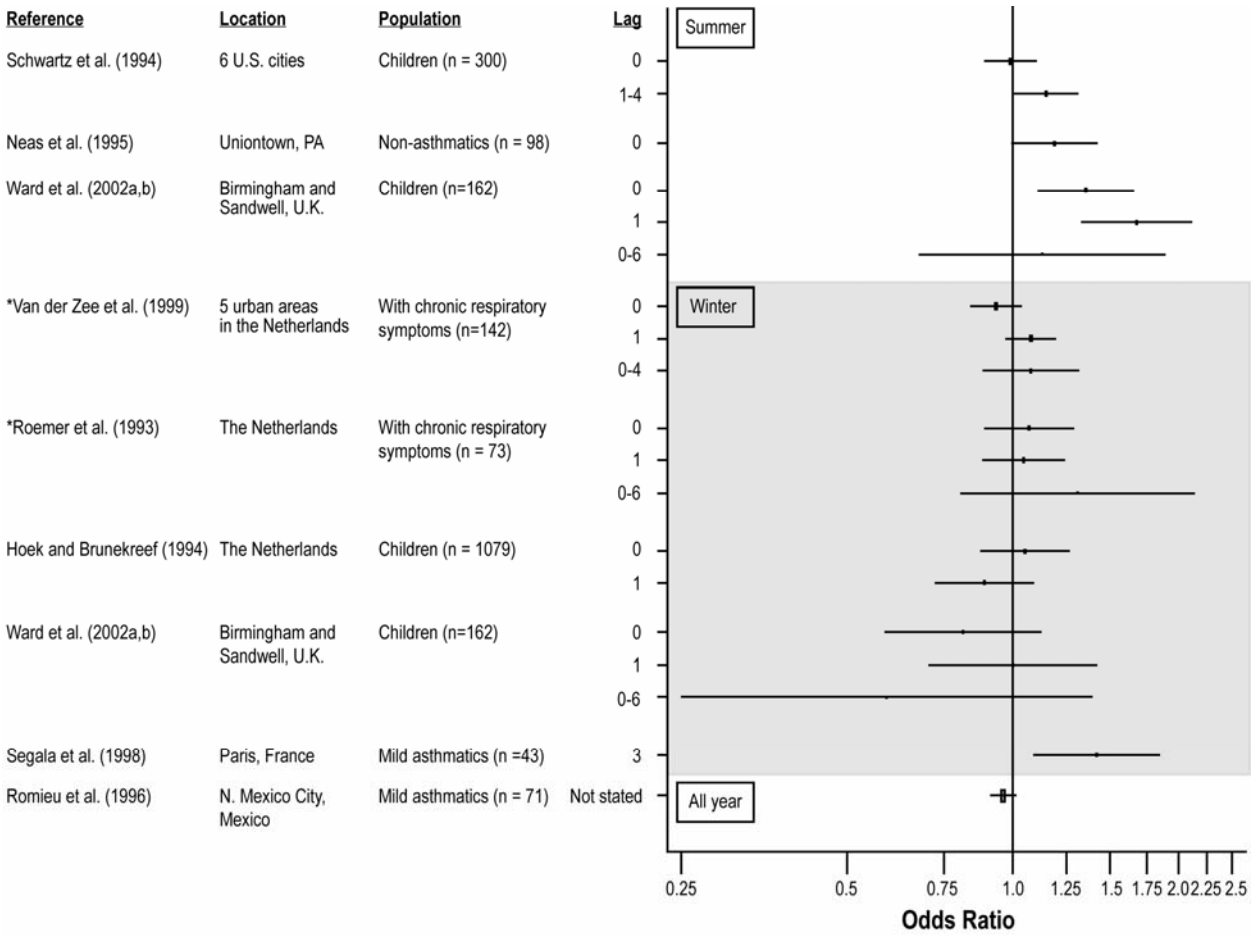

Figure 3.1-3. **Odds ratios (95% CI) for the incidence of cough among children, grouped by season. For single-day lag models, current day and/or previous day SO_2 effects are shown, except for Ségala et al. (1998), which only presented results for a 3-day lag. Risk estimates are standardized per 10-ppb increase in 24-h average SO_2 level. The size of the box of the central estimate represents the relative weight of that estimate based on the width of the 95% CI.**

* Note that van der Zee et al. (1999) and Roemer et al. (1993) presented results for prevalence of cough.

asthma symptoms (Figure 3.1-4). Although there is some variability in the individual effect estimates, the majority of the odds ratios appear to be >1. Similar to cough, stronger associations with lower respiratory or asthma symptoms were observed in the summer compared to the winter. There was some variability among the different lags of exposure; however, effects were

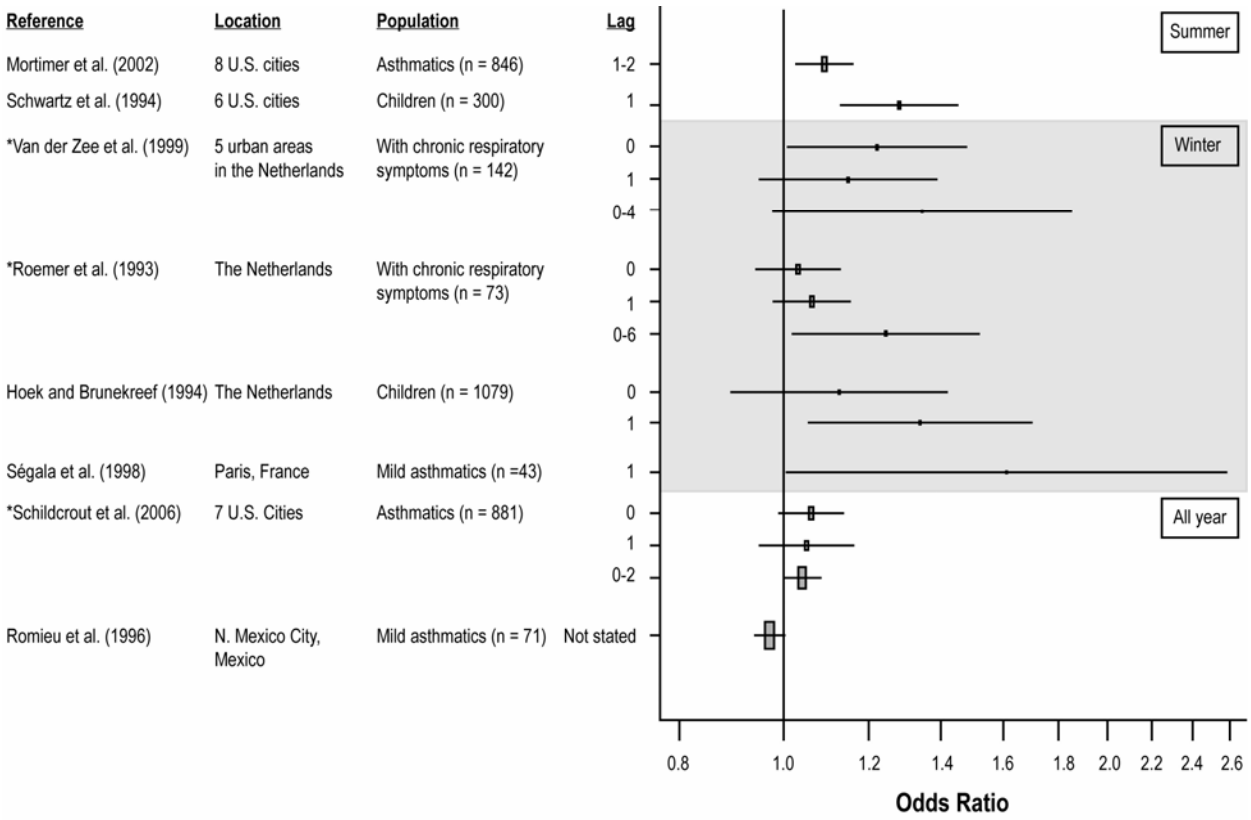

Figure 3.1-4. Odds ratios (95% CI) for the incidence of lower respiratory or asthma symptoms among children, grouped by season. For single-day lag models, current day and/or previous day SO_2 effects are shown. Risk estimates are standardized per 10-ppb increase in 24-h average SO_2 level. The size of the box of the central estimate represents the relative weight of that estimate based on the width of the 95% CI.

* Note that van der Zee et al. (1999), Roemer et al. (1993), and Schildcrout et al. (2006) presented results for prevalence of symptoms.

generally observed with current day or previous day exposure and, in some cases, with a distributed lag of 2 to 3 days.

The 1982 AQCD concluded that there was insufficient evidence on the effect of SO_2 and PM on asthma attacks but that exposure to these pollutants was associated with increases in the occurrence of upper respiratory symptoms, including exacerbation of preexisting chronic bronchitis. A study by Keles et al. (1999) evaluated the prevalence of chronic rhinitis among high school students before and after installation of a natural gas network for domestic heating

and industrial works in a polluted area of Istanbul, Turkey. Concentrations of CO, NO_2, and hydrocarbons were relatively low compared to SO_2 and TSP in this area. After the intervention, the annual mean TSP concentration declined by 23% from 89.7 $\mu g/m^3$ to 68.8 $\mu g/m^3$. An even greater decline (46%) was observed for SO_2, from an annual mean of 185.4 $\mu g/m^3$ (70.8 ppb) to 100.0 $\mu g/m^3$ (38.2 ppb). The prevalence of rhinitis decreased significantly from 62.5 to 51% of the student population ($p < 0.05$) following the installation of the natural gas network. Symptoms of rhinitis were associated with air pollution levels but not with any of the other factors considered, including sex, household crowding, heating source, and smoking status. Although the effects from TSP could not be separated from SO_2, this study demonstrated that reductions in both pollutants (with greater declines in SO_2) resulted in significant reductions in the prevalence of chronic rhinitis in a highly polluted area.

Overall, recent epidemiological studies provide evidence for an association between ambient SO_2 exposure and increased respiratory symptoms in children, particularly those with asthma or chronic respiratory symptoms. Recent U.S. multicity studies observed significant associations between SO_2 and respiratory symptoms at a median range of 17 to 37 ppb (75th percentile: ~25 to 50) across cities for 3-h average SO_2 (NCICAS, Mortimer et al., 2002) and 2.2 to 7.4 ppb (90th percentile: 4.4 to 14.2) for 24-h average SO_2 (CAMP, Schildcrout et al., 2006). However, an earlier study that examined the concentration-response function found that a statistically significant increase in the incidence of lower respiratory symptoms was not observed until concentrations exceeded a 24-h average SO_2 of 22 ppb, though an increasing trend was observed at concentrations as low as 10 ppb (Harvard Six Cities Study, Schwartz et al., 1994). In the limited number of studies that examined potential confounding by copollutants through multipollutant models, the SO_2 effect was generally found to be robust after adjusting for PM and other copollutants.

Epidemiological Studies of Adults

Compared to the number of studies conducted with children, fewer studies were performed that examined the effect of ambient SO_2 exposure on respiratory symptoms in adults. Most of these studies focused on potentially susceptible populations, i.e., those with asthma or chronic obstructive pulmonary disease (COPD). One of the larger studies was conducted by van der Zee et al. (2000) in 50- to 70-year-old adults, with (n = 266) and without (n = 223) chronic respiratory symptoms in the Netherlands. In adults both with and without chronic respiratory

symptoms, no consistent associations were observed between SO_2 levels and respiratory symptoms or medication use.

Studies by Desqueyroux et al. (2002a,b) examined the association between air pollution and respiratory symptoms in other potentially susceptible populations, i.e., those with severe asthma (n = 60, mean age 55 years) and COPD (n = 39, mean age 67 years), in Paris, France. The mean 24-h average SO_2 concentration was 7 $\mu g/m^3$ (3 ppb, range: 1, 10) in the summer and 19 $\mu g/m^3$ (7 ppb, range: 1, 31) in the winter. No associations were observed between SO_2 concentrations and the incidence of asthma attacks or episodes of symptom exacerbation in the severe asthmatics or individuals with COPD. O_3 was found to have the strongest effect in these studies.

Several other European studies did observe an association between ambient SO_2 concentrations and respiratory symptoms in adults with asthma or chronic bronchitis (Higgins et al., 1995; Neukirch et al., 1998; Peters et al., 1996; Taggart et al., 1996). However, only one of these studies examined possible confounding of the association by copollutants. Higgins et al. (1995) examined the effect of summertime air pollutant exposure on respiratory symptoms in 62 adults with either asthma, COPD, or both. The maximum 24-h average SO_2 level was 117 $\mu g/m^3$ (45 ppb). An association was observed between SO_2 and symptoms of wheeze, and it remained robust to adjustment for O_3 and NO_2. The effects of PM were not examined in this study.

Results from the epidemiological studies examining the association between SO_2 and respiratory symptoms in adults are generally mixed, with some showing positive associations and others finding no relationship at current ambient levels.

Human Clinical Studies of Adults

The 1994 Supplement to the Second Addendum described in detail several studies that evaluated respiratory symptoms following controlled human exposures to SO_2. Briefly, following 1-h exposures to 0-, 0.2-, 0.4-, and 0.6-ppm SO_2, Linn et al. (1987) reported that the severity of respiratory symptoms (i.e., cough, chest tightness, throat irritation) increased relative to air exposures only in moderate/severe asthmatics who were exposed at the highest exposure concentration (0.6 ppm). It was also observed that these symptoms abated within <1 h after exposure. Balmes et al. (1987) reported that 7/8 asthmatic adults developed respiratory

symptoms including wheezing and chest tightness following 3-min exposures to 0.5-ppm SO_2 during eucapnic hyperpnea (minute ventilation [$\dot{V}_E$] = 60 L/min).

Since the publication of the 1994 Supplement to the Second Addendum, several additional publications have evaluated the effect of SO_2 exposure on respiratory symptoms in a laboratory setting. In a human clinical study with SO_2-sensitive asthmatics, Gong et al. (1995) reported that respiratory symptoms (i.e., shortness of breath, wheeze, and chest tightness) increased with increasing SO_2 concentration (0-, 0.5-, and 1.0-ppm SO_2) following exposures of 10 min with varying levels of exercise. It was also observed that exposure to 0.5-ppm SO_2 during light exercise evoked a more severe symptomatic response than heavy exercise in clean air. In a more recent study, Tunnicliffe et al. (2003) found no association between respiratory symptoms (i.e., throat irritation, cough, wheeze) and 1-h exposures at rest to 0.2-ppm SO_2 in either asthmatics or healthy adults.

Collectively, evidence from the previous review along with a limited number of new human clinical studies indicate increased respiratory symptoms with peak (5-15 min) SO_2 exposures as low as 0.5 ppm in asthmatic subjects.

3.1.1.2 Lung Function

Most of the studies discussed in the previous section for effects of SO_2 on respiratory symptoms also examined lung function. In studies assessing the relationship between acute exposure to air pollution and lung function, self-administered PEF meters were primarily used. Since PEF follows a circadian rhythm, with the highest values found during the afternoon and lowest values during the night and early morning (Borsboom et al., 1999), these studies generally have analyzed PEF data stratified by time of day. The epidemiological studies on lung function are summarized in Annex Table AX5-1.

Children

Mortimer et al. (2002) examined 846 asthmatic children from eight U.S. urban areas in the NCICAS for changes in PEF related to air pollution. The mean 3-h average SO_2 was 22 ppb across the eight cities during the study period of June through August 1993. No associations were observed between SO_2 concentrations and morning or evening PEF. Of all the pollutants examined, including PM_{10}, O_3, and NO_2, only O_3 was associated with changes in morning PEF.

In another U.S. study (Neas et al., 1995), 83 children from Uniontown, PA reported twice-daily PEF measurements during the summer of 1990. The mean daytime 12-h average SO_2 concentration was 14.5 ppb (maximum 44.9). No associations were observed between daytime 12-h average SO_2 concentrations and mean deviation in evening PEF, even after concentrations were weighted by the proportion of hours spent outdoors during the prior 12 h. Statistically significant associations were observed for O_3, total SO_4^{2-} particles, and particle-strong acidity.

A study by van der Zee et al. (1999) observed associations between ambient SO_2 concentrations and daily PEF measurements in 7- to 11-year-old children (n = 142) with chronic respiratory symptoms living in urban areas of the Netherlands (van der Zee et al., 1999). The odds ratio (OR) for a >10% decrement in evening PEF per 10-ppb increase in 24-h average SO_2 was 1.20 (95% CI: 0.97, 1.47) with same-day exposure. A greater effect was observed at a 2-day lag, OR = 1.40 (95% CI: 1.18, 1.67), and this effect remained robust in a two-pollutant model with PM_{10}, OR = 1.34 (95% CI: 1.08, 1.64).

Multipollutant analyses also were conducted in a study by Chen et al. (1999), which examined the effects of short-term exposure to air pollution on the pulmonary function of 895 children (age 8 to 13 years) in three communities in Taiwan. The daytime 1-h max SO_2 the day before spirometry ranged from 0 to 72.4 ppb. In a single-pollutant model, 1-h max SO_2 concentration at a 2-day lag was significantly associated with FVC, −50.80 mL (95% CI: −97.06, −4.54), or a 2.6% decline, per 40-ppb 1-h max SO_2. However, in multipollutant models, only O_3 remained significantly associated with FVC and FEV_1.

While additional studies have observed associations between ambient SO_2 concentrations and changes in lung function in children (e.g., Hoek and Brunekreef, 1993; Peters et al., 1996; Roemer et al., 1993; Segala et al., 1998; Timonen and Pekkanen, 1997), several other studies did not find a significant association between SO_2 and lung function parameters (e.g., Delfino et al., 2003; Peacock et al., 2003; Romieu et al., 1996).

In a human clinical study of asthmatic adolescents (12 to 16 years old), Koenig et al. (1983) evaluated changes in FEV_1 following a 10-min exposure during moderate exercise to 0.5- and 1.0-ppm SO_2 + 1-mg/m^3 NaCl. Significant decreases of 15 and 23% were reported in FEV_1 following exposure to 0.5- and 1.0-ppm SO_2, respectively. No significant changes in FEV_1 were observed between pre- and postexposure to 1-mg/m^3 NaCl without SO_2.

The mixed results observed in epidemiological studies, along with the high to moderate correlation between SO_2 levels and other copollutants, most notably PM, reported in most studies generally suggest that short-term exposure to ambient SO_2 does not have an independent effect on lung function in children. One human clinical study provided evidence that during exercise, peak exposures (10 min) to SO_2 at concentrations of as low as 0.5 ppm in the presence of hygroscopic particles that can carry SO_2 deeper into the lung can elicit significant changes in pulmonary function in asthmatic adolescents.

Epidemiological Studies of Adults

Van der Zee et al. (2000) observed an association between SO_2 and morning PEF in 50- to 70-year-old adults (n = 138) with chronic respiratory symptoms living in urban areas of the Netherlands. No associations were observed with evening PEF. The OR for a >20% decrement in PEF was 1.21 (95% CI: 0.76, 1.92) per 10-ppb increase in 24-h average SO_2 with same-day exposure and 1.56 (95% CI: 1.02, 2.39) at a 1-day lag. No associations were observed for a >10% decrement in PEF. The authors hypothesized that while SO_2 level did not have much effect on PEF in most subjects, there was a small subgroup of individuals who experienced fairly large PEF decrements when SO_2 levels were high. No multipollutant analyses were conducted.

Higgins et al. (1995) examined the association between pulmonary function and air pollution in 75 adults with either asthma, COPD, or both. Exposure to SO_2 was associated with increased variation in PEF but not with mean or minimum PEF. The SO_2 effects on PEF variation were robust to adjustment for O_3 and NO_2. Effects of PM were not considered. Neukirch et al. (1998) also observed associations between lung function and SO_2 concentrations in a study of asthmatic adults in Paris, France, but significant associations were found for all pollutants examined, including BS, PM_{13}, and NO_2.

In a cross-sectional survey, Xu et al. (1991) investigated the effects of indoor and outdoor air pollutants on the respiratory health of 1,140 adults (aged 40 to 69 years) living in residential, industrial, and suburban areas of Beijing, China. The annual mean concentrations of SO_2 in residential, industrial, and suburban areas from 1981 to 1985 were 128 $\mu g/m^3$ (49 ppb), 57 $\mu g/m^3$ (22 ppb), and 18 $\mu g/m^3$ (7 ppb), respectively. Log-transformed SO_2 and TSP were significantly associated with reductions in FEV_1 and FVC. The authors cautioned that since SO_2 and TSP concentrations were strongly correlated, the effect of SO_2 could not be separated from that of TSP.

Others observed no relationship between ambient SO_2 concentrations and lung function in adults (Peters et al., 1996; Taggart et al., 1996). Similar to the results observed for children, the epidemiological studies examining adults do not provide strong evidence for an association between short-term exposure to ambient SO_2 and lung function. While some studies did observe significant associations between SO_2 exposure and decrements in lung function parameters, the results were not consistent across studies. In addition, the strong correlation between SO_2 and various copollutants in most studies limits interpretation of independent effects of SO_2 on lung function.

Human Clinical Studies of Adults

Healthy Individuals

In controlled SO_2 exposures of healthy human subjects under resting conditions, respiratory effects including increased respiration rates, decrements in peak flow, bronchoconstriction, and increased airway resistance have been observed. Most of these studies report effects at concentrations of >5 ppm (Abe, 1967; Andersen et al., 1974; Frank et al., 1962; Lawther, 1955; Sim and Pattle, 1957), with only a few studies reporting significant health effects at concentrations as low as 1 ppm. Snell and Luchsinger (1969) observed a significant decrease in maximum expiratory flow at 50% of forced vital capacity ($MEF_{50\%}$) in healthy resting adult subjects following 15-min inhalation exposures through a mouthpiece to 1-ppm SO_2. Amdur et al. (1953) reported an increase in respiration rate and a decrease in tidal volume at 1-ppm SO_2; however, this may be considered to be an irritant response rather than an adverse health effect of exposure.

The respiratory effects of SO_2 can be potentiated by increasing ventilation rate either through eucapnic hyperpnea or by performing light exercise during exposure. This effect is likely due to an increased uptake of SO_2 because of both the increase in $\dot{V}_E$ as well as a shift from nasal breathing to oronasal breathing. Lawther et al. (1975) found that deep breathing of 1-ppm SO_2 by mouth resulted in an increase in specific airways resistance (sRaw) compared to breathing air alone. Stacy et al. (1981) exposed 16 healthy males to 0.75-ppm SO_2 for 2 h with a 15-min period of exercise at the end of the first hour of exposure ($\dot{V}_E$ ~ 60 L/min). A separate group of 15 healthy males were exposed to clean air for 2 h and served as the control for this study. In the SO_2-exposed group, airways resistance (Raw) decreased by 2 to 55% compared to

baseline after the 15 min of exercise, but then returned to the baseline value by the end of the 2-h exposure. However, in the control group, Raw decreased throughout the 2-h exposure, resulting in statistically significant differences between the two groups in the change in Raw occurring between both baseline and post-exercise and between baseline and postexposure.

Asthmatic Individuals

During the last review, it was established that subjects with asthma are more sensitive to the effects of SO_2 exposure than healthy individuals without asthma. In fact, it has been demonstrated that asthmatic individuals exposed to <1-ppm SO_2 while performing moderate to heavy exercise for 5 min suffer significant bronchoconstriction or increases in sRaw (Bethel et al., 1983; Linn et al., 1983, 1984). Gong et al. (1995) was able to show an exposure-response relationship between SO_2 and respiratory effects by exposing 14 unmedicated, SO_2-sensitive asthmatics to 0-, 0.5-, and 1-ppm SO_2 under 3 different levels of exercise. It was shown that increasing SO_2 concentration had a greater effect on sRaw and FEV_1 than increasing exercise level. Tunnicliffe et al. (2003) evaluated the effect of a lower exposure concentration of SO_2 in resting healthy and asthmatic subjects. No significant changes in lung function as measured by FEV_1, FVC, and maximal midexpiratory flow (MMEF) were observed following 1-h exposure to 0.2-ppm SO_2. The authors reported a small but statistically significant increase in respiratory rate in the asthmatic group after SO_2 exposure compared to placebo (958.9 breaths/h with SO_2 compared to 906.8 breaths/h with air). However, this effect was counterbalanced by a reduction in tidal volume, resulting in no net change in volume breathed during exposure.

Since some of the studies involving asthmatic subjects have used change in sRaw as the endpoint of interest while others have measured changes in FEV_1 or both, a comparison of FEV_1 and sRaw based on data from Linn et al. (1987, 1990) were provided in the 1994 Supplement to the Second Addendum. Based on simple linear interpolation of the data from these two studies (Linn et al., 1987, 1990), a 100% increase in sRaw corresponded to a 12 to 15% decrease in FEV_1 and a 200% increase in sRaw corresponded to a 25 to 30% decrease in FEV_1.

One of the aims of the Linn et al. (1987) study was to determine how the intensity of response varied with asthma severity or status. In this study, 24 normal, 21 atopic (but not asthmatic), 16 mild asthmatic, and 24 moderate/severe asthmatic subjects were exposed to 0-, 0.2-, 0.4-, and 0.6-ppm SO_2. The exposure protocol consisted of 1-h exposures that included

three 10-min exercise periods ($\dot{V}_E$ ~ 40 L/min). Physiological responses were measured at approximately 15- and 55-min of exposure. Pooling data from both the mild and moderate/severe asthmatic groups (n = 40) and using only measurements made at 15 min into the exposure, the group mean sRaw was doubled with 0.6-ppm SO_2 exposure. In the project report (Hackney et al., 1987) upon which the Linn et al. (1987) article was based, individual data were presented that showed that 15/40 moderate/severe subjects (37.5%) had a doubling of the sRaw at concentrations of <0.6-ppm SO_2.

Linn et al. (1987) demonstrated that moderate and severe asthmatics had the most severe physiological and symptom responses. While the moderate/severe asthmatics were more responsive than mild asthmatics following exposure to clean air during exercise, their increases in response with increasing SO_2 concentrations were similar to the mild asthmatic group. Thus, it was concluded that SO_2 response was not strongly dependent on the clinical severity of asthma. Figure 3.1-5 illustrates the effect of varying concentrations of SO_2 on sRaw for the mild and moderate/severe asthmatics groups after adjusting for the effect of exercise. The apparent lack of correlation between SO_2 response and asthma severity should be interpreted with caution, since the SO_2 response may have been attenuated by medication usage or its persistence. Three of the moderate/severe asthmatics were unable to withhold medication usage during the exposure period. It was also suggested that individual SO_2 response could not be predicted by severity of asthma or asthma status, since a few of the atopic individuals who were not asthmatic nor had exercise-induced bronchoconstriction were reactive to SO_2. On the other extreme, a few of the asthmatics, including some in the moderate/severe group, did not react to 0.6-ppm SO_2. Nevertheless, the largest sRaw increases and most substantial decrements in FEV_1 occurred in the moderate/severe asthmatic group.

One of the key studies discussed in the 1986 Second Addendum was by Horstman et al. (1986) who exposed 27 asthmatic subjects for 10 min on different days to concentrations of SO_2 between 0- and 2-ppm SO_2 under exercising conditions ($\dot{V}_E$ = 42 L/min). These authors reported that for 25% of the subjects, the concentration of SO_2 needed to produce a doubling of the sRaw ($PC(SO_2)$) was <0.5 ppm, and for about 20% of the subjects the $PC(SO_2)$ was >1.95 ppm, with a median $PC(SO_2)$ of 0.75 ppm. Based on a cumulative frequency plot of $PC(SO_2)$ versus SO_2 concentration (Figure 3.1-6), approximately 35% of asthmatic subjects in the Horstman et al.

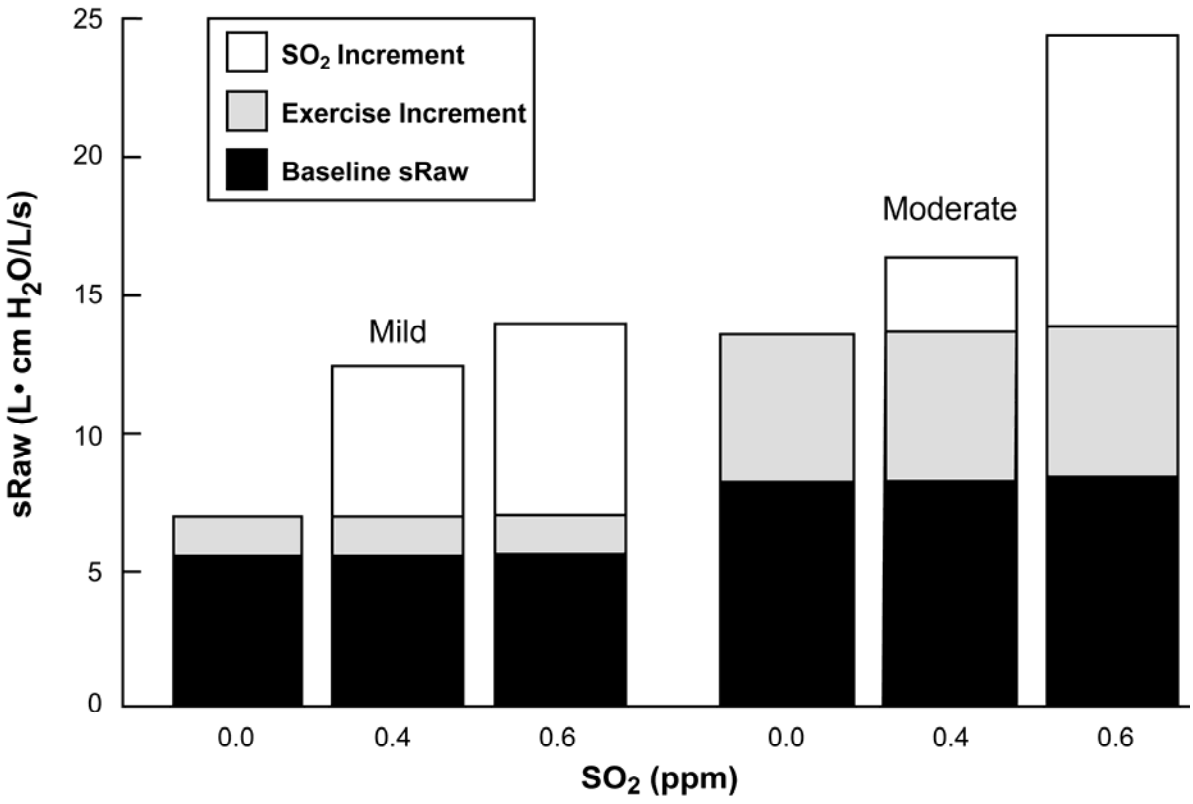

Figure 3.1-5. **Specific airways resistance (sRaw) of 16 mild and 24 moderate asthmatic subjects exposed to 0-, 0.4-, and 0.6-ppm SO_2. The exercise increment represents the increase in sRaw following exercise with exposure to clean air. Redrawn from the 1994 Supplement to the Second Addendum (U.S. Environmental Protection Agency, 1994).**

Source: Linn et al. (1987).

study (1986) reached PC(SO_2) at ≤0.6-ppm SO_2. This is consistent with the 37.5% incidence of PC(SO_2) at concentrations <0.6 ppm observed by Hackney et al. (1987).

Though Hackney et al. (1987) demonstrated the distribution of bronchial sensitivity of asthmatics to SO_2, the authors cautioned against expressing SO_2 response in terms of PC(SO_2). Hackney et al. (1987) noted several limitations to using PC(SO_2) analysis for risk assessment purposes. First, the choice of a 100% increase in sRaw is arbitrary and may not necessarily have any health significance. For example, as noted by the authors, an increase in sRaw from 2 to 4 would meet the 100% criterion but may not be of clinical significance. However, an increase from 12 to 22, while not meeting the criterion, would be of clinical significance. Second, there

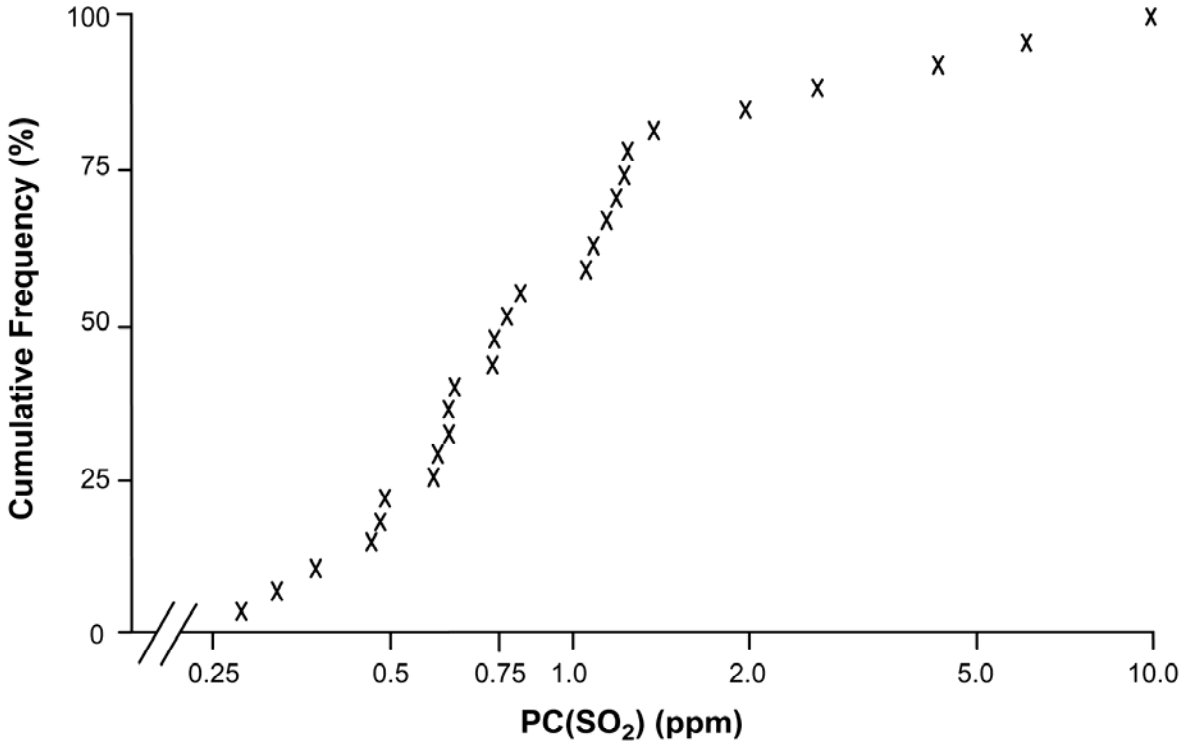

Figure 3.1-6. Distribution of individual airway sensitivity to SO_2. Each data point represents the value of $PC(SO_2)$ for an individual subject. For each subject, $PC(SO_2)$ is determined by plotting change in sRaw, corrected for exercise-induced bronchoconstriction, against SO_2 concentration. The SO_2 concentration that caused a 100% increase in sRaw is determined by linear interpolation.

Source: Horstman et al. (1986).

may be loss of information from the rest of the exposure-response curve other than the chosen point. For example, two subjects may have similar values of $PC(SO_2)$ but substantially different overall risk because of differences in threshold levels and slopes. Finally, $PC(SO_2)$ based on the Hackney et al. (1987) study was not necessarily a stable and reproducible measurement. In some cases, the sRaw change exceeded 100% at low concentrations but not at high concentrations.

Two key studies have shown that a bronchoconstrictive response to SO_2 can occur in as little as 2 min in asthmatic subjects. Horstman et al. (1988) exposed 12 SO_2-sensitive asthmatic subjects to 1.0-ppm SO_2 with exercise ($\dot{V}_E$ = 40 L/min). Correcting for exercise-induced responses, sRaw was shown to increase by 121% after a 2-min exposure and by 307% after a

5-min exposure. Balmes et al. (1987) exposed 8 asthmatic subjects to 0.5- and 1.0-ppm SO_2 during eucapnic hyperpnea (60 L/min) by mouthpiece on separate days for 1-, 3- and 5-min durations. The magnitude of bronchoconstriction increased progressively over the three time periods. At 0.5-ppm SO_2, sRaw increased by 34, 173, and 234% compared to baseline at 1, 3, and 5 min of exposure, respectively. For the 1.0-ppm SO_2 exposure, sRaw increased by 93, 395, and 580% compared to baseline at 1, 3, and 5 min of exposure, respectively.

The interaction of SO_2 with other common air pollutants or the sequential exposure of SO_2 after prior exposure to another pollutant can modify the SO_2-induced respiratory effects. However, only a few studies have looked at the interactive effects of coexisting ambient air pollutants. These few studies have been well summarized in the 1994 Supplement to the Second Addendum. In brief, Koenig et al. (1990) examined the effect of 15-min exposures to 0.1-ppm SO_2 in adolescent asthmatics engaged in moderate levels of exercise. Immediately preceding this exposure, subjects were exposed for 45 min to 0.12-ppm O_3 during intermittent moderate exercise. In this study, subjects also underwent two additional exposure sequences with the same exercise regimen: 15-min exposure to 0.1-ppm SO_2 following a 45-min exposure to clean air, and 15-min exposure to 0.12-ppm O_3 following a 45-min exposure to 0.12-ppm O_3. The authors found that the change in FEV_1 compared to baseline was significantly different following the O_3-SO_2 exposure (8% decrease) when compared to the change following the air-SO_2 or O_3-O_3 exposures (decreases of 3 and 2%, respectively). Jörres and Magnussen (1990) and Rubinstein et al. (1990) investigated the effects of a prior NO_2 exposure on SO_2-induced bronchoconstriction in asthmatic adults. While Jörres and Magnussen (1990) suggested that prior exposure to NO_2 increased the responsiveness to SO_2, Rubinstein et al. (1990) did not find that NO_2 exacerbated the effects of SO_2.

Individuals with Chronic Obstructive Pulmonary Disease

Linn et al. (1985) examined the respiratory effects of SO_2 exposure on subjects with COPD. In this controlled laboratory study, 24 subjects with COPD were exposed for 1 h to 0-, 0.4-, and 0.8-ppm SO_2 with two 15-min periods of light exercise ($\dot{V}_E$ = 18 L/min). In contrast to studies with asthmatics, most of the subjects in this study regularly used bronchodilators and were permitted their use up to 4 h prior to the study. The authors reported no SO_2 effects on sRaw, spirometric measures, or arterial oxygen saturation. While it was concluded that older

adults with COPD seem less reactive to SO_2 compared to heavily exercising young adult asthmatics, it was thought that this may be due to differences in medication usage as well as to the lower ventilation rate observed in subjects with COPD, which would itself result in a reduction in the pulmonary uptake of SO_2.

Summary of Human Clinical Studies on Lung Function in Adults

Results from human clinical studies have consistently demonstrated decreases in lung function (e.g., decreased forced expiratory volume in 1 s [FEV_1] and increased specific airways resistance [sRaw]) following peak exposures (5 to 15 min) to SO_2. These effects have clearly and consistently been shown to be exacerbated among individuals with asthma, with asthmatics exhibiting significant decrements in lung function following 5- to 15-min exposures to SO_2 concentrations of as low as 0.5 ppm while performing moderate levels of exercise (e.g., Gong et al., 1995; Horstman et al., 1986; Linn et al., 1987; Sheppard et al., 1981). The effect of peak SO_2 exposure on lung function has been shown to increase in magnitude with increasing SO_2 concentrations above 0.5 ppm. Studies have further observed significant decrements in lung function in some sensitive asthmatics following 5-15 min exposures to SO_2 concentrations of as low as 0.25 ppm while performing moderate levels of exercise (Horstman et al., 1986; Sheppard et al., 1981). Thus, the observations of increased bronchoconstriction and airway resistance in human clinical studies provide clear evidence for SO_2 effects with peak exposure.

Animal Toxicological Studies

The 1982 AQCD reported bronchoconstriction (as indicated by increased pulmonary resistance) as the most sensitive indicator of lung function effects of acute SO_2 exposure based on the observations of increased pulmonary resistance in guinea pigs that were acutely exposed to 0.16-ppm SO_2. Some of the new animal toxicological studies are consistent with these observations. These studies on lung function are summarized in Annex Table AX4-1.

Increases in pulmonary resistance and decreased dynamic compliance were the most frequently observed effects in conscious guinea pigs exposed to 1-ppm SO_2 for 1 h (Amdur et al., 1983). Studies to understand the potential role of neuronal component in SO_2-induced pulmonary resistance used the anesthetics ketamine in guinea pigs exposed to 1-ppm SO_2 for 3 h/day for 6 days (Conner et al., 1985), carbamate in rabbits exposed to 5-ppm SO_2 for 45 min (Barthélemy et al., 1988), or surgical manipulation (bivagotomy). These studies indicted that

pulmonary resistance was increased in ethyl carbamate-anesthetized rabbits exposed to SO_2 but not in ketamine-anesthetized guinea pigs and that the SO_2-induced increase in lung resistance was not mediated by the vagus nerve in rabbits. Further, observations of the elimination of reflex bronchoconstrictor response by phenyldiguanide in rabbits exposed to 5-ppm SO_2, but not the lung resistance induced by histamine, suggested that SO_2-induced bronchoconstriction in rabbits is not mediated through the vagus nerve. Though these results provided some understanding on the mechanisms involved in the development of SO_2-induced bronchoconstriction, these studies were carried out using only one SO_2 exposure dose and precluded assessment of concentration-response relationships and identification of a no-effect level.

In summary, animal studies have shown that guinea pigs exposed to 0.16- to 1-ppm and rabbits exposed to 5-ppm SO_2 have increased pulmonary resistance that is not mediated through the vagus nerve.

3.1.1.3 Airway Inflammation

One epidemiological study by Adamkiewicz et al. (2004) examined exhaled nitric oxide (eNO) as a biological marker for inflammation in 29 older adults (median age 70.7 years) in Steubenville, OH. The mean 24-h average SO_2 concentration was 12.5 ppb (IQR 11.5). The authors reported that, while significant and robust associations were observed between increased daily levels of fine PM ($PM_{2.5)}$ and increased eNO, no associations were observed with any of the other pollutants examined, including SO_2, NO_2, and O_3.

In a controlled-exposure, time-response study, Sandstrom et al. (1989) exposed 22 healthy male subjects for 20 min to 8-ppm SO_2 under light exercising conditions. Bronchoalveolar lavage was performed in all subjects at least 2 weeks prior to exposure, as well as at 4, 8, 24, and 72 h after exposure in 8/22 subjects. The authors found that as early as 4 h after exposure to SO_2, lysozyme-positive macrophages, lymphocytes, and mast cells were significantly increased compared to baseline. Twenty-four hours after exposure, these markers of inflammation, as well as the total alveolar macrophages (AM) and total cell number, were at peak levels. This study demonstrated that SO_2-induced inflammation may extend beyond the short time period often associated with SO_2 effects. A limitation of this study, however, is that the levels of exposure used are well above air pollution levels normally encountered. Tunnicliffe et al. (2003) measured levels of eNO in asthmatic and healthy adult subjects before and after 1-h

exposure to 0.2-ppm SO_2 under resting conditions. While eNO concentrations were higher in the asthmatic versus healthy subjects, no significant difference was observed between pre- and postexposure in either group.

Two recent studies that examined inflammatory responses in animals exposed to SO_2 report characteristic responses such as leukocyte influx and changes in enzyme levels or activities in the lung at high SO_2 concentrations. In brief, Meng et al. (2005) observed elevated levels of pro-inflammatory cytokines interleukin-6 and tumor necrosis factor-α in lung tissue of mice exposed to SO_2 concentrations of 5.35 and 10.7 ppm. The levels of anti-inflammatory cytokine transforming growth factor-β1 were not affected at any exposure level. For example, in rats exposed to 5, 50, or 100 ppm of SO_2 for 5 h/day for 28 days, increased leukocyte numbers in bronchoalveolar lavage fluid was observed at 100 ppm, but no such infiltration of leukocytes was observed in rats exposed to 5 or 50 ppm (Langley-Evans et al., 1996). The animal toxicological studies on airway inflammation are summarized in Annex Table AX4-2.

Overall, the limited epidemiological, human clinical, and toxicological evidence does not indicate that exposure to SO_2 at current ambient concentrations is associated with inflammation in the airways.

3.1.1.4 Airway Hyperresponsiveness and Allergy

A limited number of epidemiological studies have examined the association between SO_2 and airway hyperresponsiveness (AHR). Other studies have also considered individuals with AHR and atopy as a potentially susceptible subgroup to SO_2-related health effects. These studies are summarized in Annex Table AX5-1. Søyseth et al. (1995) investigated the effect of short-term exposure to SO_2 and fluoride on the number of capillary blood eosinophils and the prevalence of bronchial hyperresponsiveness (BHR) in schoolchildren aged 7 to 13 years (n = 620) from two regions in Norway, a valley containing an SO_2-emitting aluminum smelter and a similar but nonindustrialized valley. The median 24-h average SO_2 concentration was 22.2 $\mu g/m^3$ (8 ppb, 10th–90th percentile: 1, 33) in the exposed area and 2.5 $\mu g/m^3$ (1 ppb, 10th–90th percentile: 0, 4). The mean number of eosinophils was significantly greater in children living near the aluminum smelter compared to the nonindustrialized area. However, within children in the exposed area, a negative concentration-response relationship was observed between mean eosinophils and previous-day 24-h average SO_2. The observed association

between SO_2 and eosinophils was limited to atopic children. In children living in the exposed area, a statistically significant positive association was observed between prevalence of BHR and previous-day 24-h average SO_2 concentrations. Similar associations were observed for fluoride. The authors hypothesized that recent exposure to SO_2 may have induced changes in the airways leading to BHR, in addition to recruitment of eosinophils to the airways in atopic subjects. Exposure to PM was not assessed in this study.

A study by Taggart et al. (1996) examined the effect of summertime air pollution levels in northwestern England on BHR in nonsmoking, asthmatic subjects (n = 38) aged 18 to 80 years who were determined to be methacholine (MCh) reactors. Subjects were tested multiple times, for a total of 109 evaluable challenge tests. The maximum 24-h average SO_2 concentration during the study period was 103.7 $\mu g/m^3$ (40 ppb). This study reported that 24-h average SO_2 levels were marginally associated with a decreased dose of MCh required for a 20% drop in the postsaline FEV_1 ($PD20FEV_1$).

Other epidemiological studies investigated the effect of exposure to SO_2 on children and adults with BHR and atopy. Boezen et al. (1999) examined children (n = 459) aged 7 to 11 years old in the Netherlands and tested them for BHR using MCh and relatively high serum concentrations of total IgE (>60 kU/L, the median value). These children were a subset of a larger cohort examined in van der Zee et al. (1999). It was hypothesized that children with BHR and atopy, indicated by raised serum total IgE, may be susceptible to the effects of air pollution. One of the strengths of this study was that the use of BHR and serum IgE concentration as a marker for susceptibility was less prone to error than self-reported chronic respiratory symptoms. A total of 121 children were found to have BHR and relatively high serum total IgE, 67 had BHR and relatively low serum total IgE, 104 had no BHR but had a relatively high serum total IgE concentration, and 167 were found to have neither BHR nor relatively high serum total IgE. In the subset of children with relatively low serum total IgE with or without BHR, no associations were observed between SO_2 and any respiratory symptoms. However, for children with relatively high serum total IgE either with or without BHR, the prevalence of lower respiratory symptoms increased with increasing SO_2 concentrations. For children with BHR and relatively high serum total IgE, the OR for the prevalence of lower respiratory symptoms was 1.70 (95% CI: 1.26, 2.29) with a 5-day moving average for every 10-ppb increase in SO_2. For

children without BHR but with relatively high serum total IgE the OR was 1.82 (95% CI: 1.33, 2.50) with a 5-day moving average.

Boezen et al. (2005) did a similar study in 50- to 70-year-old adults (n = 327) in the Netherlands. Subjects underwent spirometry and MCh challenges to determine AHR. The subgroup of individuals with elevated serum total IgE, both with (n = 48) and without (n = 112) AHR were found to be more susceptible to air pollutants compared to those who did not have elevated serum total IgE (n = 167). Significant associations were observed between previous-day 24-h average SO_2 concentrations and the prevalence of upper respiratory symptoms in those with elevated serum total IgE. Stratified analyses by gender indicated that, among those with AHR and elevated IgE, only males (n = 25) were at a higher risk for respiratory symptoms. The OR for these males was 3.54 (95% CI: 1.79, 7.07) increase in 24-h average SO_2 for a 5-day moving average, compared to 1.05 (95% CI: 0.59, 1.91) for the females.

One human clinical study investigated the relationship between hyperresponsiveness to SO_2 and AHR to MCh (Nowak et al., 1997). Responsiveness to both MCh and SO_2 were tested on 790 subjects between the ages of 20 and 44. The authors reported that among subjects with AHR to MCh, 22.4% were hyperresponsive to SO_2, whereas among the MCh-nonresponsives only 0.4% were hyperresponsive to SO_2. Using a logistic regression model, they also determined that a positive skin test ($p < 0.05$), a positive history of respiratory symptoms ($p < 0.05$), and hyperresponsiveness to MCh ($p < 0.0001$) were significant predictors of a positive SO_2 response.

A limited number of animal studies also suggest acute SO_2-induced increases in airway obstruction and hypersensitivity in allergen-sensitized guinea pigs and sheep. These toxicological studies are summarized in Annex Table AX4-3. Bronchial responses (pulmonary resistance or reduced dynamic compliance to agonists (i.e., histamine, MCh, 5-hydroxytryptamine) are examined after exposure to evaluate toxic effects of pulmonary toxicants. Exposure of rabbits to 5-ppm SO_2 for 2 h had no effect on airway responsiveness to histamine (Douglas et al., 1994). Even at higher concentrations of 10-ppm SO_2 for 5 min, hyperresponsiveness and hyperreactivity effects to aerosolized MCh or 5-hydroxytryptamine were not observed in dogs (Lewis and Kirchner, 1984), but positive responses were observed at the higher concentration of 30 ppm. Studies with chronic exposure of dogs suggest no increased sensitivity to agonists at SO_2 concentrations of $\geq$15 ppm (Scanlon et al., 1987).

Riedel et al. (1988) studied the effect of SO_2 exposure in ovalbumin-sensitized guinea pigs exposed to SO_2 at 0.1, 4.3, or 16.6 ppm for 8 h/day for 5 days. On bronchial provocation, they observed increased bronchial obstruction in animals exposed to 0.1-ppm SO_2 compared to air-exposed animals. In addition, increased amounts of anti-ovalbumin IgG antibodies were detected in bronchoalveolar lavage fluid of animals exposed to $\geq$4.3-ppm SO_2 and in the serum of animals exposed to $\geq$0.1-ppm SO_2.

Similar findings were observed in studies in which guinea pigs were exposed to a single SO_2 concentration. Airway obstruction induced by an ovalbumin challenge was higher in ovalbumin-sensitized guinea pigs exposed to 0.1-ppm SO_2 for 5 h/day for 5 days compared to sensitized guinea pigs that were not exposed to SO_2 (Park et al., 2001). In guinea pigs sensitized with *Candida albicans*, exposure to 5-ppm SO_2 for 4 h/day on 5 days/week for 6 weeks resulted in an increased number of animals displaying prolonged expiration or inspiration after an inhalation challenge with *C. albicans* (Kitabatake et al., 1992, 1995).

The effect of SO_2 on antigen-induced sensitivity reactions was assessed in sheep. A 4-h exposure to 5-ppm SO_2 increased airway reactivity in response to carbachol in sheep that had been sensitized to *Ascaris suum* antigen 24-h postexposure, but increased sensitivity was not observed in nonsensitized sheep (Abraham et al., 1981).

Limited epidemiological evidence suggests that exposure to SO_2 may lead to AHR in atopic individuals. Toxicological studies that observed increased airway obstruction and hypersensitivity in allergen-sensitized animals provide biological plausibility. The epidemiological evidence further indicates that atopic individuals may be at increased risk for SO_2-induced respiratory symptoms.

3.1.1.5 Lung Host Defense

An additional concern has been the potential for SO_2 exposure to enhance susceptibility to, or the severity of illness resulting from, respiratory infections, especially in children. School absenteeism is an indicator of morbidity in children resulting from acute conditions. Respiratory conditions are the most frequent cause, particularly influenza and the common childhood infectious diseases. Park et al. (2002) examined the association between air pollution and school absenteeism in 1,264 first- to sixth-grade students attending school in Seoul, Korea. The study period extended from March 1996 to December 1999, with a mean 24-h average SO_2

concentration of 9.19 ppb (SD 4.61). Note that analyses were performed using Poisson Generalized Additive Model (GAM) with default convergence criteria. Same-day SO_2 concentrations were positively associated with illness-related absences (9% increase [95% CI: 7, 12] per 5.68-ppb increase in 24-h average SO_2), but inversely associated with non-illness–related absences (5% decrease [95% CI: 1, 8]). PM_{10} and O_3 concentrations also were positively associated with illness-related absences. In two-pollutant models containing SO_2 and either PM_{10} or O_3, the SO_2 estimates were robust. These results are consistent with those of Pönka (1990), who observed that absenteeism due to febrile illnesses among children in day care centers and schools and in adults was significantly higher on days of higher SO_2 concentrations (>21.1 $\mu g/m^3$ [8.1 ppb] weekly mean of 1-h average) compared to days of lower SO_2 concentrations. In addition, on days of higher SO_2 concentrations, the mean weekly number of cases of upper respiratory infections and tonsillitis reported from health centers increased. Temperature, but not NO_2, was also found to be associated with febrile illnesses and respiratory tract infections. From these epidemiological studies, it is unknown whether SO_2 increases susceptibility to infection or whether they exacerbate preexisting morbidity following infection.

Pino et al. (2004) examined the association between air pollution and respiratory illnesses in a cohort of 504 infants recruited at 4 months of age from primary health care units in southeastern Santiago, Chile. The infants were followed through the first year of life. The mean 24-h average SO_2 concentration was 11.6 ppb (5th–95th percentile: 3.0, 29.0). The most frequent diagnosis during follow-up was wheezing bronchitis. No associations were observed between current-day or previous-day SO_2 and wheezing bronchitis, but with a 7-day lag, a 21% (95% CI: 8, 39) increased risk in wheezing bronchitis was observed per 10-ppb increase in 24-h average SO_2. However, it should be noted that stronger associations were observed with $PM_{2.5}$, which was well correlated with SO_2 ($r = 0.73$). These epidemiological studies are summarized in Annex Table AX5-1.

The animal toxicological studies reviewed in the 1982 AQCD on the effects of SO_2 on lung defenses reported concentration and species-specific differential effects. In rats exposed to 0.1-ppm SO_2 for ~2 to 3 weeks, clearance of labeled particles from the lung was accelerated at 10 and 23 days following exposure. While this clearance was accelerated at 10 days, it slowed down at 25 days in rats exposed to 1 ppm for ~2 to 3 weeks. No difference in macrophage-containing particles was observed in rats chronically-exposed to up to 3-ppm SO_2. Only one

study published after the last review evaluated mucociliary clearance in rats after exposure to SO_2. In this subchronic study, no effect on clearance of radiolabeled particles from the lung was observed in rats exposed to 5-ppm SO_2 for 2 h/day for 4 weeks (Wolff et al., 1989), which is in contrast to the altered clearance reported in the 1982 AQCD. The current studies are summarized in Annex Table AX4-4.

There was only limited data available in the 1982 AQCD from animal toxicological studies on effects of SO_2 on immune and macrophage function. The studies reviewed there indicated no effect on susceptibility to bacterial infection with exposure to SO_2 at $\leq$5 ppm for 3 months and alterations in pulmonary immune system were reported with chronic exposure of mice to 2-ppm SO_2. At high-dose exposures to 7- to 10-ppm SO_2 for 7 days, impairment of antiviral defenses was observed in mice.

Two recent studies using a 10-ppm SO_2 exposure regimen in mice found no effect on bactericidal activity toward *Staphylococcus aureus* following acute (4 h) exposure (Clarke et al., 2000; Jakab et al., 1996). However, increased mortality rate and decreased survival time were observed in mice that were exposed to the same dose for 1 day or 1, 2, or 3 weeks and then challenged with an aerosol of *Klebsiella pneumoniae* (Azoulay-Dupuis et al., 1982). No effects on macrophage phagocytosis of red blood cells were observed in mice exposed to 10-ppm SO_2 for 4 h (Clarke et al., 2000; Jakab et al., 1996).

Although the limited epidemiologicical evidence weakly suggests a possible association between ambient SO_2 concentrations and increased respiratory illnesses, there is little toxicological evidence to support this observed relationship.

3.1.1.6 Emergency Department Visits and Hospitalizations for Respiratory Diseases

Total respiratory causes for ED visits typically include asthma, pneumonia, bronchitis, and emphysema (collectively referred to as COPD), upper and lower respiratory infections, and other minor categories (U.S. Environmental Protection Agency, 2006d). Temporal associations between ED visits or hospital admissions for respiratory diseases and the ambient concentrations of SO_2 have been the subject of >50 well-conducted research publications since 1994. In addition to considerable statistical and analytical refinements, the more recent studies have examined responses of morbidity in different age groups, the effect of seasons on ED and

hospital usage, and multipollutant models to evaluate potential confounding effects of copollutants.

All Respiratory Diseases

Relatively few studies of ED visits for all respiratory causes were conducted in comparison with studies that examined hospital admissions for all respiratory causes as the outcome. Collectively, studies of ED visits and hospitalizations provide suggestive evidence of an association between ambient SO_2 levels and ED visits and hospitalizations for all respiratory causes among children (0 to 14 years) and older adults (65+ years). The studies that examined the association of these outcomes and SO_2 levels among adults (15 to 64 years) overwhelmingly reported null results. When all age groups were combined, the results of ED and hospitalization studies were mixed; it is likely that any significant effect estimates found in these studies were driven by increases in the very young and/or older adult subpopulations. The epidemiological studies of ED visits and hospital admissions for respiratory causes are summarized in Annex Tables AX5-2.

The results from the hospitalization and ED studies, separated by analyses among all ages or age-specific analyses, are shown in Figures 3.1-7 and 3.1-8. Wilson et al. (2005) examined ED visits for all respiratory causes in Portland, ME from 1996 through 2000 and in Manchester, NH from 1998 through 2000. The mean 1-h max SO_2 concentration in Portland was 11.1 ppb (SD 9.1), and it was higher during the winter months (mean 17.1 ppb (SD 12.0]) and lower in the summer months (mean 9.1 ppb [SD 8.0]). In Manchester, the mean 1-h max SO_2 concentration was 16.5 ppb (SD 14.7 ppb), and it was higher in the winter months (mean 25.7 ppb [SD 15.8]) compared to the summer months (mean 10.6 ppb [SD 15.1]). When all ages where included in analyses, Wilson et al. (2005) found positive associations between ED visits and SO_2, with an 8% (95% CI: 3.0, 11) and 11% (95% CI: 0.0, 20.0) increased risk per 10-ppb increase in 24-h average SO_2 at a 0-day lag in Portland, ME and Manchester, NH, respectively.

Peel et al. (2005) investigated ED visits for all respiratory causes in Atlanta, GA from 1993 through 2000. This study included 484,830 ED visits. The mean 1-h max SO_2 concentration during the study period was 16.5 ppb (SD 17.1). Peel et al. (2005) found a weak positive relationship between ED visits and SO_2, though the increased risk was not statistically significant (1.6% [95% CI: −0.6, 3.8]). Tolbert et al. (2007 in press) recently reanalyzed these

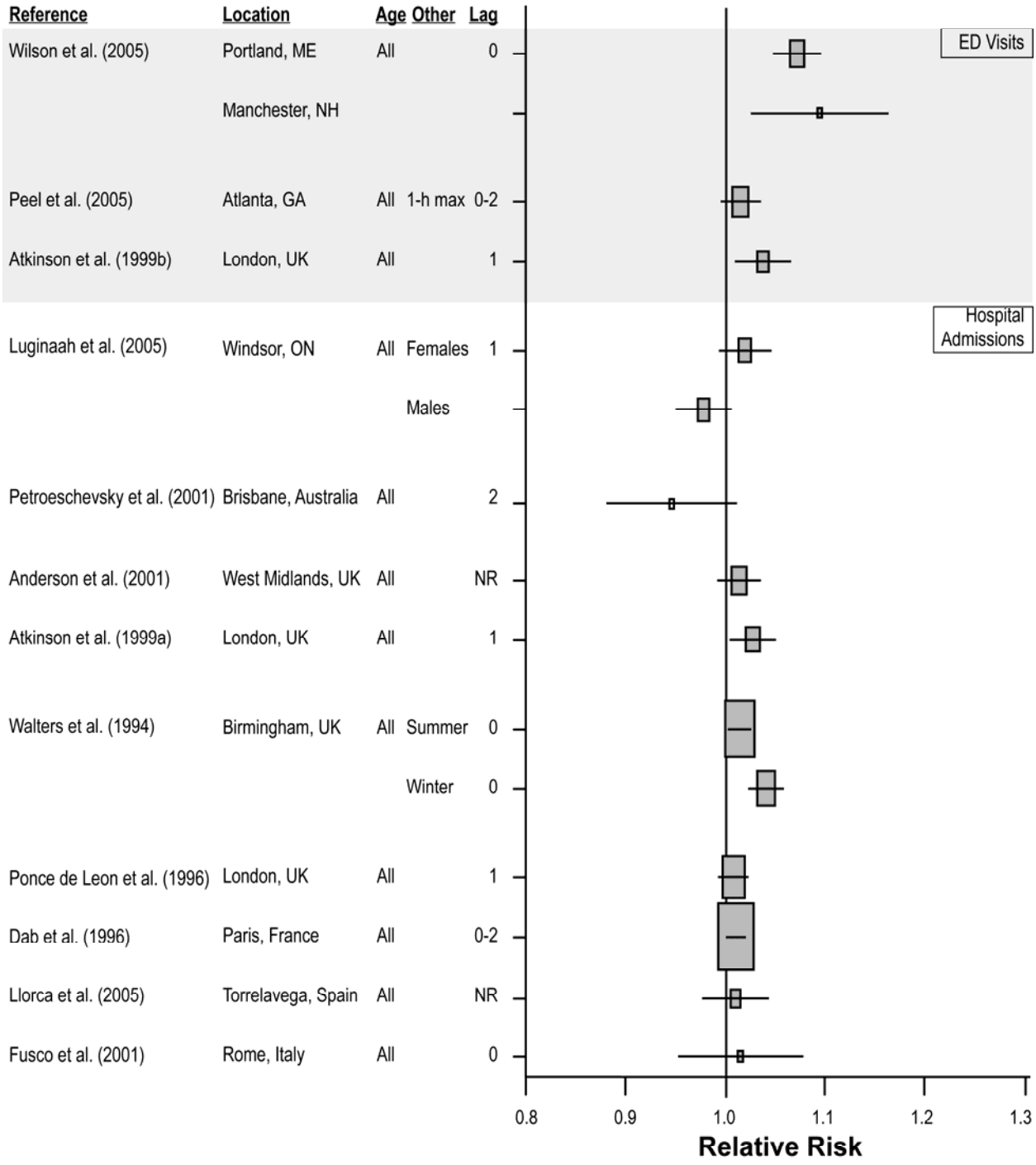

Figure 3.1-7. **Relative risks (95% CI) of SO_2-associated emergency department visits (*) and hospitalizations for all respiratory causes among all ages. Risk estimates are standardized per 10-ppb increase in 24-h average SO_2 concentrations or 40-ppb increase in 1-h max SO_2. The size of the box of the central estimate represents the relative weight of that estimate based on the width of the 95% CI.**

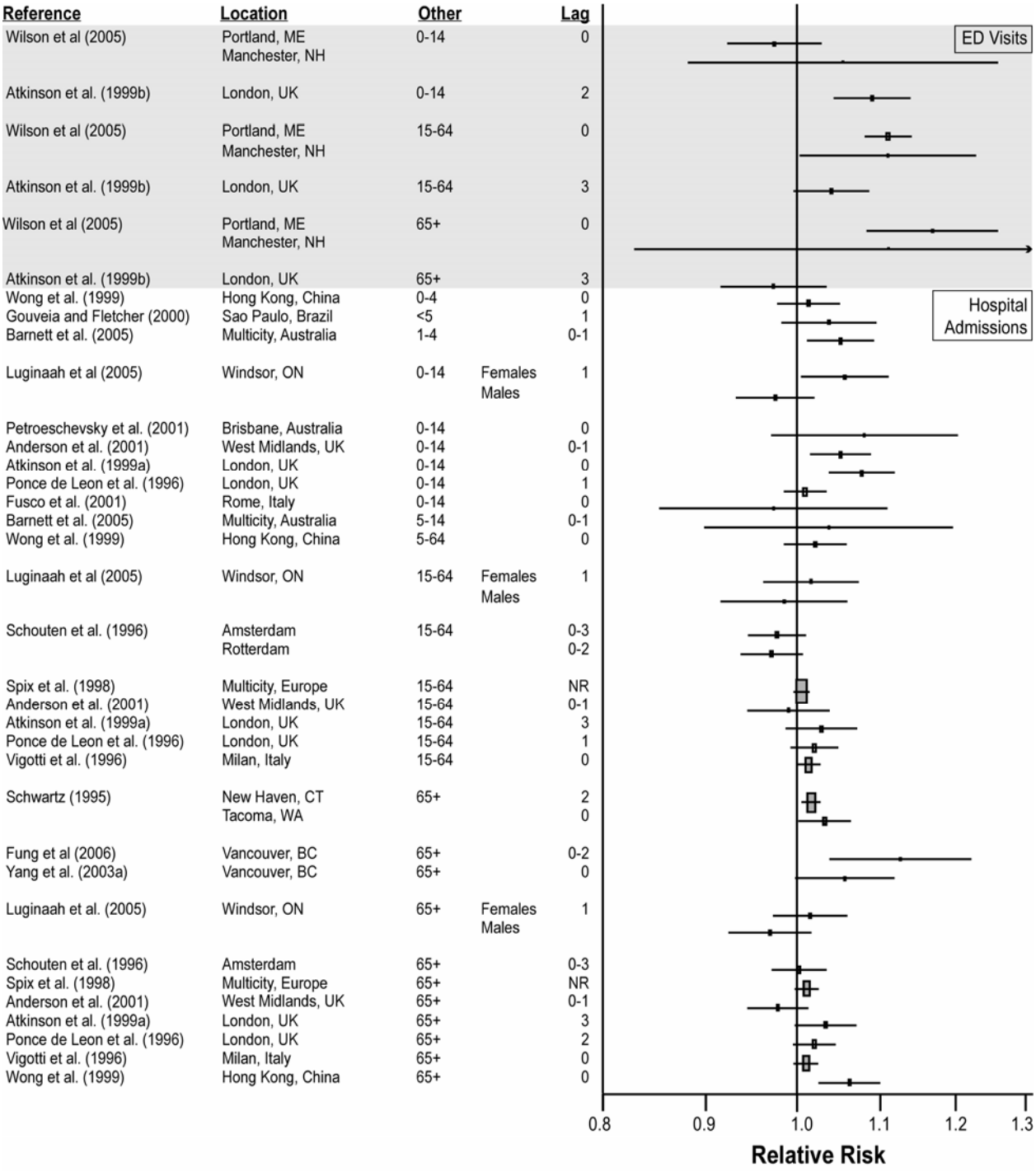

Figure 3.1-8. Relative risks (95% CI) of SO_2-associated emergency department visits and hospitalizations for all respiratory causes, stratified by age groups. Risk estimates are standardized per 10-ppb increase in 24-h average SO_2 concentrations or 40-ppb increase in 1-h max SO_2. The size of the box of the central estimate represents the relative weight of that estimate based on the width of the 95% CI.

data with 4 additional years of data and found the same results. An analysis by Dab et al. (1996) examined the association between SO_2 and hospital admissions for all respiratory causes using both the 24-h average and 1-h max. It should be noted that they observed similar effect estimates for both exposure metrics, but only the estimate using 24-h average was statistically significant (1.1% [95% CI: 0.1, 2.0] per 10-ppb increase in 24-h average SO_2 versus 1.9% [95% CI: −1.3, 5.0]) per 40-ppb increase in 1-h max SO_2).

When analyses were stratified to include only children (0 to 14 years), Wilson et al. (2005) did not find statistically significant associations between ED visits and SO_2 in Portland, ME or Manchester, NH. Additional evidence of a modest association between SO_2 and ED visits or hospitalizations for all respiratory causes in children from several Australian (Barnett et al., 2005; Petroeschevsky et al., 2001) and European (Anderson et al., 2001; Atkinson et al., 1999a,b) studies. Increased risks ranging from 3 to 22% per 10-ppb increase in 24-h average SO_2 were reported by these studies. In a multicity study spanning Australia and New Zealand, Barnett et al. (2005) compared hospital admission data collected from 1998 through 2001 with ambient SO_2 concentrations, where the mean 24-h average SO_2 concentration ranged from 0.9 to 4.8 ppb. The authors found a 5% (95% CI: 1, 9) increased risk per 10-ppb increase in 24-h average SO_2 among children (1 to 4 years) in these cities. However, some additional European (Fusco et al., 2001; Ponce de Leon et al., 1996) and Latin American (Braga et al., 1999, 2001) studies did not find statistically significant associations between ambient SO_2 concentrations and hospitalizations for all respiratory causes among children.

Wilson et al. (2005) found a positive association between ED visits and SO_2, with a 16% (95% CI: 8.0, 25.0) increased risk per 10-ppb increase in 24-h average SO_2 at a 0-day lag in Portland, ME and a null association in Manchester, NH when only older adults (65+ years) were considered. In another two-city study, Schwartz (1995) compared 13,740 hospital admissions in New Haven, CT and Tacoma, WA from 1988 through 1990 with ambient SO_2 concentrations. The mean 24-h average SO_2 concentration was 29.8 ppb (90th percentile: 159) in New Haven and 16.8 ppb (90th percentile: 74) in Tacoma. Schwartz found positive associations between hospitalizations and SO_2, with a 2% (95% CI: 1.0, 3.0) and 3% (95% CI: 1.0, 6.0) increased risk per 10-ppb increase in 24-h average SO_2 at a 0-day lag in New Haven and Tacoma, respectively. In two-pollutant models, the SO_2 effect estimate from New Haven, but not Tacoma, was found to be robust to adjustment for PM_{10}. Here, the term robust is used to indicate that there was little

change in the magnitude of the central estimate, though statistical significance may have been lost. In Vancouver, BC, both Fung et al. (2006) and Yang et al. (2003a) also found positive associations between hospitalizations and SO_2. In a multipollutant model including coefficient of haze (CoH), NO_2, O_3, and CO, the SO_2 effect estimate diminished slightly (Yang et al., 2003a).

Additional evidence of a positive association between ED visits or hospitalizations for all respiratory causes among older adults and SO_2 comes from several European (Spix et al., 1998; Sunyer et al., 2003a; Vigotti et al., 1996) and Australian (Petroeschevsky et al., 2001) studies. Increased risks ranging from 1 to 12% per 10-ppb increase in 24-h average SO_2 were reported by these studies. Petroeschevsky et al. (2001) examined 33,710 hospital admissions in Brisbane, Australia from 1987 through 1994. The mean 24-h average SO_2 concentration was 4.1 ppb and was highest in the winter months (4.8 ppb) and lowest in the spring months (3.7 ppb). Petroeschevsky et al. found a 12% (95% CI: 2.0, 23.0) increased risk per 10-ppb increase in 24-h SO_2 at 0-day lag. Additional European studies did not find statistically significant associations between ambient SO_2 concentrations and hospitalizations for all respiratory causes among older adults (Schouten et al., 1996; Anderson et al., 2001; Atkinson et al., 1999a; Ponce de Leon et al., 1996).

In summary, many studies have observed positive, though not statistically significant associations between ambient SO_2 concentrations and ED visits and hospitalizations, particularly among children and older adults (age 65+ years).

Asthma

Studies of ED visits and hospitalizations provide suggestive evidence of an association between ambient SO_2 levels and ED visits and hospitalizations for asthma among children (0 to 14 years). The studies that examined the association of these outcomes and SO_2 levels among adults (15 to 64 years) and older adults (65+ years) overwhelmingly reported null results. When all age groups were combined, the results of ED and hospitalization studies were mixed, and it is likely that any significant effect estimates found in these studies were driven by increases in the young subpopulations.

The results from the hospitalization and ED studies, separated by analyses among all ages and age-specific analyses, are shown in Figures 3.1-9 and 3.1-10. When all ages were included in analyses, Wilson et al. (2005) found a positive association between ED visits and SO_2, with a

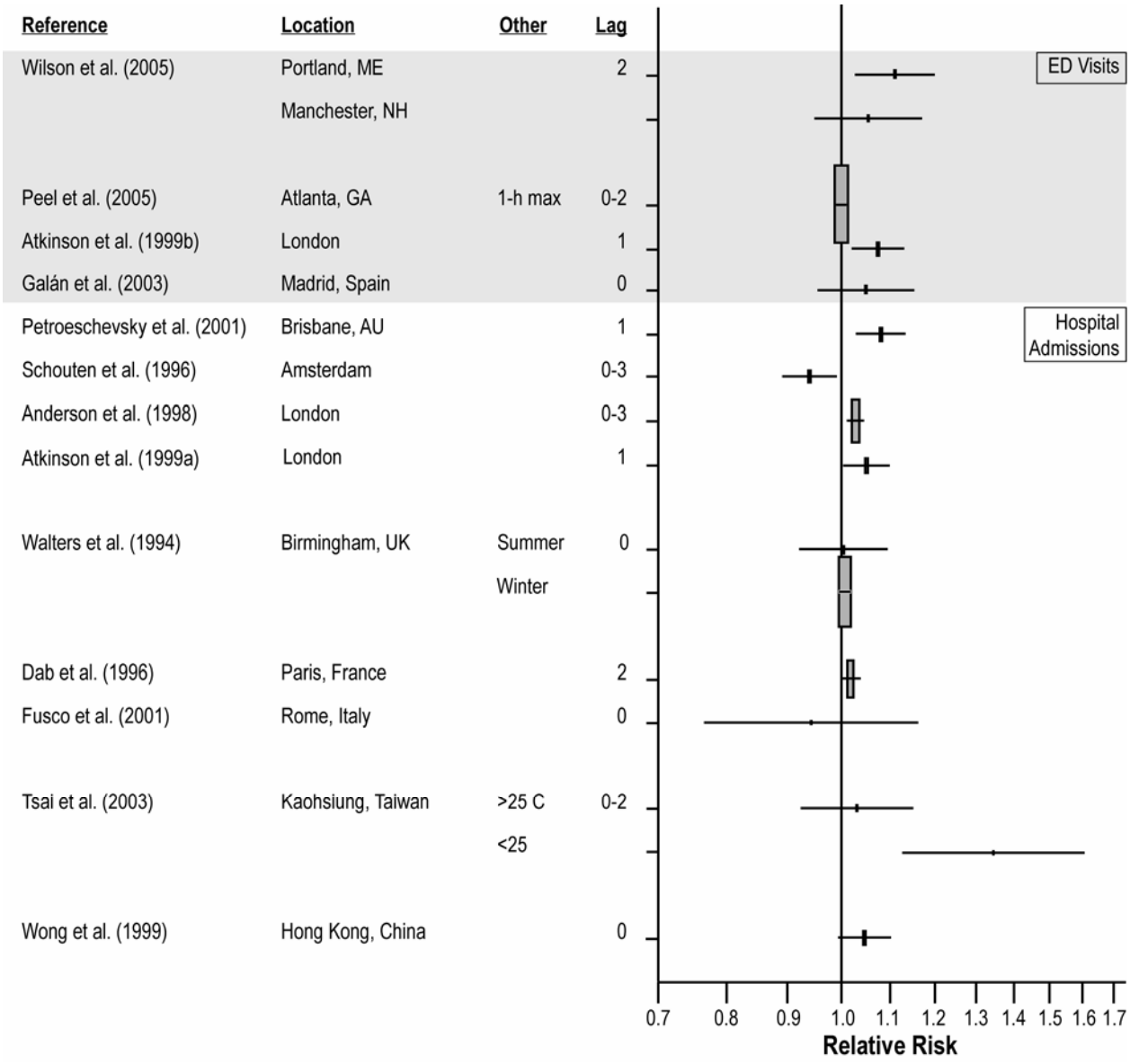

Figure 3.1-9. **Relative risks (95% CI) of SO_2-associated emergency department visits (*) and hospitalizations for asthma among all ages. Risk estimates are standardized per 10-ppb increase in 24-h average SO_2 concentrations or 40-ppb increase in 1-h max SO_2. The size of the box of the central estimate represents the relative weight of that estimate based on the width of the 95% CI.**

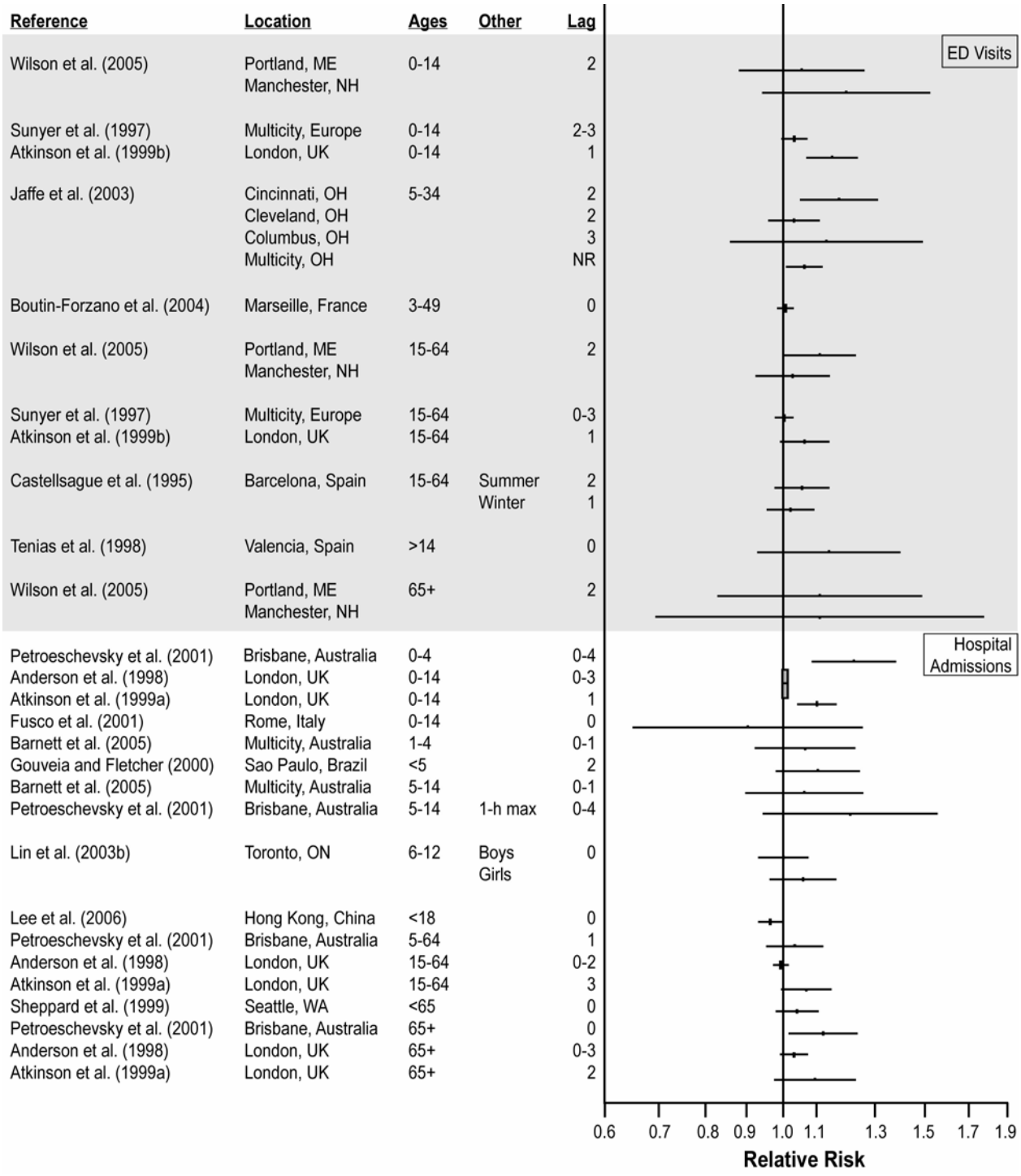

Figure 3.1-10. **Relative risks (95% CI) of SO_2-associated emergency department visits (*) and hospitalizations for asthma, stratified by age groups. Risk estimates are standardized per 10-ppb increase in 24-h average SO_2 concentrations or 40-ppb increase in 1-h max SO_2. The size of the box of the central estimate represents the relative weight of that estimate based on the width of the 95% CI.**

10% (95% CI: 2.0, 20.0) increased risk per 10-ppb increase in 24-h average SO_2 at a 0-day lag in Portland, ME and a null association in Manchester, NH. Peel et al. (2005) found a null relationship between asthma ED visits and 1-h max SO_2.

When analyses were stratified to include only children (0 to 14 years), Wilson et al. (2005) found positive, but not statistically significant, associations between ED visits and SO_2 in Portland, ME or Manchester, NH. Similarly, Lin et al. (2003a) (Toronto, ON; mean 24-h average SO_2 of 5.36 ppb [SD 5.90]) observed a weak positive association between hospitalizations for asthma and SO_2 among girls and a null association for boys.

A study by Jaffe et al. (2003) examined the association between SO_2 and ED visits for asthma in three cities in Ohio, i.e., Cincinnati, Cleveland, and Columbus, in asthmatics aged 5 to 34 years. The mean 24-h average SO_2 concentrations were 14 ppb (range: 1, 50) in Cincinnati, 15 ppb (range: 1, 64) in Cleveland, and 4 ppb (range: 0, 22) in Columbus. A positive association was observed in the multicity analysis, with a 6.1% (95% CI: 0.5, 11.5) increase in asthma visits observed per 10-ppb increase in 24-h average SO_2. In the city-stratified analyses, significant associations were only observed for Cincinnati (17.0% [95% CI: 4.6, 30.8]).

Stronger evidence of a positive association between ED visits or hospitalizations for asthma and SO_2 comes from several European (Anderson et al., 1998; Atkinson et al., 1999a,b; Hajat et al., 1999; Sunyer et al., 1997, 2003b; Thompson et al., 2001) and Asian (Lee et al., 2002) studies. Increased risks ranging from 2 to 10% per 10-ppb increase in 24-h average SO_2 were reported by these studies. Several of these studies observed that the SO_2 effect estimate was robust to adjustment for BS and NO_2 (Anderson et al., 1998; Sunyer et al., 1997), but one study observed that the SO_2 effect diminished considerably with adjustment for PM_{10} and benzene (Thompson et al., 2001). Atkinson et al. (1999a) compared 165,032 hospital admissions in London from 1992 through 1994 with ambient SO_2 levels (mean 24-h average of 7.2 ppb [SD 4.7]). They found a 10% (95% CI: 4.0, 16.0) increased risk per 10-ppb increase in 24-h average SO_2 at 1-day lag. Additional European (Fusco et al., 2001), Australian (Barnett et al., 2005; Petroeschevsky et al., 2001), Asian (Lee et al., 2006), and Latin American (Gouveia and Fletcher 2000) studies did not find statistically significant associations between ambient SO_2 concentrations and hospitalizations for all respiratory causes among children.

In general, positive associations were observed between ambient SO_2 concentrations and ED visits and asthma hospitalizations, particularly among children, in various epidemiologic studies conducted in different study locations and during varying time periods.

Chronic Obstructive Pulmonary Disease

Relatively few studies have examined the association of ED visits and hospitalizations for COPD and ambient SO_2 levels, and very little evidence exists for an association. Only three studies reported positive and statistically significant results for COPD and SO_2, and all three of these studies included asthma in their diagnostic definition of COPD (Anderson et al., 2001; Moolgavkar 2003; Sunyer et al., 2003b). Anderson et al. (2001) reported a 12% (95% CI: 5.0, 20.0) increased risk per 10-ppb increase in 24-h average SO_2 among children, while Moolgavkar (2003) and Sunyer et al. (2003b) found a 5 and 2% increased risk per 10-ppb increase in 24-h average SO_2 among older adults populations, respectively. All of the other studies examining this outcome reported null results (Atkinson et al., 1999a; Burnett et al., 1999; Michaud et al., 2004; Peel et al., 2005; Tenias et al., 2002).

Overall, this limited evidence does not support a relationship between ED visits and hospitalizations for COPD and ambient SO_2 levels.

Respiratory Diseases Other than Asthma or COPD

Emergency visits or hospital admissions for respiratory diseases include upper respiratory infections (URIs), pneumonia, bronchitis, allergic rhinitis, and lower respiratory disease (LRD). There are limited studies with mixed results for URIs (Burnett et al., 1999; Hajat et al., 2002; Lin et al., 2005; Peel et al., 2005), pneumonia (Barnett et al., 2005; Moolgavkar et al., 1997; Peel et al., 2005), bronchitis (Barnett et al., 2005; Michaud et al., 2004), and allergic rhinitis (Hajat et al., 2001; Villeneuve et al., 2006). The evidence for an association between SO_2 levels and ED visits for LRD, though limited, is suggestive of an effect. All of the studies that characterized this relationship found a positive and statistically significant increase in risk associated with increases in SO_2 (Farhat et al. 2005, Martins et al., 2002; Lin et al., 1999; Hajat et al., 1999; Atkinson et al., 1999a). Increased risks ranging from 3 to 33% per 10-ppb increase in 24-h average SO_2 were reported in these studies.

In summary, there were limited studies providing mixed results for many of the health outcomes other than asthma and COPD, making it difficult draw conclusions about the effects of

SO_2 on these diseases. Limited evidence does exist to support a suggestive association between ambient SO_2 levels and ED visits for LRD.

Potential Confounding by Copollutants

Multipollutant regression analyses indicated that SO_2 risk estimates for respiratory ED visits and hospitalizations, in general, were not sensitive to the inclusion of copollutants, including O_3 (Anderson et al., 1998; Hajat et al., 1999; Yang et al., 2003a, 2005), PM (Lin et al., 2003a, 2005; Hagen et al., 2000; Schwartz, 1995), CO (Farhat et al., 2005), and NO_2 (Anderson et al., 1998; Lin et al., 2004a; Sunyer et al., 1997). There is limited evidence that the inclusion of benzene in copollutant models attenuates SO_2 risk estimates (Hagen et al., 2000; Thompson et al., 2001). Figure 3.1-11 presents SO_2 risk estimates with and without adjustment for various copollutants, with a focus on PM and NO_2 as these pollutants tend to be moderately to highly correlated with SO_2 and have known respiratory health effects. Although the studies show that copollutant adjustment had varying degrees of influence on the SO_2 effect estimates, among the studies with tighter confidence intervals (an indicator of study power), the effect of SO_2 on respiratory health outcomes appears to be generally robust and independent of the effects of ambient particles or other gaseous copollutants.

Seasonal Effects of SO_2

The results of several studies (Anderson et al., 1998; Hajat et al., 1999; Schouten et al., 1996; Spix et al., 1998; Wong et al., 1999) have demonstrated a greater increase in ED visits and hospitalizations for respiratory illnesses during the summer months despite the fact that the average concentrations for SO_2 in some of the areas were greater in the winter months (Anderson et al., 1998; Schouten et al., 1996; Wong et al., 1999). In contrast, some studies found the associations between ED visits and hospital admission and respiratory disease with similar increases in SO_2 to be greater in winter than in summer months (Vigotti et al. 1996; Walters et al., 1994). Additional studies were unable to discern a seasonal difference in ED visits and hospitalizations for respiratory causes (Castellsague et al., 1995; Tenías et al., 1998; Wong et al., 2002). These effects were not consistent across age groups. Warmer months were more likely to show evidence of an association with adverse respiratory outcomes in children, while older adults appeared to be more likely to be affected during the cooler months. These seasonal associations remain somewhat uncertain and require additional investigation.

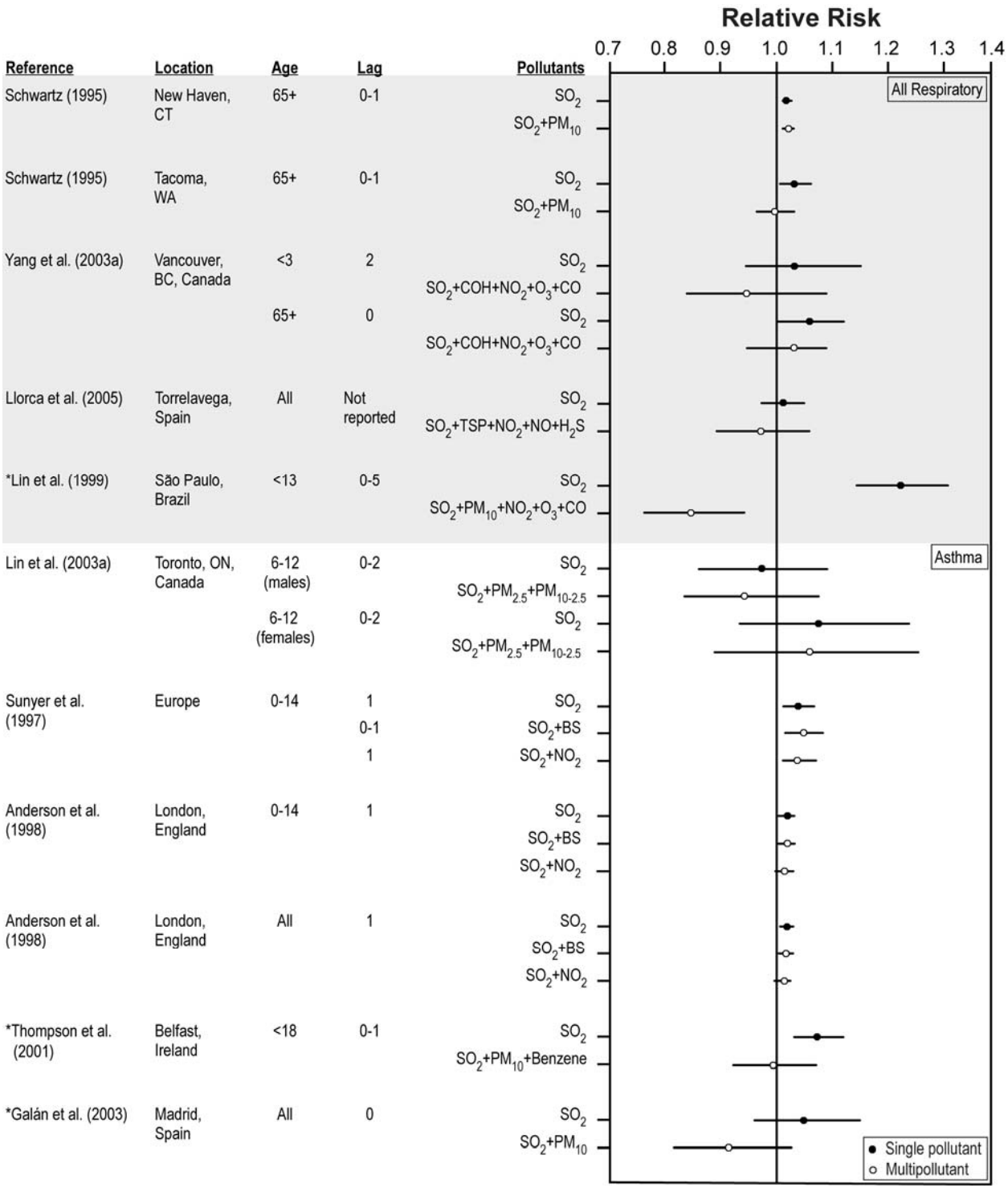

Figure 3.1-11. **Relative risks (95% CI) of SO_2-associated emergency department visits and hospitalizations for all respiratory causes and asthma, with and without copollutant adjustment. Risk estimates are standardized per 10-ppb increase in 24-h average SO_2 concentrations or 40-ppb increase in 1-h max SO_2.**

Summary of ED Visits and Hospitalizations for Respiratory Diseases

A large number of epidemiologic studies provide evidence of positive, but not always statistically significant, associations between ambient SO_2 concentrations and ED visits and hospitalizations for all respiratory causes and asthma, particularly among children and older adults. These findings are generally robust when additional copollutants are included in the model. Biologic plausibility for these findings of increased ED visits and hospitalizations is found in the epidemiologic and human clinical studies that observed increased respiratory symptoms and decreased lung function, and the animal toxicological studies that observed SO_2-induced altered lung host defenses. Season may modify the effect of SO_2 on ED visits and hospitalizations for children in warmer months, and for older adults in cooler months.

3.1.1.7 Integration of Respiratory Effects Associated with Short-Term SO_2 Exposure

The previous reviews examining adverse health effects associated with short-term exposures of SO_2 have shown some biological plausibility and coherent evidence in the epidemiological, human clinical, and animal toxicological studies completed to that time for a limited number of respiratory effects. New studies of associations between SO_2 exposure and respiratory symptoms, lung function, airway inflammation, AHR, lung host defenses, and ED visits/hospitalizations have added modestly to this evidence base.

Respiratory symptoms. Two important new multicity studies (Mortimer et al., 2002; Schildcrout et al., 2006) and several other studies (e.g., Delfino et al., 2003; Neas et al., 1995) have shown an association between short-term (24-h average) ambient SO_2 concentrations and respiratory symptoms in children. However, some other studies (e.g., Hoek and Brunekreef, 1993; Romieu et al., 1996) found no consistent association. Several new studies (e.g., Desqueyroux et al., 2002a,b; van der Zee et al., 2000) found no association between SO_2 levels and respiratory symptoms in adults. These findings suggest supportive evidence for an association between short-term (24-h average) exposure to ambient SO_2 exposure and respiratory symptoms in children, particularly those with asthma, but not in adults. Evidence from the previous review along with a limited number of new human clinical studies indicate increased respiratory symptoms with peak (5-15 min) SO_2 exposures as low as 0.5 ppm in asthmatic subjects.

Lung function. Epidemiological studies do not provide strong evidence of associations between short-term (24–h average) ambient SO_2 exposures and lung function in either children

(e.g., Mortimer et al., 2002; Roemer et al., 1998) or adults (e.g., Peters et al., 1996; Taggart et al., 1996). Though several other studies reported positive findings, the mixed results and correlation between SO_2 levels and other ambient copollutants suggests a lack of independent effects on lung function. In human clinical studies of lung function in healthy resting adults, a few studies reported effects at 1 ppm, but most effects were observed at concentrations of >5 ppm. In asthmatic adults, significant bronchoconstriction and increases in sRaw have been observed with 5- to 15-min peak (5-15 min) exposures to < 1-ppm SO_2, with some studies reporting a bronchoconstrictive response to SO_2 within minutes of the start of exposure (Balmes et al., 1987; Horstman et al., 1988). Increasing SO_2 levels from 0 to 0.5 ppm has been shown to have a greater effect on sRaw and FEV_1 than increasing the level of exercise (Gong et al., 1995). Moderate to severe asthmatics have greater exercise-induced sRaw increases and FEV_1 decrements compared to normal and mild asthmatics; however, respiratory response with increasing SO_2 concentration has not been shown to differ significantly between mild and moderate/severe asthmatics (Linn et al., 1987). Lung function has been shown to be unaffected by SO_2 exposures up to 0.8 ppm in individuals with COPD (Linn et al., 1985). Thus, the observations of increased bronchoconstriction and airway resistance in human clinical studies provide biological plausibility for SO_2 effects with peak exposure.

Airway inflammation. Only one epidemiological study (Adamkiewicz et al., 2004) evaluated inflammation, as indexed by eNO, and found no association with SO_2 exposure. One human clinical study observed increased markers of inflammation (i.e., increased macrophages, lymphocytes, mast cells), but only at a concentration of 8-ppm SO_2 in healthy adults (Sandström et al., 1989). A study at more environmentally relevant levels (0.2 ppm) found no effects in either healthy or asthmatic adults (Tunnicliffe et al., 2003). One animal study found increases in inflammatory cytokines at 5.35 ppm but may not be relevant due to the inherent limitations of high-concentration studies. Thus, the limited epidemiological, human clinical, and toxicological evidence does not suggest that exposure to SO_2 at environmentally relevant concentrations is associated with inflammation in the airways. However, studies of other ambient pollutants indicate that influx of macrophages and other inflammatory cells, with the related release of inflammatory cytokines, is a common mechanism of injury.

Airway hyperresponsiveness. Only a limited number of epidemiological studies have found an association between SO_2 exposure and AHR. Søyseth et al. (1995) observed an

association between low (8 ppb) ambient SO_2 levels and eosinophil numbers in atopic children. Taggart et al. (1996) found a marginal association between 40-ppb SO_2 concentrations and decreased responses to MCh challenge in adult asthmatics. Boezen et al. (1999, 2005) reported complex associations between SO_2 concentrations, BHR, and serum IgE levels in both children and adults. As with other respiratory endpoints, a limited toxicological database provides some biological plausibility for these findings. Bronchial responses were not observed in rabbits at 5-ppm SO_2 (Douglas et al., 1994) or in dogs at 10-ppm SO_2 (Lewis and Kirchner, 1984). Ovalbumin-sensitized guinea pigs demonstrated increased bronchial obstruction following exposure to 0.1-ppm SO_2 (Park et al., 2001; Riedel et al., 1988). Guinea pigs, as a species, are typically more sensitive to air pollution than other laboratory animals (U.S. Environmental Protection Agency, 2006d) and, thus, may provide a better model for characterizing the effects of air pollutants on AHR. The finding of increased pulmonary resistance in this species is in concordance with the limited epidemiological findings of SO_2-induced AHR.

Lung host defenses. Two epidemiological studies (Park et al., 2002; Pönkä, 1990) provide limited evidence of an association between school absences due to respiratory illness and ambient SO_2. Scant animal evidence, typically at levels much higher than ambient, provides weak biological plausibility for these epidemiological findings. SO_2-induced modulation of clearance and macrophage function were found in some subchronic and chronic studies but does little to inform the mechanism(s) of action occurring in humans with short-term exposures.

ED visits/hospitalizations. Epidemiological studies provide suggestive evidence for an association between ambient SO_2 levels and ED visits and hospitalizations for all respiratory diseases, particularly among children and older adults (65+ years of age). A modest association between ambient SO_2 and ED visits and hospitalizations for asthma particularly among children <14 years old is also suggested. No relationship is apparent in the limited number of studies evaluating ED visits and hospitalizations for COPD or other respiratory diseases, though there is a somewhat suggestive association between ambient SO_2 levels and ED visits for LRD. Overall, SO_2 risk estimates were not sensitive to the inclusion of copollutants, including PM, O_3, CO, and NO_2, indicating that the observed effects of SO_2 on respiratory endpoints is independent of the effects of other ambient air pollutants. Biologic plausibility for these findings of increased ED visits and hospitalizations is found in the epidemiologic and human clinical studies that observed

increased respiratory symptoms and decreased lung function, and the animal toxicological studies that observed SO_2-induced altered lung host defenses.

3.1.2 Cardiovascular Effects Associated with Short-Term SO_2 Exposure

The studies reviewed in the 1982 AQCD primarily investigated respiratory health outcomes. No epidemiological studies linking exposure to SO_2 with cardiovascular physiological endpoints or CVD ED visits or hospital admissions were examined in the last review. There were also key human clinical and animal toxicological studies available at the last review to address effects of SO_2 exposure on the cardiovascular system. The only report from a study in dogs exposed to air pollutant mixtures (SO_2 + sulfuric acid [H_2SO_4], with or without nonirradiated or irradiated auto exhaust) reported no changes in cardiovascular function at the end of 3 years of exposure and 3 years after exposure.

A few recent animal toxicological studies have investigated the potential effects of SO_2 exposure on physiological and biochemical parameters of cardiovascular effects and reported oxidation (Meng et al., 2003a) and glutathione (GSH) depletion (Langley-Evans et al., 1996; Meng et al., 2003a; Wu and Meng, 2003) in the hearts of rodents (see Annex Table AX4-5). Several recent epidemiological studies also have examined the association between air pollution and cardiovascular effects, including increased heart rate (HR), reduced heart rate variability (HRV), incidence of ventricular arrhythmias, changes in blood pressure, incidence of myocardial infarctions (MI), and ED visits and hospitalizations due to cardiovascular causes. The results of these cardiovascular studies are summarized in Annex Tables AX5-3 and AX5-4.

3.1.2.1 HR and HRV

HRV is generally determined by analyses of time (e.g., standard deviation of normal R-R intervals [SDNN]) and frequency domains (e.g., low frequency [LF] / high frequency [HF] ratio by power spectral analysis, reflecting autonomic balance) measured during 24 h of electrocardiography (ECG). Brook et al. (2004) state that HRV, resting HR, and blood pressure are modulated by a balance between the two determinants of autonomic tone (the sympathetic and parasympathetic nervous systems). They note that decreased HRV predicts an increased risk of cardiovascular morbidity and mortality in older adults and those with significant heart disease.

Liao et al. (2004) investigated short-term associations between ambient pollutants and cardiac autonomic control from the fourth cohort examination (1996 through 1998) of the

population-based Atherosclerosis Risk in Communities (ARIC) study using a cross-sectional study design. Men and women aged 45 to 64 years (n = 6,784) from three U.S. study centers in North Carolina, Minnesota, and Mississippi were examined. Resting, supine, 5-min beat-to-beat R-R interval data were collected. The mean 24-h average SO_2 level measured 1 day prior to the HRV measurement was 4 ppb (SD 4). In addition to SO_2, the potential effects of PM_{10}, O_3, CO, and NO_2 were evaluated. Previous-day SO_2 concentrations were positively associated with HR and inversely associated with SDNN and LF power. Consistently more pronounced associations were suggested between SO_2 and HRV among persons with a history of coronary heart disease. Significant associations with HRV indices also were observed for PM_{10} and the other gaseous pollutants. When the regression coefficients for each individual pollutant model were compared, the effects of PM_{10} on HRV were considerably larger than the effects for the gaseous pollutants, including SO_2. No multipollutant analyses were conducted.

Gold et al. (2000; reanalysis Gold et al., 2003) examined the effect of short-term changes in air pollution on HRV in a panel study of 21 older adults (aged 53 to 87 years) in Boston, MA. The study participants were observed up to 12 times from June to September 1997. The mean 24-h average SO_2 concentration was 3.2 ppb (range: 0, 12.6). The 24-h average SO_2 concentration was associated with decreased HR in the first 5-min rest period, but not in the overall 25-min study protocol. The effect estimate for SO_2 slightly diminished but remained marginally significant in a two-pollutant model with $PM_{2.5}$. The inverse association between SO_2 and HR observed in this study are in contrast to the SO_2-related increases in HR observed by Liao et al. (2004) and Peters et al. (1999). No associations were observed between HRV and SO_2. The strongest associations with HRV were observed for $PM_{2.5}$ and O_3.

Another study of air pollutants and HRV was conducted in Boston, MA on 497 men from the VA Normative Aging Study (NAS) (Park et al., 2005). The best 4-consecutive-min interval from a 7-min sample was used for the HRV calculations. For the exposure variable, 4-, 24-, and 48-h moving averages matched on the time of the ECG measurement for each subject were considered. The mean 24-h average SO_2 concentration was 4.9 ppb (range: 0.95, 24.7). Associations with measures of HRV were reported for $PM_{2.5}$ and O_3, but not with SO_2 for any of the averaging periods. In another study conducted in Boston, MA, Schwartz et al. (2005) found significant effects of increases in $PM_{2.5}$ on measures of HRV, while no associations with SO_2 were observed. Other studies have examined the relationship of SO_2 with HRV (Chan et al.,

2005; de Paula Santos et al., 2005; Holguín et al., 2003; Luttmann-Gibson et al., 2006). Most of these studies, with the exception of de Paula Santos et al. (2005), did not observe associations with SO_2.

A limited number of human clinical studies examined the effect of SO_2 on HRV. During a controlled exposure of 12 healthy subjects and 12 subjects with asthma to 0.2-ppm SO_2 for 1 h under resting conditions, Tunnicliffe et al. (2001) reported that HF power, LF power, and total power were higher with SO_2 exposures compared to air exposure in the healthy subjects, but that these indices were reduced during SO_2 exposure in the subjects with asthma. The LF/HF ratios were unchanged in both groups. The authors postulated that these results suggest that there are two autonomic pathways for SO_2-mediated bronchoconstriction. The investigators proposed that in healthy subjects, the dominant pathway was via the rapidly adapting receptor/C-fiber route, which results in a central nervous system reflex with an increase in vagal tone. In the asthmatic subjects, proximal airway narrowing was proposed as the dominant response, possibly through neurogenic inflammation. This likely causes a compensatory central nervous system-mediated reduction in vagal tone, resulting in bronchodilation of the distal airways. While there were no detectable changes in symptoms or lung function in either of the groups, this study suggests that exposure to SO_2 can provoke autonomic responses at these low levels (0.2 ppm).

In a similar study, Routledge et al. (2006) exposed patients with stable angina as well as healthy subjects to 50-$\mu g/m^3$ carbon particles and to 0.2-ppm SO_2, alone and in combination, for 1 h under resting conditions. HRV, C-reactive protein, and markers of coagulation markers were measured. These authors reported that in the healthy subjects, SO_2 exposure was associated with a decrease in HRV markers of cardiac vagal control 4 h after exposure. However, it should be noted that there was no apparent difference in the absolute value of the root mean square of successive RR interval differences (r-MSSD) at 4 h postexposure between the control, SO_2, carbon, and carbon/SO_2 groups. The significant difference reported in the change in r-MSSD from baseline to 4 h postexposure with SO_2 appears to be due to a higher baseline value of r-MSSD preceding the SO_2 exposure compared to the baseline value of r-MSSD preceding the air exposure. There were no changes in HRV among the patients with stable angina. It was noted by the authors that this lack of response in the heart patients may be due to a drug treatment effect rather than decreased susceptibility; a large portion of the angina patients were taking β-blockers, which are known to increase indices of cardiac vagal control.

In the limited number of epidemiological and human clinical studies that examined a possible effect of SO_2 on HRV, there are some suggestive findings; however, the overall evidence that SO_2 affects cardiac autonomic control is weak and inconsistent.

3.1.2.2 Repolarization Changes

In addition to the role played by the autonomic nervous system in arrhythmogenic conditions, myocardial vulnerability and repolarization abnormalities are believed to be key factors contributing to the mechanism of such diseases. Measures of repolarization include QT duration, T-wave complexity, variability of T-wave complexity, and T-wave amplitude. Henneberger et al. (2005) examined the association of repolarization parameters with air pollutants in patients with preexisting coronary heart disease (n = 56, all males) in East Germany. The patients were examined repeatedly once every 2 weeks for 6 months, for a total of 12 ECG recordings. The mean 24-h average SO_2 concentration was 4.1 $\mu g/m^3$ (2 ppb [range: 1, 4]). Ambient SO_2 concentrations during the 24-h preceding the ECG were associated with the QT interval duration, but not with any other repolarization parameters. Stronger associations were observed between PM indices and QT interval duration, T-wave amplitude, and T-wave complexity.

Two in vitro studies (Nie and Meng, 2005, 2006) conducted with a 1:3 molar:molar mixture of the SO_2 derivatives bisulfite (HSO_3^-) and sulfite (SO_3^{2-}) demonstrated effects of a 10-µm bisulfite:sulfite mixture on sodium and L-type calcium currents (which included changes in inactivation and/or activation, recovery from inactivation, and inactivation/activation time constants) in ventricular myocytes. These in vitro observations suggest a potential role for L-type calcium current in cardiac injury following SO_2 exposure; however, in vivo cardiovascular effects were observed only at high SO_2 concentrations (10 ppm and higher). Additional epidemiological and toxicological studies are necessary to evaluate the evidence of an association between SO_2 and repolarization changes.

3.1.2.3 Cardiac Arrhythmias

In a panel study of 100 patients with implanted cardioverter defibrillators (ICDs) in Eastern Massachusetts, Peters et al (2000) tested the hypothesis that patients with ICDs would experience life-threatening arrhythmias after an air pollution episode. The mean 24-h average SO_2 concentration measured at two sites in Boston during the study period was 7 ppb (5th–95th

percentile: 1, 19). ICDs monitor ECG abnormalities and treat ventricular fibrillation or ventricular tachycardias by administering shock therapy to restore the normal cardiac rhythm. The ICD device also stores information on each tachyarrhythmia and shock. There was no association between SO_2 and defibrillator discharges in the 33 subjects who had any defibrillator discharges during the follow-up period or in the 6 subjects who had at least 10 discharges. There was some evidence that NO_2 was associated with increased defibrillatory interventions in the subjects with any defibrillator discharges. Among the patients with at least 10 events, NO_2, CO, and $PM_{2.5}$ was found to be associated with defibrillator discharges.

In a follow-up study designed to confirm the findings of Peters et al. (2000), Dockery et al. (2005) used a larger sample of ICD patients in Boston (n = 203) with a longer follow-up period. The median concentration of 48-h average SO_2 averaged across multiple sites in Boston was 4.9 ppb (IQR 4.1). No significant associations were found between ventricular arrhythmic episode days and any of the air pollutants. However, when the analysis was stratified by recent arrhythmias (i.e., within 3 days), there was evidence of an increased risk of ventricular arrhythmia with SO_2, $PM_{2.5}$, black carbon, NO_2, and CO. Since $PM_{2.5}$, black carbon, NO_2, and CO were correlated with each other and SO_2, the authors noted that differentiating the independent effects of the pollutants would be difficult. A case-crossover analysis of the same data by Rich et al. (2005) also observed associations with 48-h average SO_2, but the SO_2 effect was not found to be robust to adjustment by $PM_{2.5}$. In a similar study conducted in St. Louis, MO, an increased risk was associated with SO_2 concentrations in the 24 h prior to an arrhythmia, but not with $PM_{2.5}$ and O_3 (Rich et al., 2006). In this study, none of the other measured pollutants (PM, elemental carbon, O_3, CO, NO_2) were correlated with SO_2. The authors suggested that the different effects observed in St. Louis and Boston may be due to differences in the source or mix of air pollutants in these cities.

Additional studies have examined the relationship of SO_2 with arrhythmias in Vancouver, Canada (Rich et al., 2004; Vedal et al., 2004) and observed associations at very low ambient SO_2 concentrations (mean 24-h average SO_2 of ~2.5 ppb with a maximum of 8.1 ppb). Vedal et al. (2004) stated that of all pollutants examined, the only one with somewhat consistent positive associations with arrhythmia events was SO_2. In season-stratified analyses, SO_2 was positively associated with arrhythmias in the winter, while in the summer the association was negative. On

the other hand, in the Rich et al. (2004) study, positive associations were observed in the summer but not in the winter. The authors stated that it was difficult to interpret these findings.

One toxicological study examined the effects of PM, ultrafine carbon, and SO_2 on spontaneous arrhythmia frequency in 18-month-old rats (Nadziejko et al., 2004). The rats were exposed to 1-ppm SO_2 for 4 h. No significant change in the frequency of spontaneous arrhythmias was found with SO_2 and ultrafine carbon exposure. However, rats exposed to concentrated ambient PM had a significantly greater increase in the frequency of delayed beats than rats exposed to air.

Collectively, the epidemiological evidence for an association between short-term exposure to SO_2 and arrhythmias is inconsistent. The limited toxicological evidence did not provide biological plausiblity of an effect of SO_2 on arrhythmias.

3.1.2.4 Blood Pressure

Ibald-Mulli et al. (2001) examined the association between blood pressure and SO_2 using survey data from the MONICA (Monitoring Trends and Determinants in Cardiovascular Disease) Project. Blood pressure measurements were taken from 2,607 men and women. The mean 24-h average SO_2 concentration was 60.2 $\mu g/m^3$ (23 ppb [range: 5, 91]). An increase in systolic blood pressure was associated with 24-h average SO_2 and TSP. However, in a two-pollutant model with TSP, the effect of SO_2 on blood pressure was substantially reduced and became nonsignificant while the effect of TSP was robust.

In a study by de Paula Santos et al. (2005), changes in blood pressure in association with SO_2 were investigated in vehicular traffic controllers (n = 48) aged 31 to 55 years living in São Paulo, Brazil, where vehicles are the primary source of air pollution. The mean 24-h average SO_2 level, measured at six different stations around the city, was 17.1 $\mu g/m^3$ (7 ppb [SD 3]). Blood pressure was measured every 10 min when subjects were awake (6 a.m. to 11 p.m.) and every 20 min during sleep (11 p.m. to 6 a.m.). Results indicated that SO_2, as well as CO, were associated with increases in systolic and diastolic blood pressure. However, when a two-pollutant model was used to test the robustness of the associations, only the CO effect remained statistically significant.

Several animal toxicological studies examined the effect of SO_2 on blood pressure. Hälinen et al. (2000a) examined blood pressure changes in guinea pigs that were exposed to 1-, 2.5-, or 5-ppm SO_2 in cold, dry air while being hyperventilated to simulate exercise. Animals

received 10-min exposures to each SO_2 concentration that were separated by 15-min exposures to clean warm, humid air. A transient increase in blood pressure was observed during exposure to 5-ppm SO_2 in cold, dry air. In a second study (Hälinen et al., 2000b), guinea pigs were exposed to cold, dry air alone or 1-ppm SO_2 in cold, dry air for 60 min while being hyperventilated. The study reported similar increases in blood pressure and HR with exposure to cold, dry air or cold, dry air plus SO_2. The increase in HR was gradual, while increases in blood pressure generally occurred during the first 10 to 20 min of exposure. Similar effects were observed with exposure to cold, dry air or SO_2 in cold, dry air, suggesting that effects were associated with cold, dry air rather than SO_2. Opposite effects (a transient decrease in blood pressure) was observed when rats were exposed to a higher dose (10-ppm SO_2) in air that was presumably at room temperature for 3 days (Meng et al., 2003b).

Collectively, the limited epidemiological and toxicological evidence does not suggest that short-term exposure to SO_2 has effects on blood pressure.

3.1.2.5 Blood Markers of Cardiovascular Risk

Folsom et al. (1997) demonstrated that elevated levels of fibrinogen, white blood cell count, factor VIII coagulant activity (factor VIII-C), and von Willebrand factor were associated with risk of CVD. Schwartz (2001) investigated the association between various blood markers of cardiovascular risk and air pollution among subjects in the Third National Health and Nutrition Examination Survey (NHANES III) in the United States conducted between 1989 and 1994 across 44 counties. The NHANES III is a random sample of the U.S. population with oversampling for minorities (30% of NHANES sample) and the elderly (20% of the sample). The mean SO_2 concentration was 17.2 ppb (IQR 17) across the 25 counties where data were available. This study looked at fibrinogen levels, platelet counts, and white blood cell counts. After controlling for age, ethnicity, gender, body mass index, and smoking status and number of cigarettes per day, SO_2 was found to be positively associated with white blood cell counts. PM_{10} was associated with all blood markers. In two-pollutant models, PM_{10} remained a significant predictor of white blood cell counts after controlling for SO_2, but not vice versa.

A recent cross-sectional study by Liao et al. (2005) investigated the effects of air pollution on plasma hemostatic and inflammatory markers in the ARIC study (n = 10,208). The authors hypothesized that short-term exposure to air pollutants was associated with increased levels of inflammatory markers and lower levels of albumin, as serum albumin is inversely

associated with inflammation. The mean 24-h average SO_2 concentration was 5 ppb (SD 4). Significant curvilinear relationships were observed between SO_2 and factor VIII-C, white blood cell counts, and serum albumin. The authors noted that since no biological explanation could be offered for the "U"-shaped curve between SO_2 and factor VIII-C and the "inverse U"-shape between SO_2 and albumin, generalization of the association should be exercised with caution. No associations were observed between SO_2 and fibrinogen or von Willebrand factor.

In another large cross-sectional study of 7,205 office workers in London, Pekkanen et al. (2000) examined the association between plasma fibrinogen and ambient air pollutants. The mean 24-h average SO_2 was 23.2 $\mu g/m^3$ (9 ppb [10th–90th percentile: 5, 19]). Associations with fibrinogen were observed for all pollutants examined, either in all-year or summer-only analyses, except for SO_2 and O_3. Taken together, results from the limited number of studies do not suggest that SO_2 is associated with various blood markers of cardiovascular risk.

3.1.2.6 Acute Myocardial Infarctions

The association between air pollution and the incidence of MI was examined in a small number of studies. As part of the Determinants of Myocardial Infarction Onset Study, Peters et al. (2001) examined 772 patients with MI living in greater Boston, MA. A case-crossover design was used to assess changes in the risk of acute MI after exposure to potential triggers. The mean 24-h average SO_2 was 7 ppb (range: 1, 20) during the study period. Similarly, the mean 1-h average SO_2 was 7 ppb (range: 0, 23). In an analysis that considered both the 2-h average (between 60 and 180 min before the onset of symptoms) and 24-h average (between 24 and 48 h before the onset) concentrations jointly, the study found no significant association between risk of MI and SO_2. Of all the pollutants considered, only $PM_{2.5}$ and PM_{10} were found to be associated with an increased risk of MI.

In the MONICA Project, the effect of air pollution on acute MI was studied in Toulouse, France, using a case-crossover study design (Ruidavets et al., 2005). The mean 24-h average SO_2 level was 8.3 $\mu g/m^3$ (3 ppb [5th–95th percentile: 1, 5]). A total of 399 cases of acute MI were recorded during the study period. O_3, but not SO_2 nor NO_2, was found to be associated with the incidence of acute MI. Exposure to PM was not considered in this study.

Only a limited number of studies examined the association between ambient SO_2 concentrations and incidence of acute MI. These studies provide no evidence that exposure to SO_2 increases the risk of MI.

3.1.2.7 ED Visits and Hospitalizations for CVD

The current review includes more than 30 studies that address the effect of sulfur oxides (SO_x) exposure on ED visits or hospitalizations for CVD. Cases of CVD are typically identified using ICD codes recorded on hospital discharge records. However, counts of hospital or ED admissions are also used. Studies of ED visits include cases that may be less severe than those requiring hospitalization and may be subject to greater misclassification compared to studies that rely on confirmed doctors diagnoses coded on discharge records. Studies of hospital admissions and ED visits are clearly distinguished on figures and in the Annex Tables AX5-4.

All CVD

The disease grouping "All CVD" typically includes all diseases of the circulatory system (e.g., heart diseases and cerebrovascular diseases, ICD9 Codes 390-459). A summary of the results are presented in Figure 3.1-12.

In a study of 11 cities in Spain, an increase of 3.6% (95% CI: 0.6, 6.7) per 10-ppb increase in 24-h average SO_2 at a 0-1 day lag was observed for all CVD admissions (Ballester et al., 2006). The mean 24-h average SO_2 level in the cities studied was 6.6 ppb. In addition, time-series data linking SO_2 with hospital admissions for CVD in three metropolitan areas in the United States (i.e., Cook, Maricopa, Los Angeles Counties) was conducted (Moolgavkar, 2000; reanalysis, Moolgavkar, 2003). A 13.7% (95% CI: 11.3, 16.1) increase in admissions per 10-ppb increase in 24-h average SO_2 at lag 0 day, using Generalized Linear Model(s) (GLM) and natural splines to adjust for temporal trends, was observed among older adults (65+ years) in Los Angeles County. The median 24-h average SO_2 level for Los Angeles County was 2 ppb during the study period. Results for Maricopa and Cook counties were not presented in the reanalysis. However, in previous GAM analyses, increases of 4.1% (95% CI: 2.7, 5.3) and 7.5% (95% CI: 4.1, 10.8) were reported for Cook and Maricopa Counties, respectively (Moolgavkar, 2000), per 10-ppb increase in 24-h average SO_2 level. The author indicates that the use of stringent convergence criteria did not appreciably change results (but increased smoothing did diminish effect estimates) (Moolgavkar, 2003).

Metzger et al. (2004) examined approximately 4.4 million hospital visits to 31 hospitals from 1993 to 2000 in Atlanta, GA and reported null associations between SO_2 and ED visits for all CVD. A 1.4% (95% CI: −1.5, 4.4) increase in admissions per 40-ppb increase in 1-h max

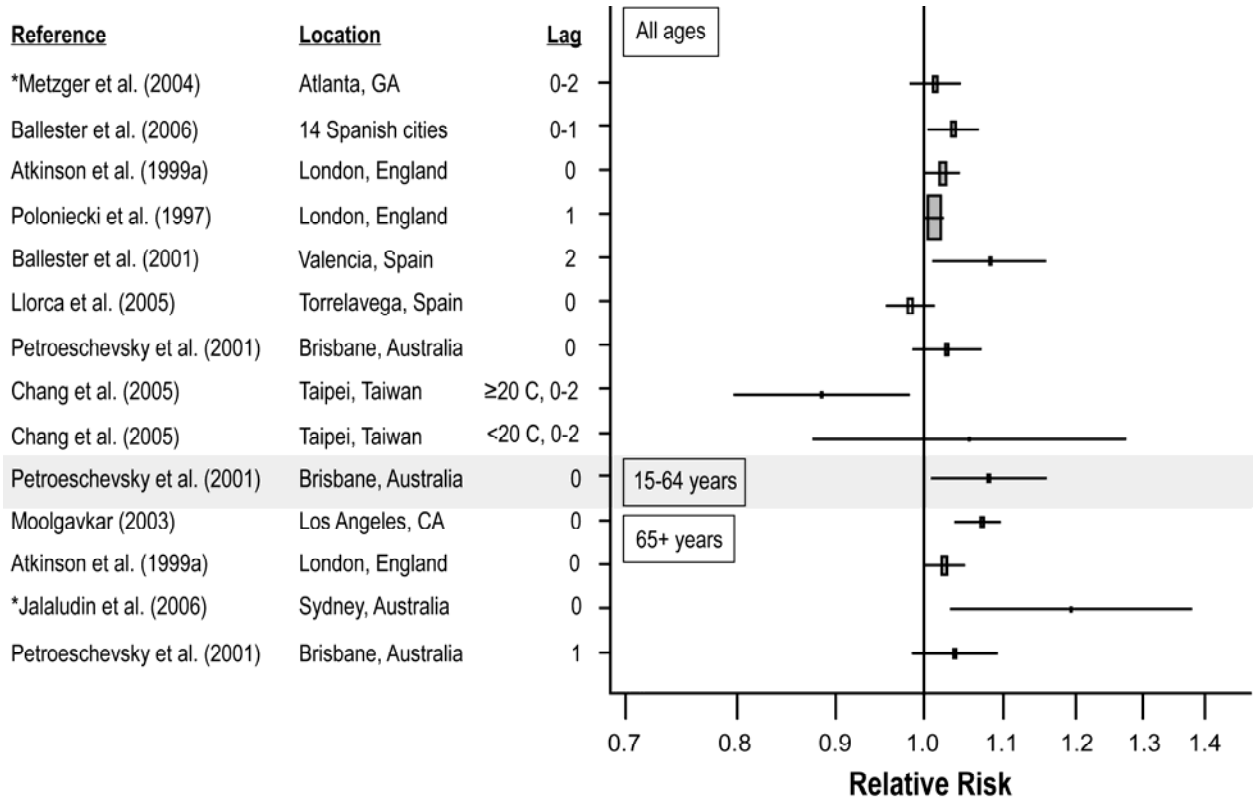

Figure 3.1-12. Relative risks (95% CI) of SO_2-associated emergency department visits and hospitalizations for all cardiovascular causes. Risk estimates are standardized per 10-ppb increase in 24-h average SO_2 concentrations or 40-ppb increase in 1-h max SO_2. The size of the box of the central estimate represents the relative weight of that estimate based on the width of the 95% CI.

SO_2 level was observed. The median 1-h max SO_2 level in Atlanta during the study period was 11 ppb (10th–90th percentile: 2, 39).

Results from single-city studies in Europe, Australia, and Taiwan are inconsistent. Atkinson et al. (1999a) reported a significant increase in CVD admissions in London (2.3% [95% CI: 0.3, 4.3] per 10-ppb increase in 24-h average SO_2), while Llorca et al. (2005) reported a null association in Torrelavega, Spain. A time-series analysis conducted in Sydney, Australia, reported an increase in all CVD admissions of 19.3% (95% CI: 3.3, 38) per 10-ppb increase in 24-h average SO_2 at lag 0 day among those 65+ years of age (Jalaludin et al., 2006). The mean 24-h average SO_2 level in Sydney during the study period was 1.07 ppb (IQR 0.75) (the authors'

estimates related the percent increase in admissions to an incremental increase in SO_2 equivalent to the IQR [1.33%, 95% CI: 0.24, 2.43]). A study conducted in Brisbane reported a nonsignificant increase of 3.8% (95% CI: −1.2, 9.1) at lag 1-day for all CVD per 10-ppb increase in 24-h average SO_2, among those 65+ years (Petroeschevsky et al., 2001). In a study conducted in Taipei, Taiwan, Chang et al. (2005) reported a significant decrease in CVD admissions of −11.5% (95% CI: −20.2, −1.8) per 10-ppb increase in 24-h average SO_2 at a lag of 0 to 2 days, among all ages, when the temperature was greater than 20 ºC. A nonsignificant increase of 5.6% (95% CI: −12.4, 27.2) was reported for cooler days. The mean 24-average SO_2 level in Taiwan during the study period was 4.3 ppb.

Some studies have observed positive associations between ambient SO_2 concentrations and ED visits and hospital admissions for all CVD, particularly among individuals 65+ years of age. Given the limited number of studies that assessed potential confounding by copollutants for this outcome, which is of concern given the moderate to strong correlation between SO_2 and various copollutants in most studies, and the lack of supportive data from panel/field studies and human clinical studies on cardiovascular health effects, the collective evidence that ambient SO_2 has an effect of CVD ED visits and hospitalizations is weak.

Specific Cardiac Diseases

Cardiac disease (ICD9 Codes 390-429) is defined to exclude diseases of the cerebrovascular system and is further restricted in some studies to include only ischemic heart disease (IHD, ICD9 Codes 410-414), dysrhythmia (ICD9 Code 427), congestive heart failure (CHF, ICD9 Code 428) or MI (410).

In a study of seven European cities (Milan, Paris, Rome, London, Birmingham, the Netherlands, and Stockholm), an increase of 1.9% (95% CI: 0.8, 2.9) per 10-ppb increase in 24-h average SO_2 lagged 0-1 day, was observed for cardiac disease hospital admissions (Sunyer et al., 2003b; used GAM with default convergence criteria). The mean 24-h average SO_2 level in the cities studied was 5.2 ppb. Ballester et al. (2006) reported a 4.6% (95% CI: 1.3, 8.0) increased risk of cardiac disease admissions per 10-ppb increase in 24-h average SO_2 at lag 0-1 day, pooled across 14 Spanish cities. Adjustment for PM_{10} and CO in two-pollutant models diminished the effect estimate by approximately half.

In a time-series study of cardiac disease and SO_2 in Windsor, Ontario, similar results were observed for those aged <65 years (4.5% [95% CI: −3.7, 14.1) per 40-ppb increase in 1-h max SO_2] and 65+ years (5.5% [95% CI: 0.0, 11.3]) (Fung et al., 2005). These results were found to be generally robust to adjustment for PM_{10}. The mean 1-h max SO_2 level in Windsor during the study period was 27.5 ppb (range: 0, 129). Michaud et al. (2004) conducted a study of hospital visits for cardiac disease in Hilo, HI, where volcanic eruptions contribute to ambient SO_2 levels. A −5.0% (95% CI: −13.5, 4.4) change in hospital visits for cardiac disease was observed per 10-ppb increase in SO_2 (averaging time 12:00 p.m. to 6:00 a.m.). The mean daily SO_2 level in Hilo during the study period was 1.97 ppb (range: 0, 108.5). In Sydney, Australia, an increase in cardiac admissions among those 65+ years of age of 1.6% (95% CI: 0.33, 2.93) was reported per 0.75-ppb increase (an IQR change) in 24-h average SO_2 level (Jalaludin et al., 2006). Standardized to a 10-ppb increase in 24-h average SO_2, the increased risk is 23.9% (95% CI: 4.5, 46.9). The mean 24-h average SO_2 level in Sydney during the study period was 1.07 ppb (range: 0.09, 3.94). Llorca et al. (2005) reported a null association for cardiac disease hospital admissions and SO_2 in Torrelavega, Spain.

Analyses restricted to diagnoses of IHD (Jalaludin et al., 2006; Lee et al., 2003a; Lin et al., 2003b; Metzger et al., 2004; Peel et al., 2007), CHF (Koken et al., 2003; Metzger et al., 2004; Peel et al., 2007; Wellenius et al., 2005a), dysrhythmia (Koken et al., 2003; Metzger et al., 2004; Peel et al., 2007), MI (Koken et al., 2003; Lin et al., 2003b), and angina pectoris (Hosseinpoor et al., 2005) were conducted. Two studies conducted in Atlanta, GA reported no significant associations between SO_2 and admissions for specific cardiac outcomes (Metzger et al. 2004; Peel et al. 2007). Metzger et al. observed null associations of 1-h max SO_2 with IHD, CHF, and dysrhythmia. Using the same dataset, Peel et al. (2007) investigated effect modification of CVD outcomes across comorbid disease status categories, including hypertension, diabetes, COPD, dysrhythmia, and CHF. Authors observed no significant associations for any cardiac disease outcome studied (i.e., IHD, CHF, dysrhythmia) with ambient 1-h max SO_2 level in any comorbid disease category.

SO_2-associated increases in admissions for CHF, IHD, and dysrhythmia were reported in a limited number of studies (Jalaludin et al., 2006; Koken et al., 2003; Wellenius et al., 2005a). Results from other analyses of specific cardiac disease endpoints were null (Hosseinpoor et al., 2005; Lee et al., 2003a; Lin et al., 2003b).

In conclusion, the strongest evidence comes from a large multicity study conducted in Spain (Ballester et al., 2006) that observed statistically significant positive associations between ambient SO_2 and cardiac disease; however, the SO_2 effect was found to diminish by half with PM_{10} and CO adjustment. Overall, findings on the relationship between ambient SO_2 and cardiac disease are generally inconsistent.

Cerebrovascular Disease and Stroke

Cerebrovascular diseases include diseases of the blood vessels supplying the brain (ICD9 Codes 430-438). Separate analyses for ischemic stroke (ICD9 434-436), hemorrhagic stroke (ICD9 Codes 431-432), and transient ischemic attack (ICD9 435) are often conducted.

Positive findings were reported for ischemic stroke and SO_2 in a study of nine U.S. cities (Wellenius et al., 2005a). This study examined time-series data including more than 155,500 ischemic stroke hospitalizations between 1986 and 1999 in the cities of Birmingham, AL, Chicago, IL, Cleveland, OH, Detroit, MI, New Haven, CT, Pittsburgh, PA, Salt Lake, UT, and Seattle, WA. The median 24-h average SO_2 level in these cities was 6.2 ppb (10th, 90th percentile: 2.17, 16.17). The study reported a 1.2% (95% CI: 0.1, 2.4) increase of ischemic stroke hospitalizations per 10-ppb increase in 24-h average SO_2 level at lag 0-2 days. Wellenius et al. did not analyze multipollutant models, but the authors noted that other pollutants studied (i.e., NO_2, CO) were more strongly were associated with increased admissions for ischemic stroke. In a study in Edmonton, Canada, Villeneuve et al. (2006) found significantly increased risk of ischemic stroke during the warm season among older adults and a significant association between transient ischemic attacks and SO_2 among older adults in the warm season and all year. The positive results were diminished in multipollutant models.

By contrast, Metzger et al. (2004) reported a null increase for all peripheral and cerebrovascular diseases of 0.2% (95% CI: −4.4, 5.0) per 40-ppb increase in 1-h max SO_2. Peel et al. (2007) also observed null results for this Atlanta population across comorbid disease status categories. Similarly, Jalaludin et al. (2006) observed a null association between cerebrovascular admissions and SO_2 in Sydney. Furthermore, primary intracerebral hemorrhage and ischemic stroke were not found to be significantly associated with SO_2 in a study of admissions records from 63 hospitals in Taiwan (Tsai et al., 2003).

A limited number of studies have examined the effect of ambient SO_2 on cerebrovascular disease and stroke. In general, findings relating ambient SO_2 level to these outcomes have been inconsistent.

Potential Confounding by Copollutants

Studies of all CVD or cardiac diseases that report multipollutant results are summarized in Figure 3.1-13. Overall, effects for all CVD, cardiac diseases, and specific cardiac outcomes were diminished in multipollutant models (Ballester et al., 2001, 2006; Morris et al., 1995; Wellenius et al., 2005b). In addition, Jalaludin et al. (2006) reported a 3% increase in CVD hospital admissions per 0.75-ppb incremental change in 24-h average SO_2 in single-pollutant models, which was reduced to null when CO was included. This study was not included in Figure 3.1-13, because the range of SO_2 concentrations was far below the 10-ppb increment to which other effect sizes were standardized. A study by Chang et al. (2005) examined the effect of SO_2 on all CVD hospitalizations by season and observed a nonsignificant negative association in single-pollutant models for the cool season in Taiwan. After adjusting for NO_2, PM_{10}, and CO in two-pollutant models, this negative association strengthened and achieved significance. The authors attributed this finding to possible collinearity problems between SO_2 and copollutants. Collectively, these results suggest that the effect of SO_2 on cardiovascular ED visits and hospitalizations is likely confounded by copollutant exposures.

3.1.3 Other Systemic Effects Associated with Short-Term SO_2 Exposure

The effects of SO_2 on the nervous system and other organ systems were not examined in the previous review. The 1982 AQCD presented only one chronic exposure study (68 months), in which dogs were exposed to a mixture of SO_2 and H_2SO_4. This study reported no effects on visual evoked brain potentials during or immediately after exposure to the SO_x mixture. In the past 25 years, an increased number of animal toxicological studies evaluated the effects of SO_2 exposure on neurophysiological, biochemical, and neurobehavior as well as on other organ systems in adult and developing animals. The most recent studies on SO_2 effects on various organ systems are summarized in Annex Tables AX4-6 through AX4-9.

3.1.3.1 Nervous System Effects Associated with Short-Term SO_2 Exposure

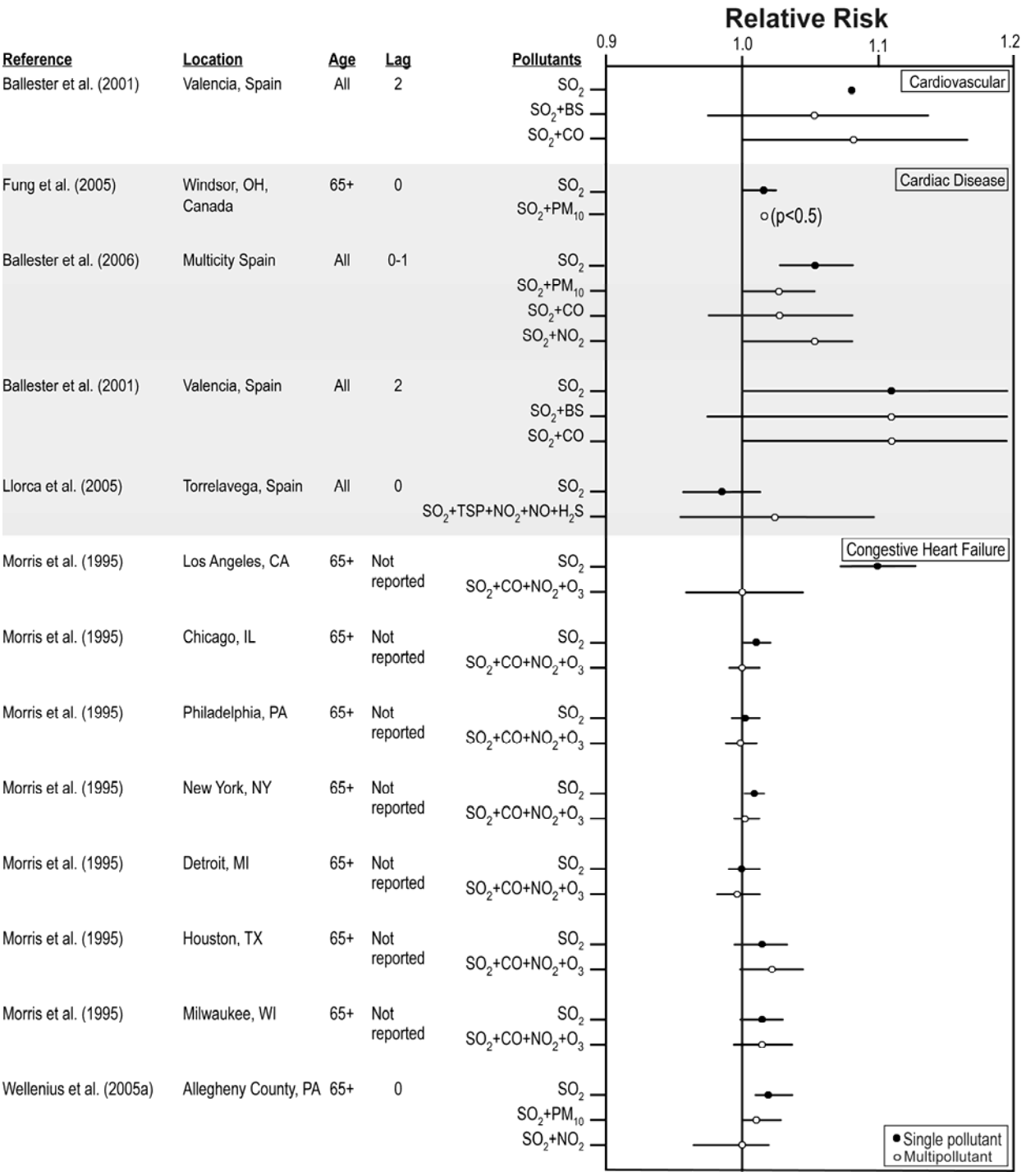

Figure 3.1-13. **Relative risks (95% CI) of SO_2-associated emergency department visits (*) and hospitalizations for cardiovascular causes, with and without copollutant adjustment. Risk estimates are standardized per 10-ppb increase in 24-h average SO_2 concentrations or 40-ppb increase in 1-h max SO_2.**

Effects of Sulfur Oxides on Neurotransmitters, Receptors, Voltage-Gated Channels, and Other Neurophysiological and Biochemical Components

The effects of SO_2 exposure (10-ppm SO_2, 1 h/day) on lipids, lipid peroxidation, and lipase activity in different regions of the brain were investigated in guinea pigs exposed for 21 to 24 days (Haider et al., 1981) and in rats exposed for 30 days (Haider et al., 1982). As summarized in Table 3.1-1, exposure to SO_2 resulted in altered lipid profiles in both species that were qualitatively and/or quantitatively brain-region specific. While levels of total lipids and free fatty acids were generally lowered, the effects on phospholipids, cholesterol, esterified fatty acids, and gangliosides were variable. Lipase activity and lipid peroxidation (as measured by malonaldehyde content) were elevated in brain tissue due to SO_2 exposure. These studies suggest that subacute exposure to 10-ppm SO_2 can lead to degradation of brain lipids. Similar findings were observed in a study in which guinea pigs were exposed to 10-ppm SO_2 alternated daily with 20-ppm of H_2S (i.e., 15 daily 1-h exposures to each gas by itself) for 1 h/day for 30 days (Haider and Hasan, 1984). No lower concentrations were examined to determine possible concentration-response relationships or a no-effect level, and effects observed at these higher levels may be due to mechanisms not induced at more environmentally relevant concentrations.

The effect of SO_2 exposure on neuronal GSH level, antioxidant status, and antioxidant enzymes was investigated in mice and rats. Wu and Meng (2003) did not observe any exposure-induced changes in GSH level or related enzyme activity in brain at the lowest concentration (8.4 ppm) studied. Studies that investigated oxidant status (thiobarbituric acid reactive substances [TBARS] levels) in brain regions and retina in rats exposed to 10-ppm SO_2 for 1 h/day, 7 days/week, for 6 weeks also included effect of age (Kilic, 2003; Yargiçoğlu et al., 1999) and experimentally induced diabetes (Ağar et al., 2000; Küçükatay et al., 2003). These studies reported consistent increases in TBARS levels in brain regions in both normal and diabetic rats, but results from the retina were not consistent.

SO_2-induced changes in neurophysiological endpoints (i.e., somatosensory-evoked potentials, peak-to-peak amplitudes, visual-evoked potentials) were also investigated. SO_2-induced changes in somatosensory-evoked potentials and peak-to-peak amplitudes were observed in young (3 months), but not in older (24 months), rats. The effects of SO_2 exposure on visual-evoked potential in experimental diabetic rats were found to be additive.

TABLE 3.1-1. SO_2 EFFECTS ON GUINEA PIG AND RAT BRAIN

Parameter	Responses[a] in Different Brain Regions					
	Cerebral Hemisphere		Cerebellum		Brain Stem	
Total Lipids	⇩	⬇	(⇩)	⬇	⇩	⬇
Free Fatty Acids	⇩	—	⇩	—	⇩	—
Phospholipids	⇧	↔	⇩	⬆	⇔	↔
Cholesterol	⇧	⬆	⇩	⬆	⇩	(⬆)
Esterified Fatty Acids	⇩	—	⇧	—	⇩	—
Gangliosides	—	⬇	—	⬆	—	⬆
Lipid Peroxidation	⇧	⬆	⇧	⬆	⇧	(⬆)
Lipase Activity	⇧	⬆	⇧	—	⇧	—

[a] Open symbols = guinea pig, closed symbols = rat; vertical arrows = significant changes ($p < 0.001$–0.05), vertical arrows in parentheses = statistically nonsignificant changes ≥10%, horizontal arrows = statistically nonsignificant changes < 10%, dashes = parameter not measured.

Source: Haider et al. (1981, 1982).

Three ex vivo acute exposure studies using SO_2 derivatives on hippocampal or dorsal root ganglion neurons isolated from Wistar rats (Du and Meng, 2004a,b, 2006) observed perturbations in potassium-, sodium-, and calcium-gated channels. These authors speculated that such effects might correlate with the neurotoxicity that has been associated with SO_2 inhalation. Details about all the above studies are presented in Table AX4-6.

Neurodevelopmental and Neurobehavioral Effects

Three studies conducted in rodents provide some information on possible neurodevelopmental effects. In offspring of mice exposed to ≥5-ppm SO_2 from 9 days before mating through the 12th to 14th day of gestation, there were no effects on somatic and neurobehavioral development (e.g., eyelid and ear opening, incisor eruption, reflex development) or passive avoidance testing of adult males (Petruzzi et al., 1996). A second study reported delayed righting and negative geotaxis reflexes in offspring of mice exposed to ≥32-ppm SO_2 on gestation days 7 through 18 (Singh, 1989).

Neurobehavioral responses were examined in adult male offspring of mice exposed to ≥5-ppm SO_2 from 9 days before mating through gestation day 14 (Fiore et al., 1998). Compared to controls, SO_2-exposed male offspring displayed an increased duration of self-grooming (5-ppm group), decreased frequency and duration of tail rattling (≥5-ppm groups), and decreased duration of defensive postures in response to an intruder mouse (≥12-ppm groups).

Studying the influence of age and diabetes on SO_2-induced lipid peroxidation, antioxidant enzyme status, and active avoidance learning in rats, Yargiçoğlu et al. (2001) and Küçükatay et al. (2007) reported that TBARS levels (indicative of lipid peroxidation) was significantly increased and antioxidant status was altered in all the experimental groups studied. The authors also concluded that SO_2 exposure induces impairments in learning in young (3 month old) animals and potentiates diabetes-induced learning impairments in rats.

Behavioral effects in adult animals were examined in male and female mice exposed to ≥5-ppm SO_2 from 9 days before mating through gestation days 12 through 14 (Petruzzi et al., 1996). No effects were observed at concentrations of <30 ppm.

Summary of Nervous System Effects

In a limited number of toxicological studies, exposure to SO_2 has been shown to affect certain neurodevelopmental and cognitive effects. There was suggestive evidence that young animals and those with preexisting conditions such as diabetes were more susceptible to these effects. These effects were observed only at high concentrations of SO_2.

3.1.3.2 Other Organ System Effects Associated with Short-Term SO_2 Exposure

A review of animal toxicological studies published since the 1982 AQCD indicates a limited number of research inquiries were conducted into the systemic effects of SO_2 exposure in various other organ systems such as reproductive, hematological, gastrointestinal, renal, lymphatic, and endocrine systems. The majority of these studies examined alteration profiles of lipid peroxidation and antioxidant levels (Langley-Evans et al., 1996; Meng and Bai, 2004; Meng et al., 2003c).

Though limited, the overall animal toxicological database on SO_2 exposure suggests no adverse effects on development or reproduction. Acute exposure to SO_2 (0.87 ppm) in rats has been found to induce hematological alterations such as increased hematocrit and decreased whole blood and packed cell viscosities (Baskurt, 1988).

No overt pathological changes were observed in the liver and gastrointestinal system of rats in acute or subchronic exposure studies (Gunnison et al., 1987; Langley-Evans et al., 1996). Decreases in the expression of certain cytochrome P450s (CYP1A2 and CYP1A1) in liver were reported at higher concentrations (Qin and Meng, 2005). Smith et al. (1989) did not find any significant effects on spleen weight or mitogen-induced activation of peripheral blood lymphocytes or spleen cells in Sprague-Dawley rats exposed to 1-ppm SO_2 for 5 h/day, 5 days/week for 4 months. Two studies that examined the effects of SO_2 exposure in rodents (Langley-Evans et al., 1996; Wu and Meng, 2003) reported alterations in GSH levels or GSH-related enzymes.

The available studies that examined the effects of SO_2 exposures on the endocrine system evaluated insulin-related parameters in diabetic rats that were fed a standard diet (normal), a high cholesterol diet, or treated with streptozotocin to induce diabetes (Lovati et al., 1996). Exposure to $\geq$5-ppm SO_2 had been found to lower plasma insulin levels in normal and hypercholesterolemic rats and to result in a nonsignificant increase in plasma insulin levels in diabetic rats.

3.2 MORTALITY ASSOCIATED WITH SHORT-TERM SO_2 EXPOSURE

The studies available to review in the 1982 AQCD were mostly from historical data including London, England, and New York City air pollution episodes. Effects of SO_x (mainly SO_2) were investigated along with PM indices because they shared a common source, coal burning, and separating their associations with mortality was a challenge that many of the earlier episodic studies could not necessarily resolve. The SO_2 levels observed in these air pollution episodes were several tens of times higher than the current average levels observed in U.S. cities (e.g., in the 1962 New York City episode, SO_2 in Manhattan peaked at 400 to 500 ppb). Some of these London and New York City studies suggested that PM, not SO_2, was associated with observed mortality, but the 1982 AQCD could not resolve the relative roles of these two pollutants and suggested that the clearest mortality associations were seen when both pollutants were at high levels (24-h average values of both BS and SO_2 exceeding 1000 $\mu g/m^3$ [~ 400 ppb for SO_2]) and less so at lower ranges although the review of the studies and reanalyses found no clear evidence of a threshold for SO_2.

The 1986 Second Addendum to the 1982 AQCD reviewed more reanalyses of the London data and analyses of New York City, Pittsburgh, and Athens data. While these reanalyses and some new analyses confirmed earlier findings (and suggested stronger evidence of BS effects than of the SO_2 effects), given the remaining uncertainties with exposure error and statistical modeling, there was not sufficient information to quantitatively determine concentration-response relationships at lower concentrations of either PM or SO_2. In the analysis of nonepisodic London data, there was an indication that mortality effects were seen at BS levels as low as 150 to 200 $\mu g/m^3$.

A series of short-term mortality effects studies in the late 1980s and early 1990s (e.g., Pope, 1989; Fairley, 1990; Dockery et al., 1992; Pope et al., 1992; Schwartz and Dockery, 1992a,b) showed associations between mortality and PM indices at relatively low levels. Since then, a large number of epidemiological studies have investigated the adverse health effects of air pollution with hypotheses mainly focused on PM, and SO_2 was often analyzed as one of the potential confounders in these studies.

3.2.1 Associations of Mortality and Short-Term SO_2 Exposure in Multicity Studies and Meta-Analyses

In reviewing the range of SO_2 mortality risk estimates, multicity studies provide especially useful information, because they analyze data from multiple cities using a consistent method, avoiding potential publication bias. There have been several multicity studies from the United States, Canada, and Europe, some of which will be discussed in the sections below. Meta-analysis studies also provide useful information on describing heterogeneity of risk estimates across studies; however, unlike multicity studies, the heterogeneity of risk estimates seen in meta-analysis may reflect the variation in analytical approaches across studies. These studies, as well as many other single-city studies, are summarized in Annex Table AX5-5.

3.2.1.1 Multicity Studies

National Morbidity, Mortality, and Air Pollution Study of 90 U.S. Cities

The time-series analysis of the largest 90 U.S. cities (Samet et al., 2000; Dominici et al., 2003) in the National Morbidity, Mortality, and Air Pollution Study (NMMAPS) is by far the largest multicity study conducted to date to investigate the mortality effects of air pollution, but

its primary interest was PM_{10}. It should also be noted that, according to the table of mean pollution levels in the original report (Samet et al., 2000), SO_2 was missing in 28/90 cities. Annual 24-h average mean SO_2 levels ranged from 0.4 ppb (Riverside, CA) to 14.2 ppb (Pittsburgh, PA), with a mean of 5.9 ppb during the study period of 1987 to 1994. The analysis in the original report used GAM models with default convergence criteria. Dominici et al. (2003) reanalyzed the data using GAM with stringent convergence criteria as well as using GLM. It should be noted that this model's adjustment for weather effects employs more terms than other time-series studies in the literature, suggesting that the model adjusts for potential confounders more aggressively than the models in other studies.

PM_{10} and O_3 (in summer) appeared to be more strongly associated with mortality than the other gaseous pollutants. The authors stated that the results did not indicate associations of SO_2, NO_2, and CO with total mortality. However, as with PM_{10}, the gaseous pollutants SO_2, NO_2, and CO each showed the strongest association at a 1-day lag (for O_3, a 0-day lag). In contrast to PM_{10} and NO_2, the inclusion of copollutants in the regression models generally resulted in reduced SO_2 risk estimates. Figure 3.2-1 shows the total mortality risk estimates for SO_2 from Dominici et al. (2003). The mortality risk estimate with a 1-day lag was 0.60% (95% CI: 0.26, 0.95) per 10-ppb increase in 24-h average SO_2. The model with PM_{10} and NO_2 resulted in an appreciably reduced SO_2 risk estimate, 0.38% (95% CI: −0.62, 1.38) per 10-ppb increase in 24-h average SO_2. These results suggest that the observed SO_2-mortality association could be confounded by PM_{10} and NO_2.

Canadian Multicity Studies

There have been three Canadian multicity studies examining the association between mortality and short-term exposure to air pollutants: (1) an analysis of gaseous pollutants in 11 cities from 1980 to 1991 (Burnett et al., 1998); (2) an analysis of $PM_{2.5}$, coarse PM ($PM_{10-2.5}$), and gaseous pollutants in 8 cities from 1986 to 1996 (Burnett et al., 2000); and (3) an analysis of $PM_{2.5}$, $PM_{10-2.5}$, and gaseous pollutants in 12 cities from 1981 to 1999 (Burnett et al., 2004). The first two studies utilized GAM with default convergence criteria. Only the PM indices were reanalyzed for the Burnett et al. (2000) study by Burnett and Goldberg (2003).

Burnett et al. (2004) is the most extensive Canadian multicity study, both in terms of the length and coverage of cities. The discussion in this study focused on NO_2, because NO_2 was the

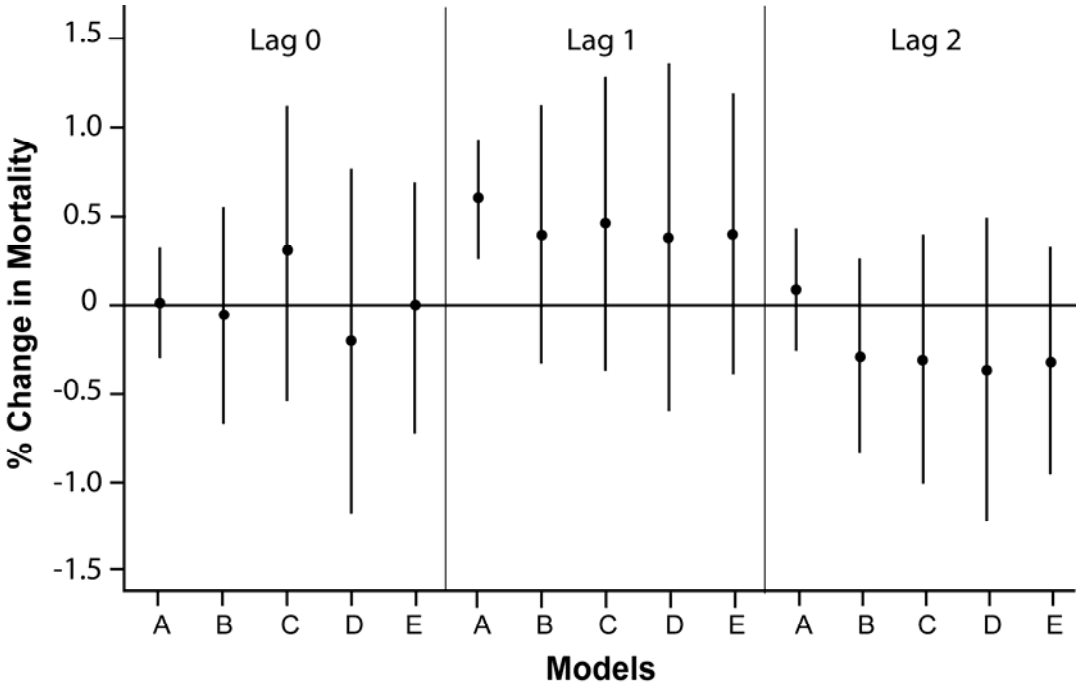

Figure 3.2-1. Posterior means and 95% posterior intervals of national average estimates of SO_2 effects on total mortality from non-external causes per 10-ppb increase in 24-h average SO_2 at 0-, 1-, and 2-day lags within sets of the 62 cities with pollutant data available. Models A = SO_2 alone; B = SO_2 + PM_{10}; C = SO_2 + PM_{10} + O_3; D = SO_2 + PM_{10} + NO_2; E = SO_2 + PM_{10} + CO.

Source: Dominici et al. (2003).

best predictor of short-term mortality fluctuations among the pollutants. This was also the case in the Burnett et al. (1998) study of the gaseous pollutants in 11 Canadian cities. The mean 24-h average SO_2 levels across the 12 cities was 5.8 ppb, with city means ranging from 1 ppb in Winnipeg to 10 ppb in Halifax. The population-weighted average was 5 ppb. The mean SO_2 levels in this study were similar to those in the NMMAPS (mean 24-h average SO_2 levels across the 62 NMMAPS cities was 5.9 ppb).

Total (nonaccidental), cardiovascular, and respiratory mortality were analyzed in Burnett et al. (2004). For SO_2, $PM_{2.5}$, $PM_{10-2.5}$, PM_{10} (arithmetic addition of $PM_{2.5}$ and $PM_{10-2.5}$), CoH, and CO, the strongest mortality association was found at a 1-day lag, whereas for NO_2, it was the 3-day moving average (i.e., average of 0-, 1-, and 2-day lags), and for O_3, it was the 2-day moving average. The daily 24-h average values showed stronger associations than the daily 1-h

max values for all the gaseous pollutants and CoH except for O_3. The SO_2 total mortality risk estimate was 0.74% (95% CI: 0.29, 1.19) per 10-ppb increase in the 24-h average SO_2 with a 1-day lag. After adjusting for NO_2, the SO_2 risk estimate was reduced to 0.42% (95% CI: 0.01, 0.84), while the NO_2 risk estimate was only slightly affected. In this analysis, no regression analysis using both SO_2 and PM was conducted. The Burnett et al. (2000) analysis observed that the simultaneous inclusion of SO_2 and $PM_{2.5}$ in the model reduced the SO_2 risk estimate by half, whereas the $PM_{2.5}$ estimate was only slightly reduced. Overall, these results suggest that SO_2 was not an important predictor of daily mortality in the Canadian cities and that its mortality associations could be confounded by NO_2 or PM.

Air Pollution and Health: A European Approach, Studies 1 and 2

Several Air Pollution and Health: a European Approach (APHEA) analyses have reported SO_2 mortality risk estimates. Katsouyanni et al. (1997) examined the association of PM_{10}, BS, and SO_2 with total mortality in 12 European cities using the standard APHEA1 (GLM) approach. The same data set was reanalyzed using nonparametric smooth functions in GAM models with default convergence criteria to adjust for the seasonal cycles (Samoli et al., 2001) and using GAM with more stringent convergence criteria as well as a parametric smoother in GLM (Samoli et al., 2003). An analysis of cardiovascular and respiratory mortality in 10/12 APHEA cities was conducted by Zmirou et al. (1998). The reanalysis by Samoli et al. (2003) produced results that were similar to those in the original analysis by Katsouyanni et al. (1997). Since the original analysis presented more results, including multipollutant model results, discussion will focus on this analysis.

The study by Katsouyanni et al. (1997) includes seven western European cities (Athens, Barcelona, Cologne, London, Lyon, Milan, and Paris) and five central eastern European cities (Bratislava, Kracow, Lodz, Poznan, and Wroclaw). The data covered at least 5 consecutive years for each city within the years 1980 through 1992. The SO_2 levels in these cities were generally higher than in the United States or Canada, with the median 24-h average SO_2 ranging from 13 $\mu g/m^3$ (5 ppb) in Bratislava to 74 $\mu g/m^3$ (28 ppb) in Kracow. Analysis was restricted to days when PM and SO_2 concentrations did not exceed 200 $\mu g/m^3$ (76 ppb for SO_2). The data were analyzed by each center separately following a standardized method, but the lag for the "best" model was allowed to vary in these cities from 0 to 3 days. The city-specific risk estimates were then examined in the second stage for source of heterogeneity using city-specific

variables such as mean pollution and weather variables, accuracy of the air pollution measurements, health of the population, smoking prevalence, and geographical differences.

The city-specific estimates were found to be heterogeneous and, among the explanatory variables, only the separation between western and central eastern European cities resulted in more homogeneous groups. The total mortality risk estimates were 1.14% (95% CI: 0.88, 1.39), 1.99% (95% CI: 1.15, 2.83), and 0.46% (95% CI: −0.23, 1.15) for all the 12 cities combined, western cities, and central eastern cities, respectively, per 10-ppb increase in the 24-h average SO_2 at variable single-day lags. Seasonal analyses indicated that the summer estimate was slightly higher than the winter estimate in the western cities, but the difference was not statistically significant. The results for the two-pollutant model with SO_2 and BS were presented for the western cities, with a similar extent (~30%) of reductions in the estimates of both pollutants (1.31% [95% CI: 0.40, 2.23] for SO_2). Furthermore, for western cities, they estimated effects for SO_2 for days with high or low BS levels and the corresponding BS effects for days with high or low SO_2 levels and found that their effects were similar for days with low or high levels of the other pollutant. From these results, Katsuoyanni et al. (1997) suggested that the effects of the two pollutants were independent.

Overall, the APHEA studies provide some suggestive evidence that the effect of short-term exposure to SO_2 on mortality is independent of PM. This is somewhat in contrast to the U.S. and Canadian studies. The SO_2 levels were much higher in the European cities, but the type of PM constituents also might be different.

The Netherlands Study

In the Netherlands studies by Hoek et al. (2000, 2001; reanalysis Hoek, 2003), the association between air pollutants and mortality were examined in a large population (14.8 million for the entire country) over the period of 1986 through 1994. The Netherlands were not part of the APHEA SO_2 analysis. The median 24-h average SO_2 level in the Netherlands was 4 ppb (6 ppb for the four major cities). All the pollutants examined, including PM_{10}, BS, O_3, NO_2, SO_2, CO, SO_4^{2-}, and nitrate, were associated with total mortality, and for single-day models, a 1-day lag showed the strongest associations for all the pollutants. The following risk estimates are all from the GLM models with natural splines for smoothing functions. The SO_2 risk estimate in a single-pollutant model was 1.31% (95% CI: 0.69, 1.93) per 10-ppb increase in 24-h

average SO_2 at a 1-day lag and 1.78% (95% CI: 0.86, 2.70) at an average of 0- to 6-day lag. Seasonal analyses showed slightly greater effect estimates during the summer compared to the winter. SO_2 was most highly correlated with BS (r = 0.70). The correlation pattern of SO_2 with other pollutants was similar to that for NO_2, but weaker (e.g., correlation between NO_2 and BS was 0.87). The simultaneous inclusion of SO_2 and BS reduced the risk estimates for both pollutants (SO_2 risk estimate was 1.07% [95% CI: −0.27, 2.42] per 10-ppb increase with an average of 0- to 6-day lag of 24-h average SO_2). PM_{10} was less correlated with SO_2 (r = 0.65), and the simultaneous inclusion of these pollutants resulted in an increase in the SO_2 risk estimate. These results from the analysis of the Netherlands data suggested some indication of confounding between SO_2 and BS. Generally, the SO_2-mortality associations resembled the pattern for NO_2-mortality associations, but weaker.

Other European Multicity Studies

Other European multicity studies were conducted in 8 Italian cities (Biggeri et al., 2005), 9 French cities (Le Tertre et al., 2002), and 13 Spanish cities (Ballester et al., 2002). The studies by Le Tertre et al. (2002) and Ballester et al. (2002) were conducted using GAM methods with the default convergence setting.

Biggeri et al. (2005) analyzed eight Italian cities (Turin, Milan, Verona, Ravenna, Bologna, Florence, Rome, and Palermo) for mortality and hospital admissions (mortality data were not available for Ravenna and Verona). The study period varied from city to city between 1990 and 1999. Only single-pollutant models were examined in this study. The SO_2 risk estimates were 4.14% (95% CI: 1.05, 7.33), 4.94% (95% CI: 0.41, 9.67), and 7.37% (95% CI: −3.58, 19.57) per 10-ppb increase with an average of 0-1-day lag of 24-h average SO_2 for total, cardiovascular, and respiratory deaths, respectively. Since all the pollutants showed positive associations with these mortality categories and the correlations among the pollutants were not presented, it is not clear how much of the observed associations are shared or confounded. The mortality risk estimates were not heterogeneous across cities for all the gaseous pollutants. It should be noted that in Turin, Milan, and Rome, the mean SO_2 values declined by 50% from the first half to the second half of the study period, while the levels of other pollutants declined by smaller fractions. This also complicates the interpretation of SO_2 risk estimates in this study, which are much higher than those from the APHEA studies.

The French nine cities study by Le Tertre et al. (2002) examined BS, SO_2, NO_2, and O_3 by generally following the APHEA protocol, but using GAM with default convergence criteria and using the average of lags 0 and 1 day for combined estimates. SO_2 data were not available in one of the nine cities (Toulouse). All four pollutants were positively associated with mortality outcomes. The study did not report descriptions of correlation among the pollutants or conduct multipollutant models, and therefore, it is difficult to assess the potential extent of confounding among these pollutants. The SO_2 risk estimates were homogeneous across cities, with the exception of Bordeaux, which was the only city that used strong acidity as a proxy for SO_2.

The Spanish Multicentre Study on Air Pollution and Mortality (EMECAM) examined the association of PM indices (i.e., PM_{10}, TSP, BS) and SO_2 with mortality in 13 cities (Ballester et al., 2002). These studies followed the APHEA protocol, but using the GAM approach. The daily mean 24-h average SO_2 concentrations ranged from 8.1 to 44.5 $\mu g/m^3$ (3 to 17 ppb). In the seven cities where 1-h max SO_2 data were also available, mean concentrations ranged from 54.9 to 113.2 $\mu g/m^3$ (21 to 43 ppb). The combined effect estimates for total and respiratory mortality were statistically significant for both 24-h average SO_2 and 1-h max SO_2. Controlling for PM indices substantially diminished the risk estimates for 24-h average SO_2, but not for 1-h max SO_2. The authors reported that these results could indicate an independent impact of peak values of SO_2 more than an effect due to a longer exposure.

3.2.1.2 Meta-Analyses of Air Pollution-Related Mortality Studies

Meta-Analysis of All Criteria Pollutants (1985 to 2000)

Stieb et al. (2002) reviewed time-series mortality studies published between 1985 and 2000, and conducted a meta-analysis to estimate combined effects for PM_{10}, CO, NO_2, O_3, and SO_2. Since many of the studies reviewed in that analysis used GAM wth default convergence parameters, Stieb et al. (2003) updated the estimates by separating the GAM versus non-GAM studies. In addition, separate combined estimates were presented for single- and multipollutant models. There were more GAM estimates than non-GAM estimates for all the pollutants except for SO_2. For SO_2, there were 29 non-GAM estimates from single-pollutant models and 10 estimates from multipollutant models. The lags and multiday averaging used in these estimates varied. The combined estimate for total mortality was 0.95% (95% CI: 0.64, 1.27) per 10-ppb increase in the daily average SO_2 from the single-pollutant models and 0.85% (95% CI: 0.32,

1.39) from the multipollutant models. Because these estimates are not from an identical set of studies, the difference (or lack of a difference, as in this case) between the two estimates may not necessarily be due to the effect of adding a copollutant in the model. Note that the data extraction procedure of this meta-analysis for the multipollutant models was to include from each study the multipollutant model that resulted in the greatest reduction in risk estimates compared with that observed in single-pollutant models. It should also be noted that all the multicity studies whose combined estimates have been discussed in the previous section were published after this meta-analysis.

Health Effects Institute Review of Air Pollution Studies in Asia

The Health Effects Institute (HEI) conducted a comprehensive review of air pollution health effects studies (HEI, 2004). They summarized the results from mortality and hospital admission studies of the health effects of ambient air pollution in Asia (East, South, and Southeast) published in peer-reviewed scientific literature from 1980 through 2003. Of the 138 papers the report identified, most were studies conducted in East Asia (mainland China, Taipei, Hong Kong, South Korea, and Japan). The levels of SO_2 in these Asian cities were generally higher than in U.S. or Canadian cities, with more than half of these studies reporting mean 24-h average SO_2 levels of >10 ppb. Based on a comparison of the reported mean SO_2 levels from the same cities in different time periods, it is clear that the SO_2 levels declined significantly in the 1990s. However, the meta-analysis used the most recent estimate for each city to reflect recent pollution levels. Based on the criteria of having at least 1 year of data, model adjustment for major time-varying confounders, and reporting risk estimates per unit increase in air pollution, the meta-analysis included 28 time-series studies (11 from South Korea, 6 from mainland China, 6 from Hong Kong, and 1 each from Taipei, India, Singapore, Thailand, and Japan). The lags selected to compute combined estimates were inevitably variable; a systematic approach was used to favor the a priori lag stated in the study, followed by the most significant lag, and then the largest effect estimate. Eleven mortality risk estimates were used to compute a combined estimate for SO_2. In general, the report focused on the results of single-pollutant models only, as there were too few studies with results of comparable multipollutant models to allow meaningful analysis. The SO_2 mortality risk estimates were found to be heterogeneous. The publication bias test suggested some indication of bias. The combined estimate for total mortality was 1.49% (95% CI: 0.86, 2.13) per 10-ppb increase in 24-h average SO_2. The report mentioned that the

resulting combined risk estimates for PM and SO_2 were similar to those found in Western countries.

3.2.1.3 Summary of Risk Estimates from Multicity Studies and Meta-Analyses

Figure 3.2-2 shows combined estimates for total mortality per the standardized increments (10-ppb increase for 24-h average SO_2) from the multicity studies and meta-analyses discussed above. The mortality risk estimates from single-pollutant models range from 0.6% (the NMMAPS) to 4.1% (the Italian 8-cities study), but given the large confidence band in the Italian study, a more stable range may be 0.6 to 2%. The heterogeneity of estimates in these studies may be due to several factors, including the differences in model specifications, averaging/lag time, SO_2 levels, and effect-modifying factors. However, given the variability of SO_2 and copollutants concentrations and differences in other effect-modifying factors, the range of SO_2 risk estimates appear to be rather narrow. It is noteworthy that the SO_2 risk estimates for the NMMAPS and Canadian 12-city studies are quite comparable (0.6 and 0.7%, respectively), considering the difference in the modeling approach. This is in contrast to the pattern for the PM_{10} (U.S. Environmental Protection Agency, 2004) and NO_2 (U.S. Environmental Protection Agency, draft, 2007) mortality risk estimates, in which the risk estimates for NMMAPS tended to be smaller than those from the Canadian or other multicity studies.

There was not enough evidence to suggest a difference in risk estimates due to lag or averaging time. In the Netherlands study, the estimate for the average of 0 to 6 days (1.8%) was larger than that for the 1-day lag (1.3%). In the APHEA1 study, the estimate for "cumulative effects" (2.3%, for the average of 2 to 4 consecutive days including the current day) for the western cities was only slightly larger than that for the single-day lag estimate (2%). Thus, while the risk estimates for multiday effects may be larger than the single-day estimates, the evidence so far indicates that the magnitude of such multiday effects is not substantial.

Only the APHEA study examined possible source of effect modifications for SO_2 in multicity or meta-analyses. They examined several potential effect modifiers such as the mean levels of pollution and weather variables, accuracy of the air pollution measurements, health of the population, smoking prevalence, and geographical differences. The only variable that could explain the heterogeneity of city-specific risk estimates was the geographic separation (western

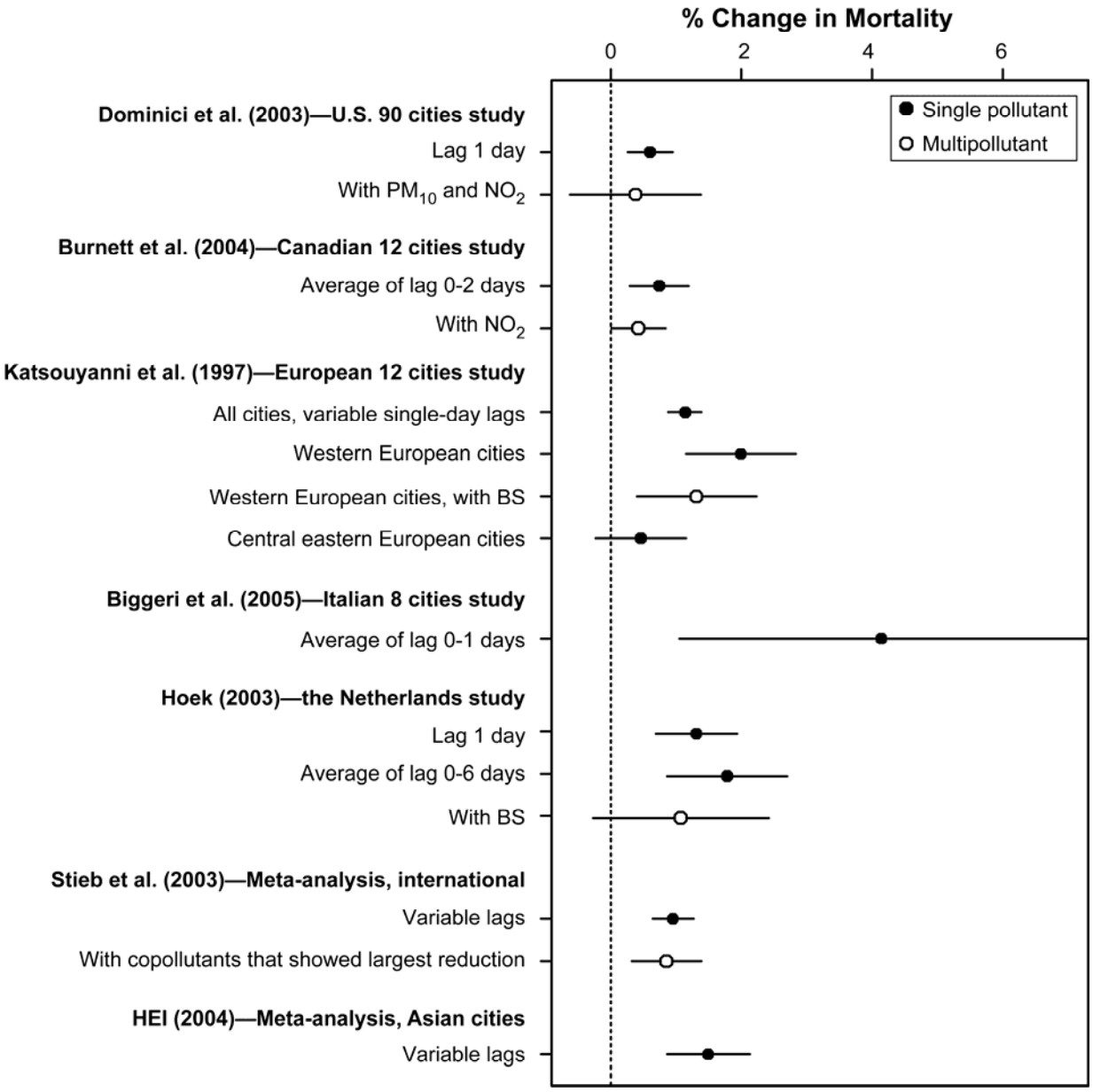

Figure 3.2-2. **All cause (nonaccidental) SO_2 mortality risk estimates (95% CI) from multicity and meta-analysis studies. Risk estimates are standardized per 10-ppb increase in 24-h average SO_2 concentrations. For multipollutant models, results from the models that resulted in the greatest reduction in SO_2 risk estimates are shown.**

versus central eastern European cities) for both SO_2 and BS, but heterogeneity in the SO_2 risk estimates remained within the western cities.

In summary, the range of SO_2 total mortality risk estimates is 0.4 to 2% per 10-ppb increase in 24-h average SO_2. There was some suggestion of confounding between SO_2 and PM and/or NO_2. The extent of multiday effects, if they exist, is not substantial. There is no clear effect modifier, but the larger European study suggested that the observed heterogeneity in SO_2 risk estimates is at least in part regional.

3.2.1.4 Potential Confounding by Copollutants of the Association of Mortality and Short-Term SO_2 Exposure

As shown in Figure 3.2-2, the mortality risk estimates from the multipollutant models in the multicity studies suggest some extent of confounding between SO_2 and PM and/or NO_2, as indicated by the reduced magnitude of the SO_2 risk estimates. NMMAPS and the Canadian study showed a similar extent of reductions in the SO_2 risk estimates in the multipollutant models (from 0.6 to 0.4% in the NMMAPS and from 0.7 to 0.4% in the Canadian study). In both the European APHEA1 analysis and the Netherlands analysis, the SO_2 mortality associations were reduced (though not eliminated) when BS was added to the model. The meta-analysis by Stieb et al. (2003) does not suggest confounding of SO_2 by copollutants, but this was not a direct comparison of estimates from the same set of studies (29 studies for single pollutant models and 10 studies for multipollutant models). Thus, the results from multicity studies suggest some evidence of confounding, in the sense of instability of risk estimates in multipollutant models.

Additional single-city studies have also examined potential confounding of the SO_2 effect on mortality by copollutants through multipollutant analyses. The studies that examined SO_2 and PM indices and did not find substantial (i.e., more than 50%) reductions in SO_2 risk estimates after adjustment for PM include analyses of data from Philadelphia, PA, with TSP (Kelsall et al., 1997, using GAM with default convergence criteria; Moolgavkar et al., 1995); Cook County, IL, with PM_{10} (Moolgavkar, 2003, using GAM with default convergence criteria); and Los Angeles, CA, with PM_{10} or $PM_{2.5}$ (Moolgavkar, 2003, using GAM with default convergence criteria). Other studies that analyzed SO_2 and PM indices and did find major reductions in SO_2 risk estimates after adjustment for PM include analyses of data from Philadelphia, PA, with TSP (Schwartz, 2000); New York City, NY, with PM_{10} (De Leon et al., 2003); and Santiago, Chile, with $PM_{2.5}$ (Cifuentes et al., 2000). It is difficult to find a consistent pattern of evidence of

confounding with PM in these single-city results. It is also possible that the constituents of PM (e.g., relative contribution of traffic-related pollution to PM mass) vary from city to city, and hence correlations of PM with SO_2 vary, contributing to apparently inconsistent results.

Fewer single-city studies examined multipollutant models with SO_2 and other gaseous pollutants. Most studies observed that adjusting for other gaseous pollutants generally did not substantially influence the SO_2 risk estimate (Bremner et al., 1999; Kelsall et al., 1997; Kwon et al., 2001; Wong et al., 2001). However, one study by Cifuentes et al. (2000) did find that the SO_2 risk estimate was reduced substantially by adding any of CO, O_3, or NO_2 in the two-pollutant model in Santiago, Chile. Again, the results from these single-city studies are too limited to exhibit a consistent pattern.

In summary, because of the lack of consistency in the way multipollutants were examined (e.g., lags examined, combination of pollutants examined, model specification) and because of the limited statistical power in individual cities, it is difficult to extract information that help elucidate a pattern of confounding between SO_2 and other pollutants from these single-city studies. The multipollutant results from multicity studies provide more useful information on this issue. As noted before, the results from the multicity studies from the United States, Canada, and Europe generally suggest that SO_2 mortality risk estimates may be confounded by copollutants.

3.2.2 Cause-Specific Mortality Associated with Short-Term SO_2 Exposure

Assessing cause-specific mortality is complicated by the lack of clarifying information on contributing causes of death. That is, attribution to one or the other of the more specific cardiopulmonary causes may underplay contributions of chronic CVD to respiratory-related deaths (e.g., a heart attack victim succumbing to acute pneumonia) or vice versa. Several multicity studies provided risk estimates for broad cause-specific categories, typically respiratory and cardiovascular mortality. A summary of these risk estimates, along with the all-cause mortality estimates for comparison, are presented in Figure 3.2-3. These results from multicity studies suggest that the mortality risk estimates for cardiovascular and respiratory causes were generally larger than that for all-cause mortality, though in some cases the effects were not statistically significant, possibly because of reduced statistical power by which to examine cause-specific associations. In these studies, the effect estimates for respiratory mortality were also

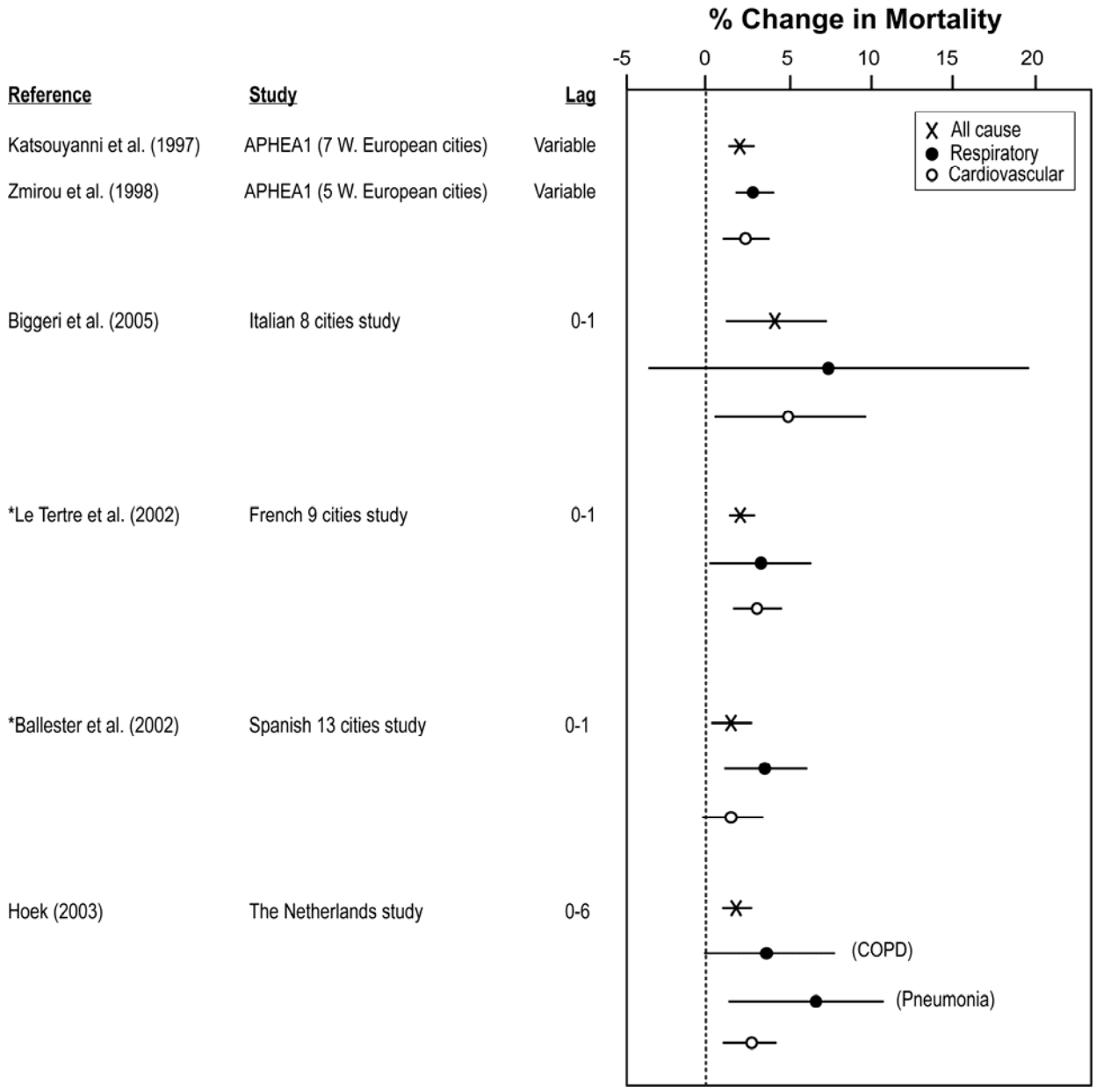

Figure 3.2-3. **All-cause (nonaccidental) and broad cause-specific (respiratory and cardiovascular) SO_2 mortality risk estimates (95% CI) from multicity studies. Risk estimates are standardized per 10-ppb increase in 24-h average SO_2 concentrations.**

*Note: Le Tertre et al. (2002) and Ballester et al. (2002) performed analyses using Poisson GAM with default convergence criteria.

found to be larger than the cardiovascular mortality risk estimates, suggesting a stronger association of SO_2 with respiratory mortality compared to cardiovascular mortality. However, this pattern was not unique to SO_2; other pollutants often showed similar patterns. There were numerous single-city studies that also examined broad specific causes (cardiovascular and respiratory), but the patterns were not always consistent, likely due to smaller sample size, or the lags reported were not consistent across the specific causes examined.

Some studies examined more specific causes within cardiovascular or respiratory causes. In the Netherlands study (Hoek et al. 2001; reanalysis Hoek, 2003), the risk estimates for heart failure (7.1% [95% CI: 2.6, 11.7] per 10-ppb increase in the average of 0- through 6-day lags of 24-h average SO_2) and thrombosis-related deaths (9.6% [95% CI: 3.1, 16.6]) were larger than that for total cardiovascular (2.7% [95% CI: 1.3, 4.1]) causes. However, a similar pattern was seen for PM_{10}, CO, and NO_2 as well. In the analysis by Goldberg et al. (2003) of Montreal data, the risk estimates for death with underlying cause of CHF and those deaths classified as having CHF 1 ear before death were compared. They did not find associations between air pollution and those with underlying cause of CHF (e.g., SO_2 risk estimate was −0.1% [95% CI: −8.9, 9.6] per 10-ppb increase in 24-h average SO_2 with a 1-day lag), but they found associations between some of the air pollutants examined (i.e., CoH, SO_2, NO_2) and the deaths that were classified as having CHF 1 year before death (SO_2 risk estimate was 5.4% [95% CI: 1.3, 9.5]). Again, the association with the specific cause of death was not unique to SO_2. This pattern of association between multiple pollutants (including, but not specific to, SO_2) and specific causes of deaths was seen for an asthma mortality (Saez et al., 1999) cohort with severe asthma (Sunyer et al. 2002), a cohort of patients with intrauterine mortality (Pereira et al., 1998), and a cohort with CHF (Kwon et al., 2001).

In summary, both cardiovascular and respiratory causes, as well as more specific causes or categories of death, have been shown to be associated with ambient SO_2 concentrations. However, since other pollutants also showed similar associations with these causes or categories, the possibility of confounding by these copollutants remains. While SO_2 may have contributed to these associations as part of the mixture of pollutants or as a surrogate index, it is difficult to evaluate the specificity of SO_2 effects on these specific causes of death.

3.2.3 Evidence from an Intervention Study

Many time-series studies provide estimates of excess risk of mortality, but a question remains as to the likelihood of a reduction in deaths when SO_2 levels are actually reduced. Hedley et al. (2002) took advantage of a sudden change in regulation in Hong Kong in July 1990 that required all power plants and road vehicles to use fuel oil with a sulfur content of $\leq$0.5% by weight. The SO_2 levels after the intervention declined about 50% (from about 17 ppb to 8 ppb), but the levels for PM_{10}, NO_2, and SO_4^{2-} did not change and O_3 levels slightly increased. The seasonal mortality analysis results showed that the apparent reduction in seasonal death rate occurred only during the first winter, and this was followed by a rebound (i.e., higher than expected death rate) in the following winter. Using Poisson regression of the monthly deaths, the average annual trend in death rate significantly declined after the intervention for all causes (2.1%), respiratory causes (3.9%), and cardiovascular causes (2.0%), but not from other causes. These results seem to suggest that a reduction in SO_2 leads to an immediate reduction in deaths. Hedley et al. (2002) estimated that the expected average gain in life expectancy per year due to the lower SO_2 levels was 20 days for females and 41 days for males.

Interpreting these results is somewhat complicated by an upward trend in mortality across the intervention point, which the authors noted was due to increased population size and aging. The results suggest that such an upward trend is less steep after the introduction of low sulfur fuel. While the Poisson regression model of monthly deaths does adjust for trend and seasonal cycles, the regression model does not specifically address the influence of influenza epidemics, which can vary from year to year. This issue also applies to the analysis of warm to cool season change in death rates. The most prominent feature of the time-series plot (or the fitted annual cycle of monthly deaths) presented in this study is the lack of a winter peak for respiratory and all-cause mortality during the year immediately following the intervention. Much could be made of this lack of a winter peak, but no discussion of the potential impact of (or a lack of) influenza epidemics is provided. These issues make the interpretation of the estimated decline in upward trend of mortality rate or the apparent lack of winter peak difficult.

Further, the decline in mortality following the intervention does not preclude the possibility that other constituents of the pollution mixture that share the same source as SO_2 is responsible for the adverse effects. Even though the PM_{10} levels before and after the intervention were stable in Hong Kong, it is possible that constituents that do not explain a major

fraction of PM may have declined. Lippmann et al. (2006) mentioned that unpublished data from Hedley and coworkers reported large reductions in nickel and vanadium but not in other metals in Hong Kong after the intervention. SO_2 also may be serving as a modifier of the effect of respirable particles. Thus, while the Hong Kong intervention data are supportive of SO_2 mortality effects, the possibility of mortality effects by other constituents that are associated with SO_2 sources remains.

3.2.4 Summary of Effects of Short-Term SO_2 Exposure on Mortality

The 1982 AQCD could not resolve the relative effects of short-term exposure to PM and SO_2 on mortality and suggested that the clearest mortality associations were seen when both pollutants were at high levels (24-h average values of both BS and SO_2 exceeding 1000 $\mu g/m^3$ [~400 ppb for SO_2]), and less so at lower ranges. The 1986 Secondary Addendum reviewed more reanalyses of the London data and analyses of New York City, Pittsburgh, and Athens data, but it concluded that there was not sufficient information to quantitatively determine concentration-response relationships at lower concentrations of either PM or SO_2. However, in the analysis of nonepisodic London data, there was an indication that mortality effects were seen at BS levels as low as 150 to 200 $\mu g/m^3$.

Recent epidemiological studies have reported associations between mortality and SO_2, often at mean 24-h average levels of <10 ppb. The range of SO_2 all cause (nonaccidental) mortality risk estimates is 0.4 to 2% per 10-ppb increase in 24-h average SO_2 in several large multicity studies and meta-analyses. Limited information suggests that the extent of multiday effects, if present, is not substantial. The risk estimates for more specific categories may be larger. In the large multicity time-series studies, the SO_2 risk estimates were generally reduced when copollutants, either PM indices and/or NO_2, were added in the model. Thus, some extent of confounding among these pollutants is suggested.

The APHEA analysis of 12 European cities sought possible sources of heterogeneity in the city-specific risk estimates, but the only important effect modifier was the geographical area, with western cities showing larger SO_2 risk estimates than central eastern cities. However, this pattern was also seen for BS. Both SO_2 and BS showed slightly larger estimates in the warm season.

The intervention study from Hong Kong supports the idea that a reduction in SO_2 levels results in a reduction in deaths, but this does not preclude the possibility that the causal agent is not SO_2 but rather something else that is associated with SO_2 sources. Overall, the evidence that SO_2 is causally related to mortality at current ambient levels is suggestive but limited by potential confounding in the epidemiological data and the absence of strong biological plausibility.

3.3 MORBIDITY ASSOCIATED WITH LONG-TERM SO_2 EXPOSURE

3.3.1 Respiratory Effects Associated with Long-Term Exposure to SO_2

In the 1982 AQCD, only a few studies provided sufficient quantitative evidence relating respiratory symptoms or pulmonary functions changes to long-term exposure to SO_2. Briefly, a study by Lunn et al. (1967) in Sheffield, England, provided the strongest evidence of an association between pulmonary function decrements and increased frequency of lower respiratory symptoms in 5- to 6-year-old children chronically exposed to ambient BS (annual level of 230 to 301 $\mu g/m^3$) and SO_2 levels (181 to 275 $\mu g/m^3$ [69 to 105 ppb]). A follow-up study in 1968 by Lunn found no effect with much lower levels of BS (range: 48, 169 $\mu g/m^3$) and SO_2 (range: 94, 253 $\mu g/m^3$ [36, 97 ppb]); it was suggested that this might be due to insufficient power to detect small health effect changes.

The 1986 Second Addendum presented three additional studies that examined the effects of long-term exposure on respiratory health. A study by Ware et al. (1986) reported that respiratory symptoms were associated with annual average TSP in the range of ~30 to 150 $\mu g/m^3$ in children (n = 8,380) from six U.S. studies. Only cough was found to be significantly associated with SO_2. Although the increase in symptoms did not appear concomitantly with any decrements in lung function, this may indicate different mechanisms of effect. Other studies by Chapman et al. (1985) and Dodge et al. (1985) also observed increased prevalence of cough among children and young adults living in areas of higher SO_2 concentrations; however, it was noted the observed effects might have been due to intermittent high SO_2 peak concentrations.

The 1982 AQCD noted no remarkable pulmonary pathological findings in animals (monkeys and dogs) following chronic exposures to SO_2 at $\leq$5.1 ppm; however, this could have been due to the conventional light microscopic examination applied, which could not detect

alterations in surface membranes or cilia. Nasal mucosal alterations were observed in mice exposed to 10-ppm SO_2 for 72 h by inhalation. Lack of data on morphological effects of SO_2 at near ambient concentrations was noted.

Since the 1982 AQCD and the 1986 Second Addendum, long-term exposure studies of SO_2 have investigated effects on asthma, bronchitis and respiratory symptoms, lung function, and morphological effects. The epidemiological studies are summarized in Annex Table AX5-6.

3.3.1.1 Asthma, Bronchitis, and Respiratory Symptoms

In the Six Cities Study of Air Pollution and Health, cross-sectional associations between air pollutants and respiratory symptoms were examined in 5,422 white children aged 10 to 12 years old from Watertown, MA, St. Louis, MO, Portage, WI, Kingston-Harriman, TN, Steubenville, OH, and Topeka, KS (Dockery et al., 1989). Annuals means of 24-h average SO_2 concentrations ranged from 3.5 ppb in Topeka to 27.8 ppb in Steubenville. Except for O_3, the correlations among pairs of pollution measures varied between 0.53 and 0.98. No associations were observed between SO_2 and a variety of respiratory symptoms, including bronchitis, chronic cough, chest illness, persistent wheeze, and asthma. Stronger associations were observed for PM indices.

Dockery et al. (1996) examined the respiratory health effects of acid aerosols in 13,369 white children aged 8 to 12 years old from 24 communities in the United States and Canada between 1988 and 1991. The city-specific annual mean SO_2 concentration was 4.8 ppb, with a range of 0.2 to 12.9 ppb. 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. For SO_2, the only significant association found was with chronic phlegm, with an OR of 1.19 (95% CI: 1.00, 1.40) per 5-ppb increase in SO_2.

As part of the international SAVIAH (Small-Area Variation in Air Pollution and Health) study, Pikhart et al. (2001) examined the respiratory health effects from long-term exposure to SO_2 in children (n = 6,959) from two central European cities with high pollution levels (Prague, Czech Republic, and Poznan, Poland). A novel technique was used to estimate the outdoor concentrations of SO_2 at a small-area level. Outdoor SO_2 was measured by passive samplers at 130 sites in the two cities during 2-week periods. Concentrations of SO_2 at each location in the

study areas were estimated from these data by modeling using a geographic information system (GIS). The estimated mean exposure to outdoor SO_2 was 84 $\mu g/m^3$ (32 ppb), with a range of 66 to 97 $\mu g/m^3$ (25, 37 ppb), in Prague and 80 $\mu g/m^3$ (31 ppb), with a range of 44 to 140 $\mu g/m^3$ (17, 53 ppb) in Poznan. The prevalence of wheezing or whistling in the past 12 months was associated with SO_2 (OR of 1.08 [95% CI: 1.03, 1.13] per 5-ppb increase in SO_2). Moreover, the lifetime prevalence of wheezing or whistling (OR 1.03 [95% CI: 1.00, 1.07]) and lifetime prevalence of physician-diagnosed asthma (OR 1.09 [95% CI: 1.00, 1.19]) also were associated with SO_2 levels.

Pénard-Morand et al. (2005) examined the effect of long-term exposures to air pollution and prevalence of exercise-induced bronchial reactivity (EIB), flexural dermatitis, asthma, allergic rhinitis, and atopic dermatitis in 9,615 children aged 9 to 11 years in six French communities. Using 3-year averaged concentrations of SO_2, the investigators reported that the prevalence of exercise-induced bronchial reactivity, lifetime asthma, and allergic rhinitis were significantly associated with increases in SO_2 exposure. The estimated 3-year averaged concentration of SO_2 was 4.6 $\mu g/m^3$ (2 ppb) in the low-exposure schools and 9.6 $\mu g/m^3$ (4 ppb) in the high-exposure schools. In a single-pollutant model, the ORs were 2.37 (95% CI: 1.44, 3.77) for EIB and 1.58 (95% CI: 1.00, 2.46) for lifetime asthma per 5-ppb increase in SO_2. In this study, SO_2 was moderately correlated with PM_{10} ($r = 0.76$) but not with O_3 ($r = -0.02$). Using a two-pollutant model that included PM_{10}, the associations of SO_2 with EIB and lifetime asthma were fairly robust (<5% change).

Herbarth et al. (2001) performed a meta-analysis of three cross-sectional surveys conducted in East Germany investigating the relationship between lifetime exposure (from birth to completion of questionnaire survey) to SO_2 and TSP in children and the prevalence of chronic bronchitis. Using a logistic model that included variables on parental predisposition (mother or father with bronchitis) and environmental tobacco smoke exposure, the authors reported that the OR for bronchitis due to a lifetime exposure to SO_2 was 3.51 (95% CI: 2.56, 4.82) (the concentration change for which the OR was based was not presented). No associations were found between TSP and the prevalence of bronchitis in children.

In a German study of 5,421 children, the annual mean SO_2 concentration was associated with morning cough over the last 12 months, but not bronchitis (Hirsch et al., 1999). This study further observed that the association of SO_2 and other air pollutants with respiratory symptoms

were stronger in nonatopic than in atopic children. The authors noted that these findings were in line with the hypothesis that these air pollutants induce nonspecific irritative rather than allergic inflammatory changes in the airway mucosa, as irritative effects would affect the clinical course in nonatopic children more strongly than in atopics whose symptoms are also determined by allergen exposure.

In a cross-sectional analysis, Heinrich et al. (2002) examined the influence of decreased air pollution levels on respiratory symptoms in children aged 5 to 14 years (n = 7,632) in the reunified Germany. Questionnaires were collected from the children during 1992-1993, 1995-1996, and 1998-1999 in three study areas. Improvements in air quality were associated with decreasing prevalence of nonallergic respiratory symptoms. The effect estimates were stronger among children without indoor exposures. For those without indoor exposures, ORs of 1.21 (95% CI: 1.11, 1.32) were observed for prevalence of bronchitis and 1.11 (95% CI: 1.02, 1.22) for frequent colds per 5-ppb increase in the annual mean of SO_2. The authors concluded that the decreasing prevalence of respiratory symptoms following decreases in air pollution levels might indicate the reversibility of adverse health effects in children.

In France, Ramadour et al. (2000) performed a cross-sectional epidemiological survey of 2,445 children aged 13 to 14 years living in communities with contrasting levels of air pollution to determine the relationship between long-term exposure to gaseous air pollutants and prevalence rate of rhinitis, asthma, and asthma symptoms. The average SO_2 concentrations during the 2-month survey period ranged from 17.3 $\mu g/m^3$ (7 ppb) to 57.4 $\mu g/m^3$ (22 ppb) across the seven communities. This study found no relationship between the mean levels of SO_2, NO_2, or O_3 and the above-mentioned symptoms. Another study conducted in eight nonurban communities in Austria observed no consistent associations between SO_2 and prevalence of asthma and symptoms (Studnicka et al., 1997).

In California, Euler et al. (1987) studied the effects of long-term cumulative exposure to TSP and SO_2 on COPD symptoms in 7,445 nonsmoking non-Hispanic white adult participants in the Adventist Health Study. Using indices of cumulative exposure, this study reported that cumulative exposure levels of SO_2 above 400 ppb (the former California 24-h standard) resulted in an increased risk of chronic obstructive pulmonary disease symptoms. Exposure levels >400 ppb for 500 h/year resulted in an 18% increased risk of having COPD symptoms, 250 h/year, a 9% increased risk, and 100 h/year, a 3% risk.

Goss et al. (2004) conducted a cohort study to examine the effect of air pollutants on 11,484 patients (mean age 18.4 years) with cystic fibrosis. Study participants were enrolled in the Cystic Fibrosis Foundation National Patient Registry in 1999-2000. Exposure was assessed by linking air pollution values from ambient monitors with the patient's home ZIP code. During the study period, the mean SO_2 concentration was 4.9 ppb (SD 2.6, IQR: 2.7, 5.9). This study found no association between SO_2 and the odds of having two or more pulmonary exacerbations. One of the limitations addressed by the authors was the lack of information regarding tobacco use or environmental tobacco smoke, an important risk factor for pulmonary exacerbations.

Several studies that examined the effects of long-term exposure to SO_2 on asthma, bronchitis, and respiratory symptoms observed positive associations in children, with the notable exception of the Harvard Six Cities study. However, there are inconsistencies in the findings observed, with some finding effects on bronchitic but not asthma symptoms and vice versa. A major limitation of some studies is that subjects were asked to recall prevalence of symptoms in the last 12 months or in a lifetime; such long recall periods may result in significant recall bias. Overall, while the evidence is suggestive, the variety of outcomes examined and the inconsistencies in the observed results make it difficult to assess the impact of long-term exposure of SO_2 on respiratory health.

3.3.1.2 Lung Function

Two major U.S. studies, the Harvard Six Cities Study by Dockery et al. (1989) and a cross-sectional analysis of NHANES II data by Schwartz (1989), reported that no associations were observed between long-term exposure to SO_2 and lung function. Additional studies conducted in Europe observed mixed results.

In a longitudinal cohort study of 1,150 children in nine communities in Austria, Frischer et al. (1999) examined the effect of long-term exposure to air pollutants on lung function. Lung function was measured in the spring and fall over a 3-year period from 1994 through 1996. Annual mean SO_2 concentrations ranged from 2 to 6 ppb across the nine communities. The authors reported no consistent associations between SO_2, PM_{10}, or NO_2 and lung function. Horak et al. (2002a,b) extended the study of Frischer et al. (1999) with an additional year of data. The mean SO_2 concentration was 16.8 $\mu g/m^3$ (6 ppb) in the winter and 6.9 $\mu g/m^3$ (3 ppb) in the summer. This study found a positive association between wintertime SO_2 concentrations and changes in FVC, which became null with PM_{10} in a two-pollutant model.

Frye et al. (2003) observed changes in lung function parameters associated with declines in SO_2 concentrations in a cross-sectional study of children (n = 2,493) conducted in East Germany. During the period from 1992-1993 to 1998-1999, the annual mean SO_2 level dramatically declined from 113 $\mu g/m^3$ (42 ppb) to 6 $\mu g/m^3$ (2 ppb) and corresponding increases in FVC and FEV_1 were observed. The annual mean of TSP declined from 79 $\mu g/m^3$ to 25 $\mu g/m^3$ as well. This study reported a 4.9% (95% CI: 0.7, 9.3) increase in FVC and a 3.0% (95% CI: −1.1, 7.2) increase in FEV_1 per 100-$\mu g/m^3$ (38 ppb) decrease in the annual mean of SO_2. Results from this study indicated that a reduction of air pollution in a short time period may improve children's lung function; however, the observed increases in lung function parameters were likely not solely attributable to decreases in SO_2.

Ackermann-Liebrich et al. (1997) examined the effect of long-term exposure to air pollutants in a cross-sectional population-based sample of adults aged 18 to 60 years old (n = 9,651) residing in eight different areas in Switzerland (Study on Air Pollution and Lung Diseases in Adults [SAPALDIA]). They observed a 1.2% decrease in FEV_1 per 109-$\mu g/m^3$ (42 ppb) increase in SO_2 for adults. Significant associations also were observed for PM_{10} and NO_2. The limited number of study areas and high intercorrelation between the pollutants made it difficult to assess the effect of an individual pollutant. The authors concluded that air pollution from fossil fuel combustion, which was the main source of air pollution for SO_2, NO_2, and PM_{10} in Switzerland, was associated with decrements in lung function parameters in this study.

An animal toxicological study in rabbits that were exposed to 5-ppm SO_2 for 13 weeks beginning in the neonatal period (Douglas et al., 1994) did not observe any alterations in pulmonary function or respiratory parameters, i.e., lung resistance, dynamic compliance, trans-pulmonary pressure, tidal volume, respiration rate, minute volume. These results, taken together with the epidemiological evidence, do not indicate that long-term exposure to SO_2 has a detrimental effect on lung function.

3.3.1.3 Morphological Effects

Three animal toxicological studies published since the 1982 AQCD reported some histopathological changes in the respiratory system following acute (<24 h) to chronic (>6 month) exposures and lesions were primarily observed in airways. No alveolar lesions (including electron microscopic evaluation) were observed in guinea pigs exposed to 1-ppm SO_2

for 3 h/day for 6 days (Conner et al., 1985). No pulmonary or nasal lesions were observed in rats exposed to 5-ppm SO_2 for 5 days/week for 4 weeks (Wolff et al., 1989). A weakness of the study is that histopathological methods were not reported. Smith et al. (1989) exposed rats for 4 to 8 months to 1-ppm SO_2 and observed increased incidence of bronchiolar epithelial hyperplasia and a small increase (12%) in numbers of nonciliated epithelial cells in terminal respiratory bronchioles at 4 but not 8 months of exposure. A limitation of the study was the examination of a single concentration, which does not allow for concentration-response assessment or identification of a no-effect-level. The studies on the morphological effects are summarized in Annex Table AX4-10.

3.3.2 Carcinogenic Effects Associated with Long-Term Exposure to SO_2

The 1982 AQCD concluded that little or no clear epidemiological evidence substantiated the hypothesized links between SO_2 or other SO_x and cancer. From the toxicological studies, it was noted that while there were some indications of carcinogenicity for both SO_2 and SO_2 + benzo[*a*]pyrene (B[*a*]P), complex exposure regimens, problematic dose determinations, and/or inadequately reported experimental details led to the conclusion that SO_2 could only be considered a suspect carcinogen/cocarcinogen. More recent studies on SO_2-related carcinogenicity are summarized in Annex Tables AX5-7 (epidemiological studies) and AX4-11 (toxicological studies).

A limited number of recent epidemiological studies have investigated the relationship between long-term exposure to SO_2 and lung cancer incidence. Nyberg et al. (2000) conducted a case-control study of men aged 40 to 75 years with (n = 1,042) and without (n = 2,364) lung cancer in Stockholm County, Sweden. They mapped residence addresses to a GIS database to assign individual exposures to SO_2 from defined emission sources (mainly local oil-fueled residential heating). Available SO_2 measurement data were used to calibrate the model. In this study, SO_2 was considered an indicator of air pollution from residential heating. Exposure to NO_2, considered to be a marker of traffic pollution, also was evaluated in this study. The 90th percentile 30-year average SO_2 level was 78.20 $\mu g/m^3$ (30 ppb). After adjusting for potential confounders (e.g., smoking, occupational exposures), long-term average heating-related SO_2 exposure was not associated with an increase in risk of lung cancer. A weak association for the 30-year average traffic-related NO_2 exposure was observed.

Very similar results were reported in a Norwegian study by Nafstad et al. (2003). The study population is a cohort of 16,209 men who enrolled in a study of CVD in 1972. The Norwegian cancer registry identified 422 incident cases of lung cancer. SO_2 exposure data were modeled based on residence using data for observed concentrations and emission from point sources (e.g., industry and heating of buildings and private homes) and traffic. Once again, no association was observed between long-term exposure to SO_2 and lung cancer incidence.

The carcinogenic potential of SO_2 was examined more extensively in animal toxicological studies. Gunnison et al. (1988) conducted a two-part study in which rats were exposed either for 21 weeks (6 h/day, 5 days/week) to 0-, 10-, or 30-ppm SO_2, or for 21 weeks to two tungsten-supplemented, molybdenum-deficient diets. This latter regimen induces a condition of sulfite oxidase deficiency, resulting in elevated systemic levels of sulfite:bisulfite relative to control values (e.g., in plasma, from 0 to 44 µM; and in tracheal tissue, from 33 to 69 or 550 nmol/g wet wt.). Beginning with week 4, some groups from each regimen received weekly tracheal installations of 1-mg B[*a*]P for 15 weeks. Overall results indicated that squamous cell carcinoma was not induced, or in the B[*a*]P groups coinduced or promoted, by SO_2 inhalation or elevated systemic sulfite:bisulfite. Due to the very high incidences of animals with tumors in the groups exposed to only B[*a*]P (65/27, 63/72), carcinogenicity or cocarcinogenicity of SO_2 or sulfite:bisulfite could only have been detected as a shortening of tumor induction time and/or an increase in rate of tumor appearance, and neither was observed. As noted by the authors, these findings do not support the hypothesis that SO_2 exposure might enhance the carcinogenicity of B[*a*]P by elevating systemic sulfite:bisulfite that could generate glutathione-*S*-sulfonates, which in turn could inhibit glutathione *S*-transferase (GST) and reduce intracellular GSH and, thus, interfere with a major detoxication pathway.

Two similar studies were published that investigated the ability of 10 to 11 months of exposure (16 h/day) to 4-ppm SO_2, 6-ppm NO_2, or their combination to affect the carcinogenicity of either urban suspended PM (SPM) (Ito et al., 1997) or diesel exhaust particle (DEP) (Ohyama et al., 1999) extract-coated carbon particles. The former study found that, while exposure to SPM extract-coated carbon particles significantly increased pulmonary endocrine cell (PEC) hyperplasia, coexposure to SO_2, NO_2, or their combination was without additional affect. Also, irrespective of gas coexposure, SPM extract-coated carbon particles demonstrated a few PEC papillomas versus control frequencies of zero.

Using Syrian golden hamsters, Heinrich et al. (1989) investigated whether coexposure to 10-ppm SO_2 and 5-ppm NO_2 for 6 to 8 months (5 days/week, 19 hours/day) could enhance tumorigenesis induced by a single subcutaneous injection of diethylnitrosamine (DEN) during week 2. The combined gas exposure did not affect body weight gain and only minimally shortened survival times. Compared to the DEN groups, serial sacrifices of gas-exposed animals demonstrated progressively increasing numbers of tracheal mucosal cells and aberrant tracheal cell cilia. In the lung, gas-mixture–related effects were largely limited to a progressing type of alveolar lesion that involved a lining of bronchiolar epithelium and the appearance of pigment-containing AM and to a mild, diffuse thickening of the alveolar septa. Exposure to the combined gases by itself did not induce tumors of the upper respiratory tract, nor did it enhance the induction of such tumors by DEN.

In conclusion, the epidemiological studies did not provide any evidence that long-term exposure to SO_2 is associated with an increased risk of lung cancer. The toxicological studies indicate that any potential pathways of SO_x to induce carcinogenesis, cocarcinogenesis, or tumor promotion appear complex and may be highly situational. SO_2 and its derivatives appear unlikely to have significant carcinogenic potential.

3.3.3 Prenatal and Neonatal Outcomes Associated with Long-Term SO_2 Exposure

In recent years, the effects of prenatal and neonatal exposure to air pollution have been examined by several investigators. The most common endpoints studied are low birth weight, preterm delivery, and measures of intrauterine growth. Preterm birth and low birth weight may result in serious long-term health outcomes for the infant. Preterm birth is the leading cause of infant mortality and is a major determinant of a variety of adverse neurodevelopmental outcomes and chronic respiratory effects (Berkowitz and Papiernik, 1993). Low birth weight has also been linked with increased risk of infant mortality and morbidity. Additional studies have examined sudden infant death syndrome (SIDS) and neonatal hospitalizations. Epidemiological studies of ambient SO_2 effects on prenatal and neonatal exposure are summarized in Annex Table AX5-8.

Usually, these studies have used routinely collected air pollution data and birth certificates from a given area for their analysis. In evaluating the results of these studies, the limitations of both fixed site monitoring for routine air pollution and the limitations of data on birth certificates must be kept in mind. The reliability and validity of birth certificate data has

been reviewed (Buescher et al., 1993; Piper et al., 1993) and found to vary in degrees of reliability by specific variables. Variables rated the most reliable included birth weight, maternal age, race, and insurance status. Gestational age, parity, and delivery type (vaginal versus cesarean) were reasonably reliable, while obstetrical complications and personal exposures such as smoking and alcohol consumption, were not.

While most studies analyzed average SO_2 exposure for the whole pregnancy, many also considered exposure during specific trimesters or other time periods. Fetal growth, for example, is much more variable during the third trimester. Thus, studies of fetal growth might anticipate that exposure during the third trimester would have the greatest likelihood of an association. However, growth can also be affected through placentation, which occurs in the first trimester. Similarly, preterm delivery might be expected to be related to exposure early in pregnancy affecting placentation, or through acute effects occurring just prior to delivery.

Epidemiological studies examining the effects of air pollutants on low birth weight are summarized in Figure 3.3-1. Maisonet et al. (2001) examined the association between air pollution and low birth weight in six northeastern cities of the United States, i.e., Boston, MA, Hartford, CT, Philadelphia, PA, Pittsburgh, PA, Springfield, MA, and Washington, DC. The study population consisted of 89,557 singleton, term live births (37 to 44 weeks of gestation) born between January 1994 and December 1996. Low birth weight was classified as <2500 g. This large multicity study observed an association between low birth weight and SO_2 concentrations among whites during each trimester. This association was not robust to the inclusion of all races and ethnicities. A consistent concentration-response relationship was not observed.

An increased risk for low birth weight associated with ambient SO_2 concentrations was reported by Dugandzic et al. (2006) in a large cohort study of 74,284 women with term, singleton births from 1988 through 2000 in Nova Scotia, Canada. The mean 24-h average SO_2 concentration over the study period was 10 ppb (IQR 7). These investigators found that SO_2 concentrations during the first trimester, but not the other two trimesters, were associated with increased risk of low birth weight. The effect estimate was 1.14 (95% CI: 1.04, 1.26) per 5-ppb increase in SO_2 level.

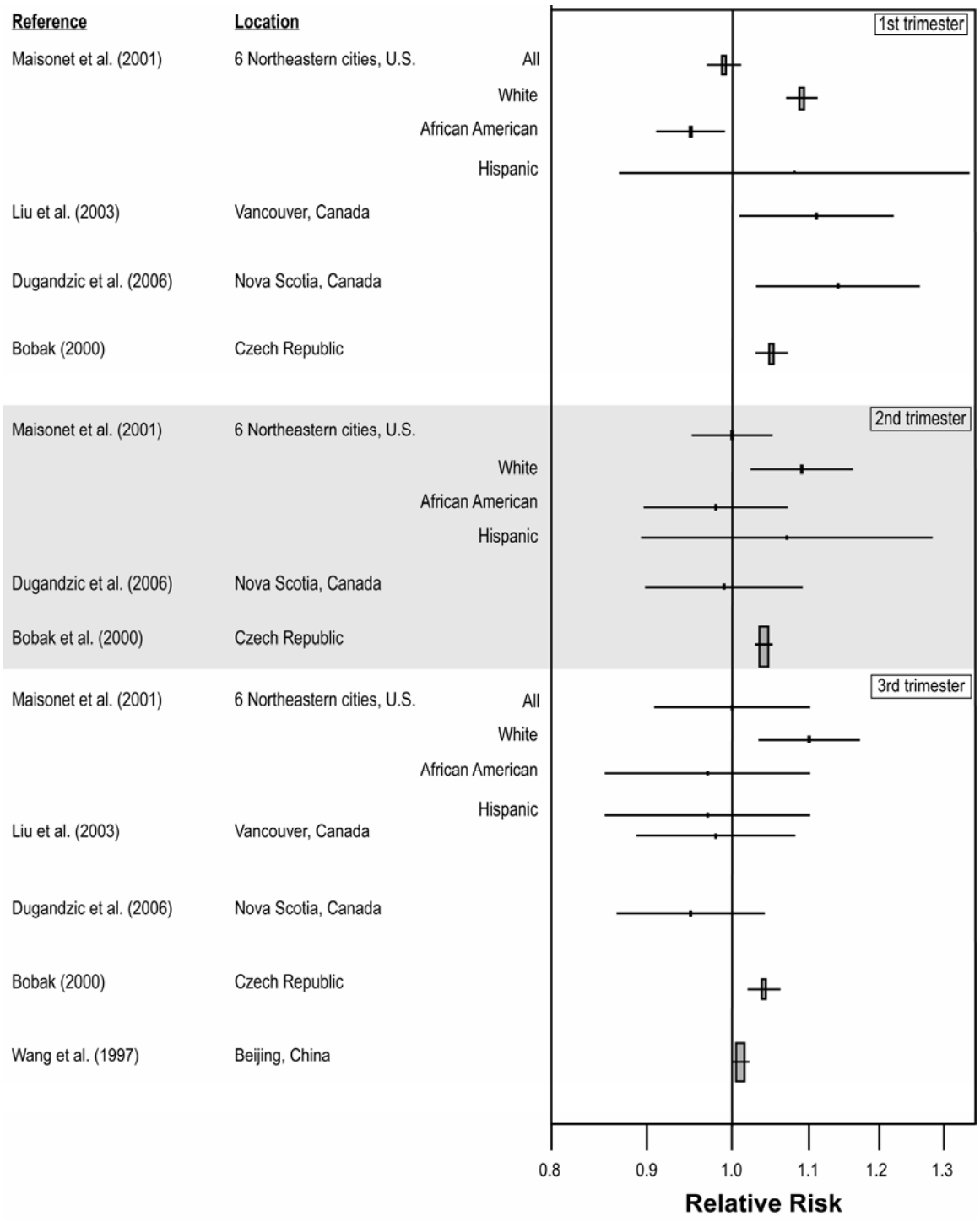

Figure 3.3-1. **Relative risks (95% CI) for low birth weight, grouped by trimester of SO_2 exposure. Risk estimates are standardized per 5-ppb increase in SO_2 concentrations. The size of the box of the central estimate represents the relative weight of that estimate based on the width of the 95% CI.**

Liu et al. (2003) found similar results in a study of pregnancy outcomes and air pollution in Vancouver, Canada. The mean 24-h average SO_2 concentration was 4.9 ppb (IQR 7.7) from 1985 to 1998. Maternal exposure during the first month was associated with an increased risk of low birth weight (OR 1.11 [95% CI: 1.01, 1.22]). Additional studies from the United States, Europe, Latin America, and Asia have reported positive associations between low birth weight and maternal exposure during the first (Bell et al., 2007; Bobak, 2000; Ha et al., 2001; Mohorovic, 2004; Yang et al., 2003b), second (Bobak, 2000; Gouveia et al., 2004; Lee et al., 2003b), and third (Bobak, 2000; Lin et al., 2004b; Wang et al., 1997) trimesters.

Preterm delivery, intrauterine growth retardation (IUGR), and birth defects are additional adverse birth outcomes that have been associated with ambient SO_2 levels. In a time-series analysis using data from four Pennsylvania counties, Sagiv et al. (2005) reported that the mean 6-week SO_2 exposure prior to birth was associated with increased risk of preterm birth with a relative risk (RR) of 1.05 (95% CI: 1.00, 1.10) per 5-ppb increase in SO_2. A 5-ppb increase in SO_2 concentrations 3 days before birth was associated with an RR of 1.02 (95% CI: 0.99, 1.05). The authors discussed two plausible mechanisms for the effects of air pollution on preterm birth: (1) changes in blood viscosity due to inflammation as a result of air pollution (citing Peters et al., 1997), and (2) maternal infection during pregnancy as a consequence of impaired immunity from air pollution exposure. Liu et al. (2003) reported that SO_2 exposure during the last month of pregnancy was associated with preterm birth with an OR of 1.09 (95% CI: 1.01, 1.19) for a 5-ppb increase in SO_2, in Vancouver, Canada. Similar results were found for studies conducted in the Czech Republic (Bobak, 2000), Korea (Leem et al., 2006), and Beijing (Xu et al., 1995).

Liu et al. (2003) further reported that SO_2 exposure during the last month of pregnancy was associated with IUGR (OR = 1.07 [95% CI: 1.01, 1.13]). However, in a later study in the Canadian cities of Calgary, Edmonton, and Montreal, Liu et al. (2006) did not observe associations between maternal exposure to SO_2 and increased risk of IUGR.

Pereira et al. (1998) found a positive association between SO_2 and intrauterine mortality in São Paulo, Brazil, during a 2-year period, though the effect was sensitive to model specifications and did not support a concentration-response relationship. The most robust association was observed for an index of three gaseous pollutants (i.e., NO_2, SO_2, CO) with mortality.

Gilboa et al. (2005) conducted a population-based case-control study to investigate the association between maternal exposure to air pollutants during weeks 3 through 8 of pregnancy and the risk of selected cardiac birth defects and oral clefts in live births and fetal deaths between 1997 and 2000 in seven Texas counties. When the highest quartile of exposure was compared to the lowest, the authors observed a positive association between SO_2 and isolated ventricular septal defects (OR = 2.16 [95% CI: 1.51, 3.09]). This study supports the notion that the developing embryo and growing fetus constitute a subpopulation susceptible to air pollution exposure.

Several studies have examined adverse health outcomes in relation to SO_2 concentrations during the neonatal period. Dales et al. (2006) evaluated hospitalizations for respiratory disorders in neonates <4 weeks of age from hospitals in 11 large Canadian cities during a 15-year study period (population-weighted average 24-h average SO_2 of 4.3 ppb). They observed a 5.5% (95% CI: 2.8, 8.3) increase in respiratory hospitalizations associated with a 10-ppb increase in 24-h average SO_2 concentrations with a 2-day lag. This effect was slightly attenuated after adjusting for PM_{10} and gaseous copollutants. To investigate the influence of ambient SO_2 concentrations on SIDS, Dales et al. (2004) conducted a time-series analysis comparing daily rates of SIDS and daily SO_2 concentrations from 12 large Canadian cities during a 16-year period. The mean 24-h average SO_2 level across the 12 cities was 5.51 ppb (IQR 4.92). There was an 18.0% (95% CI: 4.4, 33.4) increase in SIDS incidence for a 10-ppb increase in 24-h average SO_2 levels. The authors concluded that the effect of SO_2 was independent of sociodemographic factors, temporal trends, and weather.

In summary, studies on birth outcomes have found suggestive positive associations between SO_2 exposure and low birth weight. While most of these studies adequately controlled for maternal education, parity, age, and sex of child, many could not adjust for socioeconomic status, occupational exposures, indoor pollution levels, maternal smoking, alcohol use, or prenatal care. This may make comparisons across studies difficult to interpret. Additional limitations affecting the interpretation of these studies is a lack of evidence for biological plausibility of an effect, inconsistencies across trimesters of pregnancy, and a lack of evidence to evaluate confounding by copollutants. The limited number of studies addressing preterm delivery, IUGR, birth defects, neonatal hospitalizations, and infant mortality make it difficult to draw conclusions regarding these outcomes.

3.4 MORTALITY ASSOCIATED WITH LONG-TERM SO_2 EXPOSURE

At the time of the 1982 AQCD, the available studies on the effects of long-term exposure to SO_2 on mortality were all ecological cross-sectional studies. This study design could not take into consideration such confounders as cigarette smoking, occupational exposures, and social status. In addition, there were questions regarding how representative the aerometric data used were for community exposure. Therefore, it was concluded that the epidemiological studies did not provide valid quantitative data relating respiratory disease or other types of mortality to long-term (annual average) exposures to SO_2 or PM.

The 1986 Secondary Addendum reviewed more studies of this type, with information on more detailed components of PM (inhalable and fine particles and particulate SO_4^{2-}). While some studies suggested importance of the size of PM, the fundamental problem of the study design made it difficult to interpret the risk estimates. The 1986 Secondary Addendum also reviewed a Japanese study in which the death rates from asthma and chronic bronchitis in a highly polluted section of Yokkaichi, an industrial city with large SO_2 emissions from the largest oil-fired power plant in Japan, were compared with those in a less polluted area of the same city. SO levels in the polluted harbor area ranged from around 1.0 to 2.0 mg/day (annual average) during 1964 through 1972 and then steadily declined to less than 0.5 mg/day in 1982. This is in contrast to levels consistently <0.3 mg/day in the low pollution areas throughout 1967 through 1982. Annual average levels for other pollutants (i.e., NO_2, TSP, oxidants) monitored in the high pollution area were consistently low from 1974 through 1982. The results indicated elevated rates of chronic bronchitis mortality in the highly polluted area compared to the less polluted area, but the 1986 Secondary Addendum could not conclude that this was due to SO_2 alone, because SO_4^{2-} or other sulfur agents such as H_2SO_4 could have been responsible.

Several, more recent studies have examined long-term exposure effects of air pollution, including SO_2, on mortality. These studies are summarized in Annex Table AX5-9. As with short-term exposure studies, the focus of most of these studies was mainly on PM though some focused on traffic-related air pollution. They all used Cox-proportional hazards regression models with adjustment for potential confounders. The designs of these studies are epidemiologically better than earlier cross-sectional studies in that the outcome and most of the potential confounders (e.g., smoking history, occupational exposure) are measured on an

individual basis. However, the geographic scale and method for exposure estimates varied across these studies.

3.4.1 Associations of Mortality and Long-Term SO_2 Exposure in Key Studies

3.4.1.1 U.S. Cohort Studies

Harvard Six Cities Studies

Dockery et al. (1993) conducted a prospective cohort study to study the effects of air pollution with the main focus on PM components in six U.S. cities. These cities were chosen based on the levels of air pollution, with Portage, WI and Topeka, KS representing the less polluted cities and Steubenville, OH representing the most polluted city. Mean SO_2 levels ranged from 1.6 ppb in Topeka to 24.0 ppb in Steubenville from 1977 to 1985. Cox proportional hazards regression was conducted with data from a 14- to 16-year follow-up of 8,111 adults in the six cities. Dockery et al. reported that lung cancer and cardiopulmonary mortality were more strongly associated with the levels of inhalable and fine PM and SO_4^{2-} particles than with the levels of TSP, SO_2, NO_2, or acidity of the aerosol.

Krewski et al. (2000) conducted a sensitivity analysis of the Harvard Six Cities study and examined associations between gaseous pollutants (i.e., O_3, NO_2, SO_2, and CO) and mortality. 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) and cardiopulmonary (1.05 [95% CI: 1.00, 1.10]) deaths, but in this dataset SO_2 was highly correlated with $PM_{2.5}$ (r = 0.85), SO_4^{2-} (r = 0.85), and NO_2 (r = 0.84).

American Cancer Society Cohort Studies

Pope et al. (1995) investigated associations between long-term exposure to PM and the mortality outcomes in the American Cancer Society (ACS) 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. $PM_{2.5}$ and SO_4^{2-} were associated with total, cardiopulmonary, and lung cancer mortality, but not with mortality for all other causes. Gaseous pollutants were not analyzed in the 1995 Pope et al. study. Krewski and co-investigators

(Krewski et al., 2000; Jerrett et al., 2003) conducted an extensive sensitivity analysis of the Pope et al. (1995) ACS data, augmented with additional gaseous pollutants data. The mean SO_2 concentrations were 7.18 ppb in the warm season (April to September) and 11.24 ppb in the cool season (October to March). Among the gaseous pollutants examined, only SO_2 showed positive associations with mortality. 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. Analysis using SO_2 measured in different seasons produced a somewhat higher estimate for the warm season than that for the cool season (7% compared to 5% per 5-ppb increase). Although the subjects in the ACS cohort came from all regions of the United States, the majority of the cities fall in the eastern United States, where both SO_2 and SO_4^{2-} tend to be higher. $PM_{2.5}$ levels are also higher in the East. To address the influence of these spatial patterns, which may confound associations between mortality and these pollutants, Krewski et al. (2000) conducted extensive two-stage regression modeling. In these models, the association between SO_2 and mortality persisted after adjusting for SO_4^{2-}, $PM_{2.5}$, and other variables. For example, in the spatial filtering model (which resulted in the largest reduction of SO_2 risk estimate when SO_4^{2-} was included), the SO_2 total mortality RR 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 SO_4^{2-} in the two-pollutant model. The risk estimates for $PM_{2.5}$ and SO_4^{2-} were diminished when SO_2 was included in the models. The results also showed that SO_2 risk estimates were generally insensitive to adjustment for spatial correlation. Thus, these results suggest that the association between SO_2 and mortality may be confounded with PM, but the association cannot be accounted for by $PM_{2.5}$ or SO_4^{2-} alone. Krewski et al. (2000) noted that their reanalysis of the ACS and Harvard Six Cities studies suggested that mortality might be attributed to more than one component of the complex mixture of ambient air pollutants in urban areas in the United States.

The original Pope et al. (1995) study and the Krewski et al. (2000) reanalysis both used the air pollution exposure estimates that are based on the average over the Metropolitan Statistical Area (MSA), which consists of multiple counties. To investigate the effects of geographic scale over which the air pollution exposures are averaged, Willis et al. (2003) reanalyzed the ACS cohort data using the exposure estimates averaged over the county scale, and compared the results with those based on the MSA-scale average exposure. Less than half of the cohort used in the MSA-based study was used in the county-scale based analysis, because of the

limited availability of SO_4^{2-} monitors and because of the loss of subjects with the use of five-digit ZIP codes. The mean (9.3 ppb versus 10.7 ppb) and range (0.0 to 29.3 ppb versus 0.0 to 27.2 ppb) of the MSA- and county-level SO_2 data sets were similar. In the analysis comparing the two-pollutant model with SO_4^{2-} and SO_2, they found that the inclusion of SO_2 reduced SO_4^{2-} risk estimates substantially (>25%) in the MSA-scale model but not substantially (<25%) in the county-scale model. In the MSA-level analysis (with 113 MSAs), the SO_2 RR estimate was 1.04 (95% CI: 1.02, 1.06) per 5-ppb increase, with SO_4^{2-} in the model. In the county-level analysis (91 counties) with SO_4^{2-} in the model, the corresponding estimate was smaller (1.02 [95% CI: 1.00, 1.05]). It should also be noted that the correlation between covariates are different between the MSA-level data and county-level data. The correlation between SO_2 and SO_4^{2-} was 0.48 in the MSA-level data, but it was 0.56 in the county-level data. The correlation between poverty rate and SO_2 was −0.16 in the MSA-level data, but it was 0.15 in the county-level data. Thus, the extent of confounding between SO_2 and PM components as well as among other covariates in the model can be affected by the geographic scale of aggregation of exposure estimates. It is not clear, however, if the smaller geographic scale increases or decreases exposure characterization error for SO_2, because a certain extent of smoothing (averaging) over distance may reduce very local concentration peaks that are not relevant to the city-wide population.

Pope et al. (2002) extended analysis of the ACS cohort with double the follow-up time (to 1998) and triple the number of deaths compared to the original Pope et al. (1995) study. In addition to $PM_{2.5}$, all the gaseous pollutants were retrieved for the extended period and analyzed for their associations with death outcomes. As in the 1995 analysis, the air pollution exposure estimates were based on the MSA-level averages. $PM_{2.5}$ was associated with total, cardiopulmonary, and 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. The SO_2 RR estimate for total mortality was 1.03 (95% CI: 1.02, 1.05) per 5-ppb increase (1982 to 1998 average). The association of SO_2 with mortality for all other causes (SO_4^{2-} also showed this pattern) makes it difficult to interpret the risk estimates. The sensitivity analysis by Krewski et al. (2000) did not provide SO_2 risk estimates for all other causes, and it is not clear whether this pattern is found in other data sets.

Women's Health Initiative Cohort Study

Miller et al. (2007) studied 65,893 postmenopausal women between the ages of 50 and 79 years without previous CVD 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 air pollutant concentrations. Subjects' 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, which allowed estimation of effects due to both within-city and between-city variation of air pollution (this was only done for $PM_{2.5}$).

A total of 1,816 women had one or more fatal or nonfatal cardiovascular events, including 261 deaths from cardiovascular causes. Hazard ratios (HR) for the first cardiovascular event were estimated. The results for models that only included subjects with non-missing exposure data for all pollutants (n = 28,402 subjects, resulting in 879 CVD events) are described here. In the single-pollutant models, $PM_{2.5}$ showed the strongest associations with the cardiovascular events by far among the pollutants (HR = 1.24 [95% CI: 1.04, 1.48] per 10-$\mu g/m^3$ increase in annual average), followed by SO_2 (1.07 [95% CI: 0.95, 1.20] per 5-ppb increase in the annual average). In the multipollutant model where all the pollutants (i.e., $PM_{2.5}$, $PM_{10-2.5}$, CO, SO_2, NO_2, O_3) were included in the model, the $PM_{2.5}$ association with overall cadiovascular events was even stronger (1.53 [95% CI: 1.21, 1.94]). The association with SO_2 also became stronger (1.13 [95% CI: 0.98, 1.30]). Correlations among these pollutants were not described and, therefore, the extent of confounding among these pollutants in these associations could not be examined, but $PM_{2.5}$ clearly was the best predictor of cardiovascular events. Miller et al. (2007) did not report the associations between SO_2 with cardiovascular mortality. However, because the $PM_{2.5}$ HR for cardiovascular deaths was even larger than that for the overall cardiovascular events, it also seems possible that this may be the case for SO_2, though the concern for potential confounding remains.

The EPRI-Washington University Veterans' Cohort Mortality Studies

Lipfert et al. (2000) conducted an analysis of a national cohort of ~70,000 male U.S. military veterans who were diagnosed as hypertensive in the mid 1970s and were followed up for about 21 years (up to 1996). This cohort was 35% black and 57% were current smokers (81% of the cohort had been smokers at one time). $PM_{2.5}$, PM_{10}, $PM_{10-2.5}$, TSP, SO_4^{2-}, CO, O_3, NO_2, SO_2, and lead were examined in this analysis. No mean or median level of SO_2 was reported. The

county of residence at the time of entry to the study was used to estimate exposures. Four exposure periods (1960-1974, 1975-1981, 1982-1988, and 1989-1996) were defined, and deaths during each of the three most recent exposure periods were considered. The results for SO_2 were presented only qualitatively as part of their preliminary screening regression results. Lipfert et al. (2000) noted that lead and SO_2 were consistently negative and were not considered further. They also noted that the pollution risk estimates were sensitive to the regression model specification, exposure periods, and the inclusion of ecological and individual variables. The authors reported that indications of concurrent mortality risks were found for NO_2 and peak O_3.

Lipfert et al. (2006a) examined associations between traffic density and mortality in the same cohort, whose follow-up period was extended to 2001. As in their 2000 study, four exposure periods were considered but including more recent years. The 95th percentiles of daily average in each of the exposure periods were considered for SO_2. 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 only weakly correlated with SO_2 ($r = 0.32$) and $PM_{2.5}$ ($r = 0.50$) in this data set. For the 1997-2001 data period (apparently this was the only period in which SO_2 was considered), the estimated mortality relative risk for SO_2 was 0.99 (95%CI: 0.97, 1.01) per 5-ppb increase in a single-pollutant model. The two-pollutant model with the traffic density variable did not affect SO_2 risk estimate. Interestingly, as the investigators pointed out, the risk estimates due to traffic density did not vary appreciably across these four periods. They speculated that other environmental factors such as tire particles, traffic noise, and spatial gradients in socioeconomic status might have been involved.

Lipfert et al. (2006b) further extended analysis of the veterans' cohort data to include the EPA's Speciation Trends Network (STN) data, which collected chemical components of $PM_{2.5}$. They analyzed the STN data for year 2002, again using county-level averages. $PM_{2.5}$ and gaseous pollutants data for 1999 through 2001 were also analyzed. As in the previous Lipfert et al. (2006a) study, traffic density was the most important predictor of mortality, but associations were also seen for elemental carbon, vanadium, nickel, and nitrate. O_3, NO_2, and PM_{10} also showed positive but weaker associations. The risk estimate for SO_2 was essentially the same as that reported in the Lipfert et al. (2006a) analysis (RR = 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.

Seventh-day Adventist Study

Abbey et al. (1999) investigated associations between long-term ambient concentrations of PM_{10}, O_3, NO_2, SO_2, and CO (1973 through 1992) and mortality (1977 through 1992) in a cohort of 6,338 nonsmoking California Seventh-day Adventists. Monthly indices of ambient air pollutant concentrations at 348 monitoring stations throughout California were interpolated to ZIP code centroids according to home or work location histories of study participants, cumulated, and then averaged over time. They reported associations between PM_{10} and total mortality for males and nonmalignant respiratory mortality for both sexes. SO_2 was 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, 18 for male) and, therefore, it is difficult to interpret these estimates.

3.4.1.2 European Cohort Studies

Nafstad et al. (2004) investigated the association between mortality and long-term exposure to air pollution exposure in a cohort of Norwegian men followed from 1972-1973 through 1998. Data from 16,209 men (aged 0 to 49 years) living in Oslo, Norway, in 1972-1973 were linked with data from the Norwegian Death Register and with estimates of the average annual air pollution levels at the participants' home addresses. PM was not considered in this study because measurement methods changed during the study period. Exposure estimates for nitrogen oxides (NO_x) and SO_2 were constructed using models based on subject addresses, emission data for industry, heating, and traffic, and measured concentrations. While NO_x was associated with total, respiratory, lung cancer, and ischemic heart disease deaths, SO_2 did not show any associations with mortality. The authors noted that the SO_2 levels were reduced by a factor of 7 during the study period (from 5.6 ppb in 1974 to 0.8 ppb in 1995), whereas NO_x did not show any clear downward trend. The very low levels of SO_2 may be related to the lack of association in this data set.

Filleul et al. (2005) investigated long-term effects of air pollution on mortality in 14,284 adults who resided in 24 areas from seven French cities when enrolled in the PAARC (Air Pollution and Chronic Respiratory Diseases) survey in 1974. Daily measurements of SO_2, TSP, BS, NO_2, and NO were made in the 24 areas for 3 years (1974 through 1976). Models were run

before and after exclusion of six area monitors influenced by local traffic as determined by a $NO:NO_2$ ratio of > 3. Before exclusion of the six areas, none of the air pollutants was associated with mortality outcomes. After exclusion of these areas, analyses showed associations between total mortality and TSP, BS, NO_2, and NO but not SO_2 (1.01 [95% CI: 0.97, 1.06] per 5-ppb multiyear average) or acidimetric measurements. 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 SO_2 levels in these French cities declined markedly between the 1974 through 1976 period and the 1990 through 1997 period by a factor of 2 to 3, depending on the city. The changes in air pollution levels over the study period complicate interpretation of reported risk estimates.

3.4.1.3 Cross-Sectional Analysis Using Small Geographic Scale

Elliott et al. (2007) examined associations of BS and SO_2 with mortality in Great Britain using a cross-sectional analysis. However, unlike the earlier ecological cross-sectional mortality analyses in the United States in which mortality rates and air pollution levels were compared using large geographic boundaries (i.e., MSAs or counties), in the Elliot et al. analysis, the mortality rates and air pollution were compared using a much smaller geographic unit, the electoral ward, with a mean area of 7.4 km^2 and a mean population of 5,301 per electoral ward. Death rates were computed for four successive 4-year periods from 1982 to 1994 and associated with 4-year exposure periods starting in 1966 to 1970 and ending in 1990 to 1994. The number of deaths from all causes in the 10,520 wards from 1982 to 1994 was 420,776. Of note, SO_2 levels declined from 41.4 ppb in the 1966 to 1970 period to 12.2 ppb in 1990 to 1994. This type of analysis does not allow adjustments for individual risk factors, but the study did adjust for socioeconomic status data available for each ward from the 1991 census. Social deprivation and air pollution were more highly correlated in the earlier exposure windows. They observed associations for both BS and SO_2 and mortality outcomes. The estimated effects were stronger for respiratory illness than other causes of mortality for the most recent exposure period and most recent mortality period (when pollution levels were lower). The adjustment for social deprivation reduced the risk estimates for both pollutants. The adjusted mortality 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 causes, 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 effect

estimates for the most recent mortality period using the most recent exposure windows were larger. Simultaneous inclusion of BS and SO_2 reduced risk estimates for BS but not SO_2. Elliott et al. (2007) noted that the results were consistent with those reported in the Krewski et al. (2000) reanalysis of the ACS study. This analysis was ecological, but the exposure estimates in the smaller area compared to that in the U.S. cohort studies may have resulted in less exposure misclassification error, and the large underlying population appears to be reflected in the narrow confidence bands of risk estimates. The results from this study suggest an association between long-term exposures (especially in recent years) to SO_2 and mortality.

3.4.1.4 Summary of Risk Estimates from Long-Term Exposure Studies

Figure 3.4-1 summarizes the SO_2 risk estimates per 5-ppb increase in the annual (or longer period) average SO_2 for total mortality in the studies reviewed above. The overall range of RRs spans 0.97 to 1.07, but considering the precision of estimates (width of confidence bands), relevance to the U.S. setting, representativeness of study population, and the extent of sensitivity analyses conducted of the data, the analyses of the Harvard Six Cities and the ACS cohort data likely provide the risk estimates that are most useful for evaluating possible health effects in the United States. This narrows the range of RRs to 1.02 to 1.07. Note that each of the U.S. cohort data has its own advantages and limitations. The Harvard Six Cities data have a small number of exposure estimates, but the location of the monitors were chosen carefully for epidemiological purposes. The ACS cohort had far more subjects, but the population was more highly educated than the representative U.S. population. Since educational status appeared to be an important effect modifier of air pollution effects in both studies, the overall effect estimate for the ACS cohort may underestimate that for the more general population.

Another important issue that these studies could not resolve was the possible confounding among PM indices and SO_2. The possibility that the observed effects may not be due to SO_2, but other constituents that come from the same source as SO_2, cannot be ruled out. In these long-term exposure studies, the strong correlation observed between SO_2 and PM is mainly because both SO_2, which tends to be locally impacted, and SO_4^{2-}, which is regionally distributed, tend to be higher in the eastern United States. Despite the geographic variation in the studies, most concentrated on major cities in the eastern United States, even the nationwide ACS cohort.

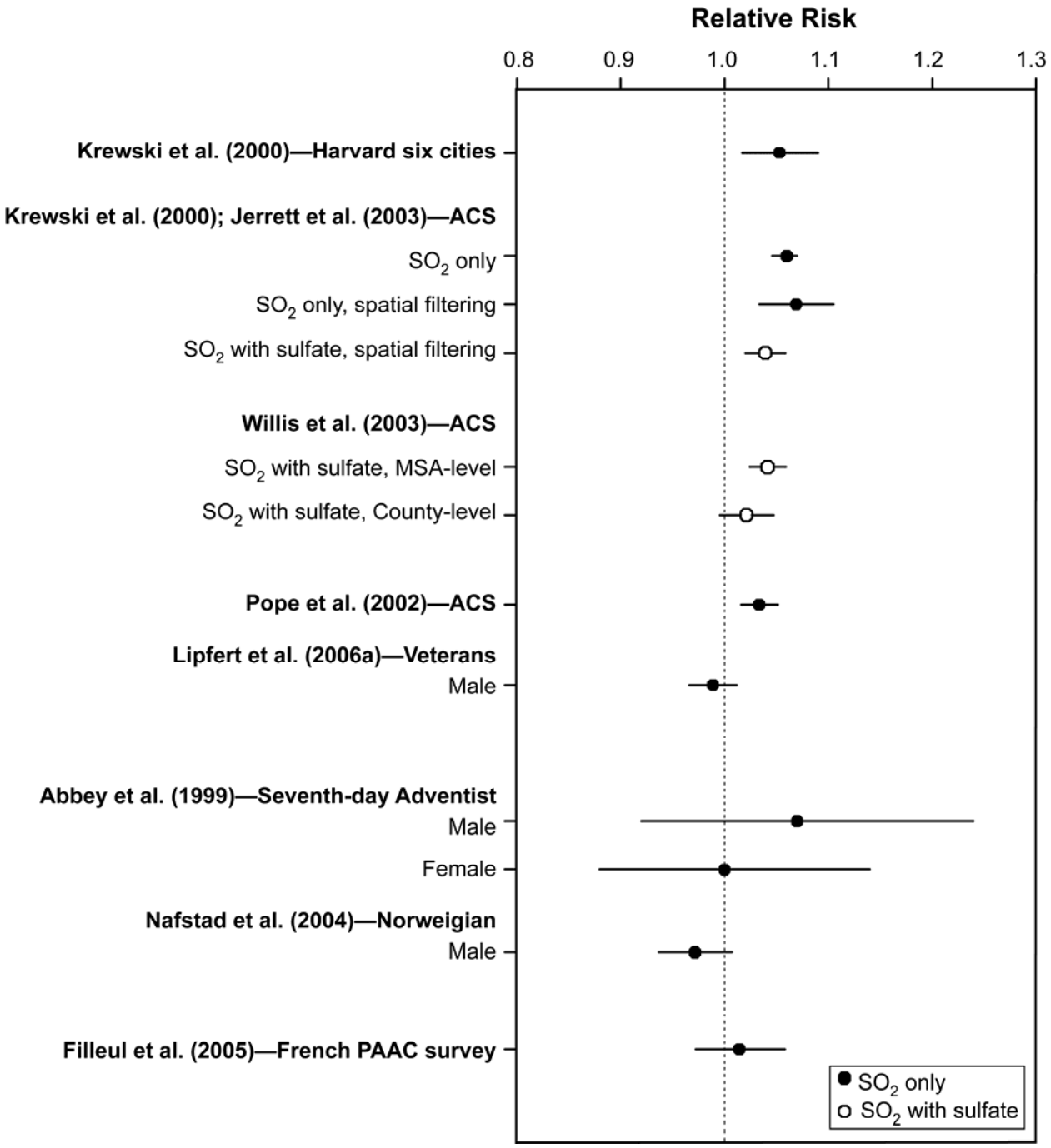

Figure 3.4-1. **Total SO_2-mortality relative risk estimates (95% CI) from longitudinal cohort studies. Risk estimates are standardized per 5-ppb increase in SO_2 concentrations. The exposure estimates for the ACS analyses in the Krewski et al. (2000) and Pope et al. (2002) studies are based on MSA-level averaging; Lipfert et al. (2006a) used county-level averaging.**

Therefore, even with sophisticated spatial modeling, separating possible confounding of SO_2 effects by PM is challenging.

Finally, the extent of uncertainty related to the geographic scale used to aggregate air pollution exposure estimates is not clear at this point. Willis et al. (2003) showed that the SO_2 risk estimate based on the county-level analysis (1.02) was smaller than that from the MSA-level analysis (1.04). For SO_4^{2-}, the opposite pattern was found. Thus, the impact of the geographic scale of analysis may also depend on the spatial distribution of air pollutants. These complications must be considered when interpretating SO_2 risk estimates.

3.4.2 Summary of Effects of Long-Term SO_2 Exposure on Mortality

The ecological cross-sectional studies examined in the 1982 AQCD and 1986 Secondary Addendum found suggestive relationships between long-term exposure to SO_2 and mortality. However, there were concerns as to whether the observed association was due to SO_2 alone, because SO_4^{2-} or other sulfur agents such as H_2SO_4 could have been responsible. In the more recent longitudinal cohort studies, once again, positive associations have been observed between long-term exposure to SO_2 and mortality; however, several issues affect the interpretation of these results.

In the limited number of available studies, the risk estimates for total mortality that are most relevant to the current U.S. population ranged from 2 to 7% per 5-ppb increase in annual or longer averages of SO_2. However, it should also be noted that several other U.S. and European studies did not observe an association between long-term exposure to SO_2 and mortality. The geographic scale of analysis appears to affect SO_2 risk estimates and also likely affects exposure error in the analysis. In a reanalysis of the ACS data, the county-level analysis showed a smaller SO_2 risk estimate than MSA-level analysis. The cross-sectional analysis in Great Britain using small-scale electoral wards observed a risk estimate similar to the lower end of the range of risk estimates for all-cause mortality from U.S. cohort studies, though it is not clear if the risk estimates from this cross-sectional study are directly comparable to those from cohort studies.

In the long-term studies of the ACS cohort, the peculiar spatial pattern of the concentration of major cities and SO_2 sources in the eastern United States dominated the overall mortality associations with $PM_{2.5}$, SO_4^{2-}, and SO_2, making it difficult to separate out the potential confounding or mixture effects. Future and on-going studies that take into

consideration within- versus between-city variation of these air pollutants may help resolve this issue.

Overall, the results from two major U.S. epidemiological studies suggest an association between long-term exposure to SO_2 or sulfur-containing particulate air pollution. However, it should be noted that authors of the reanalyses of these studies concluded that in the absence of a plausible toxicological mechanism by which SO_2 could lead to increased mortality suggested that SO_2 might be acting as a marker for other mortality-associated pollutants (Krewski et al., 2000). The inability to distinguish potential confounding by copollutants, uncertainties regarding the geographic scale of analysis and copollutant confounding limit the interpretation of a causal relationship.

4. PUBLIC HEALTH IMPACT

This chapter addresses several issues relating to the broader public health impact from exposure to ambient sulfur oxides (SO_x). First, the shape of the concentration-response relationship for sulfur dioxide (SO_2) is discussed and the evidence for a threshold value for health effects is evaluated. The next section identifies characteristics of subpopulations which may experience increased risks from SO_2 exposures, through either enhanced susceptibility (e.g., as a result of age, pre-existing disease, genetic factors) and/or differential vulnerability associated with increased exposure owing to close proximity to sources, for example. The final section defines adverse health effects associated with SO_2 and classifies them according to severity for individuals with impaired respiratory systems. The prevalence of such respiratory disorders in the U.S. population is considered to assess the impact of ambient SO_2 exposure on public health.

4.1 ASSESSMENT OF CONCENTRATION-RESPONSE FUNCTION AND POTENTIAL THRESHOLDS

An important consideration in characterizing the public health impacts associated with SO_2 exposure is whether the concentration-response relationship is linear across the full concentration range that is encountered or if there are concentration ranges where there are departures from linearity (i.e., nonlinearity). Of particular interest is the shape of the concentration-response curve at and below the level of the current SO_2 NAAQS level of a 24-h average level of 0.14 ppm or the annual average of 0.03 ppm.

Identifying possible "thresholds" in air pollution epidemiological studies is challenging. A threshold in this case would be defined as the level of SO_2 that must be exceeded to elicit a health response. Low data density in the lower concentration range, measurement error in the response, exposure measurement error, and a shallow slope near the threshold are some of the error sources that complicate determining the shape of the concentration-response curve. Biological characteristics that tend to linearize concentration-response relationships include individual differences in susceptibility to air pollution health effects additivity of SO_2-induced effects to a naturally occurring background level and additivity of effects from other pollutant

exposures. With consideration of these limitations, epidemiological and human clinical studies that examined the shape of the concentration-response function for different averaging times or exposure durations are presented below. The discussion focuses on respiratory morbidity effects associated with short-term exposure to SO_2, for which the strongest causal evidence exists.

Evidence from human clinical studies provides insights into the discussion of the concentration-response function and possible thresholds of SO_2 health effects. In human clinical studies, significant effects have been observed at the lowest levels tested (i.e., 0.2 to 0.25 ppm, 5- to 15-min exposures) in some sensitive individuals; however, there was great interindividual variability in the observed SO_2-related responses. Human clinical studies largely examined the effects of peak exposures ($\leq$1 h, typically 5 or 15 min) to SO_2 on respiratory health. The majority of these studies have involved short-term exposures of asthmatic adults to varying concentrations of SO_2 while they perform light to heavy levels of exercise. Sheppard et al. (1981) reported a significant SO_2-induced increase in specific airways resistance (sRaw) compared to filtered-air exposures among asthmatic adults following 10-min exposures to SO_2 with moderate exercise at concentrations as low as 0.25 ppm. Doubling the exposure concentration of SO_2 (0.5 ppm) increased sRaw by approximately 75% compared to the average value of sRaw following exposure to 0.25-ppm SO_2. In a similar study, Linn et al. (1982) found no significant SO_2-attributable increase in sRaw following 1-h exposures to 0.25- and 0.5-ppm SO_2 among asthmatics engaged in 10-min intervals of moderate levels of exercise. The authors suggested that the apparent contrast between their findings and those of Sheppard et al. (1981) may be explained by differences in the exposure methods used. Linn et al. (1982) conducted exposures in a chamber, allowing normal oronasal breathing, while Sheppard et al. (1981) conducted exposures through a mouthpiece, which likely resulted in a relative increase of pulmonary SO_2 uptake.

Linn et al. (1983) later evaluated the concentration-response relationship between SO_2 and respiratory effects following 5-min exposures to 0-, 0.2-, 0.4-, and 0.6-ppm SO_2 during heavy exercise (minute ventilation [$\dot{V}_E$] ~ 48 L/min). The results appeared to demonstrate an increase in sRaw attributable to increasing SO_2 concentrations. However, only exposures to 0.4 and 0.6 ppm were found to significantly differ from the control (0-ppm SO_2). Schachter et al. (1984) found the SO_2-induced respiratory response to be highly variable among asthmatic adults. These investigators exposed asthmatic and healthy, non-asthmatic subjects to 0-, 0.25-,

0.5-, 0.75-, and 1.0-ppm SO_2 for 10 min during moderate levels of exercise. No SO_2-associated respiratory effects were observed in the healthy, non-asthmatics at any of the exposure concentrations. While some asthmatic subjects exhibited a decrease in forced expiratory volume in 1 s (FEV_1) beginning at concentrations as low as 0.25 ppm, a consistent and significant reduction in FEV_1 compared to baseline was not observed at levels <0.75-ppm SO_2. Finally, in a study involving SO_2-sensitive asthmatics, Gong et al. (1995) observed a linear relationship between SO_2 concentration (0-, 0.5-, and 1.0-ppm) and both lung function (decrease in FEV_1, and increase in sRaw) and respiratory symptoms. The evidence from human clinical studies demonstrates consistent SO_2-induced respiratory effects following 5-to 15-min exposures of SO_2 at levels between 0.5 and 1.0 ppm, with weaker evidence of effects at concentrations as low as 0.25 ppm in some sensitive asthmatics.

Epidemiological studies have examined the concentration-response relationship for SO_2 using various statistical methods, including the comparison of effect estimates in increasing quartiles or quintiles, plotting the risk observed against increasing SO_2 concentrations, and using nonparametric smoothed curves to assess the nonlinearity of the SO_2-effect relationship. Most of the epidemiological studies that examined the concentration-response function between SO_2 exposure and respiratory morbidity observed that the relationship was linear across the entire concentration range, as discussed below.

Only one epidemiological study investigated the concentration-response function of peak SO_2 exposures. The association between asthma hospitalizations and ambient 1-h maximum (1-h max) SO_2 concentrations was examined in a case-control study of children in Bronx County, NY (Lin et al., 2004). The 1-h max concentration ranged from 2.9 to 66.4 ppb. Lin et al. categorized 1-h max SO_2 concentrations and estimated odds ratios (ORs) for each category using the lowest exposure group as the reference (2.9 to 9.2 ppb). They observed an increasing linear trend across the range of concentrations, suggesting that there was no threshold in the observed association between asthma hospitalizations and 1-h max SO_2 concentrations.

Most epidemiological studies investigating the concentration-response function examined the effects of short-term 24-h average exposures to SO_2. A study by Jaffe et al. (2003) examined the association between SO_2 and emergency department (ED) visits for asthma in three cities in Ohio, i.e., Cincinnati, Cleveland, and Columbus. The mean 24-h average SO_2 concentrations were 14 ppb (range: 1, 50) in Cincinnati, 15 ppb (range: 1, 64) in Cleveland, and 4 ppb (range:

0, 22) in Columbus. Significant associations were observed only in Cincinnati using the Poisson regression analysis. To examine the concentration-response function, they also conducted quintile analyses. In Cincinnati, an increasing linear trend in risk was observed across the range of concentrations.

Wong et al. (2002; using Generalized Additive Model(s) (GAM) with default convergence criteria) observed that ambient SO_2 concentrations were associated with hospital admissions for respiratory causes in adults aged 65+ years in Hong Kong (mean 24-h average SO_2 of 7 ppb [range: 0, 34]), but not London (mean 24-h average SO_2 of 9 ppb [range: 2, 43]). A plot of risk against 24-h average SO_2 concentrations was constructed to examine the concentration-response relationship in these cities. In general, a linear relationship between risk of respiratory hospitalizations and SO_2 was observed across the range of SO_2 concentrations in Hong Kong.

Burnett et al. (1997a,b) examined the relationship between adjusted hospital admission rates for respiratory diseases and ambient SO_2 concentrations for nonlinearity. A nonparametric smoothed curve using locally estimated smoothing splines (LOESS) was applied in the Toronto study (mean 1-h max SO_2 of 7.9 ppb [range: 0, 26]), while cubic polynomials and quadratic polynomials were fitted to the data in the 16 Canadian cities study (mean 1-h max SO_2 of 14.4 ppb [90th percentile: 97]. In no case did the results suggest that the association between respiratory hospitalizations and SO_2 deviated from linearity.

Additional European studies by Atkinson et al. (1999a), Hajat et al. (1999) and Hajat et al. (2002; using GAM with default convergence criteria) also did not find a threshold in the response. In Atkinson et al. (1999a), the bubble plot indicated that the relationship between hospital admission for respiratory causes and SO_2 concentrations was approximately linear. Hajat et al. (1999, 2002) reported a generally linear association between SO_2 concentrations and general practitioner visits for lower and upper respiratory conditions, using a bubble plot and a concentration-response plot across the range of SO_2 concentrations.

However, some studies did report a nonlinear relationship between SO_2 and respiratory health effects. The Harvard Six Cities study by Schwartz et al. (1994) examined the effects of summertime air pollution on the respiratory health of 1,844 schoolchildren. The median 24-h average SO_2 concentration during the study period was 4.1 ppb (10th–90th percentile: 0.8, 17.9, maximum 81.9). While SO_2 concentrations were found to be associated with increased cough

incidence and lower respiratory symptoms, the relationship was nonlinear. A figure plotting the relative odds of incidence of lower respiratory symptoms against SO_2 concentrations lagged 1 day indicated that no statistically significant increase in the incidence of lower respiratory symptoms was seen until concentrations exceeded a 24-h average SO_2 of 22 ppb (see Figure 3.1-2 in Section 3.1), though an increasing trend was observed at concentrations as low as a 24-h average SO_2 of 10 ppb.

Using time-series data, Ponce de Leon et al. (1996) studied the association between hospitalizations for respiratory causes and ambient SO_2 concentrations in London. The mean 24-h average SO_2 concentration was 32.2 ppb (5th–95th percentile: 6, 21). Bubble plots of adjusted residuals of log admission counts sorted by SO_2 level indicated that a weak relationship with SO_2 was only observable at 24-h average SO_2 concentrations above 23 ppb. In both this study and the study by Schwartz et al. (1994), a statistically significant increased risk was observable only at 24-h average SO_2 concentrations that were above the 90th percentile. These possible threshold values are dependent on only a few influential observations; so the results should be viewed with caution.

As discussed earlier in this section, many factors may obscure the presence of thresholds in epidemiological studies at the population level. Using fine particulate matter ($PM_{2.5}$) as an example, Brauer et al. (2002) examined the relationship between ambient concentrations and mortality risk in a simulated population with specified common individual threshold levels. They found that no population threshold was detectable when a low threshold level was specified. Even at high-specified individual threshold levels, the apparent threshold at the population level was much lower than specified. Brauer et al. (2002) concluded that the use of surrogate measures of exposure (i.e., those from centrally located ambient monitors) that were not highly correlated with personal exposures obscured the presence of thresholds in epidemiological studies at the population level even if a common threshold exists for individuals within the population.

The wide interindividual variability in sensitivity to SO_2 exposure further hinders the ability to find a threshold level in population studies. Human clinical studies have shown that asthmatics experience greater increases in sRaw following peak SO_2 exposures compared to healthy individuals (Linn et al., 1987). Amongst asthmatics, interindividual differences in

response also have been noted, with some asthmatics experiencing SO_2-related effects at much lower levels than others (Horstman et al., 1986).

Another factor that complicates the identification of a possible threshold of effects is that currently deployed ambient monitors may be inadequate for accurate and precise measurements at lower 24-h average SO_2 levels. Ambient concentrations of SO_2 have been declining since the 1980s and are now at or very near the limit of detection of the ambient monitors in the regulatory network. The mean 24-h average SO_2 concentration across the metropolitan statistical areas (MSAs) from 2003 through 2005 was 4 ppb (5th–95th percentile: 1, 13). Thus, there is greater uncertainty at the lower concentration range compared to the higher concentrations, which likely limits the ability to detect a threshold.

In conclusion, evidence from human clinical studies indicated wide interindividual variability in response to SO_2 exposures, with peak (5 to 10 min) exposures at levels as low as 0.25 ppm eliciting respiratory responses in some asthmatic individuals. Several epidemiological studies that examined the concentration-response function between short-term (24-h average) exposure to SO_2 and respiratory morbidity observed that the relationship was linear across the entire concentration range, suggesting a lack of a threshold in effect. However, given the various limitations in observing a possible threshold in population studies, the lack of evidence does not necessarily indicate that there is indeed no threshold in SO_2 health effects. Two epidemiological studies did report a possible threshold level of 22 to 23 ppb (24-h average) at which no statistically significant SO_2-related respiratory health effect was observed. However, as these observations were based on only a few influential data points (24-h average SO_2 concentrations above the 90th percentile), the results should be viewed with caution. The overall limited evidence from epidemiological studies examining the concentration-response function of SO_2 health effects is inconclusive regarding the presence of an effect threshold.

4.2 SUSCEPTIBLE AND VULNERABLE POPULATIONS

The previous review of the SO_2 NAAQS identified certain groups within the population that may be more susceptible to the effects of SO_2 exposure, including asthmatics, individuals not diagnosed as asthmatic but with atopic disorders (e.g., allergies), and individuals with chronic obstructive pulmonary disease (COPD) or cardiovascular disease (CVD). Other subgroups that were considered to be somewhat sensitive included children and the elderly.

Many factors such as age, preexisting disease, gender, nutritional status, smoking, and genetic variability may contribute to the interindividual variability in responses to environmental pollutants, including SO_2. Individuals in potentially sensitive groups are of concern, as they may be affected by lower levels of SO_2 than the general population or experience a greater impact with the same level of exposure. This section focuses on vulnerable groups that may be exposed to SO_2 levels above the community average and differential effects among susceptible groups, including subpopulations with asthma as well as genetic factors and age-related variability.

4.2.1 Exposure of Susceptible and Vulnerable Populations to SO_2

A limited amount of information exists on exposures of susceptible and vulnerable populations to SO_2. Indoor and personal SO_2 concentrations are generally much lower than outdoor or ambient measurements and occur near or below the detection limit of the passive samplers used in most studies (Kindzierski and Ranganathan, 2006; Sarnat et al., 2000, 2005, 2006). Infiltration of SO_2 into residences is limited (Brauer et al., 1989), partially due to its reactivity with the building envelope and indoor surfaces. Contributions of indoor sources to personal SO_2 exposures are low, with the possible exception of SO_2 emitted from indoor kerosene or gas heaters (Triche et al., 2005). Hence, individuals that spend most of their time indoors, such as older adults, are not anticipated to be vulnerable to high SO_2 exposures, though in some cases they may be more susceptible to the effects of these exposures than the general population. Other individuals with increased vulnerability include those who spend a lot of time outdoors at increased exertion levels, for example outdoor workers and individuals who exercise or play sports. Children, who generally spend more time playing outdoors, may qualify as both a susceptible population due to their developing physiology and as a vulnerable population since ambient SO_2 concentrations are several-fold higher than indoor concentrations.

Residential location is not as strong of a predictor of exposure vulnerability for SO_2 as for traffic-related pollutants, because meteorological conditions have a greater impact on pollutant plume direction from primary point sources such as coal-fired power plants.

4.2.2 Preexisting Disease as a Potential Risk Factor

Several researchers have investigated the effect of air pollution among potentially susceptible groups with preexisting medical conditions. A recent report of the National Research Council emphasized the need to evaluate the effect of air pollution on susceptible groups,

including those with respiratory illnesses and CVD (NRC 2004). Generally, asthma, COPD, conduction disorders, congestive heart failure (CHF), diabetes, and MI are conditions believed to put persons at greater risk of adverse events associated with air pollution. Asthmatics are known to be one of the most SO_2-responsive subgroups in the population; the evidence related to respiratory illness, including asthma, is discussed in further detail below.

4.2.2.1 Individuals with Respiratory Diseases

The 1982 Air Quality Criteria Document (AQCD) concluded that asthmatics are likely more susceptible to effects from SO_2 exposures than the general public. Recent epidemiological studies have strengthened this conclusion, reporting associations between a range of health outcomes with both short-term and long-term SO_2 exposures in subjects with respiratory disease.

In controlled human exposure studies, asthmatics have been shown to be more responsive to respiratory effects of SO_2 exposures than healthy, non-asthmatics. While SO_2-attributable decrements in lung function have not generally been demonstrated at concentrations <1.0 ppm in non-asthmatics (Lawther et al., 1975; Linn et al., 1987; Schachter et al., 1984), increases in respiratory symptoms and decreases in lung function have been observed in some asthmatics following peak (5 to 15 min) SO_2 exposures to concentrations $\leq$0.5 ppm (Gong et al., 1995; Horstman et al., 1986; Linn et al., 1983).

A number of epidemiological studies reported increased respiratory symptoms associated with SO_2 exposures in asthmatics and atopic individuals. In contrast, lung function generally was not positively associated with ambient SO_2 in epidemiological studies of asthmatic children (Mortimer et al., 2002) or among adults with asthma or COPD (Higgins et al., 1995; Neukirch et al., 1998; van der Zee et al., 2000). A series of epidemiological studies from the Netherlands has investigated the effect of exposure to SO_2 and other air pollutants on children and adults with airways hyperreactiveness (AHR) and atopy. In 1998, Boezen et al. found that adults with airway lability (defined as the presence of AHR or an increase in peak expiratory flow [PEF] variability) had a significantly increased prevalence of respiratory symptoms, including lower and upper respiratory symptoms, cough, and phlegm, with increasing levels of SO_2. In subsequent analyses, the authors examined whether children with AHR and elevated levels of IgE were vulnerable to the effects of SO_2 (Boezen et al., 1999). In a panel study of children aged 7 to 11 years, the authors found no associations between SO_2 and any respiratory symptoms in

the subset of children with relatively low serum total IgE with or without AHR. However, for children with relatively high serum total IgE either with or without AHR, the prevalence of lower respiratory symptoms increased in relation to increasing SO_2 concentrations. In a similar study conducted among older adults aged 50 to 70 years, Boezen et al. (2005) found that the subgroup of individuals with elevated serum total IgE, both with and without AHR, to be more susceptible to air pollutants compared to those who did not have elevated serum total IgE. Significant associations were observed between previous-day 24-h average SO_2 concentrations and the prevalence of upper respiratory symptoms in those with elevated serum total IgE. Stratified analyses by gender indicated that among those with AHR and elevated IgE, only males were at a higher risk for respiratory symptoms.

In a German study of 5,421 children, the annual mean SO_2 concentration was associated with morning cough over the previous 12 months, but not bronchitis (Hirsch et al., 1999). In contrast to the results reported by Boezen et al. (1999, 2005), this study observed that the association of SO_2 and other air pollutants with respiratory symptoms were stronger in nonatopic than in atopic children. The authors noted that these findings were in line with the hypothesis that these air pollutants induce nonspecific irritative rather than allergic inflammatory changes in the airway mucosa, as irritative effects would affect the clinical course in nonatopic children more strongly than in atopics whose symptoms are also determined by allergen exposure.

U.S. multicity studies of ambient SO_2 exposure also examined respiratory symptoms in asthmatic children (Mortimer et al., 2002; Schildcrout et al., 2006). In the National Cooperative Inner-City Asthma Study (NCICAS; Mortimer et al., 2002), the greatest effect was seen for morning symptoms, i.e., cough, wheeze, shortness of breath (range of median 3-h average SO_2 across eight cities: 17 to 37 ppb). In the Childhood Asthma Management Program (CAMP) study (Schildcrout et al., 2006), the strongest association between SO_2 and increased asthma symptoms was found for a 3-day moving average lag (range of median 24-h average SO_2 across seven cities: 2.2, 7.4 ppb [90th percentile range: 4.4, 14.2]). The Harvard Six Cities Study found an association between SO_2 concentration and cough incidence and lower respiratory symptoms among healthy children, but suggested that the relationship was nonlinear, with increased risk only observed at levels >20 ppb (Schwartz et al., 1994). These studies indicate that SO_2 effects on respiratory symptoms were observed in asthmatics at lower ambient levels of SO_2 compared to healthy children.

Other studies have examined the relationship between respiratory symptoms among subpopulations with asthma and/or COPD and ambient SO_2 concentrations. These studies generally indicated positive associations for asthma among children and included a U.S. study (Delfino et al., 2003) and several European studies (Higgins et al., 1995; Neukirch et al., 1998; Peters et al., 1996; Roemer et al., 1993; Ségala et al., 1998; Taggart et al., 1996; Timonen and Pekkanen, 1997; van der Zee et al., 1999). Studies of asthma among adults found no consistent association between respiratory symptoms among asthmatics and SO_2 concentrations (Desqueyroux et al., 2002a,b; Romieu et al., 1996; van der Zee et al., 2000).

A suggestive association between ambient SO_2 concentrations and ED visits and hospitalizations among children and the elderly provides evidence that asthmatics are susceptible to the effects of SO_2. The associations between ambient concentrations of 24-h average SO_2 and ED visits and hospitalizations for asthma in the United States are generally positive (Jaffe et al., 2003; Lin et al., 2004a; Michaud et al., 2004; Wilson et al., 2005), though a large time-series study conducted in Atlanta, GA did not find an association between ambient 1-h max SO_2 levels and ED visits (Peel et al., 2005). Studies conducted outside the United States (Atkinson et al., 1999b; Hajat et al., 1999; Sunyer et al., 1997; Thompson et al., 2001) also generally found positive results.

There was no association between SO_2 levels and asthma mortality in the general population (Saez et al., 1999) or among patients previously diagnosed with severe asthma (Sunyer et al., 2002).

In summary, there is substantial evidence from epidemiological studies that suggests that individuals with preexisting respiratory diseases, particularly asthma, are more susceptible to respiratory health effects, though not mortality, from SO_2 exposures than the general public. The observations in human clinical studies of increased sensitivity to SO_2 exposures in asthmatic subjects compared to healthy subjects provide coherence and biological plausibility for these observations in epidemiological studies.

4.2.2.2 Individuals with CVDs

Routledge et al. (2006) exposed patients with stable angina as well as healthy subjects to 50-$\mu g/m^3$ carbon particles and 0.2-ppm SO_2, alone and in combination for 1 h. Heart rate variability (HRV), C-reactive protein, and markers of coagulation were measured. There was no evidence to suggest that patients with stable angina were more susceptible to SO_2-related health

effects than healthy subjects. The authors noted that this lack of response in the heart patients may be due to a drug treatment effect rather than decreased susceptibility, as a large portion of the angina patients were taking beta blockers, which are known to increase indices of cardiac vagal control.

Liao et al. (2004) investigated short-term associations between ambient pollutants and cardiac autonomic control. Resting, supine, 5-min beat-to-beat R-R interval data were collected. Previous-day SO_2 concentrations were positively associated with heart rate and inversely associated with the standard deviation of normal R-R intervals (SDNN) and low frequency (LF) power. Consistently more pronounced associations were suggested between SO_2 and HRV among persons with a history of coronary heart disease.

Henneberger et al. (2005) examined the association of repolarization parameters with air pollutants in men with preexisting coronary heart disease in East Germany. The patients were examined repeatedly once every 2 weeks for 6 months, for a total of 12 electrocardiogram (ECG) recordings. The mean 24-h average SO_2 concentration was 4.1 $\mu g/m^3$ (2 ppb [range: 1, 4]). Ambient SO_2 concentrations during the 24-h preceding the ECG were associated with the QT interval duration, but not with any other repolarization parameters. Stronger associations were observed between PM indices and QT interval duration, T-wave amplitude, and T-wave complexity.

Evidence from ED visit and hospitalizations studies of the association between ambient levels of air pollutants and CVD is inconsistent. A recent epidemiological study investigated the association of SO_2 with cardiac hospital admissions among persons with preexisting cardiopulmonary conditions and observed no associations with ambient 1-h max SO_2 level for any cardiac disease investigated (i.e., ischemic heart disease [IHD], CHF, and dysrhythmia) across strata of comorbid disease status, including hypertension, diabetes, and COPD (Peel et al., 2007).

Goldberg et al. (2003) compared the risk estimates for death with the underlying cause of CHF and those deaths classified as having CHF 1 year before death and did not find associations between air pollution and those with CHF as an underlying cause of death. The authors found associations between some of the air pollutants examined (coefficient of haze [CoH], SO_2, and NO_2) and the deaths that were classified as having CHF 1 year before death, but the association with the specific cause of death was not unique to SO_2. This pattern of association, including but

not specific to SO_2, with specific causes of death also was observed in an additional cohort of patients with CHF (Kwon et al., 2001).

In summary, there is weak evidence from a small number of panel studies that suggests that individuals with preexisting CVD may be more susceptible to adverse health effects from ambient SO_2 exposures than the general public. The evidence from one human clinical study does not support these conclusions. Additional research is necessary to assess whether individuals with preexisting CVD constitute a susceptible group for SO_2 health effects.

4.2.3 Age-Related Variations in Susceptibility

The American Academy of Pediatrics (2004) notes that children and infants are among the most susceptible to many air pollutants, including SO_2. Eighty percent of alveoli are formed postnatal and changes in the lung continue through adolescence; furthermore, the developing lung is highly susceptible to damage from exposure to environmental toxicants (Dietert et al., 2000). Children also have increased vulnerability as they spend more time outdoors, are highly active, and have high minute ventilation, which collectively increase the dose they receive (Plunkett et al., 1992; Wiley et al., 1991a,b). In addition to children, the elderly are frequently classified as being particularly susceptible to air pollution. The basis of the increased sensitivity in the elderly is not known, but one hypothesis is that it may be related to changes in the respiratory tract lining fluid antioxidant defense network (Kelly et al., 2003).

A number of studies investigating the association between ambient SO_2 levels and ED visits or hospital admissions for all respiratory causes or asthma stratified their analyses by age group. Figure 4.2-1 summarizes the evidence of age-specific associations between SO_2 and acute respiratory ED visits and hospitalizations. Several studies demonstrated that the risk of ED visits or hospitalizations for all respiratory causes or asthma associated with a 10-ppb increase in 24-h average SO_2 levels was higher for children (Anderson et al., 2001; Atkinson et al., 1999a,b; Petroeschevsky et al., 2001; Ponce de Leon et al., 1996) and older adults (Anderson et al., 1998; Petroeschevsky et al., 2001; Ponce de Leon et al., 1996; Wilson et al., 2005) when compared to the risk for all ages together. Increased risks for children and older adults were more prevalent in the studies of all respiratory disease than those considering asthma as the outcome. Two studies investigated the association between ambient SO_2 levels and ED visits or hospital admissions for all cardio vascular causes, with analyses stratified by age (Atkinson et al., 1999a,b; Sunyer et al.,

2003b). Neither of these studies found a difference in effect estimates when analyses were stratified to ages 65+ years, compared to when all ages were included in the analyses.

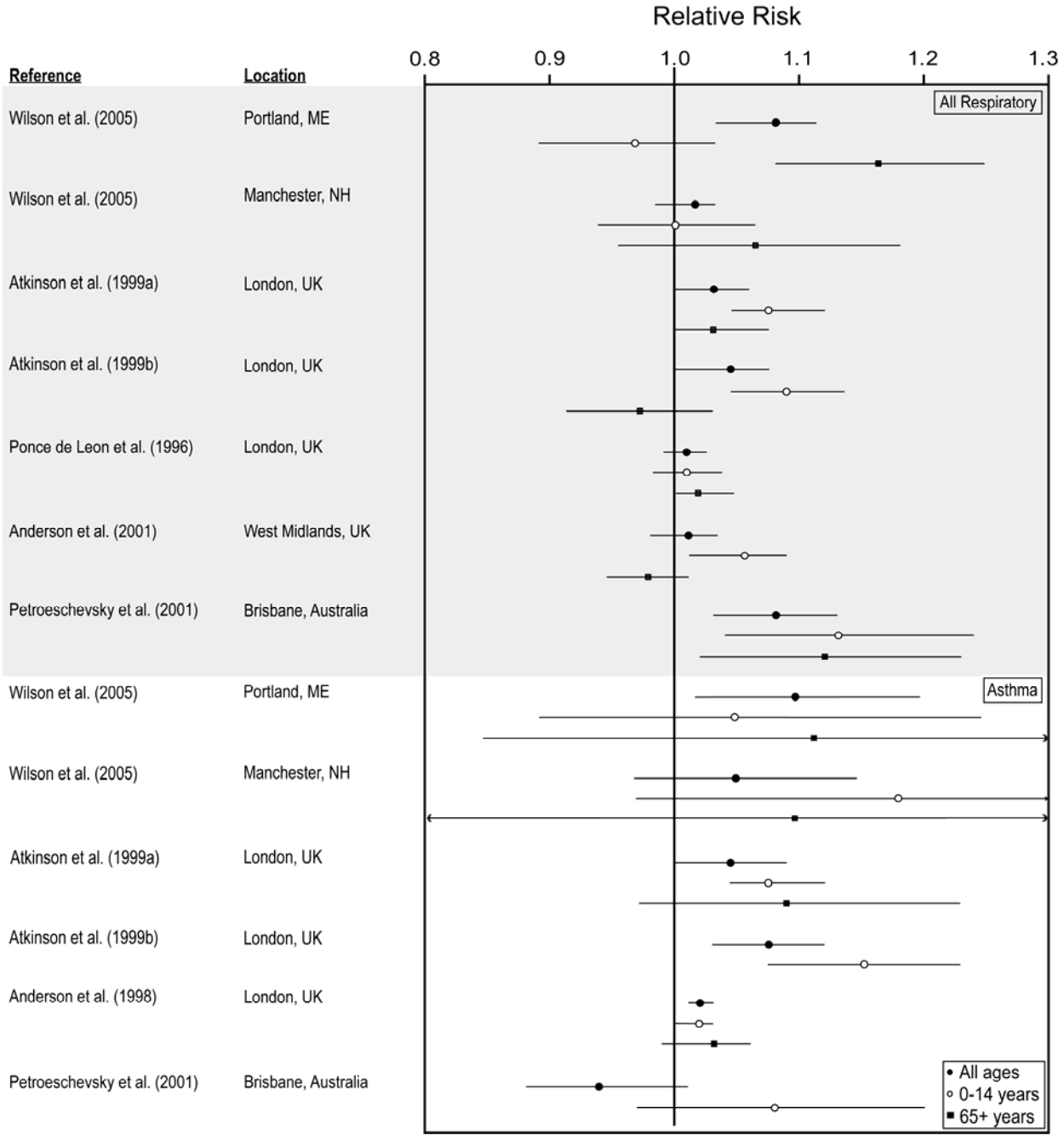

Figure 4.2-1. Relative risks (95% CI) of age-specific associations between short-term exposure to SO_2 and respiratory ED visits and hospitalizations. Risk estimates are standardized per 10-ppb increase in 24-h average SO_2 concentrations or 40-ppb increase in 1-h max SO_2.

Cakmak et al. (2007) reported that among seven Chilean urban centers, the percent increase in nonaccidental mortality associated with a 10-ppb increase in 24-h average SO_2 was 3.4% (95% CI: 0.7, 6.1) for those <65 years of age and 5.6% (95% CI: 2.2, 9.1) for those >85 years of age. The authors concluded that the elderly are particularly susceptible to dying from air pollution, and suggested that concentrations deemed acceptable for the general population may not adequately protect the very elderly.

There is limited epidemiological evidence to suggest that children and older adults (65+ years) are more susceptible to the adverse respiratory effects associated with ambient SO_2 concentrations when compared to the general population. The few studies that conducted age-stratified analyses when examining cardiovascular outcomes did not find any difference in outcomes when analyses were stratified by age.

4.2.4 Genetic Factors for Oxidant and Inflammatory Damage from Air Pollutants

A consensus now exists among scientists that genetic factors related to health outcomes and ambient pollutant exposures merit serious consideration (Gilliland et al., 1999; Kauffmann et al., 2004). Several criteria must be satisfied in selecting and establishing useful links between polymorphisms in candidate genes and adverse respiratory effects. First, the product of the candidate gene must be significantly involved in the pathogenesis of the adverse effect of interest, which is often a complex trait with many determinants. Second, polymorphisms in the gene must produce a functional change in either the protein product or in the level of expression of the protein. Third, in epidemiological studies, the issue of confounding by other genes or environmental exposures must be carefully considered.

Several glutathione *S*-transferase (GST) families have common, functionally important polymorphic alleles (e.g., homozygosity for the null allele at the GSTM1 and GSTT1 loci, homozygosity for the A105G allele at the GSTP1 locus) that significantly reduce expression of function in the lung. Exposure to radicals and oxidants in air pollution induces decreases in GSH that increase GST transcription. Individuals with genotypes that result in enzymes with reduced or absent glutathione peroxidase activity are likely to have reduced oxidant defenses and increased susceptibility to inhaled oxidants and radicals.

Gilliland et al. (2002) examined effects of GSTM1, GSTT1, and GSTP1 genotypes and acute respiratory illness, specifically respiratory illness-related absences from school. The goal was to examine potential susceptibilities on this basis, but not specifically to air pollutants. They concluded that fourth grade schoolchildren who inherited a GSTP1 Val-105 variant allele had a decreased risk of respiratory illness-related school absences, indicating that GSTP1 genotype influences the risk and/or severity of acute respiratory infections in school-aged children.

Lee et al. (2004) studied ninth grade schoolchildren with asthma in Taiwan for a gene-environmental interaction between GSTP1-105 genotypes and outdoor pollution. They examined general district air pollution levels of low (mean SO_2 level of 3.6 ppb from 1994 to 2001), moderate (mean SO_2 of 6.2 ppb), and high (mean SO_2 of 8.6 ppb) in the analysis and found that compared with individuals with any Val-105 allele in the low air pollution district, Ile-105 homozygotes in the high air pollution district had a significantly increased risk of asthma.

Gauderman et al. (2007) describe a study method that uses principal components analysis computed on single nucleotide polymorphism (SNP) markers to test for an association between a disease and a candidate gene. For example, they evaluated the association between respiratory symptoms in children and four SNPs in the GSTP1 locus, using data from the Southern California Children's Health Study (CHS). The authors observed stronger evidence of an association using the principal components approach ($p = 0.044$) than using either a genotype-based ($p = 0.13$) or haplotype-based ($p = 0.052$) approach. This method may be applied to relationships in this and other databases to evaluate aspects of air pollutants such as SO_2.

In 2001, Winterton et al. (2001) attempted to identify a genetic biomarker for susceptibility to SO_2. They screened 62 asthmatic subjects for SO_2 responsiveness using an inhalation challenge and collected genetic material via buccal swabs to test for associations between SO_2 sensitivity and specific gene polymorphisms. Subjects inhaled 0.5-ppm SO_2 by mouthpiece for 10 min while wearing noseclips during moderate exercise on a treadmill. Subjects were defined as SO_2-sensitive if FEV_1 dropped $\geq$12%. Genetic polymorphisms as biomarkers of susceptibility were evaluated in five regions coding for the β2-adrenergic receptor, the α subunit of the interleukin-4 (IL-4) receptor, the Clara cell secretory protein (CC16), tumor necrosis factor-α (TNF-α), and lymphotoxin-α (also known as TNF-β). The authors found a significant association between response to SO_2 and the homozygous wild-type allele of TNF-α.

All of the SO_2-sensitive subjects had the homozygous wild-type allele for TNF-α, while 61% of the nonresponders had this genotype. Homozygosity for the TNF-1 allele was associated with a 5-fold increased risk of physician-diagnosed asthma relative to other genotypes. None of the other polymorphisms showed significant trends.

In summary, the differential effects of air pollution among genetically diverse subpopulations have been examined for a number of GST genes and other genotypes. The limited number of studies may provide some insight into susceptible groups and a potential genetic role in such. Only one of these studies specifically examined SO_2 as the exposure of interest, and it found a significant association with the homozygous wild-type allele for TNF-α. Khoury et al. (2005) states that while genomics is still in its infancy, opportunities exist for developing, testing, and applying its tools to public health research of outcomes with possible environmental causes. At this time, there are only very limited data on which to base a conclusion regarding the effect of SO_2 exposure on genetically distinct subpopulations.

4.3 POTENTIAL PUBLIC HEALTH IMPACTS

Exposure to ambient SO_2 is associated with a variety of outcomes including increases in respiratory symptoms, particularly among asthmatic children, and ED visits and hospital admissions for respiratory diseases among children and older adults (65+ years). In protecting public health, a distinction must be made between health effects that are considered "adverse" and those that are not. What constitutes an adverse health effect varies for different population groups. Some changes in healthy individuals are not viewed as adverse while those of similar type and magnitude in other susceptible individuals with preexisting disease are.

4.3.1 Concepts Related to Defining Adverse Health Effects

The American Thoracic Society (ATS) published an official statement titled "What Constitutes an Adverse Health Effect of Air Pollution?" (ATS, 2000). This statement updated the guidance for defining adverse respiratory health effects that had been published 15 years earlier (ATS, 1985), taking into account new investigative approaches used to identify the effects of air pollution and reflecting concern for impacts of air pollution on specific susceptible groups. In the 2000 update, there was an increased focus on quality of life measures as indicators of adversity and a more specific consideration of population risk. Exposure to air pollution that

increases the risk of an adverse effect to the entire population is viewed as adverse, even though it may not increase the risk of any identifiable individual to an unacceptable level. For example, a population of asthmatics could have a distribution of lung function such that no identifiable single individual has a level associated with significant impairment, and exposure to air pollution could shift the distribution to lower levels that still do not bring any identifiable individual to a level that is associated with clinically relevant effects. However, this shift to a lower level would be considered adverse because individuals within the population would have diminished reserve function and, therefore, would be at increased risk if affected by another agent.

Reflecting new investigative approaches, the ATS statement also describes the potential usefulness of research into the genetic basis for disease, including responses to environmental agents that provide insights into the mechanistic basis for susceptibility and provide markers of risk status. Likewise, biomarkers that are indicators of exposure, effect, or susceptibility may someday be useful in defining the point at which one or an array of responses should be considered an adverse effect.

The 2006 O_3 AQCD (U.S. Environmental Protection Agency, 2006) provided information useful in helping to define adverse health effects associated with ambient O_3 exposure by describing the gradation of severity and adversity of respiratory-related O_3 effects. The definitions that relate to responses in impaired individuals are reproduced and presented here in Table 4.3-1. The severity of effects described in the tables and the approaches taken to define their relative adversity are valid and reasonable in the context of the new ATS (2000) statement.

As assessed in detail in earlier chapters of this document and briefly recapitulated in preceding sections of this chapter, exposures to a range of SO_2 concentrations have been reported to be associated with increasing severity of health effects, ranging from respiratory symptoms to ED visits and hospital admission for respiratory causes. Respiratory effects associated with short-term SO_2 exposures have been by far the most extensively studied and most clearly shown to be causally related to SO_2 exposure. Such effects are observed among children, older adults, and persons with respiratory impairments.

4.3.2 Estimation of Potential Numbers of Persons in At-Risk Susceptible Population Groups in the United States

Although SO_2-related health risk estimates may appear to be small, they may well be significant from an overall public health perspective due to the large numbers of individuals in

the potential risk groups. Several subpopulations have been identified as possibly having increased susceptibility or vulnerability to adverse health effects from SO_2, including children, older adults, and individuals with preexisting pulmonary diseases. One consideration in the assessment of potential public health impacts is the size of various population groups that may be at increased risk for health effects associated with SO_2-related air pollution exposure. Table 4.3-2 summarizes information on the prevalence of chronic respiratory conditions in the U.S. population in 2004 and 2005 (NHIS, 2006a,b). Individuals with preexisting cardiopulmonary disease constitute a fairly large proportion of the population, with tens of millions of people included in each disease category. Of most concern are those individuals with preexisting respiratory conditions, with approximately 10% of adults and 13% of children having been diagnosed with asthma and 6% of adults with COPD (chronic bronchitis and/or emphysema).

In addition, subpopulations based on age group also comprise substantial segments of the population that may be potentially at risk for SO_2-related health impacts. Based on U.S. census data from 2000, about 72.3 million (26%) of the U.S. population are under 18 years of age, 18.3 million (7.4%) are under 5 years of age, and 35 million (12%) are 65 years of age or older. Hence, large proportions of the U.S. population are included in age groups that are considered likely to have increased susceptibility and vulnerability for health effects from ambient SO_2 exposure.

The prevalence and number of people affected for selected respiratory disorders by age group are summarized in Table 4.3-2. In addition to their high prevalence, these diseases may be severe, resulting in deaths or hospitalizations. There are approximately 2.5 millions deaths from all causes per year in the U.S. population, with about 100,000 deaths from chronic lower respiratory diseases (Kochanek et al., 2004) and 4,000 from asthma (NCHS Health E Stats). For respiratory health diseases, there are nearly 4 million hospital discharges per year (DeFrances et al., 2005), 14 million ED visits (McCaig and Burt, 2005), 112 million ambulatory care visits (Woodwell and Cherry, 2004), and an estimated 700 million restricted activity days per year due to respiratory conditions (Adams et al., 1999). Of the total number of visits for respiratory disease, 1.8 million annual ED visits are reported for asthma, including more than 750,000 visits by children. In addition, nearly 500,000 annual hospitalizations for asthma are reported (NCHS Health E Stats summarizing 2005 NHIS data).

Centers for Disease Control and Prevention (CDC) analyses have shown that the burden of asthma has increased over the past two decades (NCHS Health E Stats 2005 NHIS data for both adults and children). In 2005, approximately 22.2 million (7.7% of the population) currently had asthma. The incidence was higher among children (8.9% of children) compared to adults (7.2%) (Note: 2004 data is shown in Table 4.3-2, with a prevalence of 6.7%). In addition, prevalence and severity is higher among certain ethnic or racial groups, such as Puerto Ricans, American Indians, Alaskan Natives, and African Americans. The asthma hospitalization rate for black people was 240% higher than that for white people. Puerto Ricans were reported to have the highest asthma death rate (360% higher than non-Hispanic white people) and non-Hispanic black people had an asthma death rate 200% higher than non-Hispanic white people. Gender and age is also a determinant of prevalence and severity, with adult females having a 40% higher prevalence than adult males, while boys had a 30% higher rate than girls. Overall, females had a hospitalization rate about 35% higher than males.

Evidence indicates that several groups are at increased risks from SO_2 exposures compared to the average population. Susceptible subgroups include individuals with preexisting disease, especially asthma, and children and older adults. Other individuals with increased vulnerability include those who spend a lot of time outdoors at increased exertion levels (e.g., outdoor workers, children, individuals who exercise or play sports) and those in proximity to large uncontrolled or poorly controlled sources. The considerable size of the population groups at risk indicate that exposure to ambient SO_2 could have a significant impact on public health in the United States.

TABLE 4.3-1. GRADATION OF INDIVIDUAL RESPONSES TO SHORT-TERM SO_2 EXPOSURE IN INDIVIDUALS WITH IMPAIRED RESPIRATORY SYSTEMS

Functional Response	None	Small	Moderate	Large
FEV_1 change	Decrements of <3%	Decrements of 3 to ≤10%	Decrements of >10 but <20%	Decrements of ≥20%
Nonspecific bronchial responsiveness[a]	Within normal range	Increases of <100%	Increase of ≤300%	Increases of >300%
Airways resistance (sRaw)	Within normal range (±20%)	sRaw increased <100%	sRaw increased up to 200% or up to 15 cm H_2O·s	sRaw increased >200% or more than 15 cm H_2O·s
Duration of response	None	<4 h	>4 h but ≤24 h	>24 h
Symptomatic Response	**Normal**	**Mild**	**Moderate**	**Severe**
Wheeze	None	With otherwise normal breathing	With shortness of breath	Persistent with shortness of breath
Cough	Infrequent cough	Cough with deep breath	Frequent spontaneous cough	Persistent uncontrollable cough
Chest pain	None	Discomfort just noticeable on exercise or deep breath	Marked discomfort on exercise or deep breath	Severe discomfort on exercise or deep breath
Duration of response	None	< 4 h	>4 h, but ≤24 h	>24 h
Impact of Responses	**Normal**	**Mild**	**Moderate**	**Severe**
Interference with normal activity	None	Few individuals choose to limit activity	Many individuals choose to limit activity	Most individuals choose to limit activity
Medical treatment	No change	Normal medication as needed	Increased frequency of medication use or additional medication	Physician or emergency room visit

[a]An increase in nonspecific bronchial responsiveness of 100% is equivalent to a 50% decrease in PD20 or PD100.

Source: This table is reproduced from the 1996 O_3 AQCD (Table 9-2, page 9-25) (U.S. Environmental Protection Agency, 1996).

TABLE 4.3-2. PREVALENCE OF SELECTED RESPIRATORY DISORDERS BY AGE GROUP AND BY GEOGRAPHIC REGION IN THE UNITED STATES (2004 [U.S. ADULTS] AND 2005 [U.S. CHILDREN] NATIONAL HEALTH INTERVIEW SURVEY)

			Age (Years)				Region			
	Adults (18+ Years)		18-44	45-64	65-74	75+	Northeast	Midwest	South	West
Chronic Condition/Disease	Cases ($\times 10^6$)	%	%	%	%	%	%	%	%	%
Respiratory Conditions										
Asthma	14.4	6.7	6.4	7.0	7.5	6.6	6.8	6.8	6.0	7.5
COPD										
Chronic Bronchitis	8.6	4.2	3.2	4.9	6.1	6.3	4.0	4.7	4.4	3.5
Emphysema	3.5	1.7	0.3	2	4.9	6.0	1.5	1.7	2.0	1.1

			Age (Years)			Region			
	Children (<18 years)		0-4	5-11	12-17	Northeast	Midwest	South	West
Chronic Condition/Disease	Cases ($\times 10^6$)	%	%	%	%	%	%	%	%
Respiratory Conditions									
Asthma	6.5	8.9	6.8	9.9	9.6	10.1	8.5	9.3	7.9

Source: National Center for Health Statistics (2006a,b).

5. KEY FINDINGS AND CONCLUSIONS

The previous chapters have presented the most policy-relevant information related to the atmospheric chemistry and exposures to sulfur dioxide (SO_2) and have discussed the health effects of SO_2 exposure. This chapter provides concise summaries of key findings and reports conclusions drawn from atmospheric sciences, ambient air data analyses, exposure assessment, dosimetry, and health evidence in consideration of the review of the National Ambient Air Quality Standards (NAAQS) for SO_2.

5.1 SUMMARY OF KEY FINDINGS RELATED TO THE SOURCE-TO-DOSE RELATIONSHIP

Key elements linking sources to health effects are: emission source identification, atmospheric chemistry and transport of a pollutant, techniques for ambient measurement, spatial and temporal patterns in concentrations, correlations to other relevant chemical species, and patterns of human exposures to ambient pollutants.

5.1.1 Emission Sources, Atmospheric Science, and Ambient Monitoring Methods

The characteristics of anthropogenic sources and atmospheric chemistry and monitoring methods for SO_2 are relatively well known.

- Anthropogenic SO_2 is emitted mainly by fossil fuel combustion (chiefly coal and oil) and metal smelting, with its largest emissions coming from elevated point sources like the stacks of power plants and industrial facilities.
- Anthropogenic SO_2 emissions from electric generating utilities and smelters have declined substantially since 1990
- SO_2 is a soluble gas that is oxidized mainly in the aqueous phase in cloud drops with gas phase oxidation being of secondary importance. Both pathways lead quantitatively to sulfate formation in cloud drops and/or in particles. Sulfur dioxide and sulfate are removed from the atmosphere by wet and dry deposition.
- Ambient SO_2 is most commonly monitored in regulatory networks using the pulsed fluorescence technique and reported with a 1-h frequency, although finer time-scales are

sometimes available at selected sites. More sensitive techniques for measuring SO_2 are available, but most of these systems are too complex and expensive for routine monitoring applications.

5.1.2 Ambient Concentrations

The decline in SO_2 emissions from electric generating utilities and smelters since 1990 has lowered ambient SO_2 concentrations and improved air quality dramatically, as demonstrated in the data collected from the State and Local Air Monitoring Stations (SLAMS) and National Air Monitoring Stations (NAMS) networks.

- Measured annual mean SO_2 values have not been observed to exceed the annual primary NAAQS (0.03 ppm) since 2000. Ambient concentrations decreased 48% between 1990 and 2005 owing to controls administered by EPA's Acid Rain Program and Clean Air Markets Division. In addition, means and maxima of the 24-h concentrations in the 12 consolidated metropolitan statistical areas (CMSAs) with >4 monitors in the years 2003 through 2005 were never in excess of the 24-h primary SO_2 NAAQS (0.14 ppm). The ambient monitors currently deployed in the regulatory networks are fully adequate to determine compliance with these standards.
- Monitors deployed in the current regulatory network are adequate to detect SO_2 concentrations above 3 ppb. But their detection technique is inadequate for accurate and precise measurements at or near the current mean 24-h SO_2 levels (~3 ppb). The U.S. Environmental Protection Agency (EPA) through its National Core Monitoring Network (NCore) initiative is engaged in a program to install and operate trace-level SO_2 instruments with lower limits of detection that will increase the accuracy and precision of observations at current low ambient levels.
- Ambient annual average concentrations reported in the regulatory monitoring networks of the continental U.S. (CONUS) over the years 2003 to 2005 ranged from a low of ~1 ppb (reported) on the West Coast to a high of ~3 ppb (reported) in the Mid-Atlantic region where SO_2 emissions remain highest. Both emissions and ambient concentrations demonstrate a strong east-to-west gradient, owing to the overrepresentation of SO_2-emitting electric generating units in the Ohio River Valley and upper South regions.

- SO_2 concentrations demonstrate no correlation to concentrations of sulfate (SO_4^{2-}) at the 12 CMSAs with more than four SO_2 monitors except at Riverside, CA. This exception likely arises from Riverside's geographic location downwind of the regionally important SO_2 sources near Los Angeles, and the strongly correlated seasonality of SO_2 with SO_4^{2-}, each showing peaks in summer when SO_2 oxidation would be maximized during transport to Riverside.
- Policy relevant background levels of SO_2 are estimated to be <1% of typical ambient levels (or in the range of a few hundredths of a ppb) across most of the United States. However, much higher values are found in areas affected by volcanic or geothermal activity as in Hawaii (>30 ppb) or in the Pacific Northwest, or in areas affected by trans-Pacific or trans-Arctic transport from Eurasia.

5.1.3 Exposure Assessment

The amount of time a person spends in different microenvironments and the infiltration characteristics of these microenvironments are strong determinants of the association between ambient SO_2 concentrations and human exposures. Relatively few studies have been conducted since the last review examining the relationships among personal exposures, and indoor, outdoor, and ambient concentrations of SO_2.

- In studies in which personal exposure concentrations were above detection limits, or in studies using active denuder systems, reasonably strong associations were found between personal exposure and ambient SO_2 concentrations.
- Passive badges used to monitor personal exposures generally cannot accurately measure concentrations of SO_2 over commonly used sampling periods because concentrations typically encountered by the subjects wearing them are often well below limits of detection. Hence, associations between ambient concentrations and personal exposure, using commonly deployed passive methods, can be incorrectly or inadequately characterized.
- The main source of SO_2 in indoor environments is infiltration from outdoors, as evidenced by relatively high correlations between indoor and outdoor values and lower values indoors than outdoors. However, a wide range of indoor-outdoor ratios was reported in the studies examined here: from 0.03 to 1.01. A number of factors including instrument measurement error contribute to these results.

- In addition to ambient SO_2, people could also be exposed to SO_2 produced by indoor heating sources. Exposures of this sort would be limited, though, because the chief identified source activity, kerosene space heater use, is not widespread. However, disparities in socioeconomic status and behavior, and any differential susceptibilities related to such disparities may result in increased exposure of selected groups.
- The effect of exposure error on community time-series epidemiology studies has been investigated in a limited number of studies, although not specifically for SO_2. Variations in non-ambient exposure and in the fractional contribution of ambient pollutants to exposure will not influence the observed health effect estimate, unless they are correlated with the ambient concentration.

5.1.4 Dosimetry

Dosimetry of SO_2 is the measurement or estimation of the amount of SO_2 or its reaction products reaching and persisting at specific sites in the respiratory tract following exposures.

- Due to its high solubility, SO_2 is readily removed in the moist surfaces of the nose and other respiratory passages. With quiescent nasal breathing, almost all inhaled SO_2 is removed in the extrathoracic (head) region. This limits the potential for direct effects on the more sensitive thoracic regions of the respiratory tract. Factors that can increase penetration of SO_2 to these regions include oral and oronasal breathing, increased ventilation rates and the presence of particles or fog droplets that may act as carriers for SO_2.

5.2 SUMMARY OF KEY HEALTH EFFECTS FINDINGS

5.2.1 Findings from the Previous Review of the NAAQS for SO_2

In the previous review of the NAAQS for SO_2, the following conclusions were reached regarding health effects of SO_2 (U.S. Environmental Protection Agency, 1982b, 1994b):

- Although SO_2 may produce effects through several mechanisms, the most striking acute effects observed appear to result from stimulation of receptors in the tracheobronchial region, leading to a neurally mediated reflex bronchoconstriction.
- The major effects categories of concern associated with high exposures to SO_2 include sensory and other nonrespiratory responses, effects on respiratory mechanics and symptoms,

aggravation of existing respiratory and cardiovascular disease, effects on clearance and other host defense mechanisms, and mortality.

- The major subgroups of the population that appear likely to be most sensitive to the effects of SO_2 include asthmatics, individuals not diagnosed as asthmatic but with atopic disorders (e.g., allergies), and individuals with chronic obstructive pulmonary or cardiovascular disease. Other subgroups that may be somewhat sensitive include the elderly and children.
- The major effects observed in human clinical studies following peak exposures (1 h or less, generally 5 to 15 min) are increases in airway resistance and decreases in other functional measures indicative of significant bronchoconstriction in relatively healthy asthmatic or atopic subjects. At 0.4-0.6 ppm SO_2, changes in functional measures were accompanied by mild increases in perceptible symptoms such as wheezing, chest tightness, and coughing. At higher concentrations, effects were more pronounced and the fraction of asthmatic subjects who responded increased, with clearer indications of clinically or physiologically significant effects at 0.6 to 0.75 ppm and above.
- A substantial percentage (25 to 50 percent) of mild to moderate asthmatic individuals exposed for 5 to 15 minutes to 0.6 to 1.0 ppm SO_2 during moderate exercise would be expected to have respiratory function changes. The effects observed after exposure to 0.6 to 1.0 ppm SO_2 are relatively transient (not lasting more than a few hours) and are not likely to worsen or to reoccur with the same magnitude of response if re-exposure to another SO_2 peak occurred within the next several hours after the initial exposure. At SO_2 concentrations at or below 0.5 ppm with moderate exercise, only a relatively small percentage ($\geq$l0 to 20 percent) of mild and moderate asthmatic individuals are likely to experience lung function changes distinctly larger than those they typically experience. Furthermore, compared to the response at 0.6 to 1.0 ppm SO_2, the response at or below 0.5 ppm SO_2 is less likely to be perceptible and of immediate health concern.
- In the epidemiological studies, an association of short-term (generally hours to days) SO_2 exposure with daily mortality was likely at levels of 0.19 to 0.38 ppm, an association with aggravation of bronchitis was likely at levels of 0.19 to 0.23 ppm and possible at levels below 0.19 ppm, and small, reversible declines in lung function in children were possible at 0.10 to 0.18 ppm.

- Although the possibility of effects from long-term (generally months to years) lower level exposures to SO_2 could not be ruled out, no quantitative rationale could be offered to support a specific range of interest for an annual standard. The limited available epidemiological data indicated associations between respiratory illnesses and symptoms and persistent exposures to SO_2 in areas with long-term averages exceeding 0.04 ppm.

5.2.2 New Findings on the Health Effects of Exposure to SO_2

New evidence developed since the previous NAAQS review for SO_2 has confirmed and extended the conclusions articulated in the 1982 Air Quality Criteria Document (AQCD), 1986 Second Addendum, and 1994 Supplement to the Second Addendum. In the time since the previous review, the epidemiological evidence has grown substantially, including new field or panel studies on respiratory health outcomes, numerous time-series epidemiological studies of effects including emergency department (ED) visits and hospital admissions, and a substantial number of studies evaluating mortality risk with short-term (generally 24-h average) SO_2 exposures. Several new studies have reported findings from prospective cohort studies on respiratory health effects and mortality with long-term (generally months to years) SO_2 exposure. While not as marked as the growth in epidemiological literature, a number of new human clinical and animal toxicological studies provide some additional biological plausibility for the observed relationships between SO_2 exposure and health effects in epidemiological studies.

The key findings of this draft Integrated Science Assessment (ISA) on the health effects of SO_2 exposure are presented below. Here, we build upon the discussions in Chapter 3 to draw conclusions regarding the overall strength of the body of evidence and the extent to which causal inferences may be made. Strong evidence from human clinical studies can lead to a conclusion of a "causal" relationship between exposure and adverse health effects. Where the epidemiological evidence is strong and there is coherent and plausible clinical or toxicological evidence, we have concluded that the relationship is "likely causal." Where the epidemiological findings are generally strong and consistent, but the available experimental evidence is too limited to draw conclusions regarding coherence, mechanism(s) of action, or plausibility of the results, we have concluded that this relationship is "suggestive." In some situations, the evidence from epidemiological and experimental studies is not found to be strong or consistent (sometimes with very limited available evidence) and there is limited support for coherence and plausibility; these relationships we judge to

be "inconclusive." Where possible, we have also included observations about the general levels or ranges of concentrations at which effects have been observed. A series of tables with information supporting these observations are presented in the appendix following this chapter. Table 5A-1 summarizes key animal toxicological studies and the lowest levels at which effects have been seen for a series of effect categories. Table 5A-2 summarizes the key findings of human clinical studies, and the exposure levels at which those effects have been observed. The results of key new epidemiological studies on respiratory health effects are presented in Tables 5A-3 (panel studies of respiratory symptoms) and 5A-4 (population studies of ED visits and hospital admissions for respiratory causes) and include information about the distribution of SO_2 levels (generally provided as mean and range) as presented in the study.

5.2.2.1 Peak (5-15 min) Exposure to SO_2 and Respiratory Health Effects

We conclude that there is a *causal* relationship between peak (1-h or less, typically 5 to 15 min) exposure to SO_2 and effects on the respiratory system, based on evidence from human clinical studies. Human clinical studies provide clear evidence that peak exposures to SO_2 at levels of 0.5 to 1.0 ppm cause effects on the respiratory system, namely decrements in lung function and increases in respiratory symptoms in exercising asthmatic adults.

Respiratory Symptoms

- The human clinical studies have reported increased respiratory symptoms with SO_2 concentrations of as low as 0.5 ppm in asthmatic subjects (Section 3.1.1.1). One human clinical study with SO_2-sensitive asthmatics reported that respiratory symptoms (i.e., shortness of breath, wheeze, and chest tightness) increased with increasing SO_2 concentration (0-, 0.5-, and 1.0-ppm SO_2) following exposures of 10 min with varying levels of exercise (Gong et al., 1995). It was also observed that exposure to 0.5-ppm SO_2 during light exercise evoked a more severe symptomatic response than heavy exercise in clean air.

Lung Function

- Human clinical studies have consistently demonstrated decreases in lung function (e.g., decreased forced expiratory volume in 1 s [FEV_1] and increased specific airways resistance [sRaw]) following peak exposures (5 to 15 min) to SO_2 (Section 3.1.1.2). These effects have clearly and consistently been shown to be exacerbated among individuals with asthma,

with asthmatics exhibiting significant decrements in lung function following 5- to 15-min exposures to SO_2 concentrations of as low as 0.5 ppm while performing moderate levels of exercise (e.g., Gong et al., 1995; Horstman et al., 1986; Linn et al., 1987; Sheppard et al., 1981). The effect of peak SO_2 exposure on lung function has been shown to increase in magnitude with increasing SO_2 concentrations above 0.5 ppm. Studies have further observed significant decrements in lung function in some sensitive asthmatics following 5-15 min exposures to SO_2 concentrations of as low as 0.25 ppm while performing moderate levels of exercise (Horstman et al., 1986; Sheppard et al., 1981). Thus, the observations of increased bronchoconstriction and airway resistance in human clinical studies provide clear evidence for SO_2 effects with peak exposure.

5.2.2.2 Short-Term (24-h average) Exposure to SO_2 and Respiratory Health Effects

We conclude that there is a *likely causal* relationship between short-term exposure to SO_2 at ambient concentrations and effects on the respiratory system, based on consideration of all the data. Numerous new epidemiological studies, supported by evidence from toxicological and human clinical studies provide evidence of a relationship between short-term (24-h average) exposures to SO_2 and respiratory health effects, ranging from respiratory symptoms and increasing in severity to ED visits and hospital admissions for respiratory causes. These effects were observed particularly in individuals with preexisting respiratory diseases, children, and older adults (65+ years). Associations between short-term exposure to SO_2 and respiratory morbidity were generally robust to adjustment for potential confounding by copollutants, as assessed using multipollutant models. As shown in Tables 5A-3 and 5A-4, almost all of the epidemiologic studies have been conducted in areas where the maximum ambient 24-h average SO_2 concentration was below the current 24-h average NAAQS level of 0.14 ppm. Evidence related to specific types of respiratory effects is highlighted below.

Respiratory Symptoms

- Recent epidemiological studies provide evidence for an association between ambient SO_2 exposure and increased respiratory symptoms in children, particularly those with asthma or chronic respiratory symptoms (Section 3.1.1.1, see Figures 3.1-3 and 3.1-4). Recent U.S. multicity studies observed significant associations between SO_2 and respiratory symptoms at a median range of 17 to 37 ppb (75th percentile: ~ 25 to 50) across cities for 3-h average

SO_2 (National Cooperative Inner-City Asthma Study [NCICAS], Mortimer et al., 2002) and 2.2 to 7.4 ppb (90th percentile: 4.4 to 14.2) for 24-h average SO_2 (Childhood Asthma Management Program [CAMP], Schildcrout et al., 2006). The SO_2 effect was generally found to be robust after adjusting for particulate matter (PM) and other copollutants.

- Results from the epidemiological studies examining the association between SO_2 and respiratory symptoms in adults are generally mixed, with some showing positive associations and others finding no relationship at current ambient levels (Section 3.1.1.1).

Lung Function

- Epidemiological studies observed mixed results for the association between 24-h average ambient SO_2 and lung function in children and adults (Section 3.1.1.2). A limited number of animal studies and human clinical studies of >1-h exposures provide some degree of biologic plausibility and no concentration-response information to allow an understanding of the inconclusive epidemiological findings.

Airway Hyperresponsiveness

- Very limited epidemiological evidence suggests that exposure to SO_2 may lead to airway hyperresponsiveness in atopic individuals (Section 3.1.1.4). Toxicological studies that observed increased airway obstruction and hypersensitivity at low levels (0.1 ppm) in allergen-sensitized animals provide biological plausibility for these findings. The epidemiological evidence further observed that atopic individuals may be at increased risk for SO_2-induced respiratory symptoms.

Inflammation

- The limited epidemiological, human clinical, and toxicological evidence does not suggest that exposure to SO_2 at current ambient concentrations is associated with inflammation in the airways (Section 3.1.1.3).

Respiratory ED Visits and Hospitalizations

- A large number of epidemiologic studies provide evidence of positive, but not always statistically significant, associations between ambient SO_2 concentrations and ED visits and hospitalizations for all respiratory causes and asthma, particularly amount children and older

adults (Section 3.1.1.6, see Figures 3.1-7 through 3.1-10). These findings are generally robust when additional copollutants are included in the model (Figure 3.1-11). Biologic plausibility for these findings of increased ED visits and hospitalizations is found in the epidemiologic and human clinical studies that observed increased respiratory symptoms and decreased lung function, and the animal toxicological studies that observed SO_2-induced altered lung host defenses (Section 3.1.1.5).

5.2.2.3 Short-Term Exposure to SO_2 and Cardiovascular Health Effects

The collective evidence with regard to the effect of SO_2 on the cardiovascular system is *inconclusive*.

- Evidence from epidemiological studies of heart rate variability (HRV), cardiac repolarization changes, and cardiac rhythm disorders provide limited evidence of associations with SO_2 exposure (Section 3.1.2.1 to 3.1.2.3). The parameters measured in these studies were associated most strongly with PM compared to other ambient pollutants, so the effects observed for SO_2 may have been confounded. Two human clinical studies provided weak and inconsistent evidence for an effect of SO_2 on HRV, while one animal toxicological study did not provide support for an effect on spontaneous arrhythmias. Overall, evidence that SO_2 affects cardiac autonomic control and cardiac rhythm is inconclusive.
- Some studies have observed positive associations between ambient SO_2 concentrations and ED visits and hospital admissions for all cardiovascular diseases (CVDs), particularly among individuals 65 years or greater (Section 3.1.2.7, see Figure 3.1-12). Given the limited number of studies that assessed potential confounding by copollutants for this outcome (Figure 3.1-13), which is of concern because of the moderate to strong correlation between SO_2 and various copollutants in most studies, and the lack of supportive data from panel studies and human clinical studies on cardiovascular health effects, the collective evidence that ambient SO_2 has an effect of CVD ED visits and hospitalizations is weak.

5.2.2.4 Short-Term Exposure to SO_2 and Other Systemic Effects

The limited toxicological evidence for SO_2-related effects on the nervous system and other organ systems is *inconclusive*.

- In a limited number of toxicological studies, exposure to SO_2 has been shown to affect certain neurodevelopmental and cognitive effects (Section 3.1.3.1). There was suggestive evidence that young animals and those with preexisting conditions such as diabetes were more susceptible to these effects. These effects were observed only at high concentrations of SO_2.
- Though limited, the overall animal toxicology database on SO_2 exposure suggests no overt adverse effects on the reproductive, hematological, gastrointestinal, renal, lymphatic, and endocrine systems (Section 3.1.3.2).

5.2.2.5 Effects of Short-Term Exposure to SO_2 on Mortality

Epidemiological evidence is *suggestive* of associations between SO_2 and nonaccidental all-cause and cardiopulmonary-related mortality, but additional research is needed to more fully establish underlying mechanisms by which such effects occur.

- Recent epidemiological studies have reported associations between mortality and SO_2, often at mean 24-h average levels below 10 ppb (Section 3.2.1, see Figure 3.2-2). The range of SO_2 all cause (nonaccidental) mortality risk estimates is 0.4 to 2% per 10-ppb increase in 24-h average SO_2 in several large multicity studies and meta-analyses. In the large multicity time-series studies, the SO_2 risk estimates were generally reduced when copollutants, either PM indices and/or nitrogen dioxide (NO_2), were added in the model. Thus, some extent of confounding among these pollutants is suggested.
- Results from multicity studies indicate that the SO_2 effect estimates for respiratory mortality were generally larger than the cardiovascular mortality risk estimates, suggesting a stronger association of SO_2 with respiratory mortality compared to cardiovascular mortality; however, similar associations were observed for other pollutants, including PM and NO_2 (Section 3.2.2, See Figure 3.2-3). There is some biological plausibility for the stronger associations observed between ambient SO_2 and respiratory mortality given the likely causal relationship between SO_2 and respiratory morbidity outcomes.
- An intervention study from Hong Kong (Hedley et al., 2002) supports the notion that a reduction in SO_2 levels results in a reduction in deaths, but this does not preclude the possibility that the causal agent is not SO_2 but rather something else that is emitted along with SO_2, such as the trace metals vanadium and nickel (Section 3.2.3). Overall, the

evidence that SO_2 is causally related to mortality at current ambient levels is suggestive but limited by potential confounding in the epidemiological data and the absence of strong biological plausibility.

5.2.2.6 Effects of Long-Term Exposure to SO_2 on Morbidity

The epidemiological findings, along with the very limited toxicological findings, provide *inconclusive* evidence that long-term exposure to SO_2 has adverse health effects.

- Several epidemiological studies that examined the effects of long-term exposure to SO_2 on asthma, bronchitis, and respiratory symptoms observed positive associations in children (Section 3.3.1.1). However, there are inconsistencies in the findings observed, with some finding effects on bronchitic symptoms but not asthma symptoms and vice versa. Overall, while the evidence is suggestive, the variety of outcomes examined and the inconsistencies in the observed results make it difficult to assess the impact of long-term exposure of SO_2 on respiratory health.
- The epidemiological evidence reported mixed results on the effect of long-term exposure on lung function (Section 3.3.1.2). An animal toxicological study in rabbits that were exposed to 5-ppm SO_2 for 13 weeks did not observe any alterations in pulmonary function or respiratory parameters. These results, collectively, do not indicate that long-term exposure to SO_2 has a detrimental effect on lung function.
- A very limited number of animal toxicological studies examined histopathological changes in the respiratory system following exposure to SO_2 (Section 3.3.1.3). In one study, rats were exposed for 4 to 8 months to 1-ppm SO_2 and an increased incidence of bronchiolar epithelial hyperplasia and a small increase (12%) in numbers of nonciliated epithelial cells in terminal respiratory bronchioles were observed at 4 but not at 8 months of exposure. Two other toxicological studies with shorter exposure periods (6 days and 4 weeks) did not report any alveolar or other pulmonary lesions.
- The epidemiological studies did not provide any evidence that long-term exposure to SO_2 is associated with an increased risk of lung cancer (Section 3.3.2). The toxicological studies indicate that any potential pathways for sulfur oxides (SO_x) to induce carcinogenesis, cocarcinogenesis, or tumor promotion appear to be complex and may be highly situational. SO_2 and its derivatives appear unlikely to have significant carcinogenic potential.

- Epidemiological studies on birth outcomes have found suggestive positive associations between SO_2 exposure and low birth weight (Section 3.3.3, see Figure 3.3-1). One concern, however, is that many of these studies could not adjust for potential confounding factors. Additional limitations affecting the interpretation of these studies is a lack of evidence for biological plausibility of an effect, inconsistencies across trimesters of pregnancy, and a lack of evidence to evaluate confounding by copollutants.

5.2.2.7 Effects of Long-Term Exposure to SO_2 on Mortality

Results from the limited number of epidemiological studies are *inconclusive* regarding the association between long-term exposure to SO_2 and mortality.

- The results from two major U.S. epidemiological studies (Harvard Six Cities Study [Dockery et al., 1993; reanalysis, Krewski et al., 2000] and the American Cancer Study [ACS] [Pope et al., 1995; reanalysis, Krewski et al., 2000]) observed associations between long-term exposure to SO_2 and mortality (Section 3.4.1, see Figure 3.4-1). However, Krewski et al. concluded that in the absence of a plausible toxicological mechanism by which SO_2 could lead to increased mortality suggested that SO_2 might be acting as a marker for other mortality-associated pollutants. The inability to distinguish potential confounding by copollutants, inconsistent observations across the various U.S. and European studies and the remaining uncertainties regarding the geographic scale of analysis and copollutant confounding limit the interpretation of a causal relationship.

5.2.2.8 Concentration-Response Function and Potential Thresholds

The limited evidence from epidemiological studies examining the concentration-response function of SO_2 health effects is inconclusive regarding the presence of an effect threshold (Section 4.1).

- Evidence from human clinical studies indicated wide interindividual variability in response to SO_2 exposures (Horstman et al., 1986; Linn et al., 1987). The evidence from human clinical studies demonstrates consistent SO_2-induced respiratory effects following 5 to 15 min exposures of SO_2 at levels between 0.5 and 1.0 ppm, with weaker evidence of effects at concentrations as low as 0.25 ppm in some sensitive asthmatics.
- Several epidemiological studies that examined the concentration-response function between short-term (24-h average) exposure to SO_2 and respiratory morbidity observed a linear

relationship across the entire concentration range, suggesting a lack of a threshold in effect. However, given the various limitations in observing a possible threshold in population studies, the lack of evidence for a threshold does not necessarily indicate that there is indeed no threshold for SO_2 health effects. Two epidemiological studies did report a possible threshold level of 22 to 23 ppb (24-h average) at which no statistically significant SO_2-related respiratory health effect was observed. However, as these observations were based on only a few influential data points (24-h average SO_2 concentrations above the 90th percentile), the results should be viewed with caution.

- In considering the factors that influence the dosimetry of SO_2, a mechanistic argument for individual thresholds in SO_2-related health effects can be made. The individual thresholds for response may not necessarily translate to a detectable population threshold. Additivity of SO_2-induced responses to a background level of response and interindividual differences in susceptibility to SO_2-related health effects will tend to linearize the concentration-response relations and obscure any population threshold that exists.

5.2.2.9 Susceptible and Vulnerable Populations

Certain subgroups within the population have been found to be more susceptible or vulnerable to the effects of SO_2 exposure, including individuals with preexisting respiratory diseases, children, and older adults (65+ years) (Section 4.2). It should be further noted that other individuals who may not generally be susceptible to SO_2-related health effects may experience transient airways reactivity to respiratory irritants such as SO_2 following a recent viral respiratory infection (Stempel and Boucher, 1981).

- Substantial evidence from epidemiological studies suggests that subjects with respiratory illnesses, particularly asthma, are more susceptible to respiratory health effects from SO_2 exposures than the general public (Section 4.2.2.1). The observations in human clinical studies of increased sensitivity to SO_2 exposures in asthmatic subjects compared to healthy subjects provide coherence and biological plausibility for these observations in epidemiological studies.
- There is weak evidence from a small number of panel studies that suggests that individuals with preexisting CVD may be more susceptible to adverse health effects from ambient SO_2 exposures than the general public (Section 4.2.2.2). Additional research is necessary to

assess whether individuals with preexisting CVD constitutes a susceptible group for SO_2 health effects.

- Limited epidemiological evidence suggests that children and older adults (65+ years) are more susceptible to the adverse respiratory effects associated with ambient SO_2 concentrations when compared to the general population (Section 4.2.3, see Figure 4.2-1). The few studies that conducted age-stratified analyses when examining cardiovascular outcomes did not find any difference in outcomes when analyses were stratified by age.
- Differential effects of air pollution among genetically diverse subpopulations have been examined for a number of glutathione S-transferase (GST) genes and other genotypes in a limited number of studies (Section 4.2.4). Only one of these studies specifically examined SO_2 as the exposure of interest, and it found a significant association with the homozygous wild-type allele for tumor necrosis factor-α (TNF-α). At this time there are only very limited data on which to base a conclusion regarding the effect of SO_2 exposure on genetically distinct subpopulations.

5.3 CONCLUSIONS

This draft ISA focused on scientific information that has become available since the last review and reflects the current state of knowledge on the most relevant issues pertinent to the review of the primary NAAQS for SO_2. The current primary SO_2 NAAQS has two parts – a 24-h average of 0.14 ppm, not to be exceeded more than once per year, and an annual average of 0.03 ppm. Exceedances in recent years have become rare, as the mean 24-h average and annual average SO_2 concentrations in the United States for the years 2003 to 2005 were ~4 ppb, with maximum values of >120 ppb for the 24-h average and ~14-15 ppb for the annual average. For the monitors reporting a 1-h max in these years, the mean concentration was ~13 ppb, with a maximum value of >600 ppb.

In the review of the scientific literature for SO_2, evidence from the various disciplines of atmospheric sciences, exposure assessment, dosimetry, human and animal toxicology, and epidemiology was integrated and collectively considered in formulating conclusions. Overall, we conclude that there is a *causal* relationship between *peak* (1 h or less, typically 5 to 15 min) exposure to SO_2 and effects on the respiratory system, based on evidence from human clinical studies. Human clinical studies provide clear and consistent evidence of a causal relationship

between peak exposures to SO_2 at levels of 0.5 to 1.0 ppm and effects on the respiratory system, namely decrements in lung function in exercising asthmatic adults. We further conclude that there is a *likely causal* relationship between *short-term* (generally 24-h average) SO_2 exposure at ambient levels and respiratory health effects, mostly based on the epidemiological studies. A large body of new epidemiological studies provides evidence of consistent and robust associations between short-term exposure to ambient SO_2 and respiratory health endpoints, ranging from increased respiratory symptoms in children with asthma or chronic respiratory symptoms, and increasing in severity to ED visits and hospital admissions for respiratory causes particularly in children and older adults (65+ years of age). The public health impact of ambient SO_2 exposures may be large, owing to the fact that these potentially susceptible subgroups constitute a large part of the general population. Associations of health effects with ambient SO_2 exposure have been reported in locations where the maximum 24-h average SO_2 concentration was below the levels of the current NAAQS (see Tables 5A-3 and 5A-4).

However, much uncertainty remains in the interpretation of the health evidence related to ambient SO_2 exposures. Exposure error is one key source of uncertainty, as typical indoor 24-h average SO_2 concentrations are often below the detection limit of personal exposure monitors, and ambient SO_2 concentrations in locations with low levels may be at or below the detection limit of existing monitors in the regulatory networks. Other sources of uncertainty include the magnitude of SO_2 risk estimates and the shape of concentration-health response relationships. Together, these uncertainties complicate our ability to attribute observed health effects to SO_2 directly.

The epidemiological observations of SO_2 health effects can be interpreted in several ways that are not mutually exclusive. First, the reported SO_2 effect estimates in epidemiological studies may be attributable to SO_2 per se, reflecting independent SO_2 effects on respiratory health. Available human clinical and animal toxicological studies are conducted at higher than average ambient SO_2 exposures, and do not examine the most susceptible populations. Due to its high solubility, SO_2 is readily removed in the moist surfaces of the nose and other respiratory passages, limiting the potential for direct effects on the more sensitive thoracic regions of the respiratory tract during nasal breathing. Factors that can increase penetration of SO_2 to these regions, including oral and oronasal breathing, increased ventilation rates, and the presence of high levels of particles or fog droplets that may act as carriers for SO_2. Evidence from human clinical studies indicate that peak exposures (5 to 15 min) to SO_2 at levels as low as 0.5 ppm have been associated with

increased respiratory symptoms and decreased lung function in exercising asthmatics, with levels as low as 0.25 ppm eliciting respiratory responses in some sensitive individuals. These findings provide supportive evidence that peak concentrations of SO_2 may be driving the observed associations in epidemiological studies. SO_2 at levels such as these are found in only a very few areas in the United States and under specific meteorological conditions.

Second, ambient SO_2 may be serving as an indicator of complex ambient air pollution mixtures that share the same source as SO_2 (i.e., combustion of sulfur-containing fuels or metal smelting). Other components of mixed emissions from these sources include trace elements such as vanadium, nickel, selenium, and arsenic. It should be noted that particulate SO_4^{2-} was found not to be correlated with SO_2 in ambient data for 12 CMSAs with multiple monitors. In multipollutant models adjusting for PM indices, SO_2 effect estimates generally were found to be robust. However, in the event that one or more pollutants act as surrogates for an unmeasured component of a mixture actually responsible for the observed association, the strongest predictor in a multipollutant model could indicate simply which measured pollutant is the best surrogate for the unmeasured pollutant of interest. Therefore, reported SO_2-related effects may represent those of the overall mixture.

Third, in the presence of complex pollution mixtures, copollutants may enhance the toxic capability of SO_2 or SO_2 may influence the toxicity of copollutants. For example, water-soluble gases such as SO_2 that are usually largely removed by deposition to wet surfaces in the upper portion of the respiratory tract could be dissolved in particle-bound water and, thereby, be carried into the lower regions of the respiratory tract. In turn, SO_2 can acidify particles, increasing the bioavailability of soluble transition metals capable of inducing lung injury.

Assessment of the health effects directly attributable to SO_2 at current average ambient concentrations is difficult at present, particularly due to the uncertainties related to exposure characterization in epidemiological studies using ambient SO_2 concentration data and the inability to discern the shape of the concentration-response function in the available epidemiology studies. Lack of clear mechanistic understanding for low level exposures increases the difficulty with which available findings can be integrated in assessing the coherence of SO_2-related evidence. Despite these difficulties, the epidemiological evidence, along with limited toxicological and human clinical information, indicates a likely causal association between short-term exposure to SO_2 and respiratory health outcomes. Whether SO_2 has a direct effect, SO_2 is a surrogate for pollution mixtures with the same source, and/or the toxicity of SO_2 is influencing or influenced by the

presence of copollutants, reduction of ambient SO_2 concentrations will result in decreased frequency and severity of SO_2-related respiratory health effects.

APPENDIX 5A.

SUMMARY OF NEW ANIMAL TOXICOLOGICAL, HUMAN CLINICAL, AND EPIDEMIOLOGICAL STUDIES OF HEALTH EFFECTS ASSOCIATED WITH EXPOSURES TO SULFUR DIOXIDE

TABLE 5A-1. KEY RESPIRATORY HEALTH EFFECTS OF EXPOSURE TO SULFUR DIOXIDE OBSERVED IN ANIMAL TOXICOLOGICAL STUDIES

SO_2 Concentration & Exposure Duration	Species	Observed Effects	References
MORPHOLOGY			
1 ppm, 3 h/day/6 day Evaluated up to 72 h postexposure	Male Hartely guinea pigs	No alveolar lesions.	Conner et al. (1985)
5 ppm, 2 h/day, 5 day/wk/4 wk	Male and female F344 rats	No nasal or pulmonary lesions. No effect on mucociliary clearance of radiolabeled aluminosilicate particles.	Wolff et al. (1989)
LUNG INJURY AND INFLAMMATION			
1 ppm, 5 h/day, 5 day/wk up to 4 and 8 mos	Male Sprague-Dawley rats	Increased bronchial epithelial hyperplasia and number of nonciliated epithelial cells observed at 4 mos.	Smith et al. (1989)
5-21 ppm, 4 h/day/7 day Effects observed at as low as 5 ppm	Male Kunming albino mice	Elevated levels of pro-inflammatory cytokines IL-6 and TNF-α in lung and TNF-α in serum.	Meng et al. (2005a)
5, 50, and 100 ppm, 5 h/day/28 day	Male Wistar rats	No evidence of lung injury and lung epithelial permeability. Significant elevation in neutrophil number of 5-ppm group at day 14.	Langley-Evans et al. (1996)
AIRWAY HYPERRESPONSIVENESS AND ALLERGY			
0.1, 4.3, and 16.6 ppm 8 h/day/5 day With ovalbumin challenge in the last 3 days	Perlbright-female white guinea pigs	Bronchial obstruction with ovalbumin challenge in all the SO_2 groups. SO_2-induced potentiation of allergic sensitization of airway.	Riedel et al. (1988)
0.1 ppm, 5 h/day/5 day With or without ovalbumin exposure	Male, Dunkin-Hartley guinea pigs	Enhanced eosinophil count in SO_2-exposed, and SO_2 + ovalbumin-exposed group of animals. Infiltration of inflammatory cells. SO_2 potentiates ovalbumin-induced asthmatic reaction in guinea pigs.	Park et al. (2001)
5 ppm, whole body 4 h/day/5 day/6 wk Sensitization with Candida albicans after 2 wks of exposure to SO_2	Male Hartley guinea pigs	The number of SO_2-exposed animals with prolonged expiration and inspiration increased after 15 h of challenge with the antigen. SO_2 exposure increases dyspneic symptoms in guinea pigs.	Kitabatake et al. (1995)
5 ppm SO_2 for 4 h Sensitized to Ascaris suum	Sheep	SO_2 exposure significantly increased airway reactivity in allergic sheep.	Abraham et al. (1981)

TABLE 5A-1 (cont'd). KEY RESPIRATORY HEALTH EFFECTS OF EXPOSURE TO SULFUR DIOXIDE OBSERVED IN ANIMAL TOXICOLOGICAL STUDIES

SO_2 Concentration & Exposure Duration	Species	Observed Effects	References
LUNG FUNCTION			
1 ppm SO_2 for 1 h	Male Hartley guinea pigs	Increase in pulmonary resistance and decrease in dynamic compliance up to 1 h following exposure. No effect of SO_2 exposure on breathing frequency, tidal volume or minute volume.	Amdur et al. (1983)
1 ppm, nose only 3 h/day/6 day Analyses up to 48 h following exposure	Ketamine-anesthetized male Hartley guinea pigs	No effect of SO_2 exposure on residual volume, functional reserve capacity, vital capacity, total lung capacity, respiratory frequency, tidal volume, pulmonary resistance, or pulmonary compliance.	Conner et al. (1985)
5 ppm for 45 min	Adult rabbits	SO_2 exposure results in increased lung resistance. Bivagotomy had no effect on this phenomenon, indicating the noninvolvement of vagal reflex in this process. SO_2 had no effect on the lung resistance induced by intravenously administered histamine.	Barthelemy et al. (1988)
5 ppm, 2 h/day for 13 wks	New Zealand white male and female rabbits	SO_2 exposure had no effect on lung resistance, dynamic compliance, transpulmonary pressure, tidal volume, respiration rate, or minute volume.	Douglas et al. (1994)
HOST DEFENSE			
10 ppm for 4 h, nose only	White Swiss mice	No effect on red blood cell Fc-receptor mediated phagocytosis or bactericidal activity.	Jakab et al. (1996)
10 ppm for 4 h, nose only	Male Wistar rats	No effect of SO_2 exposure on alveolar macrophage phagocytosis or bactericidal activity to *Staphylococcus aureus*.	Clarke et al. (2000)
10 ppm for 24 h, 1, 2, and 3 wks	OF1 mice	Respiratory challenge with *Klebsiella pneumoniae* resulted in increased mortality and decreased survival time in SO_2-exposed animals.	Azoulay-Dupuis et al. (1982)

TABLE 5A-2. KEY HUMAN HEALTH EFFECTS OF PEAK EXPOSURE TO SULFUR DIOXIDE OBSERVED IN CLINICAL STUDIES

SO_2 Concentration (ppm)	Exposure Duration	Observed Effects	References
0.2-0.4	5 min–1 h	Significant reductions in FEV_1 and increases in specific airways resistance (sRaw) observed among some asthmatic adults. Some weak and inconsistent evidence to suggest that SO_2 exposure may lead to changes in heart rate variability.	Bethel et al. (1985); Horstman et al. (1986); Linn et al. (1982, 1983, 1987); Routledge et al. (2006); Schachter et al. (1984); Sheppard et al. (1981); Tunnicliffe et al. (2001, 2003)
0.4-0.6	1 min–2 h	Decrements in lung function observed between 0.4- and 0.6-ppm SO_2 in asthmatic adults and adolescents during exercise. Significant interindividual variability in response has been consistently demonstrated. Effects observed within 1-5 min of exposure are generally not enhanced by increasing exposure duration. Respiratory symptoms (e.g., wheezing and chest tightness) increase with increasing exposure concentrations above 0.4 ppm. No respiratory effects reported in healthy, non-asthmatics.	Balmes et al. (1987); Bedi et al. (1979); Gong et al. (1995); Horstman et al. (1986); Koenig et al. (1983); Linn et al. (1982, 1983, 1987); Magnussen et al. (1990); Schachter et al. (1984); Sheppard et al. (1981)
0.6-1.0	1 min–2 h	Specific airway resistance shown to double following 10-min exposures to SO_2 concentrations between 0.25 and 0.75 ppm with moderate exercise in 50% of asthmatics tested. Some evidence of an increase in airway resistance in healthy, non-asthmatic subjects exposed to SO_2 concentrations of as low as 0.75 ppm during heavy exercise. Respiratory effects attributed to SO_2 among asthmatics during exercise may be diminished after cessation of exercise, even with continued SO_2 exposure.	Balmes et al. (1987); Gong et al. (1995); Hackney et al. (1984); Horstman et al. (1986, 1988); Koenig et al. (1983); Linn et al. (1985, 1987); Schachter et al. (1984); Stacy et al. (1981)
≥1.0	3 min–1 h	Among healthy adults, SO_2-attributed decrements in lung function generally occur at concentrations above 1 ppm during exercise and above 5 ppm at rest. Markers of airway inflammation are significantly elevated at 4 h postexposure, reaching peak levels 24 h postexposure.	Amdur et al. (1953); Kreisman et al. (1976); Lawther et al. (1955, 1975); Sandström et al. (1989); Sim and Pattle (1957); Snell and Luchsinger (1969)

TABLE 5A-3. EFFECTS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE ON RESPIRATORY SYMPTOMS AMONG CHILDREN

Reference, Study Location, and Period	Study Population	Averaging Time, Mean (SD) SO_2 Levels (ppb)	Statistics for SO_2 Air Quality Data (ppb)				Standardized Odds Ratio (95% CI)a
			98th %	99th %	Range	Upper Percentile	
UNITED STATES							
Schildcrout et al. (2006) Eight North American Cities 1993-1995	Asthmatic children (n = 990)	24-h avg: 2.2-7.4 (range of city-specific medians)	NR	NR	NR	75th: 3.1, 10.7 90th: 4.4, 14.2 (range in city specific estimates)	Asthma symptoms: SO_2 alone: 1.04 (1.00, 1.08), 3-day sum SO_2 + NO_2: 1.04 (1.00, 1.09), 3-day sum SO_2 + PM_{10}: 1.04 (0.99, 1.08), 3-day sum
Schwartz et al. (1994) Six cities, U.S. Apr-Aug 1985, 1986, 1987 (depends on the city)	Children in grades 2-5 (n = 1,844)	24-h avg: 4.1 (median)	NR	NR	NR	75th: 8.2 90th: 17.9 Max: 81.9	Cough incidence: SO_2 alone: 1.15 (1.02-1.31), 4-day avg SO_2 + PM_{10}: 1.08 (0.93, 1.25), 4-day avg SO_2 + NO_2: 1.09 (0.94, 1.30), 4-day avg
Neas et al. (1995) Uniontown, PA Summer 1990	Children in grades 4-5 (n = 83)	12-h avg: 10.2 5.9 overnight 14.5 daytime	NR	NR	IQR: 11.1	Max: 44.9	Evening cough: 1.19 (1.00, 1.42), lag 12 h
Mortimer et al. (2002) Eight urban areas, U.S. Jun-Aug 1993	Asthmatic children, aged 4-9 (n = 846)	3-h avg: 22 (shown in figure)	NR	NR	0-75 ppb (shown in graph)	NR	Asthma symptoms: SO_2 alone (8 cities): 1.19 (1.06, 1.35), lag 1-2 SO_2 + O3 + NO_2 (7 cities): 1.19 (1.04, 1.37), lag 1-2 SO_2 + O3 + NO_2 + PM_{10} (3 cities): 1.23 (0.94, 1.62), lag 1-2

TABLE 5A-3 (cont'd). EFFECTS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE ON RESPIRATORY SYMPTOMS AMONG CHILDREN

Reference, Study Location, and Period	Study Population	Averaging Time, Mean (SD) SO_2 Levels (ppb)	Statistics for SO_2 Air Quality Data (ppb)				Standardized Odds Ratio (95% CI)a
			98th %	99th %	Range	Upper Percentile	
EUROPE							
Timonen and Pekkanen (1997) Kuopio (urban and suburban), Finland 1994	Children 7-12 yrs with asthma or cough symptoms (n = 169)	24-h avg: 2.3	NR	NR	NR	75th: 2.7 Max: 12.3	Upper respiratory symptoms: 2.71 (1.19, 6.17), lag 0 3.17 (1.21, 8.78), lag 1
Ward et al. (2002) Birmingham and Sandwell, England Jan-Mar 1997 May-Jul 1997	Children, age at enrollment 9 yrs (n = 162)	24-h avg: Median 5.4, Winter 4.7, Summer	NR	NR	2, 18 Winter 2, 10 Summer	NR	Cough: 0.59 (0.25, 1.40), Winter 0.90 (0.49, 1.66), Summer Shortness of breath: 0.59 (0.32, 1.09), Winter 0.81 (0.30, 2.17), Summer Wheeze: 0.79 (0.38, 1.63), Winter 0.77 (0.28, 2.08), Summer (7-day avg lag for above results)
Segala et al. (1998) Paris, France Nov 1992-May 1993	Children 7-15 yrs with physician-diagnosed asthma (n = 84)	24-h avg: 8.3 (5.2)	NR	NR	1.7-32.2	NR	Prevalent asthma: 1.32 (1.08, 1.62), lag 0 1.26 (0.93, 1.71), lag 1 Prevalent shortness of breath: 1.17 (0.53, 2.62), lag 0 1.21 (0.99, 1.49) lag 1 Incident asthma 1.73 (1.15, 2.60), lag 0 1.60 (1.01, 2.53), lag 1 Incident wheeze 1.22 (0.95, 1.58), lag 0 1.13 (0.68, 1.88), lag 1

TABLE 5A-3 (cont'd). EFFECTS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE ON RESPIRATORY SYMPTOMS AMONG CHILDREN

Reference, Study Location, and Period	Study Population	Averaging Time, Mean (SD) SO_2 Levels (ppb)	Statistics for SO_2 Air Quality Data (ppb)				Standardized Odds Ratio (95% CI)a
			98th %	99th %	Range	Upper Percentile	
EUROPE (cont'd)							
Boezen et al. (1998) Amsterdam and Meppel (urban and rural), Netherlands Winter 1993-1994	Children 7-11 yrs, with and without BHR and high serum concentrations of total IgE (n = 632)	24-h avg: Means: 1.7, 8.7 Medians: 1.4, 8.3 (range in city-specific estimates)	NR	NR	1.9, 23.6	NR	Among children with BHR and relatively high serum total IgE: Lower respiratory symptoms: 1.27 (1.09, 1.49), lag 0 1.25 (1.06, 1.48), lag 1 1.69 (1.26, 2.28), 5-day avg
Roemer et al. (1993) Wageningen, the Netherlands Winter 1990-1991	Children with chronic respiratory conditions 6-12 yrs (n = 73)	24-h avg 1-h max	NR	NR	0, 40.4 (24-h avg)	Max: 56.5 (1-h max)	Asthma attack: 1.79 (1.35, 2.38), 7-day avg Wheeze: 1.97 (1.42, 2.72), 7-day avg Waken with symptoms: 1.79 (1.12, 2.87), 7-day avg Shortness of breath: 1.48 (1.06, 2.07), 7-day avg Cough: 1.97 (1.03, 3.77), 7-day avg
Hoek and Brunekreff (1993) Wageningen, Netherlands Winter 1991	Children 7-11 yrs, nonurban area (n = 112)	24-h avg	NR	NR	NR	Max: 40.4	Cough: 1.22 (0.20, 7.39), lag 0 0.25 (0.04, 1.65), lag 1 3.67 (0.002, 7.331.974), 7-day avg Lower respiratory symptoms: 1.82 (0.14, 24.3), lag 0 0.33 (0.02, 6.05), lag 1 0.005 (0.0, 44.7), 5-day avg

TABLE 5A-3 (cont'd). EFFECTS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE ON RESPIRATORY SYMPTOMS AMONG CHILDREN

Reference, Study Location, and Period	Study Population	Averaging Time, Mean (SD) SO_2 Levels (ppb)	Statistics for SO_2 Air Quality Data (ppb)				Standardized Odds Ratio (95% CI)a
			98th %	99th %	Range	Upper Percentile	
EUROPE (cont'd)							
Van der Zee et al. (1999) Urban and nonurban areas, the Netherlands 3 winters, 1992-1995	Children 7-11 yrs, with and without chronic respiratory symptoms (n = 633)	24-h avg: 1.4, 8.8 (range in city-specific medians)	NR	NR	NR	Max: 6.5, 58.5 (range in city-specific maximums)	Lower respiratory symptoms: Urban: SO_2 alone: 1.22 (1.01, 1.46), lag 0 1.14 (0.95, 1.38), lag 1 1.34 (0.98, 1.82), 5-day avg SO_2 + PM_{10}: 1.18 (0.96, 1.45), lag 0 1.03 (0.83, 1.27), lag 1 1.08 (0.72, 1.63), 5-day avg Nonurban: 0.94 (0.79, 1.12), lag 0 0.94 (0.78, 1.13), lag 1 1.10 (0.75, 1.63), 5-day avg

TABLE 5A-3 (cont'd). EFFECTS OF SHORT-TERM EXPOSURE TO SULFUR DIOXIDE ON RESPIRATORY SYMPTOMS AMONG CHILDREN

Reference, Study Location, and Period	Study Population	Averaging Time, Mean (SD) SO_2 Levels (ppb)	Statistics for SO_2 Air Quality Data (ppb)				Standardized Odds Ratio (95% CI)[a]
			98th %	99th %	Range	Upper Percentile	
EUROPE (cont'd)							
Van der Zee et al. (1999) (cont'd)							Cough: Urban: 0.93 (0.84, 1.03), lag 0 1.08 (0.98, 1.19), lag 1 1.08 (0.89, 1.30) 5-day avg Nonurban: 1.05 (0.96, 1.15), lag 0 0.98 (0.90, 1.08), lag 1 1.04 (0.83, 1.30), 5-day avg

[a]24-h avg SO_2 and 12-h avg SO_2 standardized to 10-ppb incremental change; 3-h avg SO_2 standardized to 20-ppb incremental change; and 1-h max SO_2 standardized to 40-ppb incremental change.
NR = Not Reported
BHR = Bronchial Hyperresponsiveness
NR = Not Reported
BHR = Bronchial Hyperresponsiveness

TABLE 5A-4. EFFECTS OF SHORT-TERM SO_2 EXPOSURE ON EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR RESPIRATORY OUTCOMES

Reference, Study Location, and Period	Study Population	Averaging Time, Mean (SD) SO_2 Levels (ppb)	Statistics for SO_2 Air Quality Data (ppb)				Standardized Percent Excess Risk (95% CI)
			98th %	99th %	Range	Upper Percentile	
EMERGENCY DEPARTMENT VISITS - ALL RESPIRATORY							
UNITED STATES							
Wilson et al. (2005) Portland, ME 1998-2000 Manchester, NH 1996-2000	≈ 84,000 ED visits	1-h max: Portland: 11.1 (9.1) Manchester: 16.5 (14.7)	NR	NR	NR	NR	Portland: All ages: 8% (3, 11) 0-14: −2.6% (−10.3, 2.7) 15-64: 11% (5.4, 13.9) 65+: 16.8% (8.2, 25.8) Manchester: All ages: 6% (1, 12) 0-14: 5.4% (−12.8, 25.8) 15-64: 11.0% (0.0, 22.7) 65+: 11.0% (−15.2, 48.4)
Peel et al. (2005) Atlanta, GA Jan 1993-Aug 2000	484,830 ED visits, all ages from 31 hospitals	1-h max: 16.5 (17.1)	NR	NR	NR	90th: 39.0	1.6% (−0.6, 3.8)
EUROPE							
Atkinson et al. (1999b) London, United Kingdom Jan 1992-Dec 1994	98,685 ED visits from 12 hospitals	24-h avg: 8.0 (2.9)	NR	NR	2.8, 30.9	50th: 7.4 90th: 11.7	All Ages: 4.2% (1.1, 7.4) 0-14: 9.0% (4.4, 13.8) 15-64: 4.0% (−0.3, 8.5) 65+: −2.7% (−5.4, 3.3)

TABLE 5A-4 (cont'd). EFFECTS OF SHORT-TERM SO_2 EXPOSURE ON EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR RESPIRATORY OUTCOMES

Reference, Study Location, and Period	Study Population	Averaging Time, Mean (SD) SO_2 Levels (ppb)	Statistics for SO_2 Air Quality Data (ppb)				Standardized Percent Excess Risk (95% CI)
			98th %	99th %	Range	Upper Percentile	
EMERGENCY DEPARTMENT VISITS - ASTHMA							
UNITED STATES							
Jaffe et al. (2003) Cincinnati, Cleveland, Columbus, OH Jul 1991-Jun 1996	4,416 ED visits for asthma, age 5-34	24-h avg: Cincinnati: 13.5 (9.4) Cleveland: 14.7 (9.5) Columbus: 4.2 (3.2)	NR	NR	Cincinnati: 0.6, 49.6 Cleveland: 0.98, 62.8 Columbus: 0, 21.4	NR	Cincinnati: 17.3% (4.7, 30.8) Cleveland: 3.1% (−3.8, 10.7) Columbus: 13.1% (−14.2, 48.6) All Cities: 6.2% (0.5, 11.6)
Wilson et al. (2005) Portland, ME 1998-2000 Manchester, NH 1996-2000	≈ 84,000 ED visits	1-h max: Portland: 11.1 (9.1) Manchester: 16.5 (14.7)	NR	NR	NR	NR	Portland: All ages: 11.0% (0.0, 19.7) 0-14: 5.4% (−12.8, 25.8) 15-64: 11% (0, 22.7) 65+: 11.0% (−15.2, 48.4) Manchester: All ages: 5.4% (−2.6, 16.8) 0-14: 19.7% (−2.6, 51.8) 15-64: 2.7% (−7.8, 13.9) 65+: 11.0% (−28.8, 77.2)
Peel et al. (2005) Atlanta, GA Jan 1993-Aug 2000	Asthma ED visits, all ages and 2-18 yrs from 31 hospitals	1-h max: 16.5 (17.1)	NR	NR	NR	90th: 39.0	0.2% (−3.2, 3.4)

TABLE 5A-4 (cont'd). EFFECTS OF SHORT-TERM SO_2 EXPOSURE ON EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR RESPIRATORY OUTCOMES

Reference, Study Location, and Period	Study Population	Averaging Time, Mean (SD) SO_2 Levels (ppb)	Statistics for SO_2 Air Quality Data (ppb)				Standardized Percent Excess Risk (95% CI)
			98th %	99th %	Range	Upper Percentile	
EUROPE							
Atkinson et al. (1999b) London, United Kingdom Jan 1992-Dec 1994	98,685 ED visits from 12 hospitals	24-h avg: 8.0 (2.9)	NR	NR	2.8, 30.9	50th: 7.4 90th: 11.6	All ages: 7.4% (2.3, 12.8) 0-14: 15.0% (7.1, 23.5) 15-64: 6.3% (−0.8, 13.8)
Hajat et al. (1999) London, United Kingdom 1992-1994	General practitioner visits for asthma	All yr: 24-h avg: 8.0 (2.9) Warm: 24-h avg: 7.7 (2.4) Cool: 24-h avg: 8.3 (3.4)	NR	NR	NR	All yr: 90th: 11.6 Warm: 90th: 10.7 Cool: 90th: 12.4	All ages: 6.6% (1.3, 11.9) 0-14: 6.6% (−1.0, 14.7) 15-64: 5.2% (−1.5, 12.3) 65+: 7.2% (−4.3, 20.1)
Boutin-Forzano et al. (2004) Marseille, France Apr 1997-Mar 1998	549 ED visits for asthma	24-h avg: 8.5	NR	NR	0.0, 35.3	NR	3-49: 0.6% (−1.4, 2.7)
Galan et al. (2003) Madrid, Spain 1995-1998	4,827 ED visits for asthma	24-h avg: 8.9 (5.8)	NR	NR	1.9, 45.6	50th: 7.0 75th: 11.8 90th: 16.5	All ages: 4.9% (−4.2, 15.0)

TABLE 5A-4 (cont'd). EFFECTS OF SHORT-TERM SO_2 EXPOSURE ON EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR RESPIRATORY OUTCOMES

Reference, Study Location, and Period	Study Population	Averaging Time, Mean (SD) SO_2 Levels (ppb)	Statistics for SO_2 Air Quality Data (ppb)				Standardized Percent Excess Risk (95% CI)
			98th %	99th %	Range	Upper Percentile	
EUROPE (cont'd)							
Tenias et al. (1998) Valencia, Spain 1993-1995	734 ED visits for asthma	24-h avg: 10.0 Cold: 11.9 Warm: 8.2 1-h max: 21.2 Cold: 24.3 Warm: 18.1	NR	NR	NR	24-h avg: 50th: 9.8 75th: 12.9 95th: 16.0 1-h max: 50th: 19.6 75th: 27.1 95th: 35.8	>14 yrs: 13.9% (−7.0, 39.4)
Sunyer et al. (1997) Multicity, Europe (Barcelona, Helsinki, Paris, London) 1986-1992	All ED visits for asthma	24-h median: Barcelona: 15.4 Helsinki: 6.0 London: 11.6 Paris: 8.6	NR	NR	Barcelona: 0.8, 60.2 Helsinki: 1.1, 35.7 London: 3.4, 37.6 Paris: 0.4, 82.3	NR	0-14: 3.2% (−0.2, 6.8) 15-64: 0.2% (−2.2, 2.6)
Castellsague et al. (1995) Barcelona, Spain 1986-1989	ED visits for asthma from 4 hospitals	24-h avg: Summer: 15.3 Winter: 19.5	NR	NR	NR	Summer: 50th: 13.5 75th: 20.3 95th: 30.8 Winter: 50th: 18.4 75th: 25.2 95th: 35.3	Summer: 15-64: 5.5% (−2.1, 13.8) Winter: 15-64: 2.1% (−4.2, 9.0)

TABLE 5A-4 (cont'd). EFFECTS OF SHORT-TERM SO_2 EXPOSURE ON EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR RESPIRATORY OUTCOMES

Reference, Study Location, and Period	Study Population	Averaging Time, Mean (SD) SO_2 Levels (ppb)	Statistics for SO_2 Air Quality Data (ppb)				Standardized Percent Excess Risk (95% CI)
			98th %	99th %	Range	Upper Percentile	
EMERGENCY DEPARTMENT VISITS - COPD							
UNITED STATES							
Peel et al. (2005) Atlanta, GA Jan 1993-Aug 2000	COPD ED visits, all ages from 31 hospitals	1-h max: 16.5 (17.1)	NR	NR	NR	90th: 39.0	3.2% (−3, 10)
HOSPITAL ADMISSIONS – ALL RESPIRATORY							
UNITED STATES							
Schwartz (1995) New Haven, CT Tacoma, WA 1988-1990	≈ 13,470 Hospital admissions, ages 65+	24-h avg: New Haven: 29.8 Tacoma: 16.8	NR	NR	NR	New Haven: 75th: 37.6 90th: 59.8 Tacoma: 75th: 21.1 90th: 27.8	New Haven: 1.6% (1.1, 2.6) Tacoma: 3.2% (0.5, 6.2)
CANADA							
Fung et al. (2006) Vancouver, BC Jun 1995-Mar 1999	≈ 41,000 respiratory admissions for elderly (65+ yrs)	24-h avg: 3.46 (1.82)	NR	NR	0.0, 12.5	NR	12.6% (4.1, 22.0) 5% (−1, 12)
Yang et al. (2003) Vancouver, BC 1986-1998	Respiratory hospital admissions among young children (<3 yrs) and elderly (≥65 yrs)	24-h avg: 4.84 (2.84)	NR	NR	NR	75th: 6.25 100th: 24.00	<3 yrs: 3% (−6, 15) ≥65 yrs: 5.8% (0.0, 11.9)
*Burnett et al. (2001) Toronto, ON 1980-1994	All respiratory admissions for young children (<2 yrs)	1-h max: 11.8	NR	55	NR	75th: 15 95th: 32 100th: 110	11% (-0.3, 23.6)

TABLE 5A-4 (cont'd). EFFECTS OF SHORT-TERM SO_2 EXPOSURE ON EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR RESPIRATORY OUTCOMES

Reference, Study Location, and Period	Study Population	Averaging Time, Mean (SD) SO_2 Levels (ppb)	Statistics for SO_2 Air Quality Data (ppb)				Standardized Percent Excess Risk (95% CI)
			98th %	99th %	Range	Upper Percentile	
CANADA (cont'd)							
Luginaah et al. (2005) Windsor, ON Apr 1995-Dec 2000	All respiratory admissions ages 0-14, 15-64, and 65+ from 4 hospitals	1-h max: 27.5 (16.5)	NR	NR	0, 129	NR	All ages, female: 2.1% (−0.7, 5.0) All ages, male: -2.5% (−5.3, 0.5) 0-14, female: 5.6% (0.6, 10.9) 0-14, male: −2.5% (−6.8, 1.9) 15-64, female: 1.6% (−3.7, 7.2) 15-64, male: −4.5% (−8.4, 5.8) 65+, female: 1.5% (−2.6, 5.8) 65+, male: −3.1% (−7.5, 1.5)
AUSTRALIA							
Barnett et al. (2005) Multicity, Australia/New Zealand; (Auckland, Brisbane, Canberra, Christchurch, Melbourne, Perth, Sydney) 1998-2001	All respiratory hospital admissions	24-h avg: Auckland: 4.3 Brisbane: 1.8 Christchurch: 2.8 Sydney: 0.9 NA in Canberra, Melbourne, and Perth 1-h max: Brisbane: 7.6 Christchurch: 10.1 Sydney: 3.7 NA in Auckland, Canberra, Melbourne, and Perth	NR	NR	24-h avg: Auckland: 0, 24.3 Brisbane: 0, 8.2 Christchurch: 0, 11.9 Sydney: 0, 3.9 1-h max Brisbane: 0, 46.5 Christchurch: 0.1, 42.1 Sydney: 0.1, 20.2	NR	1-4 yrs: 5.1% (0.0, 9.1) 5-14: 3.7% (−9.9, 19.5)

TABLE 5A-4 (cont'd). EFFECTS OF SHORT-TERM SO_2 EXPOSURE ON EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR RESPIRATORY OUTCOMES

Reference, Study Location, and Period	Study Population	Averaging Time, Mean (SD) SO_2 Levels (ppb)	Statistics for SO_2 Air Quality Data (ppb)				Standardized Percent Excess Risk (95% CI)
			98th %	99th %	Range	Upper Percentile	
AUSTRALIA (cont'd)							
Petroeschevsky et al. (2001) Brisbane, Australia 1987-1994	33,710 hospital admissions	24-h avg: 4.1 1-h max: 9.2	NR	NR	NR	NR	All ages: −5.9% (−12.4, 1.1) 0-14: 8.0% (−2.9, 20.1) 15-64: −21.6% (−34.4, −6.2)
EUROPE							
Oftedal et al. (2003) Drammen, Norway 1994-2000	All respiratory hospital admissions	24-h avg: 1.1 (0.8)	NR	NR	NR	NR	All ages: 71.8% (15.5, 152.7)
Fusco et al. (2001) Rome, Italy Period of study: 1/1995-10/1997	All respiratory hospital admissions	24-h avg: 3.4 (2.2)	NR	NR	NR	50th: 3.0 75th: 4.5	All age: 1.6% (−4.9, 8.8) 0-14: −2.7% (−4.6, 10.8)
Llorca et al. (2005) Torrelavega, Spain 1992-1995	Hospital admissions from one hospital	24-h avg: 5.0 (6.3)	NR	NR	NR	NR	All ages: 1.0% (−2.8, 4.7)
Anderson et al. (2001) West Midlands conurbation, United Kingdom Oct 1994-Dec 1996	Hospital admissions stratified by age	24-h avg: 7.2 (4.7)	NR	NR	1.9, 59.8	90th: 12.3	All ages: 1.4% (−0.8, 3.8) 0-14: 5.1% (1.6, 8.7) 15-64: −1.0% (−5.3, 3.7) 65+: −2.2% (−5.4, 1.2)

TABLE 5A-4 (cont'd). EFFECTS OF SHORT-TERM SO_2 EXPOSURE ON EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR RESPIRATORY OUTCOMES

Reference, Study Location, and Period	Study Population	Averaging Time, Mean (SD) SO_2 Levels (ppb)	Statistics for SO_2 Air Quality Data (ppb)				Standardized Percent Excess Risk (95% CI)
			98th %	99th %	Range	Upper Percentile	
EUROPE (cont'd)							
Atkinson et al. (1999a) London, England 1992-1994	165,032 hospital admissions	24-h avg: 8.0 (2.9)	NR	NR	2.8, 30.9	50th: 7.4 90th: 11.7	All ages: 3.0% (0.4, 5.6) 0-14: 7.7% (3.8, 11.7) 15-64: 2.8% (−1.2, 7.0) 65+: 3.3% (−0.1, 6.9)
Schouten et al. (1996) Multicity, The Netherlands (Amsterdam, Rotterdam) Period of study: Apr 1977-Sep 1989	All respiratory hospital admissions	24-h avg: Amsterdam: 10.5 Rotterdam: 15.0 1-h max: Amsterdam: 24.4 Rotterdam: 37.2	NR	NR	NR	NR	Amsterdam: 15-64: −2.3% (−5.5, 0.9) 65+: 0.2% (−2.8, 3.3) Rotterdam: 15-64: −2.9% (−6.2, 0.5)
Spix et al. (1998) Multicity (London, Amsterdam, Rotterdam, Paris, Milan), Europe 1977-1991	All respiratory hospital admissions	24-h avg: London: 10.9 Amsterdam: 7.9 Rotterdam: 9.4 Paris: 8.6 Milan: 24.8	NR	NR	NR	NR	15-64: 0.5% (−0.4, 1.3) 65+: 1.1% (0.3, 2.4)

TABLE 5A-4 (cont'd). EFFECTS OF SHORT-TERM SO_2 EXPOSURE ON EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR RESPIRATORY OUTCOMES

Reference, Study Location, and Period	Study Population	Averaging Time, Mean (SD) SO_2 Levels (ppb)	Statistics for SO_2 Air Quality Data (ppb)				Standardized Percent Excess Risk (95% CI)
			98th %	99th %	Range	Upper Percentile	
EUROPE (cont'd)							
Dab et al. (1996) Paris, France Period of study: 1/1/87-9/30/92	Hospital admissions from 27 hospitals	All year: 24-h avg: 11.2 1-h max: 22.5 Warm season 24-h avg: 7.6 1-h max: 16.1 Cold season 24-h avg: 15.1 1-h max: 29.4	NR	NR	NR	All year: 24-h avg: 99th: 50.0 1-h max: 99th: 87.5 Warm season 99th: 18.5 1-h max: 99th: 50.3 Cold season 24-h avg: 99th: 56.0 1-h max: 99th: 100.9	All ages: 1.1% (0.1, 2.1)
Ponce de Leon et al. (1996) London, England 1987-1988 1991-1992	19,901 hospital admissions	24-h avg: 12.1 (4.7)	NR	NR	NR	50th: 11.7 75th: 14.7 90th: 17.7 95th: 20.3	All ages: 0.8 (−0.7, 2.4) 0-14: 0.9 (−1.5, 3.3) 15-64: 2.0% (−0.5, 4.7) 65+: 2.0% (−0.3, 4.4)

TABLE 5A-4 (cont'd). EFFECTS OF SHORT-TERM SO_2 EXPOSURE ON EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR RESPIRATORY OUTCOMES

Reference, Study Location, and Period	Study Population	Averaging Time, Mean (SD) SO_2 Levels (ppb)	Statistics for SO_2 Air Quality Data (ppb)				Standardized Percent Excess Risk (95% CI)
			98th %	99th %	Range	Upper Percentile	
EUROPE (cont'd)							
Walters et al. 1994 Birmingham, United Kingdom 1988-1990	All respiratory hospital admissions	24-h avg: All year: 14.7 Spring: 16.1 Summer: 14.2 Autumn: 15.4 Winter: 12.9	NR	NR	NR	Max: 47.5	All ages: Summer: 1.5% (0.3, 2.7) Winter: 4.5% (2.3, 6.5)
Hagen et al. (2000) Drammen, Norway 1994-1997	Hospital admissions for all respiratory outcomes	24-h avg: Winter: 21 Spring: 18 Summer: 15 Autumn: 19 Number of monitors: 1	NR	NR	Winter: 11, 33 Spring: 13, 29 Summer: 5, 24 Autumn: 16, 23	NR	All ages: 92.8% (16.8, 218.8)
LATIN AMERICA							
Gouveia and Fletcher (2000) São Paulo, Brazil Nov 1992-Sep 1994	All respiratory hospital admissions	24-h avg: 6.9 (3.4)	NR	NR	1.2, 22.9	50th: 6.2 75th: 8.3 95th: 13.5	<5 yrs: 3.7% (−1.7, 9.4)
ASIA							
Wong et al. (1999) Hong Kong 1994-1995	Hospital admissions from 12 hospitals	24-h avg: 6.4	NR	NR	1.0, 25.7	75th: 9.4	0-4 yrs: 1.3% (−2.4, 4.9) 5-64: 2.1% (−1.1, 5.7) 65+: 6.2% (3.2, 9.9)

TABLE 5A-4 (cont'd). EFFECTS OF SHORT-TERM SO_2 EXPOSURE ON EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR RESPIRATORY OUTCOMES

Reference, Study Location, and Period	Study Population	Averaging Time, Mean (SD) SO_2 Levels (ppb)	Statistics for SO_2 Air Quality Data (ppb)				Standardized Percent Excess Risk (95% CI)
			98th %	99th %	Range	Upper Percentile	
HOSPITAL ADMISSIONS - ASTHMA							
UNITED STATES							
Sheppard et al. (1999; reanalysis 2003) Seattle, WA 1987-1994	7,837 asthma hospital admissions for patients <65 yrs	24-h avg: 8	NR	NR	NR	75th: 10.0 90th: 13.0	<65 yrs: 4.0% (−4.0, 10.3)
CANADA							
*Burnett et al. (1999) Toronto, ON 1980-1994	Asthma hospital admissions	24-h avg: 5.35	NR	NR	NR	75th: 8 95th: 17 100th: 57	1.9% (−0.2, 4.0)
Lin et al. (2003) Toronto, ON 1981-1993	7,319 asthma hospital admissions among 6-12 yr olds	24-h avg: 5.36 (5.90)	NR	NR	0, 57.0	75th: 8.00	Boys: 0% (−7.1, 7.2) Girls: 5.8% (−4.3, 16.1)

TABLE 5A-4 (cont'd). EFFECTS OF SHORT-TERM SO_2 EXPOSURE ON EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR RESPIRATORY OUTCOMES

Reference, Study Location, and Period	Study Population	Averaging Time, Mean (SD) SO_2 Levels (ppb)	Statistics for SO_2 Air Quality Data (ppb)				Standardized Percent Excess Risk (95% CI)
			98th %	99th %	Range	Upper Percentile	
AUSTRALIA							
Barnett et al. (2005) Multicity, Australia/New Zealand; (Auckland, Brisbane, Canberra, Christchurch, Melbourne, Perth, Sydney) Period of study: 1998-2001	All respiratory hospital admissions	24-h avg: Auckland: 4.3 Brisbane: 1.8 Christchurch: 2.8 Sydney: 0.9 NA in Canberra, Melbourne, and Perth 1-h max: Brisbane: 7.6 Christchurch: 10.1 Sydney: 3.7 NA in Auckland, Canberra, Melbourne, and Perth	NR	NR	24-h avg: Auckland: 0, 24.3 Brisbane: 0, 8.2 Christchurch: 0, 11.9 Sydney: 0, 3.9 1-h max: Brisbane: 0, 46.5 Christchurch: 0.1, 42.1 Sydney: 0.1, 20.2	NR	1-4 yrs: 6.4% (−7.8, 22.5) 5-14: 6.2% (−10.1, 25.4)
Petroeschevsky et al. (2001) Brisbane, Australia 1987-1994	33,710 hospital admissions	24-h avg: 4.1 1-h max: 9.2	NR	NR	NR	NR	All ages: 8.0% (3.0, 13.1) 0-4: 22.4% (8.7, 37.7) 5-14: 21.1% (−5.5, 55.1) 15-64: 3.3% (−10.5, 11.8) 65+: 12.1% (1.9, 23.4)
EUROPE							
Fusco et al. (2001) Rome, Italy Jan 1995-Oct 1997	All respiratory hospital admissions	24-h avg: 3.4 (2.2)	NR	NR	NR	50th: 3.0 75th: 4.5	All ages: −5.7% (−23.2, 15.9) 0-14: −9.7% (−34.6, 25.2)

TABLE 5A-4 (cont'd). EFFECTS OF SHORT-TERM SO_2 EXPOSURE ON EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR RESPIRATORY OUTCOMES

Reference, Study Location, and Period	Study Population	Averaging Time, Mean (SD) SO_2 Levels (ppb)	Statistics for SO_2 Air Quality Data (ppb)				Standardized Percent Excess Risk (95% CI)
			98th %	99th %	Range	Upper Percentile	
EUROPE (cont'd)							
Atkinson et al. (1999a) London, England 1992-1994	165,032 hospital admissions	24-h avg: 8.0 (2.9)	NR	NR	2.8, 30.9	50th: 7.4 90th: 11.7	All ages: 5.0% (0.6, 9.6) 0-14: 10.1% (4.3, 16.2) 15-64: 6.8% (−0.3, 14.5) 65+: 9.5% (−2.3, 22.7)
Schouten et al. (1996) Multicity, the Netherlands (Amsterdam, Rotterdam) Period of study: Apr 1977-Sep 1989	All respiratory hospital admissions	24-h avg: Amsterdam: 10.5 Rotterdam: 15.0 1-h max: Amsterdam: 24.4 Rotterdam: 37.2	NR	NR	NR	NR	Amsterdam: All ages: −6.0% (−10.7, −1.1)
Dab et al. (1996) Paris, France Jan 1987-Sep 1992	Hospital admissions from 27 hospitals	All year: 24-h avg: 11.2 1-h max: 22.5 Warm season 24-h avg: 7.6 1-h max: 16.1 Cold season 24-h avg: 15.1 1-h max: 29.4	NR	NR	NR	All year: 24 h avg: 99th: 50.0 1-h max: 99th: 87.5 Warm season 99th: 18.5 1-h max: 99th: 50.3 Cold season 24-h avg: 99th: 56.0 1-h max: 99th: 100.9	All ages: 1.8% (0.1, 3.6)

TABLE 5A-4 (cont'd). EFFECTS OF SHORT-TERM SO_2 EXPOSURE ON EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR RESPIRATORY OUTCOMES

Reference, Study Location, and Period	Study Population	Averaging Time, Mean (SD) SO_2 Levels (ppb)	Statistics for SO_2 Air Quality Data (ppb)				Standardized Percent Excess Risk (95% CI)
			98th %	99th %	Range	Upper Percentile	
EUROPE (cont'd)							
Anderson et al. (1998) London, England Apr 1987-Feb 1992	All hospital admissions for asthma	24-h avg: 12.0 (4.4)	NR	NR	3.4, 37.6	50th: 11.6 75th: 14.3 90th: 17.3 95th: 19.5	All ages: 2.8% (1.2, 4.3) 0-14: 0.5% (0.1, 1.0) 15-64: −0.7% (−2.7, 1.3) 65+: 3.1% (−0.7, 7.0)
Walters et al. (1994) Birmingham, United Kingdom 1988-1990	All respiratory hospital admissions	24-h avg: All year: 14.7 Spring: 16.1 Summer: 14.2 Autumn: 15.4 Winter: 12.9	NR	NR	NR	Max: 47.5	Summer: All ages: 0.4% (−2.8, 9.2) Winter: All ages: 0.7% (−2.2, 1.6)
LATIN AMERICA							
Gouveia and Fletcher (2000) São Paulo, Brazil Nov 1992-Sep 1994	All respiratory hospital admissions	24-h avg: 6.9 (3.4)	NR	NR	1.2, 22.9	50th: 6.2 75th: 8.3 95th: 13.5	<5 yrs: 10.4% (−1.9, 24.2)
ASIA							
Wong et al. (1999) Hong Kong, China 1994-1995	Hospital admissions from 12 hospitals	24-h avg: 6.4	NR	NR	1.0, 25.7	75th: 9.4	All ages: 4.6% (−0.5, 9.9)
Lee et al. (2006) Hong Kong, China 1997-2002	26,663 hospital admissions for asthma	24-h avg: 6.6 (4.0)	NR	NR	NR	50th: 5.7 75th: 8.2	<18 yrs: −3.7% (−6.7, −0.6)

TABLE 5A-4 (cont'd). EFFECTS OF SHORT-TERM SO_2 EXPOSURE ON EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR RESPIRATORY OUTCOMES

Reference, Study Location, and Period	Study Population	Averaging Time, Mean (SD) SO_2 Levels (ppb)	Statistics for SO_2 Air Quality Data (ppb)				Standardized Percent Excess Risk (95% CI)
			98th %	99th %	Range	Upper Percentile	
HOSPITAL ADMISSIONS - COPD							
UNITED STATES							
Moolgavkar (2000; reanalysis 2003) Chicago, Los Angeles, Phoenix, 1987-1995	Hospital admissions	24-h avg: Chicago: 6; LA: 2; Phoenix: 2	NR	NR	Chicago: 0.5, 36 LA: 0, 16 Phoenix: 0, 14	Chicago: 75th: 8 LA: 75th: 4 Phoenix: 75th: 4	Chicago: 5% (1.9, 8.2)
CANADA							
Yang (2005) Vancouver, BC 1994-1998	COPD admissions among elderly (65+)	24-h avg: 3.79 (2.12)	NR	NR	0.75, 22.67	NR	0.3% (−26, 15) 7.3% (−7, 23) 15% (−3.9, 31.6)
Burnett et al. (1999) Toronto, ON 1980-1994	COPD hospital admissions	24-h avg: 5.35	NR	NR	NR	75th: 8 95th: 17 100th: 57	0.1% (−2.1, 2.3)

[a] 24-h avg SO_2 standardized to 10 ppb incremental change; 1-h max SO_2 standardized to 40 ppb incremental change.

* Analyses using Poisson GAM with default convergence criteria.

NA: Not Available

NR: Not Reported

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