

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

**(Second 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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# Abbreviations and Acronyms

A	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
$\beta$	beta; the calculated Health Effect Parameter
B[a]P	benzo[a]pyrene
BHR	bronchial hyperresponsiveness
BS	black smoke
CAMP	Childhood Asthma Management Program
CARB	California Air Resources Board
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 <sub>3</sub> -S-H	methyl mercaptan
CH <sub>3</sub> -S-S-CH <sub>3</sub>	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 <sub>2</sub>	carbon disulfide
CVD	cardiovascular disease
DEN	diethylnitrosamine
DEP	diesel exhaust particle
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
Fe	iron
FEMs	Federal Equivalent Methods
FEV <sub>0.75</sub>	forced expiratory volume in 0.75 second
FEV <sub>1</sub>	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 <sup>+</sup>	hydrogen ion
HEADS	Harvard-EPA Annular Denuder System
HEI	Health Effects Institute
HF	high frequency
HNO <sub>2</sub>	nitrous acid
HNO <sub>3</sub>	nitric acid
HO <sub>2</sub>	hydroperoxyl; hydroperoxy radical
H <sub>2</sub> O	water
H <sub>2</sub> O <sub>2</sub>	hydrogen peroxide
HR	heart rate
HRV	heart rate variability
H <sub>2</sub> S	hydrogen sulfide
HSO <sub>3</sub> <sup>-</sup>	hydrogen sulfite, bisulfite
HSO <sub>4</sub> <sup>-</sup>	bisulfate ion
H <sub>2</sub> SO <sub>4</sub>	sulfuric acid
hν	solar ultraviolet photon
IARC	International Agency for Research on Cancer
ICD9	International Classification of Diseases, Ninth Revision
ICDs	implanted cardioverter defibrillators
Ig	immunoglobulin (e.g., IgA, IgE, IgG)
IHD	ischemic heart disease
IIASA	International Institute for Applied Systems Analysis
IL	interleukin (e.g., IL-4, IL-6, IL-8)
IOM	Institute of Medicine
IQR	interquartile range
ISA	Integrated Science Assessment
ISAAC	International Study of Asthma and Allergies in Children

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 <sub>50%</sub>	maximal midexpiratory flow at 50% of forced vital capacity
MMEF	maximal midexpiratory flow
Mn	manganese
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 <sub>3</sub>	sodium carbonate
NADP	National Atmospheric Deposition Program
NAMS	National Air Monitoring Stations
NAPAP	National Acid Precipitation Assessment Program
NAS	National Academy of Sciences
NCAR	National Center for Atmospheric Research
NCEP	National Center for Environmental Prediction
NCICAS	National Cooperative Inner-City Asthma Study
NCore	National Core Monitoring Network
NERL	National Exposure Research Laboratory
NH <sub>4</sub> <sup>+</sup>	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 <sub>2</sub>	nitrogen dioxide
NO <sub>3</sub> <sup>·</sup>	nitrate radical
NO <sub>3</sub> <sup>-</sup>	nitrate ion
NOAA	National Oceanic and Atmospheric Administration
NO <sub>x</sub>	oxides of nitrogen
NR	not reported
NRC	National Research Council
NTN	National Trends Network
NTP	National Toxicology Program
O <sub>2</sub>	molecular oxygen, diatomic oxygen
O <sub>3</sub>	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 <sub>2</sub> )	provocative concentration of SO <sub>2</sub> that produces a 100% increase in specific airway resistance
PD20FEV <sub>1</sub>	20% decrease in forced expiratory volume in 1 second
PD20	provocative dose that produces a 20% decrease in FEV <sub>1</sub>
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 <sub>2.5</sub>	particulate matter with 50% upper cut point aerodynamic diameter of 2.5 µm for sample collection; surrogate for fine PM
PM <sub>10</sub>	particulate matter with 50% upper cut point aerodynamic diameter of 10 µm for sample collection
PM <sub>10-2.5</sub>	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 <sub>13</sub>	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, r	correlation coefficient
RAR	rapidly activating receptor
RAS	roll-around system
Raw	airway resistance
RH	relative humidity
r-MSSD	root mean square of successive differences in R-R intervals.
RR	rate ratio; relative risk
S <sup>2-</sup>	sulfur radical
SAB	Science Advisory Board
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
<sup>35</sup> S	sulfur-35 radionuclide
SLAMS	State and Local Air Monitoring Stations
SO	sulfur monoxide
SO <sub>2</sub>	sulfur dioxide
SO <sub>3</sub>	sulfur trioxide
SO <sub>3</sub> <sup>2-</sup>	sulfite ion
SO <sub>4</sub> <sup>2-</sup>	sulfate ion
SO <sub>x</sub>	sulfur oxides
S <sub>2</sub> O	disulfur monoxide
SPM	suspended particulate matter
sRaw	specific airway 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

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# Preface

## Legislative Requirements

1 Section 109 (42 U.S. Code, 2003b) directs the Administrator to propose and promulgate  
2 “primary” and “secondary” National Ambient Air Quality Standards (NAAQS) for pollutants  
3 listed under section 108. Section 109(b)(1) defines a primary standard as one “the attainment and  
4 maintenance of which in the judgment of the Administrator, based on such criteria and allowing  
5 an adequate margin of safety, are requisite to protect the public health.”<sup>1</sup> A secondary standard,  
6 as defined in section 109(b)(2), must “specify a level of air quality the attainment and  
7 maintenance of which, in the judgment of the Administrator, based on such criteria, is required to  
8 protect the public welfare from any known or anticipated adverse effects associated with the  
9 presence of [the] pollutant in the ambient air.”<sup>2</sup> The requirement that primary standards include  
10 an adequate margin of safety was intended to address uncertainties associated with inconclusive  
11 scientific and technical information available at the time of standard setting. It was also intended  
12 to provide a reasonable degree of protection against hazards that research has not yet identified.  
13 See *Lead Industries Association v. EPA*, 647 F.2d 1130, 1154 (D.C. Cir 1980), cert. denied, 449  
14 U.S. 1042 (1980); *American Petroleum Institute v. Costle*, 665 F.2d 1176, 1186 (D.C. Cir. 1981)  
15 cert. denied, 455 U.S. 1034 (1982). Both kinds of uncertainties are components of the risk  
16 associated with pollution at levels below those at which human health effects can be said to  
17 occur with reasonable scientific certainty. Thus, in selecting primary standards that include an  
18 adequate margin of safety, the Administrator is seeking not only to prevent pollution levels that  
19 have been demonstrated to be harmful but also to prevent lower pollutant levels that may pose an  
20 unacceptable risk of harm, even if the risk is not precisely identified as to nature or degree.

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

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

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

1 In setting standards that are “requisite” to protect public health and welfare, as provided in  
2 section 109(b), EPA’s task is to establish standards that are neither more nor less stringent than  
3 necessary for these purposes. In so doing, EPA may not consider the costs of implementing the  
4 standards. See generally *Whitman v. American Trucking Associations*, 531 U.S. 457, 465-472,  
5 475-76 (D.C. Cir. 2001).

6 Section 109(d)(1) requires that “not later than December 31, 1980, and at 5-year intervals  
7 thereafter, the Administrator shall complete a thorough review of the criteria published under  
8 section 108 and the national ambient air quality standards...and shall make such revisions in  
9 such criteria and standards and promulgate such new standards as may be appropriate...” Section  
10 109(d)(2) requires that an independent scientific review committee “shall complete a review of  
11 the criteria...and the national primary and secondary ambient air quality standards...and shall  
12 recommend to the Administrator any new...standards and revisions of existing criteria and  
13 standards as may be appropriate...” Since the early 1980s, this independent review function has  
14 been performed by the Clean Air Scientific Advisory Committee (CASAC) of EPA’s Science  
15 Advisory Board.

## **History of Reviews of the Primary NAAQS for Sulfur Oxides**

16 On April 30, 1971, the EPA promulgated primary NAAQS for sulfur oxides (SO<sub>x</sub>). These  
17 primary standards, which were based on the findings outlined in the original 1969 Air Quality  
18 Criteria for Sulfur Oxides, were set at 0.14 parts per million (ppm) averaged over a 24-hour  
19 period, not to be exceeded more than once per year, and 0.030 ppm annual arithmetic mean with  
20 SO<sub>2</sub> as the indicator. In 1982, EPA published the *Air Quality Criteria for Particulate Matter and*  
21 *Sulfur Oxides* (EPA, 1982) along with an addendum of newly published controlled human  
22 exposure studies, which updated the scientific criteria upon which the initial standards were  
23 based. In 1986, a second addendum was published presenting newly available evidence from  
24 epidemiologic and controlled human exposure studies (EPA, 1986b). In 1988, EPA published a  
25 proposed decision not to revise the existing standards (53 FR 14926). However, EPA specifically  
26 requested public comment on the alternative of revising the current standards and adding a new  
27 1-hour primary standard of 0.4 ppm.

28 As a result of public comments on the 1988 proposal and other post-proposal  
29 developments, EPA published a second proposal on November 15, 1994 (59 FR 58958). The

1 1994 re-proposal was based in part on a supplement to the second addendum of the criteria  
2 document, which evaluated new findings on short-term SO<sub>2</sub> exposures in asthmatics (EPA,  
3 1994b). As in the 1988 proposal, EPA proposed to retain the existing 24-hour and annual  
4 standards. The EPA also solicited comment on three regulatory alternatives to further reduce the  
5 health risk posed by exposure to high 5-minute peaks of SO<sub>2</sub> if additional protection were judged  
6 to be necessary. The three alternatives were: 1) revising the existing primary SO<sub>2</sub> NAAQS by  
7 adding a new 5-minute standard of 0.60 ppm SO<sub>2</sub>; 2) establishing a new regulatory program  
8 under section 303 of the Act to supplement protection provided by the existing NAAQS, with a  
9 trigger level of 0.60 ppm SO<sub>2</sub>, one expected exceedance; and 3) augmenting implementation of  
10 existing standards by focusing on those sources or source types likely to produce high 5-minute  
11 peak concentrations of SO<sub>2</sub>. On May 22, 1996, EPA's final decision, that revisions of the NAAQS  
12 for SO<sub>x</sub> were not appropriate at that time, was announced in the Federal Register (61 FR 25566).  
13 In that decision, EPA announced an intention to propose guidance, under section 303 of the Act,  
14 to assist states in responding to short-term peak levels of SO<sub>2</sub>. The basis for the decision, and  
15 subsequent litigation, is discussed in Annex A.

# Chapter 1. Introduction

1           This second external review draft Integrated Science Assessment (ISA) presents a concise  
2 synthesis of the most policy-relevant science to form the scientific foundation for the review of  
3 the primary (health-based) NAAQS for SO<sub>x</sub>. This document is intended to “accurately reflect the  
4 latest scientific knowledge useful in indicating the kind and extent of identifiable effects on  
5 public health which may be expected from the presence of [a] pollutant in ambient air” (Clean  
6 Air Act, Section 108, 2003a)<sup>1</sup>. Contained herein are the key information and judgments formerly  
7 contained in the Air Quality Criteria Document (AQCD) for SO<sub>x</sub>; additional details of the  
8 pertinent scientific literature published since the last review, as well as selected older studies of  
9 particular interest, are included in a series of annexes to the draft ISA. This second external  
10 review draft ISA thus serves to update and revise the information available at the time of the  
11 previous review of the NAAQS for SO<sub>x</sub> in 1996.

12           SO<sub>2</sub> is the most important of the monomeric sulfur oxides (SO<sub>x</sub>) for both atmospheric  
13 chemistry and health effects. SO<sub>x</sub> is usually defined to include SO<sub>3</sub> and H<sub>2</sub>SO<sub>4</sub> as well, but  
14 neither is present in the atmosphere in concentrations significant for human exposures.  
15 Descriptions of the atmospheric chemistry of SO<sub>x</sub> include both gaseous and particulate species; a  
16 meaningful analysis would not be possible otherwise. Most studies on the health effects of  
17 gaseous SO<sub>x</sub> focus on SO<sub>2</sub>; effects of other gaseous species are considered as information is  
18 available. The health effects of particulate SO<sub>x</sub> are included in the review of the NAAQS for  
19 particulate matter (PM). In evaluating the health evidence, this second external draft ISA  
20 considers possible influences of other atmospheric pollutants, including interactions of SO<sub>2</sub> with  
21 other co-occurring pollutants such as PM, nitrogen oxides (NO<sub>x</sub>), carbon monoxide (CO), and  
22 ozone (O<sub>3</sub>).

23           As discussed in the Integrated Plan for Review of the Primary NAAQS for SO<sub>x</sub> (EPA,  
24 2007), a series of policy-relevant questions frames this review to provide a scientific basis for a  
25 decision about whether the current primary NAAQS for SO<sub>x</sub> should be retained or revised. The  
26 primary NAAQS for SO<sub>x</sub>, with SO<sub>2</sub> serving as the indicator, is set at 0.14 parts per million (ppm),  
27 averaged over a 24-h period, not to be exceeded more than once per year, and 0.030 ppm annual  
28 arithmetic mean. This second external review draft ISA focuses on evaluation of the newly

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<sup>1</sup>A review of the secondary SO<sub>x</sub> NAAQS, in conjunction with a review of the secondary NAAQS for NO<sub>x</sub>, is underway independently, as is a review of the primary NAAQS for NO<sub>x</sub> and a review of the primary and secondary effects of PM.

1 available scientific evidence to best inform consideration of these framing questions, including  
2 the following:

- 3       ▪ How has new information altered/substantiated the scientific support for the occurrence  
4           of health effects following short- and/or long-term exposure to levels of SO<sub>x</sub> found in  
5           the ambient air?
- 6       ▪ How does new information influence conclusions from the previous review regarding the  
7           effects of SO<sub>x</sub> on susceptible populations?
- 8       ▪ At what levels of SO<sub>x</sub> exposure do health effects of concern occur?
- 9       ▪ How has new information altered conclusions from previous reviews regarding the  
10           plausibility of adverse health effects caused by SO<sub>x</sub> exposure?
- 11       ▪ To what extent have important uncertainties identified in the last review been reduced?  
12           Have new uncertainties emerged?
- 13       ▪ What are the air quality relationships between short-term and long-term exposures  
14           to SO<sub>x</sub>?

## 1.1. Document Development

15       EPA initiated the current formal review of the NAAQS for SO<sub>x</sub> on May 15, 2006 with a  
16       call for information from the public (FR, 2006). In addition to the call for information,  
17       publications are identified through an ongoing literature search process that includes extensive  
18       computer database mining on specific topics. Additional publications were identified by EPA  
19       scientists in a variety of disciplines by combing through relevant, peer-reviewed scientific  
20       literature obtained through these ongoing literature searches, reviewing previous EPA reports,  
21       and a review of reference lists from important publications. All relevant epidemiological, human  
22       clinical, and animal toxicological studies, including those related to exposure-response  
23       relationships, mechanism(s) of action, or susceptible subpopulations published since the last  
24       review were considered. Added to the body of research were EPA's analyses of air quality and  
25       emissions data, studies on atmospheric chemistry, transport, and fate of these emissions, as well  
26       as issues related to exposure to SO<sub>x</sub>. Further information was acquired from consultation with  
27       content and area experts and the public. Annex A has more discussion of search strategies and  
28       criteria for study selection.

## 1.2. Document Organization

1 This second external review draft ISA is composed of five chapters. This introductory  
2 chapter presents background information, discusses the purpose of the document, and  
3 characterizes the search, evaluation and retrieval process of policy-relevant scientific studies.  
4 Chapter 2 highlights key concepts or issues relevant to understanding the atmospheric chemistry,  
5 sources, exposure, and dosimetry of SO<sub>x</sub>, following a “source-to-dose” paradigm. Chapter 3  
6 evaluates and integrates epidemiological, human clinical, and animal toxicological information  
7 relevant to the review of the primary NAAQS for SO<sub>x</sub>. Chapter 4 has information related to the  
8 public health impact of ambient SO<sub>x</sub> exposure, with emphasis on potentially susceptible and  
9 vulnerable population groups. Finally, Chapter 5 summarizes key findings and conclusions from  
10 the atmospheric sciences, ambient air data analyses, exposure assessment, dosimetry, and health  
11 effects for consideration in the review of the NAAQS for SO<sub>x</sub>.

12 A series of annexes supplement this second external review draft ISA. The annexes provide  
13 additional details of the pertinent literature published since the last review, as well as selected  
14 older studies of particular interest. These annexes contain information on:

- 15       ▪ atmospheric chemistry of SO<sub>x</sub> as well as the sampling and analytic methods for  
16       measurement of SO<sub>x</sub><sup>1</sup>;
- 17       ▪ environmental concentrations and human exposure to SO<sub>x</sub>;
- 18       ▪ toxicological studies of health effects in laboratory animals;
- 19       ▪ human clinical studies of health effects related to peak (5-10 min) and short-term (1-h or  
20       longer) exposure to SO<sub>x</sub>; and
- 21       ▪ epidemiological studies of health effects from short- and long-term exposure to SO<sub>x</sub>.

22 Detailed information about methods and results of health studies is summarized in tabular  
23 format, and generally includes information about: concentrations of SO<sub>x</sub> and averaging times;  
24 study methods employed; results and comments; and quantitative results for relationships  
25 between effects and exposure to SO<sub>x</sub>.

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<sup>1</sup> This section also includes information on NO<sub>2</sub>, in order to support the reviews of the primary and secondary NAAQS for both SO<sub>2</sub> and NO<sub>2</sub>. The atmospheric chemistry of NO<sub>x</sub> and SO<sub>x</sub> are intricately linked; discussion of their combined chemistry is more effective and more efficient than a separate discussion of each pollutant.

### 1.3. EPA Framework for Causal Determinations

1 It is important to have a consistent and transparent basis to evaluate the causal nature of air  
2 pollution-induced health effects. The framework described below establishes uniform language  
3 concerning causality and brings more specificity to the findings. It draws standardized language  
4 from across the Federal government and wider scientific community, especially from the recent  
5 National Academy of Sciences (NAS) Institute of Medicine (IOM) document, *Improving the*  
6 *Presumptive Disability Decision-Making Process for Veterans* (IOM, 2007), the most recent  
7 comprehensive work on evaluating the causality of health effects. This section:

- 8       ▪ describes the kinds of scientific evidence used in establishing a general causal  
9       relationship between exposure and health effects;
- 10       ▪ defines cause, in contrast to statistical association;
- 11       ▪ discusses the sources of evidence necessary to reach a conclusion about the existence of a  
12       causal relationship;
- 13       ▪ highlights the issue of multifactorial causation;
- 14       ▪ identifies issues and approaches related to uncertainty; and
- 15       ▪ provides a framework for classifying and characterizing the weight of evidence in support  
16       of a general causal relationship.

17 Approaches to assessing the separate and combined lines of evidence (e.g.,  
18 epidemiological, human clinical, animal toxicological, and in vitro studies) have been formulated  
19 by a number of regulatory and science agencies, including the IOM of the National Academies of  
20 Science (IOM, 2008), International Agency for Research on Cancer (IARC, 2006), EPA  
21 Guidelines for Carcinogen Risk Assessment (EPA, 2005), Centers for Disease Control and  
22 Prevention (CDC, 2004), and National Acid Precipitation Assessment Program (NAPAP, 1991).  
23 Highlights or excerpts from the various decision framework documents are included in Annex A.

24 These formalized approaches offer guidance for assessing causality. The frameworks are  
25 similar in nature, although adapted to different purposes, and have proved effective in providing  
26 a uniform structure and language for causal determinations. Moreover, these frameworks must  
27 support decision-making under conditions of uncertainty.

### **1.3.1. Scientific Evidence Used in Establishing Causality**

1           The most compelling evidence of a causal relationship between pollutant exposures and  
2 human health effects comes from human clinical studies. This type of study experimentally  
3 evaluates the health effects of administered exposures in humans under highly-controlled  
4 laboratory conditions.

5           In epidemiological or observational studies of humans, the investigator does not control  
6 exposures or intervene with the study population. Broadly, observational studies can describe  
7 associations between exposures and effects. These studies fall into several categories: cross-  
8 sectional, prospective cohort, time-series, and panel studies. “Natural experiments” occur  
9 occasionally in epidemiology; these include comparisons of health effects before and after a  
10 change in population exposures, such as closure of a pollution source.

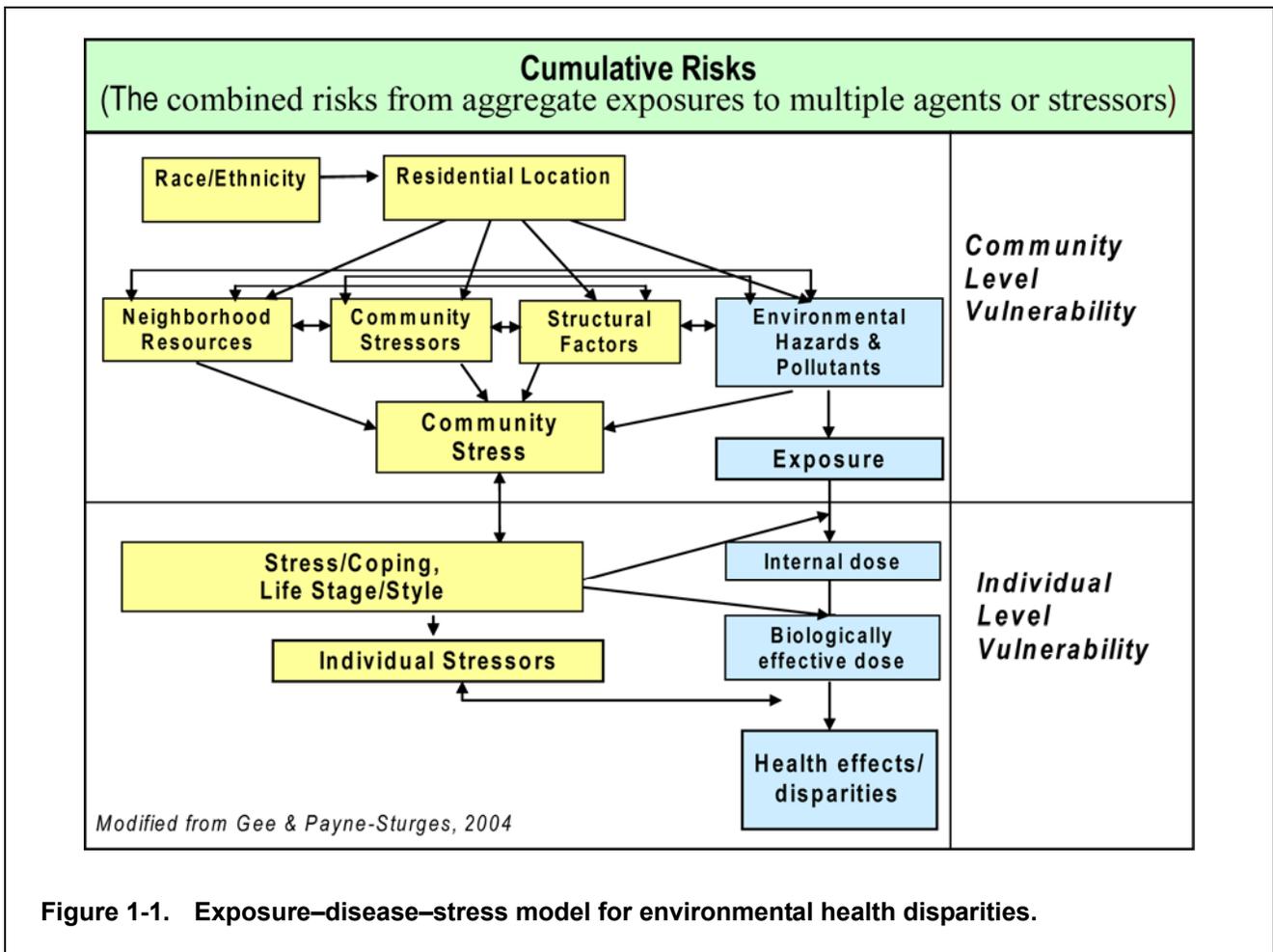
11           Experimental animal data complements the clinical and observational data; these studies  
12 can help characterize effects of concern, exposure-response relationships, sensitive  
13 subpopulations and modes of action. In the absence of clinical or epidemiological data, animal  
14 data alone may be sufficient to support a likely causal determination, assuming that humans  
15 respond similarly to the experimental species.

### **1.3.2. Association and Causation**

16           Association and causation are not the same. “Cause” conveys the notion of a significant,  
17 effectual relationship between an agent and an associated disorder or disease in the population.  
18 “Association” is the statistical dependence among multiple (two or more) events, characteristics,  
19 or other variables. An association is merely prima facie evidence for causation; alone, it is not  
20 sufficient for proof of a causal relationship between exposure and disease. Unlike an association,  
21 a causal claim supports the creation of counterfactual claims; that is, a claim about what the  
22 world would have been like under different or changed circumstances (IOM, 2008). Currently,  
23 much of the newly available health information evaluated in the draft ISA comes from  
24 epidemiological studies that report a statistical association between exposure and health  
25 outcome.

26           It is recognized that many of the health outcomes evaluated in ISAs have complex  
27 etiologies. Most diseases, such as cancer or coronary heart disease, result from a complex web of  
28 causation, whereby one or more agents can initiate a disease process. The outcome could depend

1 on many factors, including age, genetic susceptibility, nutritional status, immune competence,  
 2 social factors, and others (Gee and Payne-Sturges, 2004; IOM, 2008). Figure 1-1 shows a  
 3 diagram of a variety of etiologic factors that contribute to disease. Exposure to multiple agents  
 4 together could result in synergistic or antagonistic effects that are different from what might  
 5 result from exposure to each agent separately.<sup>1</sup> The results are the net effect of many actions and  
 6 counteractions.



### 1.3.3. Evidence for Going beyond Association to Causation

7 Moving from association to causation involves elimination of alternative explanations for  
 8 the association. Human clinical studies are experiments in which subjects in a population are

<sup>1</sup> For example, a multiplicative interaction relative risk (RR) could be defined as  $RR_{int(mult)} = RR_{joint} / RR_E \times RR_S$ . An additive interaction RR could be defined as  $RR_{int(add)} = RR_{joint} - RR_E - RR_S + 1$

1 randomly allocated into groups, usually called study and control groups, and exposed to a  
2 pollutant or a sham. The results are assessed by rigorous comparison of rates of appropriate  
3 outcomes between the study and control groups. Randomized human clinical studies are  
4 generally regarded as the most scientifically rigorous method of hypothesis testing available. By  
5 assigning exposure randomly, the study design attempts to remove the effect of any factor that  
6 might influence exposure. Done properly, and setting aside randomness, only a causal  
7 relationship between exposure and health outcome should produce observed associations in  
8 randomized clinical trials. In another type of human clinical study, the same subject is exposed to  
9 a pollutant and a sham at different time points, and the responses to the two types of exposures  
10 are compared. This study design is also effective at controlling for any potential confounders,  
11 since the subject is serving as his/her own control. A lack of observation of effects from human  
12 clinical studies does not necessarily mean that a causal relationship does not occur. Human  
13 clinical studies are often limited because the study population is generally small, which restricts  
14 the ability to discern statistically significant findings. In addition, the most susceptible  
15 individuals may be explicitly excluded (for ethical reasons), and other susceptible individuals or  
16 groups, such as those with nutritional deficits, may not be included.

17         Inferring causation from epidemiological studies requires consideration of potential  
18 confounders. When associations are found in epidemiological studies, one approach to remove  
19 spurious association from possible confounders is statistical control on characteristics that may  
20 differ between exposed and unexposed persons; this is frequently termed “adjustment.”  
21 Multivariable regression models constitute one tool for estimating the association between  
22 exposure and outcome after adjusting for characteristics of participants that might confound the  
23 results. Another way to adjust for potential confounding is through stratified analysis, i.e.,  
24 examining the association within homogeneous groups with the confounding variable. The use of  
25 stratified analyses has an additional benefit: it allows examination of effect modification through  
26 comparison of the effect estimates across different groups. If investigators successfully measured  
27 characteristics that distort the results, adjustment of these factors help separate a spurious from a  
28 true causal association. Appropriate statistical adjustment for confounders requires identifying  
29 and measuring all reasonably expected confounders. Deciding which variables to control for in a  
30 statistical analysis of the association between exposure and disease depends on knowledge about

1 possible mechanisms. Identifying these mechanisms makes it possible to control for potential  
2 sources that may result in a spurious association.

3 Measurement error is another problem encountered when adjusting for spurious  
4 associations. In multivariate analyses, the effects of a well-measured covariate may be  
5 overestimated, in contrast to a more poorly measured covariate. There are several components  
6 that contribute to exposure measurement error in these studies, including the difference between  
7 true and measured ambient concentrations, the difference between average personal exposure to  
8 ambient pollutants and ambient concentrations at central monitoring sites, and the use of average  
9 population exposure rather than individual exposure estimates.

10 It is difficult to identify and measure all potential confounders in epidemiological studies.  
11 Confidence that unmeasured confounders are not producing the findings is increased when  
12 multiple studies are conducted in various settings using different subjects or exposures; each of  
13 which might eliminate another source of confounding from consideration. Thus, multi-city  
14 studies which use a consistent method to analyze data from across locations with different levels  
15 of covariates can provide insight on potential confounding in associations. The number and  
16 degree of diversity of covariates, as well as their relevance to the potential confounders, remain  
17 matters of scientific judgment. Intervention studies, because of their experimental nature, can be  
18 particularly useful in characterizing causation.

19 In addition to clinical and epidemiological studies, the tools of experimental biology have  
20 been valuable for developing insights into human physiology and pathology. Laboratory tools  
21 have been extended to explore the effects of putative toxicants on human health, especially  
22 through the study of model systems in other species. Background knowledge of the biological  
23 mechanisms by which an exposure might or might not cause disease can prove crucial in  
24 establishing, or negating, a causal claim. At the same time, species can differ from each other in  
25 fundamental aspects of physiology and anatomy (e.g., metabolism, airway branching, hormonal  
26 regulation) that may limit extrapolation. Testable hypotheses about the causal nature of proposed  
27 mechanisms or modes of action are central to utilizing experimental data in causal  
28 determinations.

### 1.3.4. Multifactorial Causation

1 Scientific judgment is needed regarding likely sources and magnitude of confounding,  
2 together with judgment about how well the existing constellation of study designs, results, and  
3 analyses address this potential threat to inferential validity. One key consideration in this review  
4 is evaluation of the potential contribution of SO<sub>x</sub> to health effects, when it is a component of a  
5 complex air pollutant mixture. There are multiple ways by which SO<sub>x</sub> might cause or be  
6 associated with adverse health effects. First, the reported SO<sub>x</sub> effect estimates in epidemiological  
7 studies may reflect independent SO<sub>x</sub> effects on respiratory health. Second, ambient SO<sub>x</sub> may be  
8 serving as an indicator of complex ambient air pollution mixtures that share the same source as  
9 SO<sub>x</sub> (i.e., combustion of sulfur-containing fuels or metal smelting). Finally, copollutants may  
10 mediate the effects of SO<sub>x</sub> or SO<sub>x</sub> may influence the toxicity of copollutants. Epidemiologists use  
11 the term “interaction” or “effect modification” to denote the departure of the observed joint risk  
12 from what might be expected based on the separate effects of the factors. These possibilities are  
13 not necessarily exclusive. In addition, confounding can result in the production of an association  
14 between adverse health effects and SO<sub>2</sub> that is actually attributable to another factor that is  
15 associated with SO<sub>2</sub> in a particular study. Multivariate models are the most widely used strategy  
16 to address confounding in epidemiological studies, but such models are not readily interpreted  
17 when assessing effects of covarying pollutants such as PM, SO<sub>2</sub>, and nitrogen dioxide (NO<sub>2</sub>).

### 1.3.5. Uncertainty

18 The science of estimating the causal influence of an exposure on disease is an uncertain  
19 one. There are two distinct levels of uncertainty to be considered here:

- 20 ■ Model uncertainty—uncertainty regarding gaps in scientific theory required to make  
21 predictions on the basis of causal inferences.
- 22 ■ Parameter uncertainty—uncertainty as to the statistical estimates within each model.

23 Assessment of model uncertainty involves:

- 24 ■ whether exposure causes the health outcome;
- 25 ■ the set of confounders associated with exposure and health outcome;

1       ▪ which parametric forms best describe the relations of exposure and confounders with  
2       outcome; and

3       ▪ whether other forms of bias could be affecting the association.

4       Model uncertainty is not limited to the qualitative causal structure: it also involves factors  
5 such as uncertainty about the parametric form of the model specified, the variables included and  
6 whether or not measurement error is modeled. When mechanistic knowledge exists, this  
7 important source of uncertainty can be reduced. In contrast, uncertainty about the parameter  
8 estimates (regression coefficients) for a given model is a well-studied problem. The important  
9 point is that these reports of uncertainty are conditional on the model providing a sufficiently  
10 adequate approximation of reality so that inferences are valid. The overall scientific inference  
11 involves evaluation of model uncertainty and uncertainty about parameter estimates given to  
12 each model.

13       There are systematic, quantitative approaches for including uncertainty about the model in  
14 an assessment of overall uncertainty about a causal inference, such as sensitivity analysis and  
15 model averaging. Sensitivity analysis attempts to quantify the sensitivity of the parameter  
16 estimate in relation to assumptions about the model. Uncertainty ranges can be estimated using  
17 classical analysis (Robinson, 1989) or the Monte Carlo technique (Eggleston, 1993). By  
18 averaging over many different competing models, Bayesian Model Averaging incorporates  
19 model uncertainty into conclusions about parameters and prediction.

### **1.3.6. Application of Framework**

20       EPA uses a two-step approach to evaluate the scientific evidence on health effects of  
21 exposure to criteria pollutants. These two steps address two policy relevant questions noted in  
22 the beginning of this chapter – what are (if any) the effects of SO<sub>x</sub> on susceptible populations,  
23 given the total body of evidence, and at what levels of SO<sub>x</sub> exposure do health effects of concern  
24 occur. The first step determines the weight of evidence in support of causation and characterizes  
25 the strength of any resulting causal classification. The second step includes further evaluation of  
26 the quantitative evidence regarding the concentration-response relationships and the levels,  
27 duration and pattern of exposures at which effects are observed.

1 To aid judgment, various “aspects”<sup>1</sup> of causality have been discussed by many  
2 philosophers and scientists. The most widely cited aspects of causality in epidemiology, and  
3 public health in general, were articulated by Sir Austin Bradford Hill in 1965 and have been  
4 widely used (EPA, 2005; IARC, 2006; Surgeon General, 2004; IOM, 2008). These nine aspects  
5 (Hill, 1965) have been modified (below) for use in causal determinations specific to health and  
6 environmental effects and pollutant exposures.<sup>2</sup>

---

**Table 1-1 Aspects to aid in judging causality.**

1. ***Consistency of the observed association.*** An inference of causality is strengthened when a pattern of elevated risks is observed across several independent studies. The reproducibility of findings constitutes one of the strongest arguments for causality. If there are discordant results among investigations, possible reasons such as differences in exposure, confounding factors, and the power of the study are considered.
2. ***Strength of the observed association.*** The finding of large, precise risks increases confidence that the association is not likely due to chance, bias, or other factors. A modest risk, however, does not preclude a causal association and may reflect a lower level of exposure, an agent of lower potency, or a common disease with a high background level.
3. ***Specificity of the observed association.*** As originally intended, this refers to increased inference of causality if one cause is associated with a single effect or disease (Hill, 1965). Based on our current understanding this is now considered one of the weaker guidelines for causality; for example, many agents cause respiratory disease and respiratory disease has multiple causes. The ability to demonstrate specificity under certain conditions remains, however, a powerful attribute of experimental studies. Thus, although the presence of specificity may support causality, its absence does not exclude it.
4. ***Temporal relationship of the observed association.*** A causal interpretation is strengthened when exposure is known to precede development of the disease.

---

<sup>1</sup>The “aspects” describe by Hill (1965) have become, in the subsequent literature, more commonly described as “criteria.” The original term “aspects” is used here to avoid confusion with ‘criteria’ as it is used, with different meaning, in the Clean Air Act.

<sup>2</sup>The Hill aspects were developed for use with epidemiology data. They have been modified here for use with a broader array of data, i.e., epidemiological, controlled human exposure, and animal toxicological studies, as well as *in vitro* data, and to be more consistent with EPA’s Guidelines for Carcinogen Risk Assessment.

5. **Biological gradient (exposure-response relationship).** A clear exposure-response relationship (e.g., increasing effects associated with greater exposure) strongly suggests cause and effect, especially when such relationships are also observed for duration of exposure (e.g., increasing effects observed following longer exposure times). There are, however, many possible reasons that a study may fail to detect an exposure-response relationship. Thus, although the presence of a biologic gradient may support causality, the absence of an exposure-response relationship does not exclude a causal relationship.
6. **Biological plausibility.** An inference of causality tends to be strengthened by consistency with data from experimental studies or other sources demonstrating plausible biological mechanisms. A lack of biologic understanding, however, is not a reason to reject causality.
7. **Coherence.** An inference of causality may be strengthened by other lines of evidence (e.g., clinical and animal studies) that support a cause-and-effect interpretation of the association. The absence of other lines of evidence, however, is not a reason to reject causality.
8. **Experimental evidence (from human populations).** Experimental evidence is generally available from human populations for the criteria pollutants. The strongest evidence for causality can be provided when a change in exposure brings about a change in adverse health effect or disease frequency in either clinical or observational studies.
9. **Analogy.** Structure activity relationships and information on the agent's structural analogs can provide insight into whether an association is causal. Similarly, information on mode of action for a chemical, as one of many structural analogs, can inform decisions regarding likely causality.

1           While these aspects provide a framework for assessing the evidence, they do not lend  
2 themselves to being considered in terms of simple formulas or fixed rules of evidence leading to  
3 conclusions about causality (Hill, 1965). For example, one cannot simply count the number of  
4 studies reporting statistically significant results or statistically nonsignificant results for health  
5 effects and reach credible conclusions about the relative weight of the evidence and the  
6 likelihood of causality. Rather, these important considerations are taken into account with the  
7 goal of producing an objective appraisal of the evidence, informed by peer and public comment  
8 and advice, which includes weighing alternative views on controversial issues. Additionally, it is  
9 important to note that the principles in Table 1-1 cannot be used as a strict checklist, but rather to  
10 determine the weight of the evidence for inferring causality. In particular, the absence of one or  
11 more of the principles does not automatically exclude a study from consideration (e.g., see  
12 discussion in U.S. Surgeon General's Report, 2004).

### 1.3.7. First Step—Determination of Causality

1 In the ISA, EPA assesses results of recent publications, in light of evidence available  
2 during the previous NAAQS review, to draw conclusions on the causal relationships between  
3 relevant pollutant exposures and health outcomes. This second external review draft ISA uses a  
4 five-level hierarchy that classifies the weight of evidence for causation, not just association.<sup>1</sup>;  
5 that is, whether the weight of scientific evidence makes causation at least as likely as not, in the  
6 judgment of the reviewing group. In developing this hierarchy, EPA has drawn on the work of  
7 previous evaluations, most prominently the IOM’s Improving the Presumptive Disability  
8 Decision-Making Process for Veterans (IOM, 2008), EPA’s Guidelines for Carcinogen Risk  
9 Assessment (EPA, 1986a), and the U.S. Surgeon General’s smoking reports (U.S. Surgeon  
10 General’s Report, 2004). These efforts are presented in more detail in Annex A. In the draft ISA,  
11 EPA uses a series of five descriptors to characterize the weight of evidence on whether  
12 associations are in fact causal. This weight of evidence evaluation is based on various lines of  
13 evidence from epidemiological studies, animal studies, or other mechanistic, toxicological, or  
14 biological sources. These separate judgments are integrated into a qualitative statement about the  
15 overall weight of the evidence and causality. The five descriptors for causal determination are  
16 described in Table 1-2.

**Table 1-2. Weight of evidence for causal determination.**

<b>Sufficient to infer a causal relationship</b>	Evidence is sufficient to conclude that there is a causal relationship between relevant pollutant exposure and the outcome. That is, a positive association has been observed between the pollutant and the outcome in studies in which chance, bias, and confounding could be ruled out with reasonable confidence. For example, controlled human exposures, epidemiologic “natural experiments,” or observational studies supported by other lines of evidence. Generally, determination is based on multiple studies by multiple investigators.
<b>Sufficient to infer a likely causal relationship (i.e., more likely than than not).</b>	Evidence is sufficient to conclude a likely causal association between relevant pollutant exposures and the outcome. That is, a positive association has been observed between the pollutant and the outcome in studies in which chance and bias can be ruled out with reasonable confidence but potential confounding issues remain. For example, a) observational studies show positive associations but copollutant exposures are difficult to address and/or other lines of evidence (controlled human exposure, animal, or mechanism of action information) are limited or inconsistent; or b) animal evidence from multiple studies, sex, or species is positive but limited or no human data are available. Generally, determination is based on multiple studies by multiple investigators.

<sup>1</sup> It should be noted that the CDC and IOM frameworks use a four-category hierarchy for the strength of the evidence. A five-level hierarchy is used here to be consistent with the EPA Guidelines for Carcinogen Risk Assessment and to provide a more nuanced set of categories.

<b>Suggestive, but not sufficient to infer a causal relationship</b>	Evidence is suggestive of an association between relevant pollutant exposures and the outcome, but is limited because chance, bias and confounding cannot be ruled out. For example, at least one high-quality study shows a positive association but the results of other studies are inconsistent.
<b>Inadequate to infer the presence or absence of a causal relationship</b>	The available studies are of insufficient quality, consistency or statistical power to permit a conclusion regarding the presence or absence of an association between relevant pollutant exposure and the outcome. For example, studies fail to control for confounding, have inadequate exposure assessment, or fail to address latency.
<b>Suggestive of no causal relationship</b>	Several adequate studies, covering the full range of levels of exposure that human beings are known to encounter and considering sensitive subpopulations, are mutually consistent in not showing a positive association between exposure and the outcome at any level of exposures. In addition, the possibility of a very small elevation in risk at the levels of exposure studied can never be excluded.

### 1.3.8. Second Step—Evaluation of Population Response

1           Beyond judgments regarding causality are questions relevant to characterizing exposure  
2 and risk to populations (i.e., at what levels do health effects occur). Such questions include:

- 3           ▪ Under what exposure conditions (dose or exposure, duration and pattern) are effects  
4           seen?
- 5           ▪ What is the shape of the concentration-response or dose-response relationship?
- 6           ▪ What population groups appear to be affected or more susceptible to effects?

7           On the population level, causal and likely causal claims typically characterize how risk—  
8 the probability of health effects—changes in response to exposure. Initially, the response is  
9 evaluated within the range of observation. Approaches to analysis of the range of observation of  
10 epidemiological and human clinical studies are determined by the type of study and methods of  
11 exposure/dose and response measurement. Extensive human data for concentration-response  
12 analyses exists for all criteria pollutants, unlike most other environmental pollutants. Animal data  
13 also can inform concentration-response, particularly relative to dosimetry, mechanisms of action,  
14 and characteristics of sensitive subpopulations.

15           An important consideration in characterizing the public health impacts associated with  
16 exposure to a pollutant is whether the concentration-response relationship is linear across the full  
17 concentration range encountered, or if nonlinear relationships exist along any part of this range.  
18 Of particular interest is the shape of the concentration-response curve at and below the level of  
19 the current standards. The complex molecular and cellular events that underlie cancer and  
20 noncancer toxicity are likely to be both linear and nonlinear, and vary depending on dose.

1 Additionally, many chemicals and agents may act by perturbing naturally occurring background  
2 processes that lead to disease. At the human population level, however, various sources of  
3 variability and uncertainty tend to smooth and “linearize” the concentration-response function  
4 (such as the low data density in the lower concentration range, possible influence of  
5 measurement error, and individual differences in susceptibility to air pollution health effects).  
6 These attributes of population dose-response may explain why the available human data at  
7 ambient concentrations for some environmental pollutants (e.g., ozone, lead [Pb], PM,  
8 secondhand tobacco smoke, radiation) do not exhibit evident thresholds for cancer or noncancer  
9 health effects, even though likely mechanisms of action include nonlinear processes for some  
10 key events. These attributes of human population dose-response relationships have been  
11 extensively discussed in the broader epidemiological literature (e.g., Rothman and Greenland,  
12 1998).

## 1.4. Conclusions

13 This second external review draft ISA strives to present a concise review, synthesis, and  
14 evaluation of the most policy-relevant science, and communicates critical science judgments  
15 relevant to the NAAQS review. It reviews the most policy relevant evidence from  
16 epidemiological, human clinical, and animal toxicological studies, including mechanistic  
17 evidence from basic biological science. Annexes to the ISA provide additional details of the  
18 literature published since the last review. A framework for making critical judgments concerning  
19 causality is presented in this chapter. It relies on a widely accepted set of principles and  
20 standardized language to express evaluation of the evidence. This approach can bring rigor and  
21 clarity to the current and future assessments. This ISA should assist EPA and others, now and in  
22 the future, to represent accurately what is presently known—and what remains unknown—  
23 concerning the effects of sulfur oxides on human health.

## Chapter 2. Source to Tissue Dose

1           This chapter contains basic information about concepts and findings in atmospheric  
2 sciences, human exposure assessment, and human dosimetry. It is meant to serve as a prologue  
3 for the detailed discussions of health effects data in Chapters 3 and 4. Section 2.1 gives an  
4 overview of the sources of SO<sub>2</sub>. Atmospheric chemistry processes involved in the oxidation of  
5 SO<sub>2</sub> and those involved in the production of SO<sub>2</sub> from reduced sulfur gases in the atmosphere are  
6 discussed in Section 2.2. A description of SO<sub>2</sub> measurement methods and related issues are  
7 presented in Section 2.3. Data for ambient SO<sub>2</sub> concentrations are characterized in Section 2.4.  
8 Policy relevant background concentrations of SO<sub>2</sub>, i.e., those concentrations defined to result  
9 from uncontrollable emissions, are also presented in Section 2.4. Factors related to personal  
10 exposure to SO<sub>2</sub> are discussed in Section 2.5. Finally, Section 2.6 covers the dosimetry of SO<sub>2</sub> in  
11 the respiratory tract. This organization generally follows that given in the National Research  
12 Council (NRC) paradigm for integrating air pollutant research (NRC, 1998).

### 2.1. Sources of Sulfur Oxides

13           Industrial emissions of SO<sub>2</sub> in the United States are mainly due to combustion of fossil  
14 fuels by electrical utilities (~66 %) and industry (~29%); transportation-related sources  
15 contribute minimally (~5%) (2002 statistics) (EPA, 2006d). Thus, most SO<sub>2</sub> emissions originate  
16 from point sources. Annex B has a detailed breakdown of emissions by source category. Almost  
17 all of the sulfur in fuel is released as volatile components (SO<sub>2</sub> or SO<sub>3</sub>) during combustion.  
18 Hence, based on sulfur content in fuel stocks, sulfur emissions can be calculated to a higher  
19 degree of accuracy than other pollutants such as nitrogen oxides or primary PM. However, these  
20 estimates given above are national averages and may not accurately reflect the contribution of  
21 specific local sources for determining individual exposure to SO<sub>2</sub> at a particular location and  
22 time. For example, shipping and in-port activities may be a significant source of SO<sub>2</sub> in some  
23 coastal cities (Wang et al., 2007).<sup>1</sup>

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<sup>1</sup> Ships and commercial boats contribute approximately 25% of the SO<sub>2</sub> emissions in the South Coast Air Basin, and 50% of statewide SO<sub>2</sub> emissions (Dabdub and Vutukuru, 2008). Because of the importance of SO<sub>2</sub> emissions, the ports of Long Beach and Los Angeles are part of a Sulfur Emissions Control Area in which sulfur contents of fuels are not to exceed 1.5%. Modeling studies by Vutukuru (2008) also indicate that ships contribute just over 1 part per billion (ppb) SO<sub>2</sub> (for a 24-h avg) to Long Beach, and a few tenths of a ppb to locations further inland.

1 The largest natural sources of SO<sub>2</sub> are volcanoes and wildfires. Although SO<sub>2</sub> constitutes a  
2 relatively minor fraction (0.005% by volume) of total volcanic emissions (Holland, 1978),  
3 concentrations in volcanic plumes can be in the range of several to tens of ppm. Volcanic sources  
4 of SO<sub>2</sub> in the U.S. are limited to the Pacific Northwest, Alaska, and Hawaii. Emissions of SO<sub>2</sub>  
5 from burning vegetation are generally in the range of 1 to 2% of the biomass burned (Levine and  
6 Pinto, 1998). Sulfur is a component of amino acids in vegetation and is released during  
7 combustion. Gaseous sulfur emissions from this source are mainly in the form of SO<sub>2</sub>.

8 In addition to its role as an emitted primary pollutant, SO<sub>2</sub> is also produced by the  
9 photochemical oxidation of reduced sulfur compounds such as dimethyl sulfide (CH<sub>3</sub>-S-CH<sub>3</sub>, or  
10 DMS), hydrogen sulfide (H<sub>2</sub>S), carbon disulfide (CS<sub>2</sub>), carbonyl sulfide (OCS), methyl  
11 mercaptan (CH<sub>3</sub>-S-H), and dimethyl disulfide (CH<sub>3</sub>-S-S-CH<sub>3</sub>). The sources for these compounds  
12 are mainly biogenic (see Annex Table B-6). Emissions of reduced sulfur species are associated  
13 typically with marine organisms living either in pelagic or coastal zones, and with anaerobic  
14 bacteria in marshes and estuaries. Emissions of DMS from marine plankton represent the largest  
15 single atmospheric source of reduced sulfur species (Berresheim et al., 1995). Other than OCS,  
16 which is lost mainly by photolysis (e-folding lifetime, [τ] ~6 months), species are lost mainly by  
17 reaction with hydroxyl radical (OH) and NO<sub>3</sub> radicals, and are relatively short-lived; lifetimes  
18 range from a few hours to a few days (see Annex Table B-2). Reaction with NO<sub>3</sub> radicals at night  
19 most likely represents the major loss process for DMS and methyl mercaptan. Although the  
20 mechanisms for the oxidation of DMS are not completely understood, excess sulfate in marine  
21 aerosol appears related mainly to the production of SO<sub>2</sub> from the oxidation of DMS. Emissions of  
22 sulfur from natural sources are small compared to industrial emissions within the U.S. However,  
23 important exceptions occur locally as the result of volcanic activity, wildfires and in certain  
24 coastal zones as described above.

25 Because OCS is relatively long-lived, it can survive oxidation in the troposphere and be  
26 transported upward into the stratosphere. Crutzen (1976) proposed that its oxidation to sulfate in  
27 the stratosphere serves as the major source of the stratospheric aerosol layer. However, Myhre  
28 et al. (2004) proposed that SO<sub>2</sub> transported upward from the troposphere by deep convection is  
29 the most likely source, since the flux of OCS is too small. In addition, in situ measurements of  
30 the isotopic composition of sulfur in stratospheric sulfate do not match those of OCS (Leung,

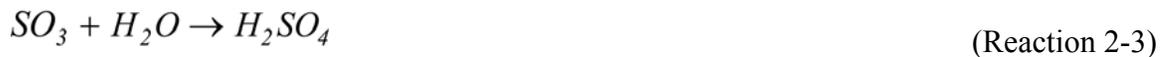
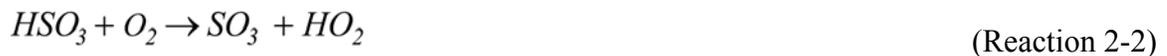
1 2002). Thus, anthropogenic SO<sub>2</sub> emissions could be important precursors to the formation of the  
2 stratospheric aerosol layer.

## 2.2. Atmospheric Chemistry

3 The only forms of monomeric sulfur oxides of interest in tropospheric chemistry are SO<sub>2</sub>  
4 and SO<sub>3</sub>. SO<sub>3</sub> can be emitted from the stacks of power plants and factories; however, it reacts  
5 extremely rapidly with H<sub>2</sub>O in the stacks or immediately after release into the atmosphere to  
6 form H<sub>2</sub>SO<sub>4</sub>, which mainly condenses onto existing particles when particle loadings are high; it  
7 can nucleate to form new particles under lower concentration conditions. Thus, only SO<sub>2</sub> is  
8 present in the tropospheric boundary layer at concentrations of concern for human exposures.  
9 The gas phase oxidation of SO<sub>2</sub> is initiated by the reaction



10 where M is an atmospheric constituent such as N<sub>2</sub> and O<sub>2</sub> that helps stabilize the reaction  
11 product. Reaction 2-1 is followed by



12 Because the saturation vapor pressure of H<sub>2</sub>SO<sub>4</sub> is extremely low, it will be removed rapidly by  
13 transfer to the aqueous phase of aerosol particles and cloud drops. Depending on atmospheric  
14 conditions and concentrations of ambient particles and gaseous species that can participate in  
15 new particle formation, it can also nucleate to form new particles. Rate coefficients for the  
16 reactions of SO<sub>2</sub> with either the hydroperoxyl radical (HO<sub>2</sub>) or NO<sub>3</sub> are too low to be significant  
17 (Jet Propulsion Laboratory, 2003).

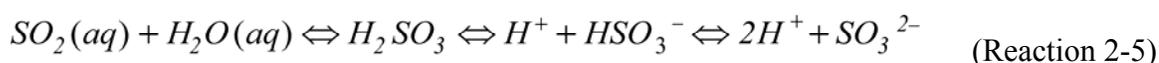
18 The major sulfur species in clouds are hydrogen sulfite (HSO<sub>3</sub><sup>-</sup>) and the sulfite ion (SO<sub>3</sub><sup>2-</sup>).  
19 Both are derived from the dissolution of SO<sub>2</sub> in water, and are referred to as S(IV); bisulfate ion  
20 (HSO<sub>4</sub><sup>-</sup>) and sulfate (sulfate) are referred to as S(VI). The chief species capable of oxidizing  
21 S(IV) to S(VI) in cloud water are O<sub>3</sub>, peroxides (either hydrogen peroxide [H<sub>2</sub>O<sub>2</sub>] or organic  
22 peroxides), hydroxyl (OH) radicals, and ions of transition metals such as iron (Fe), manganese  
23 (Mn) and copper (Cu) that can catalyze the oxidation of S(IV) to S(VI) by O<sub>2</sub>. The basic

1 mechanism of the aqueous phase oxidation of SO<sub>2</sub> has long been studied and can be found in  
2 numerous texts on atmospheric chemistry, e.g., Seinfeld and Pandis (1998), Finlayson-Pitts and  
3 Pitts (1999), Jacob (1999), and Jacobson (2002). Following Jacobson (2002), the steps involved  
4 in the aqueous phase oxidation of SO<sub>2</sub> can be summarized as

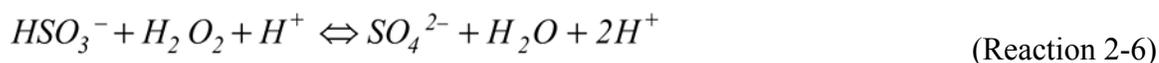
5 Dissolution of SO<sub>2</sub>



6 The formation and dissociation of H<sub>2</sub>SO<sub>3</sub>



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



9 as SO<sub>3</sub><sup>2-</sup> is much less abundant than HSO<sub>3</sub><sup>-</sup>.

10 For pH up to about 5.3, H<sub>2</sub>O<sub>2</sub> is the dominant oxidant, while at pH > 5.3, O<sub>3</sub> becomes  
11 dominant, followed by Fe(III), using characteristic values found in Seinfeld and Pandis (1998).  
12 However, differences in concentrations of oxidants result in differences in the pH at which this  
13 transition occurs. It should also be noted that the oxidation of SO<sub>2</sub> by O<sub>3</sub> and O<sub>2</sub> tends to be self-  
14 limiting: as sulfate is formed, the pH decreases and the rates of these reactions decrease. Higher  
15 pH levels are expected to be found mainly in marine aerosols. However, in marine aerosols, the  
16 chloride-catalyzed oxidation of S(IV) may be more important (Hoppel and Caffrey, 2005; Zhang  
17 and Millero, 1991). Because the ammonium ion (NH<sub>4</sub><sup>+</sup>) is so effective in neutralizing acidity, it  
18 affects the rate of oxidation of S(IV) to S(VI) and the rate of dissolution of SO<sub>2</sub> in particles and  
19 cloud drops.

20 A comparison of the relative rates of oxidation by gas and aqueous phase reactions by  
21 Warneck (1999) indicates that on average only about 20% of SO<sub>2</sub> is oxidized by gas phase  
22 reactions; the remainder is oxidized by aqueous phase reactions. In areas away from strong  
23 pollution sources, the SO<sub>2</sub> τ is ~7 days, based on measurements of the rate constant for Reaction  
24 2-1 (Jet Propulsion Laboratory, 2003) and a nominal concentration for the OH radical of 10<sup>6</sup>/cm<sup>3</sup>.

1 However, the mechanism of SO<sub>2</sub> oxidation at a particular location depends on local  
2 environmental conditions. For example, near stacks, oxidants such as OH radicals are depleted  
3 and almost no SO<sub>2</sub> is oxidized in the gas phase. Further downwind, as the plume is diluted with  
4 background air, the gas phase oxidation of SO<sub>2</sub> increases in importance. Finally, even further  
5 downwind when conditions in the plume can become more oxidizing than in background air, the  
6 SO<sub>2</sub> oxidation rate could exceed that in background air. SO<sub>2</sub> in the planetary boundary layer is  
7 also removed from the atmosphere by dry deposition to moist surfaces, resulting in an  
8 atmospheric  $\tau$  with respect to dry deposition of approximately 1 day to 1 week. Wet deposition of  
9 sulfur naturally depends on the variable nature of rainfall, but in general results in a  $\tau$  of SO<sub>2</sub> ~7  
10 days, too. These two processes, oxidation and deposition, lead to an overall lifetime of SO<sub>2</sub> in the  
11 atmosphere of 3 to 4 days.

## 2.3. Measurement Methods and Associated Issues

12 Currently, ambient SO<sub>2</sub> is measured using instruments based on pulsed ultraviolet (UV)  
13 fluorescence. The UV fluorescence monitoring method for atmospheric SO<sub>2</sub> was developed to  
14 improve on the flame photometric detection (FPD) method, which in turn had replaced the  
15 pararosaniline wet chemical method. This latter method is still the EPA's Federal Reference  
16 Method (FRM) for atmospheric SO<sub>2</sub>, but is rarely used due to its complexity and slow response,  
17 even in its automated forms. Both the UV fluorescence and FPD methods are designated as  
18 Federal Equivalent Methods (FEMs) by EPA, but UV fluorescence has largely supplanted the  
19 FPD approach because of the UV method's inherent linearity and because the FPD method needs  
20 consumable hydrogen gas.

21 In the UV fluorescence method, SO<sub>2</sub> molecules absorb UV light at one wavelength and  
22 emit UV light at longer wavelengths in the process known as fluorescence, through excitation of  
23 the SO<sub>2</sub> molecule to a higher energy (singlet) electronic state. Once excited, the molecule decays  
24 nonradiatively to a lower-energy electronic state from which it then decays to the original or  
25 electronic state by emitting a photon of light at a longer wavelength (i.e., a lower-energy photon)  
26 than the original, incident photon. The intensity of the emitted light is thus proportional to the  
27 number of SO<sub>2</sub> molecules in the sample gas.

28 In commercial analyzers, light from a high-intensity UV lamp passes through a bandwidth  
29 filter, allowing only photons with wavelengths around the SO<sub>2</sub> absorption peak (near 214

1 nanometers [nm]) to enter the optical chamber. The light passing through the source bandwidth  
2 filter is collimated using a UV lens and passes through the optical chamber, where it is detected  
3 on the opposite side of the chamber by the reference detector. A photomultiplier tube (PMT) is  
4 offset from and placed perpendicular to the light path to detect the SO<sub>2</sub> fluorescence. Since the  
5 SO<sub>2</sub> fluorescence at 330 nm is different from its excitation wavelength, an optical bandwidth  
6 filter is placed in front of the PMT to filter out any stray light from the UV lamp. A lens is  
7 located between the filter and the PMT to focus the fluorescence onto the active area of the  
8 detector and optimize the fluorescence signal. The limit of detection (LOD) for a non-trace level  
9 SO<sub>2</sub> analyzer is required to be 10 ppb (FR, 2006). However, most commercial analyzers have  
10 detection limits of about 3 ppb; many monitors might have lower effective detection limits. The  
11 EPA, through its National Core (NCore) initiative (EPA, 2005) is in the process of supporting  
12 state, local, tribal, and federal networks in the implementation of newer trace-level SO<sub>2</sub>  
13 instrumentation. These new trace-level instruments have detection limits of 0.1 ppb or lower.  
14 More information related to SO<sub>2</sub> sampling and measurement is in Annex B.5.

### 2.3.1. Sources of Positive Interference

15 The most common source of interference to the UV fluorescence method for SO<sub>2</sub> is from  
16 other gases that fluoresce in a similar fashion when exposed to UV radiation. The most signifi-  
17 cant of these are polycyclic aromatic hydrocarbons (PAHs), of which naphthalene is a prominent  
18 example. Xylene is another common hydrocarbon that can cause fluorescent interference. Conse-  
19 quently, any such aromatic hydrocarbons in the optical chamber can act as positive interference.  
20 To remove this source of interference, high-sensitivity SO<sub>2</sub> analyzers, such as those to be used in  
21 the NCore network (EPA, 2005), have hydrocarbon scrubbers to remove these compounds from  
22 the sample stream before the sample air enters the optical chamber.

23 Luke (1997) reported positive artifacts of a modified pulsed fluorescence detector  
24 generated by the coexistence of nitric oxide (NO), carbon disulfide (CS<sub>2</sub>), and a number of  
25 highly fluorescent aromatic hydrocarbons such as benzene, toluene, *o*-xylene, *m*-xylene,  
26 *p*-xylene, *m*-ethyltoluene, ethylbenzene, and 1,2,4-trimethylbenzene. The positive artifacts could  
27 be reduced by using a hydrocarbon “kicker” membrane. At a flow rate of 300 standard cc min<sup>-1</sup>  
28 and a pressure drop of 645 torr across the membrane, the interference from ppm levels of many  
29 aromatic hydrocarbons was eliminated. NO fluoresces in a spectral region close to that of SO<sub>2</sub>.

1 However, in high-sensitivity SO<sub>2</sub> analyzers, the bandpass filter in front of the PMT is designed to  
2 prevent NO fluorescence from being detected at the PMT. Care must be exercised when using  
3 multicomponent calibration gases containing both NO and SO<sub>2</sub>, so that the NO rejection ratio of  
4 the SO<sub>2</sub> analyzer is sufficient to prevent NO interference.

5 The most common source of positive bias (as contrasted with positive spectral  
6 interference) in high-sensitivity SO<sub>2</sub> monitoring is stray light in the optical chamber. Since SO<sub>2</sub>  
7 can be electronically excited by a broad range of UV wavelengths, any stray light with an  
8 appropriate wavelength that enters the optical chamber can excite SO<sub>2</sub> in the sample and increase  
9 the fluorescence signal. Furthermore, stray light at the wavelength of the SO<sub>2</sub> fluorescence that  
10 enters the optical chamber may impinge on the PMT and increase the fluorescence signal.  
11 Several design features minimize stray light, including the use of light filters, dark surfaces, and  
12 opaque tubing.

13 Nicks and Benner (2001) reported a sensitive SO<sub>2</sub> chemiluminescence detector based on a  
14 differential measurement: response from ambient SO<sub>2</sub> is determined by the difference between  
15 air containing SO<sub>2</sub> and air scrubbed of SO<sub>2</sub> when both air samples contain other detectable sulfur  
16 species. Assuming monotonic efficiency of the sulfur scrubber, all positive artifacts should also  
17 be reduced with this technique.

### **2.3.2. Sources of Negative Interference**

18 Nonradiative deactivation (quenching) of excited SO<sub>2</sub> molecules can occur from collisions  
19 with common molecules in air, including nitrogen, oxygen, and water. During collisional  
20 quenching, the excited SO<sub>2</sub> molecule transfers energy, kinetically allowing the SO<sub>2</sub> molecule to  
21 return to the original lower energy state without emitting a photon. Collisional quenching results  
22 in a decrease in the SO<sub>2</sub> fluorescence and, hence, an underestimation of SO<sub>2</sub> concentration in the  
23 air sample. Of particular concern is the variable water vapor content of air. Luke (1997) reported  
24 that the response of the detector could be reduced by an amount of ~7 to 15% at water vapor  
25 mixing ratios of 1 to 1.5 mole percent (relative humidity [RH] = 35 to 50% at 20 to 25°C and 1  
26 atmosphere [atm] for a modified pulsed fluorescence detector [Thermo Environmental  
27 Instruments, Model 43s]). Condensation of water vapor in sampling lines must be avoided, as  
28 water on the inlet surfaces can absorb SO<sub>2</sub> from the sample air. The simplest approach to avoid  
29 condensation is to heat sampling lines to a temperature above the expected dew point and to

1 within a few degrees of the controlled optical bench temperature. At very high SO<sub>2</sub>  
2 concentrations, reactions between electronically excited SO<sub>2</sub> and ground state SO<sub>2</sub> might occur,  
3 forming SO<sub>3</sub> and SO (Calvert et al., 1978). However, the possibility that this artifact might be  
4 affecting measurements at very high SO<sub>2</sub> levels has not been examined.

### 2.3.3. Other Techniques for Measuring so<sub>2</sub>

5 More sensitive techniques for measuring SO<sub>2</sub> are available, but most of these systems are  
6 too complex and expensive for routine monitoring applications. However, techniques such as  
7 those described by Luke (1997) can be used to improve the sensitivity of ambient SO<sub>2</sub> monitors  
8 by eliminating sources of common interference. See descriptions in Annex section B.5.

## 2.4. Environmental Concentrations of SO<sub>x</sub>

### 2.4.1. Design Criteria for the NAAQS so<sub>2</sub> Monitoring Networks<sup>1</sup>

9 Trace level SO<sub>2</sub> monitoring is currently required at the approximately 75 proposed NCore  
10 sites, as noted in CFR 40 Part 58 Appendices C and D. Continued operation of existing State and  
11 Local Air Monitoring Sites (SLAMS) for SO<sub>2</sub> using Federal Reference Methods (FRM) or  
12 Federal Equivalent Methods (FEM) is required until discontinuation is approved by the EPA  
13 Regional Administrator. Where SLAMS SO<sub>2</sub> monitoring is required, at least one of the sites must  
14 be a maximum concentration site for that specific area. In 2007, there were ~500 SO<sub>2</sub> monitors  
15 reporting values to the EPA Air Quality System database (AQS).

16 The appropriate spatial scales for SO<sub>2</sub> SLAMS monitoring are the microscale, middle, and  
17 possibly neighborhood scales.

18 ■ ***Micro and middle scale***—Some data uses associated with microscale and middle scale  
19 measurements for SO<sub>2</sub> include assessing the effects of control strategies to reduce  
20 concentrations (especially for the 3-hour and 24-hour averaging times), and monitoring  
21 air pollution episodes.

22 ■ ***Neighborhood scale***—This scale applies where there is a need to collect air quality data  
23 as part of an ongoing SO<sub>2</sub> stationary source impact investigation. Typical locations  
24 might include suburban areas adjacent to SO<sub>2</sub> stationary sources, for example, or for

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<sup>1</sup> This section is adapted from Code of the Federal Register 40 CFR Parts 53 and 58 and Appendix E to Part 58, as revised: Vol. 71, No. 200 / 17  
October 2006

1 determining background concentrations as part of studies of population responses to  
2 SO<sub>2</sub> exposure.

### ***Horizontal and Vertical Placement***

3 The probe, or at least 80 percent of the monitoring path, must be located between 2 and 15  
4 meters above ground level for all SO<sub>2</sub> monitoring sites. The probe, or at least 90 percent of the  
5 monitoring path, must be positioned at least 1 meter vertically or horizontally from any  
6 supporting structure, walls, parapets, penthouses, etc., and away from dusty or dirty areas. If the  
7 probe, or a significant portion of the monitoring path, is located near the side of a building, it  
8 should be located on the windward side relative to the prevailing wind direction during the  
9 season of highest concentration potential for the pollutant being measured.

### ***Spacing from Minor Sources***

10 Local minor sources of a primary pollutant such as SO<sub>2</sub> can affect concentrations of that  
11 particular pollutant at a monitoring site. If the objective for that site is to investigate these local  
12 primary pollutant emissions, then the site should be located where the spatial and temporal  
13 variability in these emissions can be captured. This type of monitoring site would likely be the  
14 microscale type. If a monitoring site is to be used to determine air quality over a much larger  
15 area, such as a neighborhood or city, a monitoring agency should avoid placing a monitor probe,  
16 path, or inlet near local, minor sources. The plume from the local minor sources should not be  
17 allowed to inappropriately influence the air quality data collected.

18 To minimize these potential interferences, the probe, or at least 90 percent of the  
19 monitoring path, must be placed away from furnace or incineration flues, or other minor sources  
20 of SO<sub>2</sub>. The separation distance should take into account the heights of the flues, type of waste or  
21 fuel burned, and the sulfur content of the fuel.

### ***Spacing from Obstructions***

22 Buildings and other obstacles may possibly scavenge SO<sub>2</sub>, and can act to restrict airflow  
23 for any pollutant. To avoid this interference, the probe, inlet, or at least 90 percent of the  
24 monitoring path must have unrestricted airflow and be located away from obstacles. The distance  
25 from the obstacle to the probe, inlet, or monitoring path must be at least twice the height of the  
26 obstruction's protrusion. An exception can be made for measurements taken in street canyons or

1 at source-oriented sites where buildings and other structures are unavoidable. Generally, a probe  
2 or monitoring path located near or along a vertical wall is undesirable, because air moving along  
3 the wall may be subject to possible removal mechanisms. A probe, inlet, or monitoring path must  
4 have unrestricted airflow in an arc of at least 180 degrees. This arc must include the predominant  
5 wind direction for the season of greatest pollutant concentration potential.

6 Special consideration must be devoted to the use of open path analyzers, due to their  
7 inherent potential sensitivity to certain types of interferences, or optical obstructions. A  
8 monitoring path must be clear of all trees, brush, buildings, plumes, dust, or other optical  
9 obstructions, including potential obstructions that may move due to wind, human activity, growth  
10 of vegetation, etc. Temporary optical obstructions, such as rain, particles, fog, or snow, should be  
11 considered when locating an open path analyzer. Any temporary obstructions that are of  
12 sufficient density to obscure the light beam will affect the ability of the open path analyzer to  
13 measure pollutant concentrations continuously. Transient, but significant obscuration of  
14 especially longer measurement paths could occur because certain meteorological conditions  
15 (e.g., heavy fog, rain, snow) and/or aerosol levels are of sufficient density to prevent the  
16 analyzer's light transmission. If certain compensating measures are not otherwise implemented at  
17 the onset of monitoring (e.g., shorter path lengths, higher light source intensity), data recovery  
18 during periods of greatest primary pollutant potential could be compromised. For instance, if  
19 heavy fog or high particulate levels are coincident with periods of projected NAAQS-threatening  
20 pollutant potential, the resulting data may not be representative for reflecting maximum pollutant  
21 concentrations, despite the fact that the site may otherwise exhibit an acceptable, even  
22 exceedingly high overall valid data capture rate.

### ***Spacing from Trees***

23 Trees can provide surfaces for SO<sub>2</sub> adsorption or reactions, and surfaces for particle  
24 deposition. Trees can also act as obstructions in cases where they are located between the air  
25 pollutant sources or source areas and the monitoring site, and where the trees are of sufficient  
26 height and leaf canopy density to interfere with normal airflow around the probe, inlet, or  
27 monitoring path. To reduce possible interference, the probe, inlet, or at least 90 percent of the  
28 monitoring path must be at least 10 meters or further from the drip line of trees.

1 For microscale sites, no trees or shrubs should be located between the probe and the source  
2 under investigation, such as a roadway or a stationary source.

### 2.4.2. Monitor Locations in Selected Areas of the U.S.

3 Figures 2-1 through 2-6 illustrate the 2005 geospatial locations of monitors for SO<sub>2</sub>, NO<sub>2</sub>,  
4 CO, particulate matter ≤ 10 μm (PM<sub>10</sub>), particulate matter ≤ 2.5 μm (PM<sub>2.5</sub>), and O<sub>3</sub>. These  
5 locations, sited in several cities in six states, were selected as relevant for SO<sub>2</sub> health effects  
6 studies; see the summaries and assessments of health effects in Chapter 4, and the discussion of  
7 intracity SO<sub>2</sub> correlations that follows. For each state, Figure A shows locations of each monitor  
8 for all six pollutants; Figure B shows only the SO<sub>2</sub> monitor locations. Totals for each monitor  
9 type are included. These figures demonstrate the important point that not all SO<sub>2</sub> monitors in any  
10 Consolidated Metropolitan Statistical Area (CMSA) are co-located with monitors for other  
11 pollutants. Two examples are given below.

---

**Table 2-1. Monitor counts for California and San Diego County, 2005.**

	SO <sub>2</sub>	NO <sub>2</sub>	O <sub>3</sub>	CO	PM <sub>10</sub>	PM <sub>2.5</sub>
California (all)	35	105	176	86	177	97
San Diego County	4	9	10	6	7	7

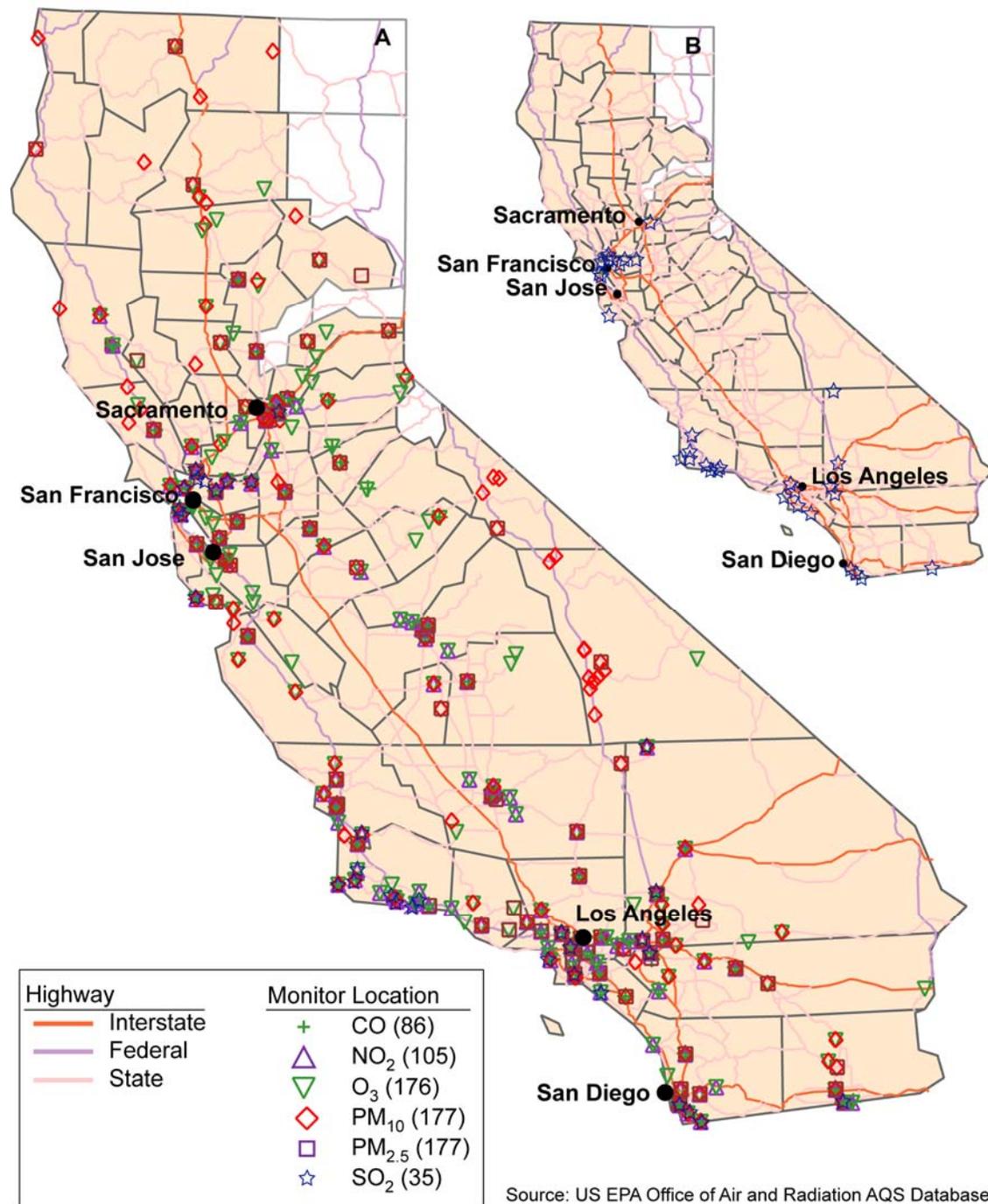
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**Table 2-2. Monitor counts for Ohio and Cuyahoga County, 2005.**

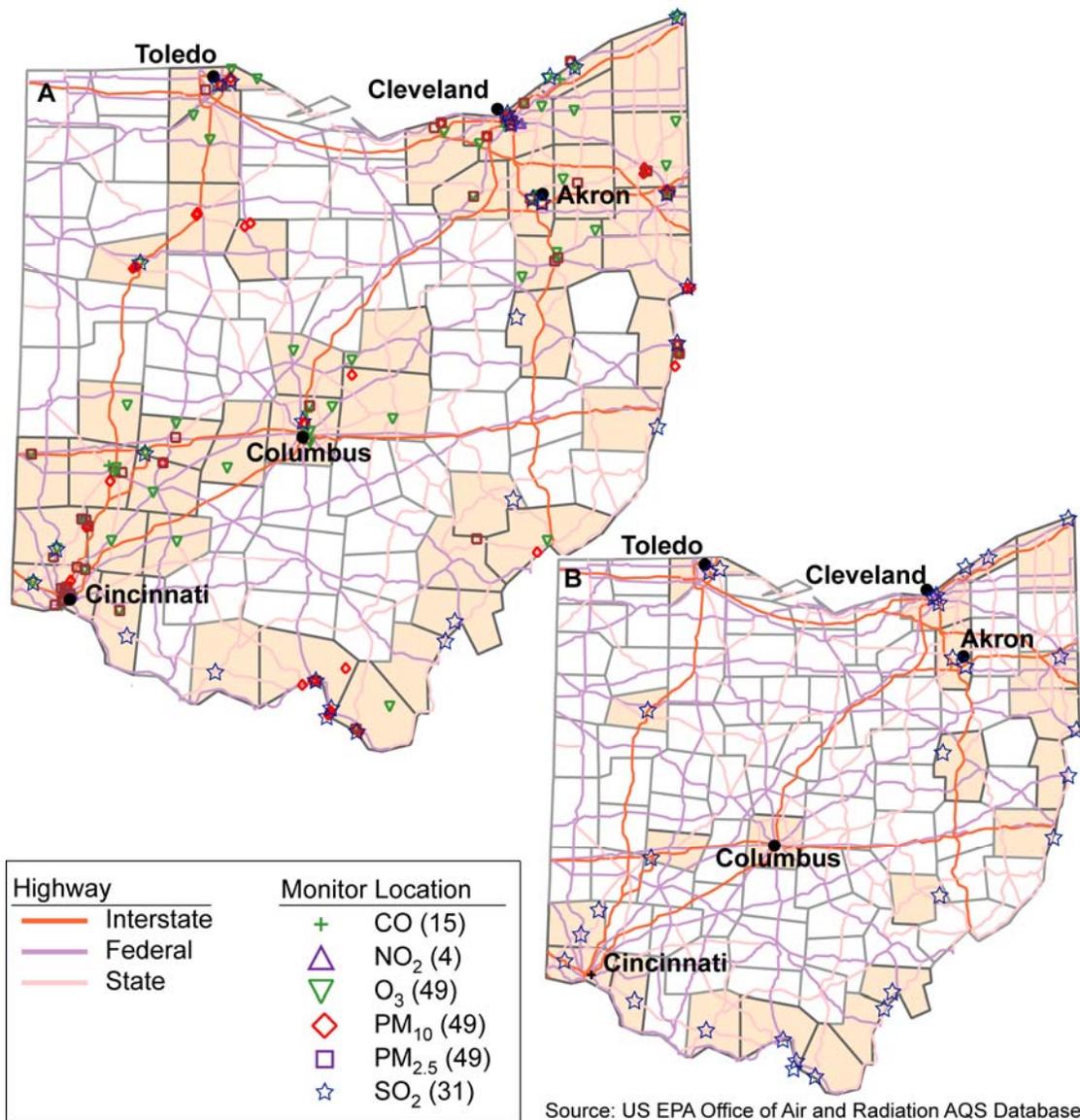
	SO <sub>2</sub>	NO <sub>2</sub>	O <sub>3</sub>	CO	PM <sub>10</sub>	PM <sub>2.5</sub>
Ohio (all)	31	4	49	15	49	49
Cuyahoga County	4	2	3	4	6	7

12 Table 2-1 lists the totals for all criteria air pollutant monitors (except Pb) in California, as  
13 well as the subset of these monitors in San Diego County. At each of the four sites where SO<sub>2</sub>  
14 was measured, NO<sub>2</sub>, CO, PM<sub>10</sub>, PM<sub>2.5</sub>, and O<sub>3</sub> were also measured, with the exception of PM<sub>2.5</sub>  
15 at one site (AQS ID 060732007) in Otay Mesa, CA. Table 2-2 lists the totals for all criteria air  
16 pollutant monitors (except Pb) in Ohio, as well as the subset of in Cuyahoga County.

1            In Cuyahoga County, PM<sub>10</sub> and PM<sub>2.5</sub> were measured at all four sites where SO<sub>2</sub> was also  
2 measured in 2005, but O<sub>3</sub> and CO were not measured at any of those four sites; NO<sub>2</sub> was only  
3 measured at one site (AQS ID 39050060) near Cleveland's city center and ~0.5 km from the  
4 intersection of Interstate Highways 77 and 90.



**Figure 2-1. Criteria pollutant monitor locations (A) and SO<sub>2</sub> monitor locations (B), California, 2005. Shaded counties have at least one monitor.**

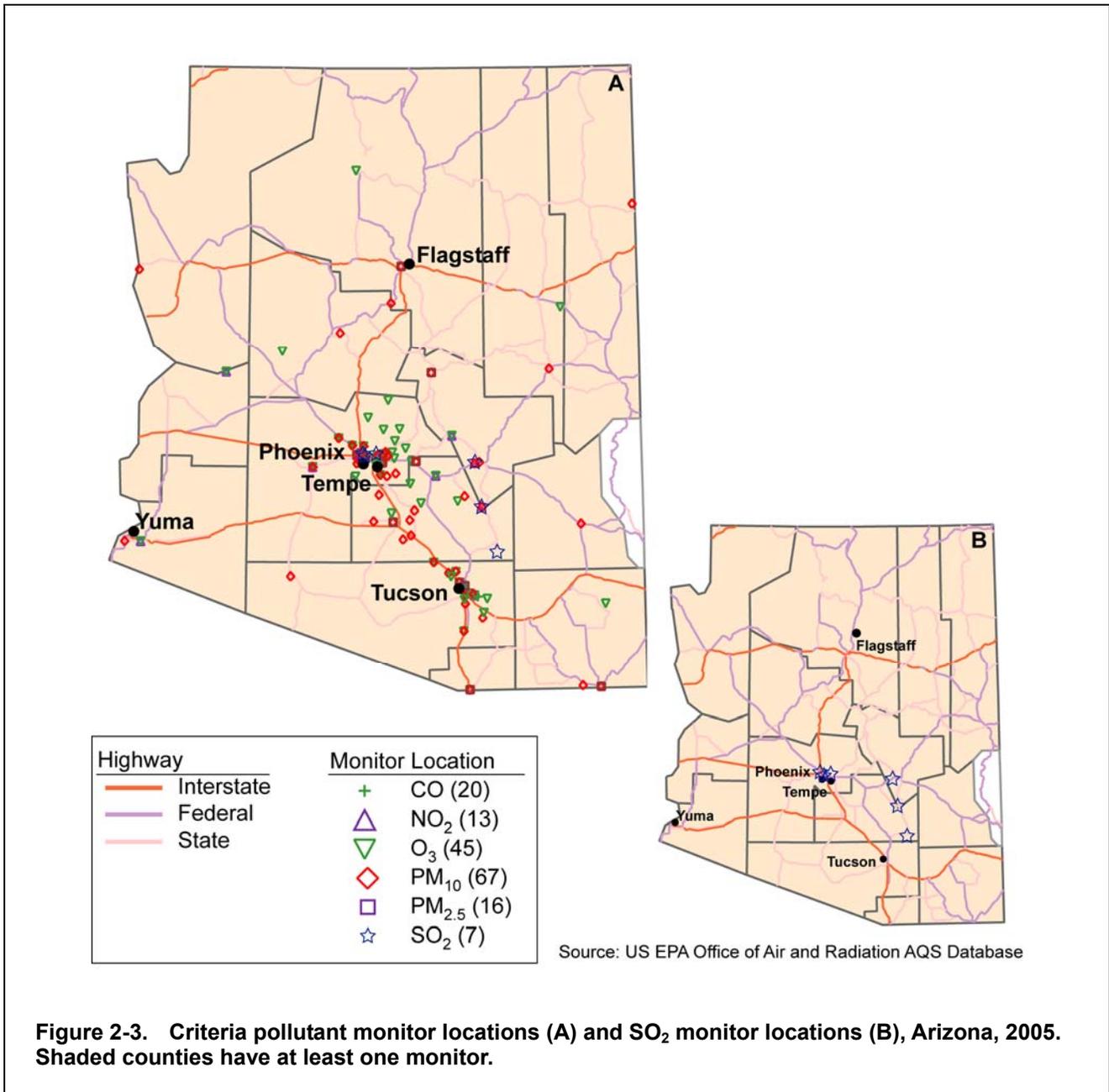


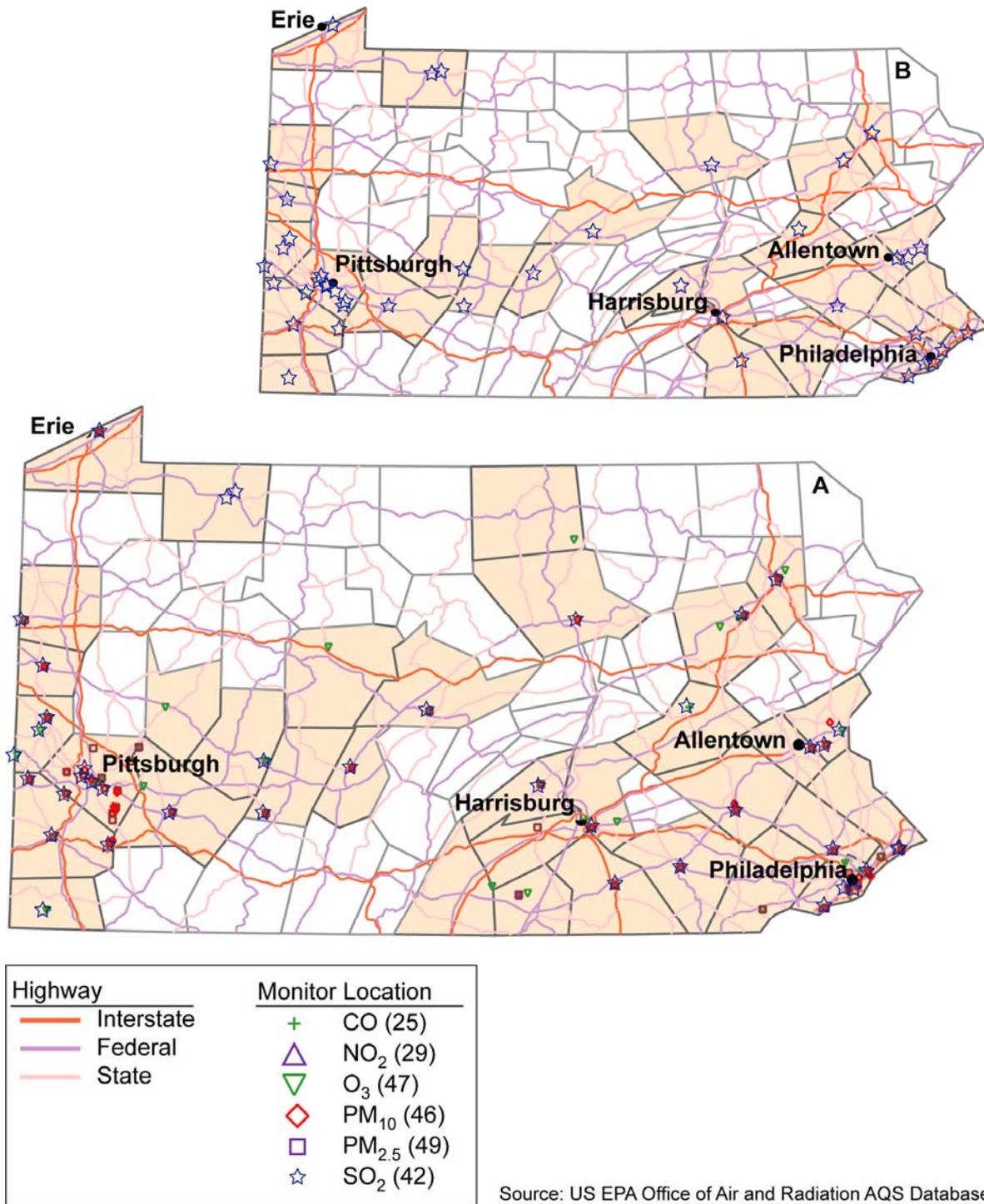
**Figure 2-2. Criteria pollutant monitor locations (A) and SO<sub>2</sub> monitor locations (B), Ohio, 2005. Shaded counties have at least one monitor.**

### 2.4.3. Ambient so<sub>2</sub> Concentrations in Relation to so<sub>2</sub> Sources

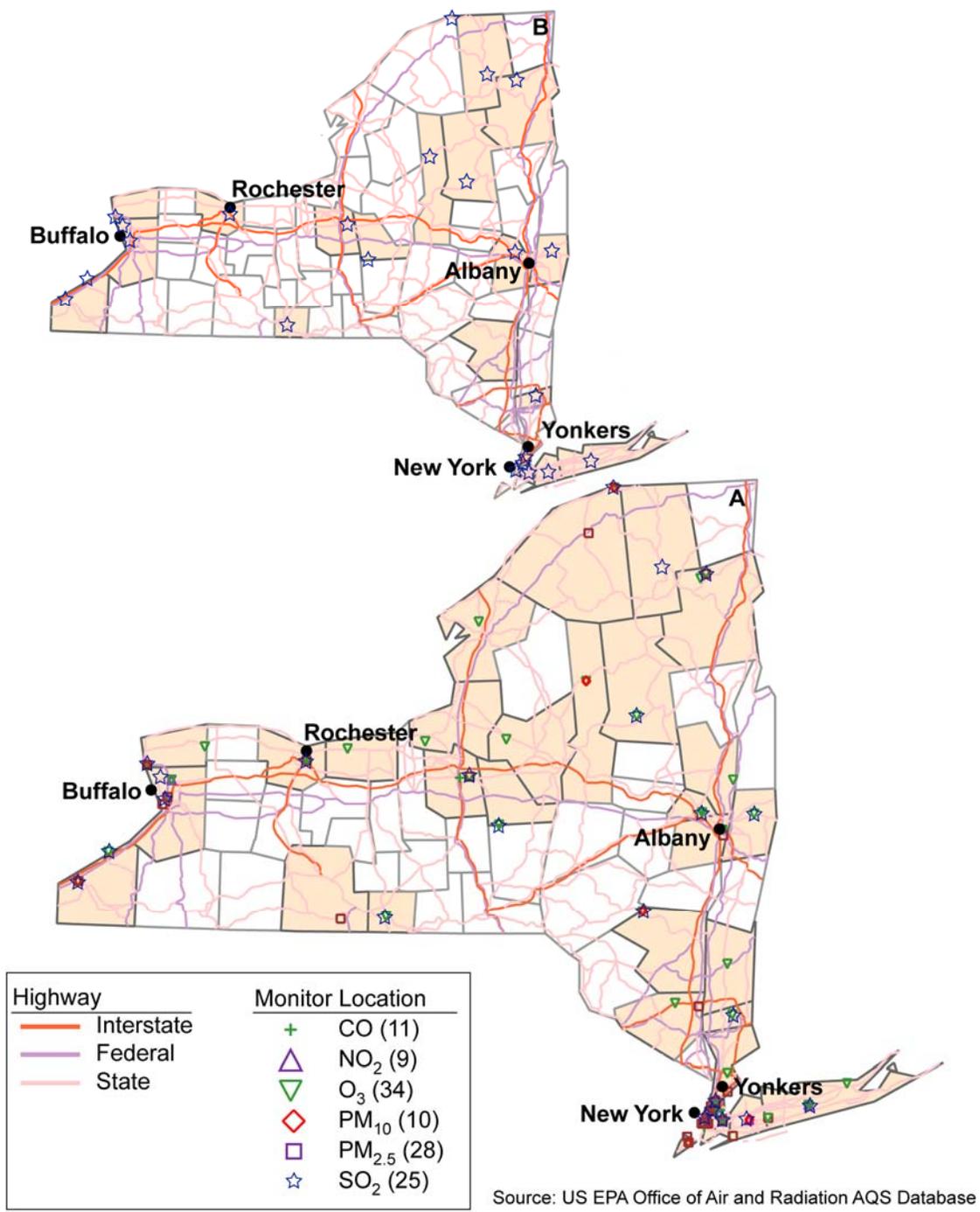
- 1 SO<sub>2</sub> data collected from the SLAMS and NAMS networks, like those illustrated in
- 2 Figures 2-1 through 2-6, show that the decline in SO<sub>2</sub> emissions from electric generating utilities
- 3 has substantially improved air quality. Not one monitored exceedance of the SO<sub>2</sub> annual ambient

1 air quality standard in the lower 48 States of the United States has been recorded since 2000,  
 2 according to the EPA Acid Rain Program (ARP) 2005 Progress Report (EPA, 2006a). EPA's  
 3 trends data ([www.epa.gov/airtrends](http://www.epa.gov/airtrends)) reveal that the national composite average SO<sub>2</sub> annual mean  
 4 ambient concentration decreased by 48% from 1990 to 2005; the largest single-year reduction  
 5 was 1994-95, the ARP's first operating year (EPA, 2006a). Figure 2-7 depicts data for SO<sub>2</sub>  
 6 emissions in the contiguous United States (CONUS) during those years, with state-level totals.

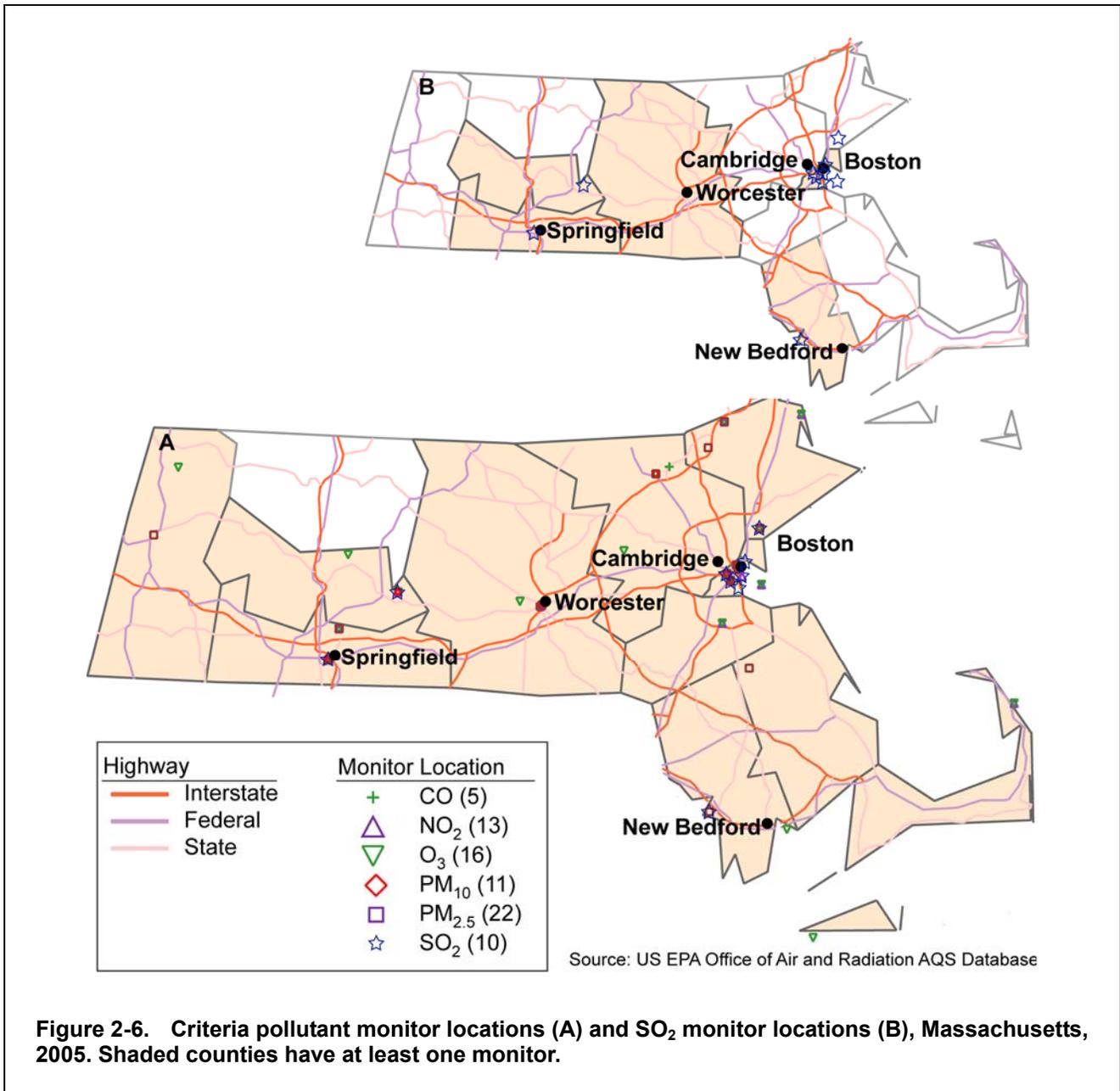




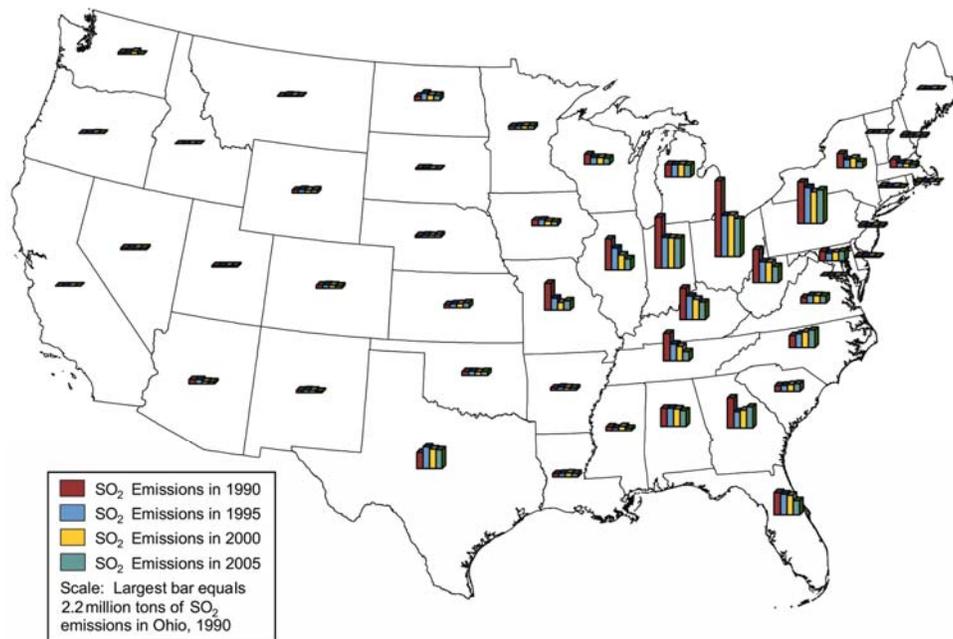
**Figure 2-4. Criteria pollutant monitor locations (A) and SO<sub>2</sub> monitor locations (B), Pennsylvania, 2005. Shaded counties have at least one monitor.**



**Figure 2-5. Criteria pollutant monitor locations (A) and SO<sub>2</sub> monitor locations (B), New York, 2005. Shaded counties have at least one monitor.**



1            These emissions data trends are consistent with the trends in the observed ambient  
2 concentrations from the Clean Air Status and Trends Network (CASTNet). Following  
3 implementation of the Phase I controls on ARP sources between 1995 and 2000, significant  
4 reductions in SO<sub>2</sub> and ambient SO<sub>4</sub><sup>2-</sup> concentrations were observed at CASTNet sites throughout  
5 the eastern United States. The mean annual concentrations of SO<sub>2</sub> and SO<sub>4</sub><sup>2-</sup> from CASTNet's  
6 long-term monitoring sites can be compared using two 3-year periods, 1989–1991 and  
7 2003–2005, shown in Figure 2-8 for SO<sub>2</sub> and Figure 2-9 for SO<sub>4</sub><sup>2-</sup>.

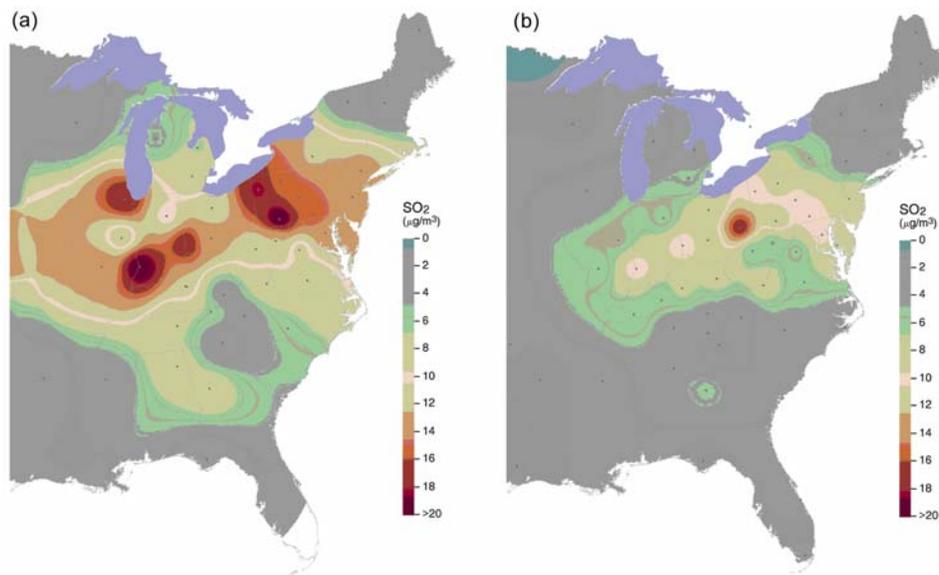


**Figure 2-7. State-level SO<sub>2</sub> emissions, 1990-2005.**

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

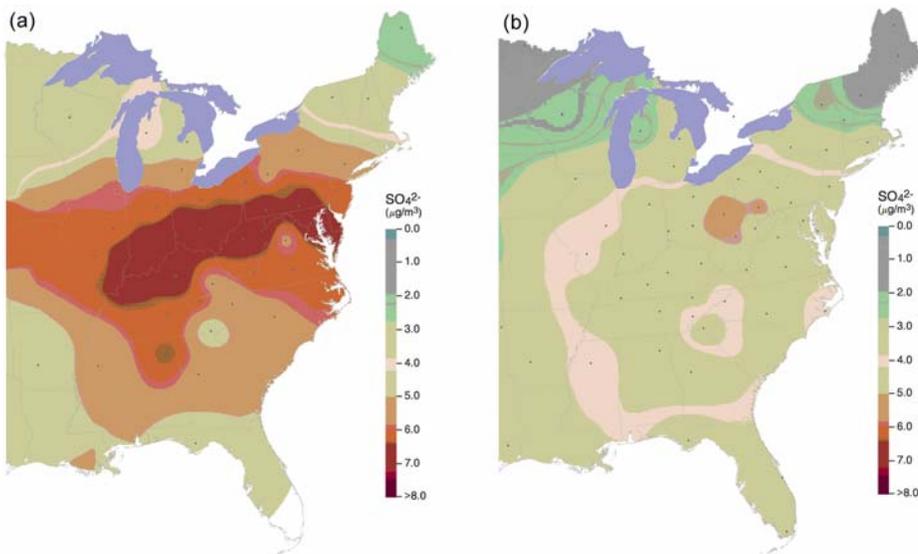
1 From 1989 through 1991—that is, in the years prior to implementation of the ARP  
 2 Phase I—the highest ambient mean concentrations of SO<sub>2</sub> and SO<sub>4</sub><sup>2-</sup> were observed in western  
 3 Pennsylvania and along the Ohio River Valley: > 20 μg/m<sup>3</sup> (~8 ppb) SO<sub>2</sub> and > 15 μg/m<sup>3</sup> SO<sub>4</sub><sup>2-</sup>.  
 4 As with SO<sub>2</sub>, in the years since the ARP controls were enacted, both the magnitude of SO<sub>4</sub><sup>2-</sup>  
 5 concentrations and their areal extent have been significantly reduced, with the largest decreases  
 6 again along the Ohio River Valley.

7 Figure 2-10 depicts the magnitude and spatial distribution of SO<sub>2</sub> emissions in 2006 from  
 8 sources in the ARP for the CONUS. This depiction clearly shows the continuing  
 9 overrepresentation of SO<sub>2</sub> sources in the United States east of the Mississippi River, a trend even  
 10 stronger in the central Ohio River Valley, as evident in the smoothed concentration plots in  
 11 Figure 2-8. As shown in Table 2-3, regional distributions of SO<sub>2</sub> and SO<sub>4</sub><sup>2-</sup> concentrations  
 12 averaged for 2003–2005 reflect this geospatial emissions source difference as well.



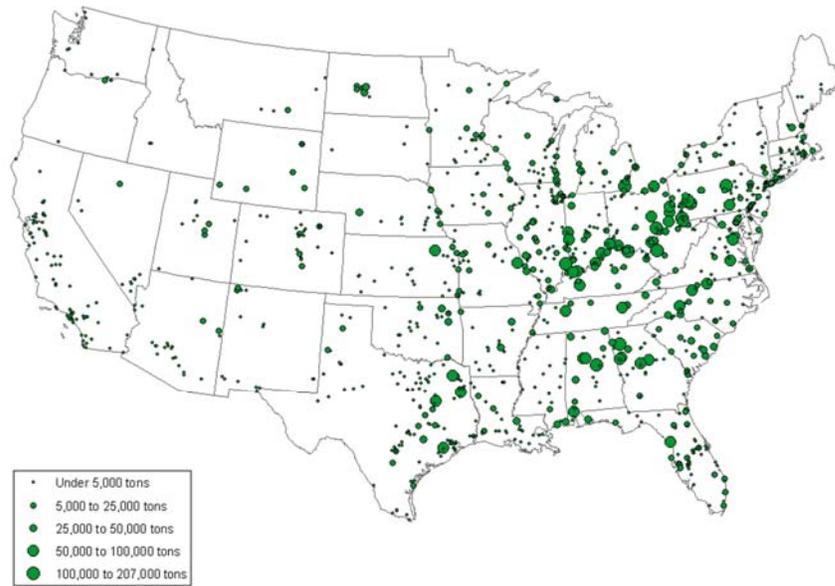
**Figure 2-8. Annual mean ambient SO<sub>2</sub> concentration, 1989 through 1991 (a), and 2003 through 2005 (b).**

Source: U.S. EPA CASTNet



**Figure 2-9. Annual mean ambient SO<sub>4</sub><sup>2-</sup> concentration, 1989 through 1991 (a), and 2003 through 2005 (b).**

Source: U.S. EPA CASTNet



**Figure 2-10. Annual SO<sub>2</sub> emissions for Acid Rain Program cooperating facilities, 2006.**

Dots represent monitoring sites. Lack of shading for Southern Florida indicates lack of monitoring coverage.  
 Source: Environmental Protection Agency, Clean Air Markets Division ([www.epa.gov/airmarkets/index.html](http://www.epa.gov/airmarkets/index.html)).

#### 2.4.4. Spatial and Temporal Variability of Ambient so<sub>2</sub> Concentrations

1 SO<sub>2</sub> concentrations have been falling throughout all regions of the CONUS, as  
 2 demonstrated by the CASTNet data reviewed above. In and around most individual CMSAs, the  
 3 trends are also toward lower SO<sub>2</sub> levels. Table 2-4 shows that many annual and even 1-h mean  
 4 concentrations for the years 2003 through 2005 were consistently at or below the operating LOD  
 5 of ~3 ppb for the standard sensitivity UV fluorescence SO<sub>2</sub> monitors deployed in the regulatory  
 6 networks, while the aggregate mean value over all 3 years and all sites in and around the CMSAs  
 7 was just above the LOD at ~4 ppb, and identical to the 1-h and 24-h means. Hence, it appears  
 8 reasonable to aggregate up in time from available 1-h samples to daily and even annual exposure  
 9 estimates.

10 Figure 2-11 shows the composite diel variation in hourly SO<sub>2</sub> concentrations in boxplot  
 11 form from all monitors reporting SO<sub>2</sub> data into AQS. The AQS contains measurements of air  
 12 pollutant concentrations in the 50 states, plus the District of Columbia, Puerto Rico, and the  
 13 Virgin Islands, for the six criteria air pollutants (SO<sub>2</sub>, NO<sub>2</sub>, PM, CO, Pb, O<sub>3</sub>), as well as for  
 14 hazardous air pollutants.

**Table 2-3. Regional distribution of SO<sub>2</sub> and SO<sub>4</sub><sup>2-</sup> ambient concentrations, averaged for 2003-05.**

REGION	CONCENTRATION	
	SO <sub>2</sub> (ppb)	SO <sub>4</sub> <sup>2-</sup> (µg/m <sup>3</sup> )
Mid-Atlantic	3.3	4.5
Midwest	2.3	3.8
Northeast	1.2	2.5
Southeast	1.3	4.1

**Table 2-4. Distributions of temporal averaging inside and outside CMSAs.**

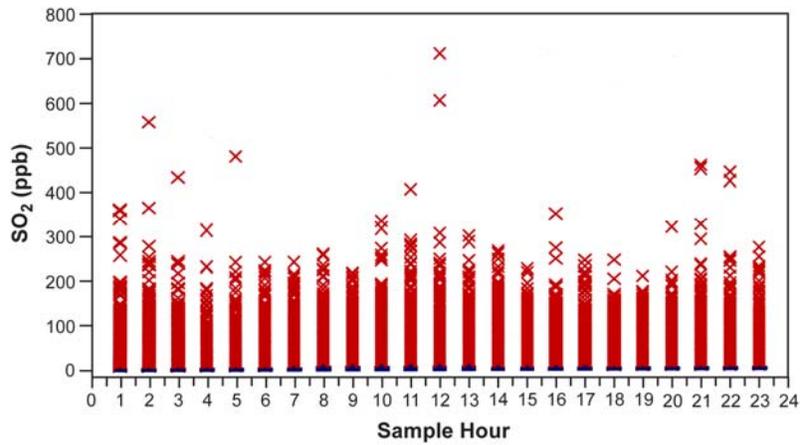
AVERAGING TIME MONITOR LOCATIONS	N	MEAN	PERCENTILES											MAX
			1	5	10	25	30	50	70	75	90	95	99	
<b>1-h Max Concentration</b>														
Inside CMSAs	332405	13	1	1	1	3	4	7	13	16	30	45	92	714
Outside CMSAs	53417	13	1	1	1	1	2	5	10	13	31	51	116	636
<b>1-h Avg Concentration</b>														
Inside 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
<b>24-h Avg Concentration</b>														
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
<b>Annual Avg Concentration</b>														
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
<b>Aggregate 3-yr Avg Concentration, 2003-2005</b>														
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

1 To be sure, the max 1-h concentration observed at some sites in and around some CMSAs  
 2 still exceeded the mean by a large margin, with max 1-h values of > 600 ppb. However, the 50th  
 3 percentile maximum value outside CMSAs, 5 ppb, was only slightly greater than the 1-h, 24-h,  
 4 and annual mean value, 4 ppb. The 50th percentile maximum value inside CMSAs, 7 ppb, was  
 5 75% greater than these longer-term averages, reflecting heterogeneity in source strength and

1 location. In addition, even with 1-h max values of > 600 ppb, the maximum annualized mean  
2 value for all CMSAs was still < 16 ppb, which is below the current annual primary SO<sub>2</sub> NAAQS.



**Figure 2-11. Boxplot of hourly SO<sub>2</sub> concentrations across all cities in focus.**

3 The strong west-to-east increasing gradient in SO<sub>2</sub> emissions described above is well-  
4 replicated in the observed concentrations in individual CMSAs. For example, Table 2-5 shows  
5 the mean annual concentrations from 2003–2005 for the 12 CMSAs with four or more SO<sub>2</sub>  
6 regulatory monitors. Values ranged from a reported low of ~1 ppb in Riverside, CA and San  
7 Francisco, CA to a high of ~12 ppb in Pittsburgh, PA and Steubenville, OH, in the highest SO<sub>2</sub>  
8 source region.

9 The Pearson correlation coefficients ( $r$ ) for multiple monitors in these CMSAs were  
10 generally very low for all cities, especially at the lower end of the observed concentration ranges,  
11 and even negative at the very lowest levels on the West Coast (see Table 2-5). This reflects  
12 strong heterogeneity in SO<sub>2</sub> ambient concentrations even within any one CMSA and, therefore,  
13 indicates possibly different exposures of spatially distinct subgroups of humans in these CMSAs  
14 to these very low concentrations of SO<sub>2</sub>. At higher concentrations, the  $r$  values were also higher.  
15 In some CMSAs, this heterogeneity may result from meteorological effects, whereby a generally  
16 well-mixed subsiding air mass containing one or more SO<sub>2</sub> plumes with relatively high  
17 concentration would be more uniformly spread than faster-moving plumes with lower  
18 concentrations. However, instrument error may also play a role, because the highest  $r$  values, i.e.,  
19 those > 0.7, correspond to the highest SO<sub>2</sub> concentrations, i.e., > 6 and > 10 ppb. Since the lowest  
20 SO<sub>2</sub> concentrations are at or below the operating LOD, and demonstrate the lowest correlation

1 across monitors that share at least some air mass characteristics most of the year, the unbiased  
 2 instrument error in this range may be confounding interpretation of any possible correlation. This  
 3 could be because the same actual ambient value would be reported by different monitors (with  
 4 different error profiles) in the CMSA as different values in this lowest concentration range.

5 To better characterize the extent and spatiotemporal variance of SO<sub>2</sub> concentrations within  
 6 each of the CMSAs having four or more SO<sub>2</sub> monitors, the means, minima, and maxima were  
 7 computed from daily mean data across all available monitors for each month for the years 2003  
 8 through 2005. Because many of these CMSAs with SO<sub>2</sub> monitors also reported SO<sub>4</sub><sup>2-</sup>, it is  
 9 possible to compute the degree of correlation between SO<sub>2</sub>, the emitted species, and SO<sub>4</sub><sup>2-</sup>, the  
 10 most prominent oxidized product from SO<sub>2</sub>. SO<sub>4</sub><sup>2-</sup> values, however, while averaged over all  
 11 available data at each site are generally available at their monitoring sites on a schedule of only 1  
 12 in 3 days or 1 in 6 days. Furthermore, SO<sub>2</sub> and SO<sub>4</sub><sup>2-</sup> monitors are not all co-located throughout  
 13 the CMSAs. For each of the five example CMSAs in Figures 2-12 through 2-16, monthly  
 14 aggregated values are depicted from daily means of: (a) the monthly mean, minimum, and  
 15 maximum SO<sub>2</sub> concentrations; (b) the monthly mean, minimum and maximum SO<sub>4</sub><sup>2-</sup>  
 16 concentrations; and (c) a scatterplot of SO<sub>2</sub> versus SO<sub>4</sub><sup>2-</sup> concentrations.

**Table 2-5. Range of mean annual SO<sub>2</sub> concentrations and Pearson correlation coefficients in urban areas having at least four regulatory monitors, 2003–2005.**

CMSA (# MONITORS)	MEAN SO <sub>2</sub> 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

1 In Steubenville, OH (Figure 2-12), the area of highest SO<sub>2</sub> concentrations of all 12 CMSAs  
2 with more than four monitors, all monthly mean SO<sub>2</sub> concentrations (a) were substantially < 30  
3 ppb, though max daily means in some months were often > 60 ppb, or even > 90 ppb. Sulfate  
4 data (b) at Steubenville were insufficient to make meaningful comparisons, though the 12  
5 months of available SO<sub>4</sub><sup>2-</sup> data suggest no correlation with SO<sub>2</sub> (c).

6 Next, consider Philadelphia, PA (Figure 2-13). SO<sub>2</sub> in Philadelphia, PA (a) is present at  
7 roughly one-half the monthly mean concentrations in Steubenville, OH, and demonstrates a  
8 strong seasonality with SO<sub>2</sub> concentrations peaking in winter. By contrast, SO<sub>4</sub><sup>2-</sup> concentrations  
9 in Philadelphia peak in the three summer seasons, with pronounced wintertime minima. This  
10 seasonal anticorrelation still contains considerable monthly scatter, however.

11 Los Angeles, CA (Figure 2-14) presents a special case, since its size and power  
12 requirements place a larger number of SO<sub>2</sub> emitters near it than would otherwise be expected on  
13 the West Coast. Concentrations of SO<sub>2</sub> demonstrate weak seasonality in these 3 years, with  
14 summertime means of ~3 to 4 ppb, and maxima generally higher than wintertime ones, though  
15 the highest means and maxima occur during the winter of 2004–2005. SO<sub>4</sub><sup>2-</sup> at Los Angeles  
16 shows stronger seasonality, most likely because the longer summer days of sunny weather allow  
17 for additional oxidation of SO<sub>2</sub> to SO<sub>4</sub><sup>2-</sup> than would be available in winter. Weak seasonal effects  
18 in SO<sub>2</sub> likely explain the complete lack of correlation between SO<sub>2</sub> and SO<sub>4</sub><sup>2-</sup> here.

19 The Riverside, CA CMSA (Figure 2-15) presents the strongest example among the 12  
20 examined for this study of correlation between SO<sub>2</sub> and SO<sub>4</sub><sup>2-</sup>, though even here the R<sup>2</sup> value is  
21 merely 0.3. Seasonal peaks are obvious in summertime for SO<sub>2</sub> and SO<sub>4</sub><sup>2-</sup>, both at roughly one-  
22 half the ambient concentrations seen in Los Angeles. This is very likely due to Riverside's  
23 geographic location just downwind of the regionally large electric generating utility sources near  
24 Los Angeles and the prevailing westerly winds in summer. Again, as with Los Angeles, the  
25 summertime peaks in SO<sub>4</sub><sup>2-</sup> are most likely due to the combination of peaking SO<sub>2</sub> and favorable  
26 meteorological conditions allowing more complete oxidation.

27 Phoenix, AZ was the CMSA with the lowest monthly mean SO<sub>2</sub> and SO<sub>4</sub><sup>2-</sup> concentrations  
28 examined here (Figure 2-16). In Phoenix, nearly all monthly mean SO<sub>2</sub> values were at or below  
29 the regulatory monitors' operating LOD of ~3 ppb. SO<sub>4</sub><sup>2-</sup> concentrations were equivalently low,  
30 roughly one-half the concentrations seen in Riverside, CA, for example. The monthly mean data  
31 show strong summertime peaks for even these very low-level SO<sub>4</sub><sup>2-</sup> observations, which, at ~1 to

1 3  $\mu\text{g}/\text{m}^3$ , were generally one-half of those in Philadelphia. This suggests some seasonality in  $\text{SO}_2$ ,  
2 though anticorrelated with  $\text{SO}_4^{2-}$ ; however, the trend is very weak, as the correlation scatterplot  
3 shows.

#### **2.4.5. 5-Minute Sample Data in the Monitoring Network**

4 Although the number of monitors across the CONUS varies somewhat each year, in 2006  
5 there were ~500  $\text{SO}_2$  monitors in the NAAQS monitoring network (<http://www.epa.gov/air/data>).  
6 The state and local agencies responsible for these monitors are required to report 1-h avg  
7 concentrations to the EPA AQS. In addition, a very small number of sites—only 108 total from  
8 1997 to 2006, and not the same sites in all years—voluntarily reported 5-min block avg to AQS.  
9 Of these, 104 reported only the max 5-minute average, 15 reported all 12 5-minute avg in each  
10 hour, and 11 of those 15 reported all 12 values each hour and maximum values for some fraction  
11 of time between 1997 and 2006. See Table 2-6 and Table 2-7 for a breakdown of these monitor  
12 locations and sampling periods, and Figure 2-17 for the geospatial distribution of these monitors  
13 across the CONUS.

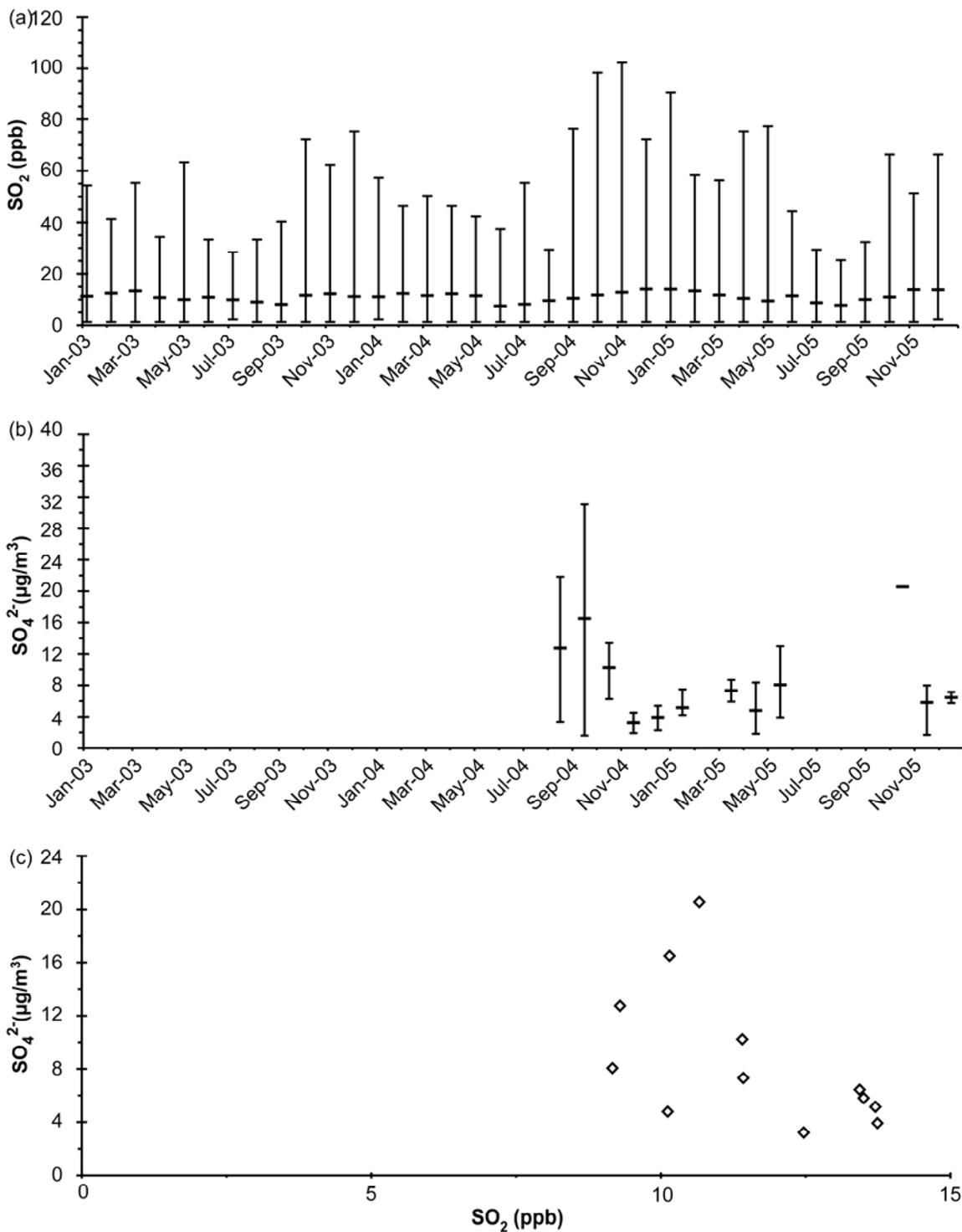
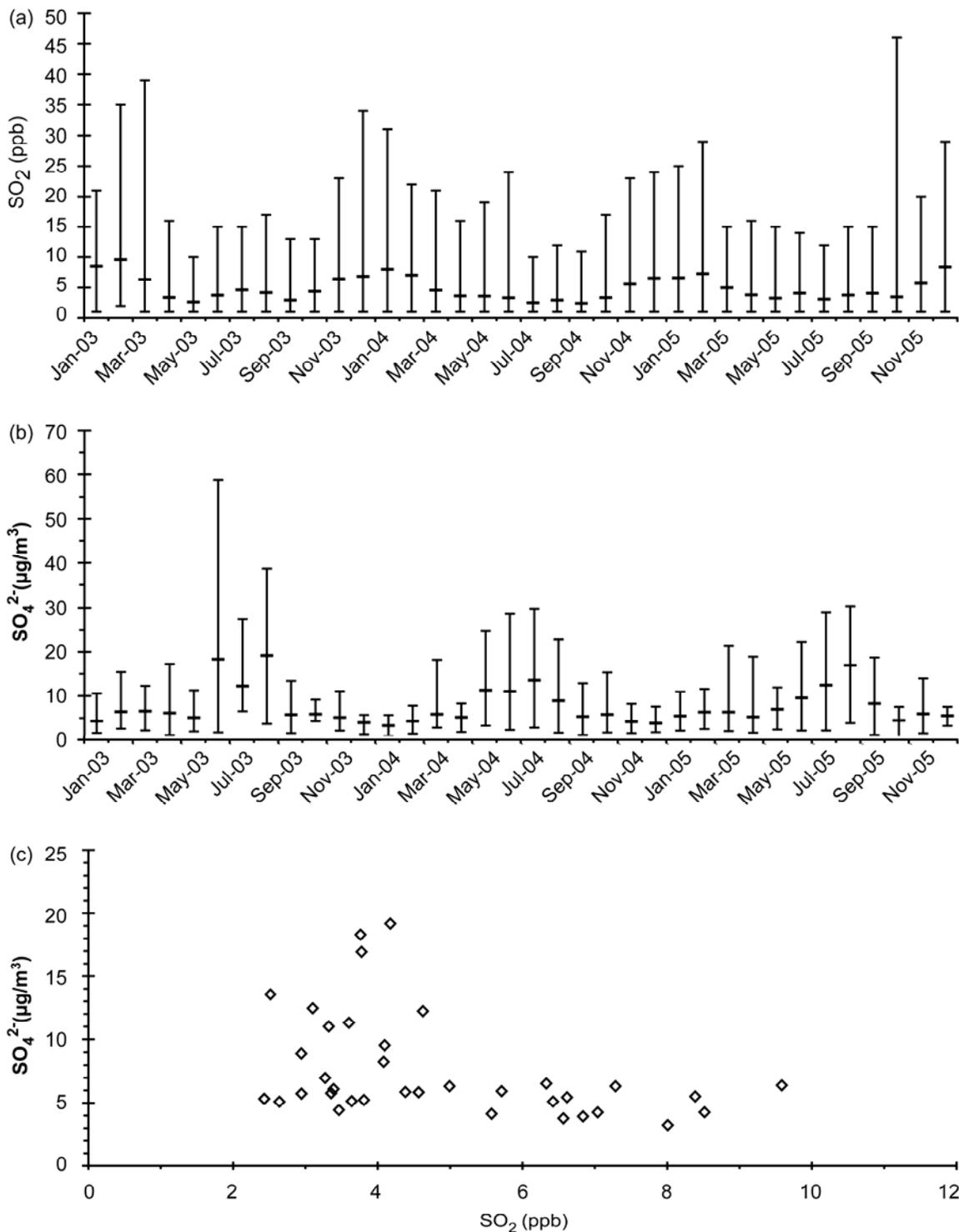


Figure 2-12. Steubenville, OH, 2003–2005. (a) Monthly mean, minimum, and maximum SO<sub>2</sub> concentrations. (b) Monthly mean, minimum, and maximum SO<sub>4</sub><sup>2-</sup> concentrations. (c) Monthly mean SO<sub>4</sub><sup>2-</sup> concentrations as a function of SO<sub>2</sub> concentrations.



**Figure 2-13. Philadelphia, 2003–2005. (a) Monthly mean, minimum, and maximum SO<sub>2</sub> concentrations. (b) Monthly mean, minimum, and maximum SO<sub>4</sub><sup>2-</sup> concentrations. (c) Monthly mean SO<sub>4</sub><sup>2-</sup> concentrations as a function of SO<sub>2</sub> concentrations.**

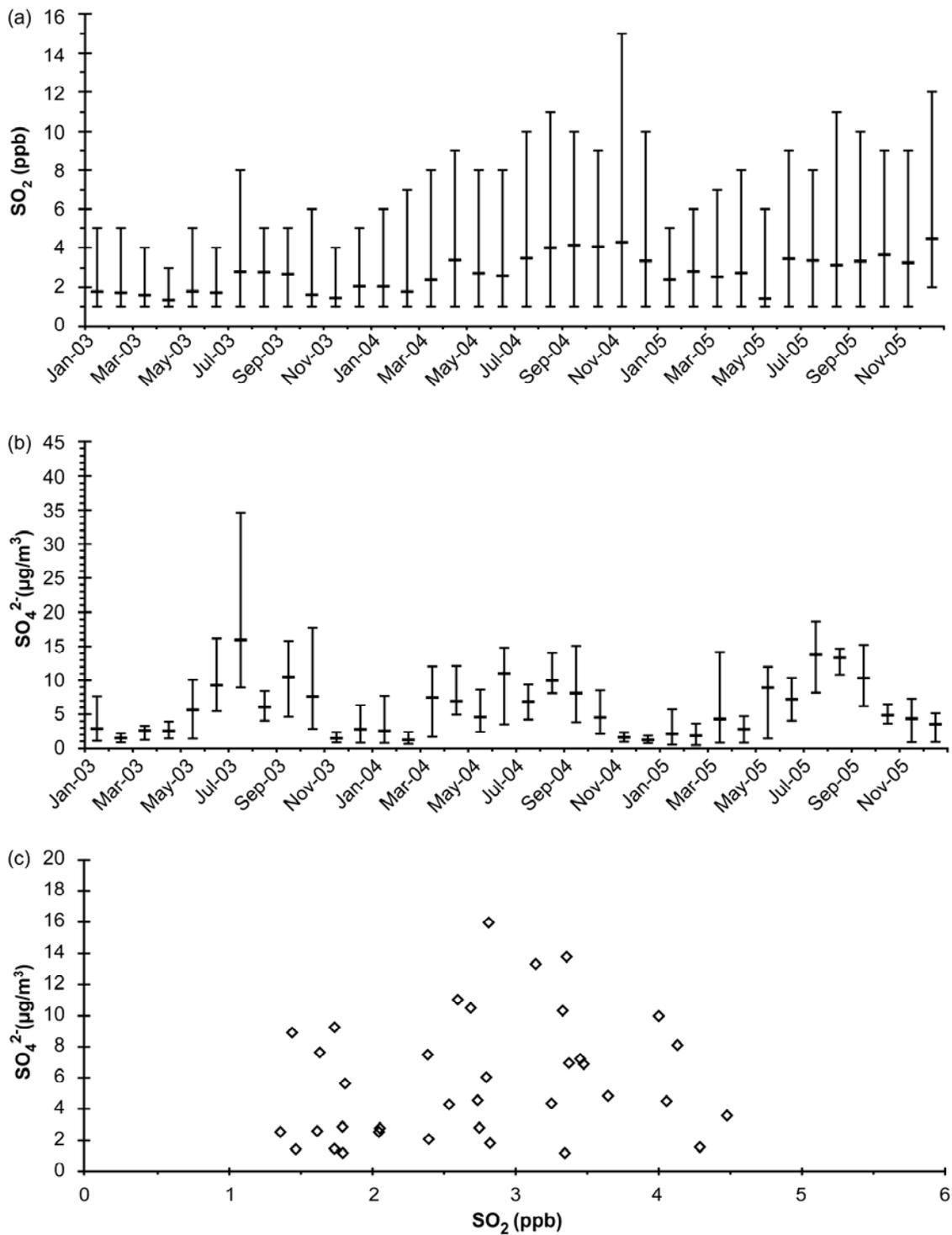


Figure 2-14. Los Angeles, 2003–2005. (a) Monthly mean, minimum, and maximum  $\text{SO}_2$  concentrations. (b) Monthly mean, minimum, and maximum  $\text{SO}_4^{2-}$  concentrations. (c) Monthly mean  $\text{SO}_4^{2-}$  concentrations as a function of  $\text{SO}_2$  concentrations.

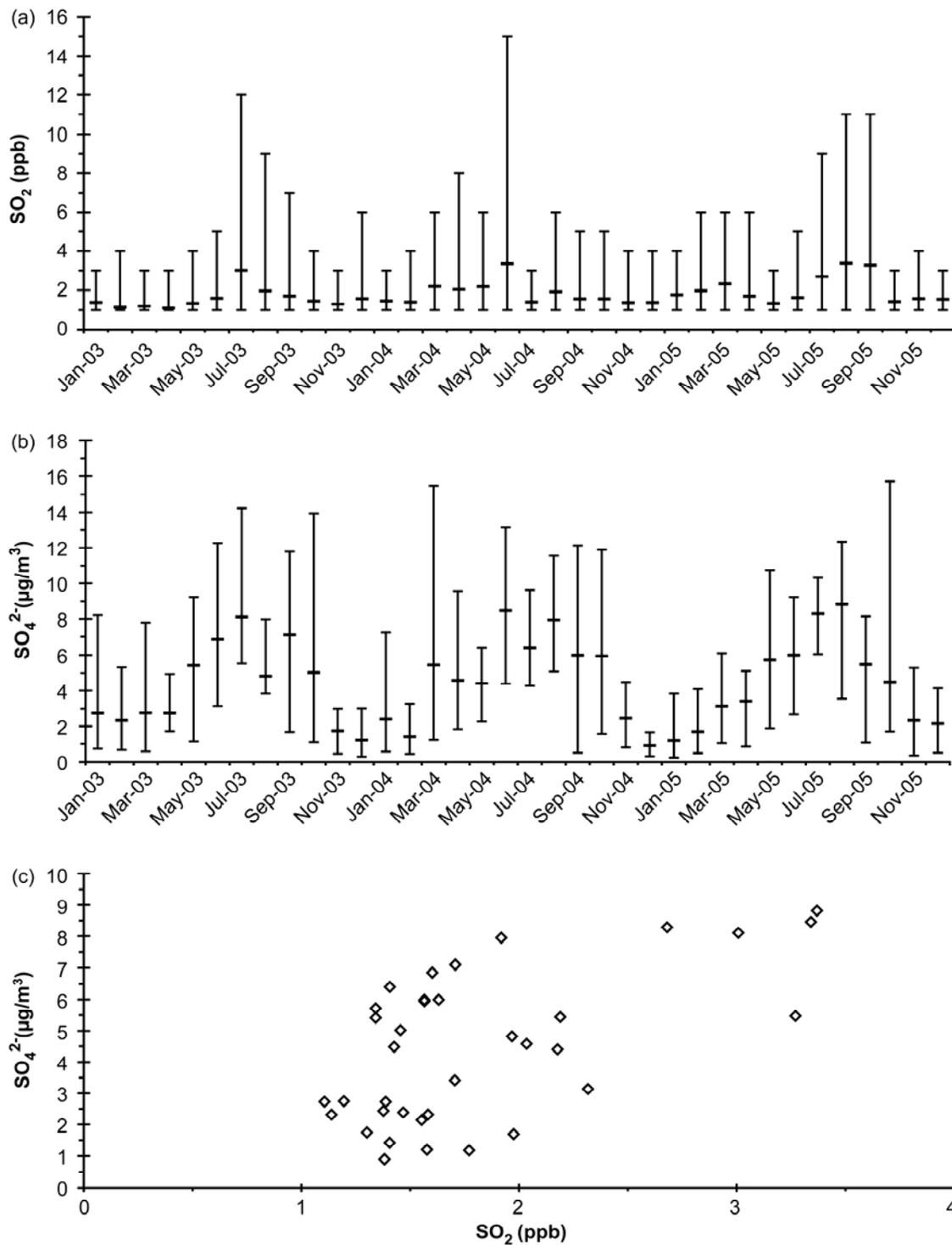
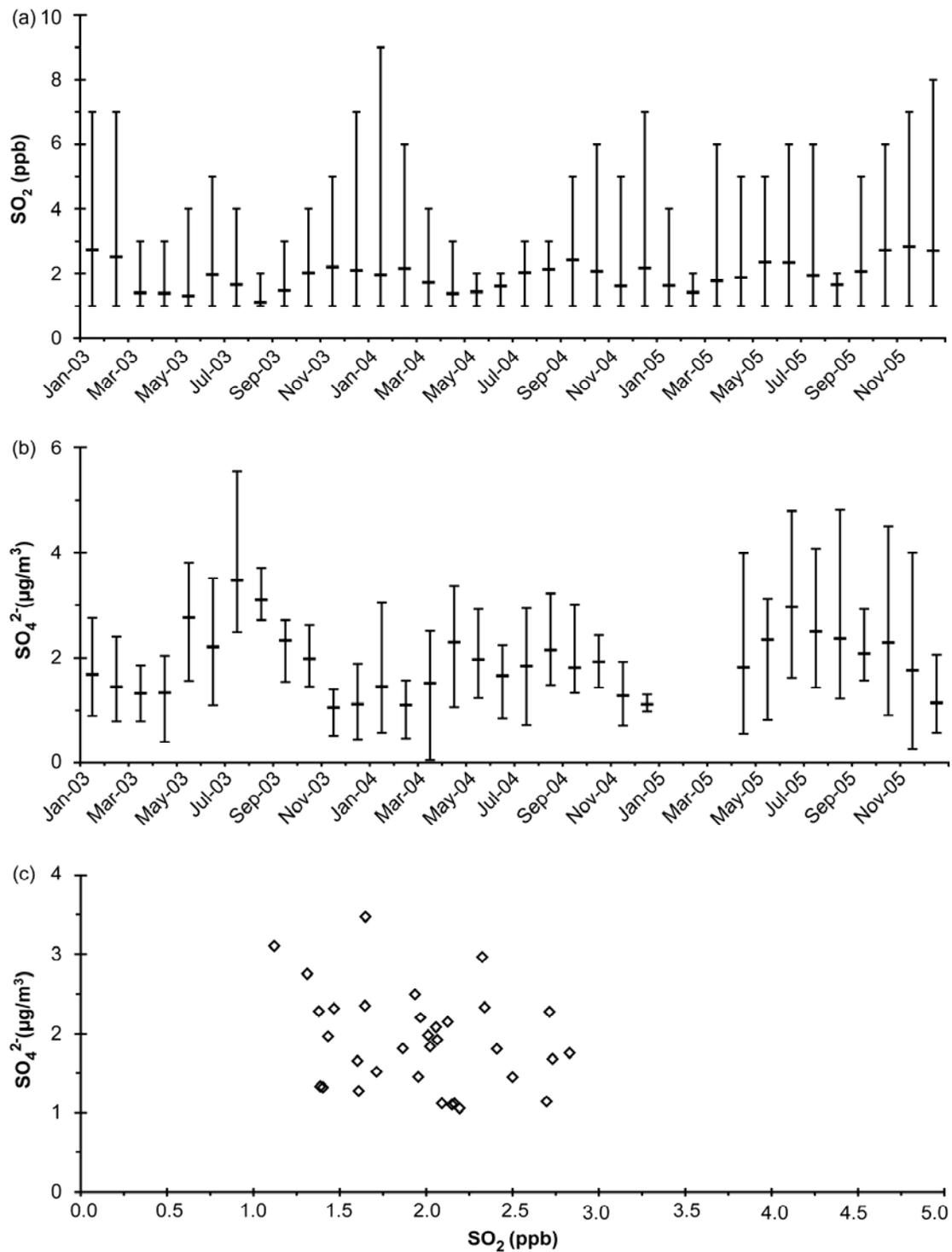


Figure 2-15. Riverside, CA, 2003–2005. (a) Monthly mean, minimum, and maximum  $\text{SO}_2$  concentrations. (b) Monthly mean, minimum, and maximum  $\text{SO}_4^{2-}$  concentrations. (c) Monthly mean  $\text{SO}_4^{2-}$  concentrations as a function of  $\text{SO}_2$  concentrations.



**Figure 2-16. Phoenix, 2003–2005. (a) Monthly mean, minimum, and maximum SO<sub>2</sub> concentrations. (b) Monthly mean, minimum, and maximum SO<sub>4</sub><sup>2-</sup> concentrations. (c) Monthly mean SO<sub>4</sub><sup>2-</sup> concentrations as a function of SO<sub>2</sub> concentrations.**

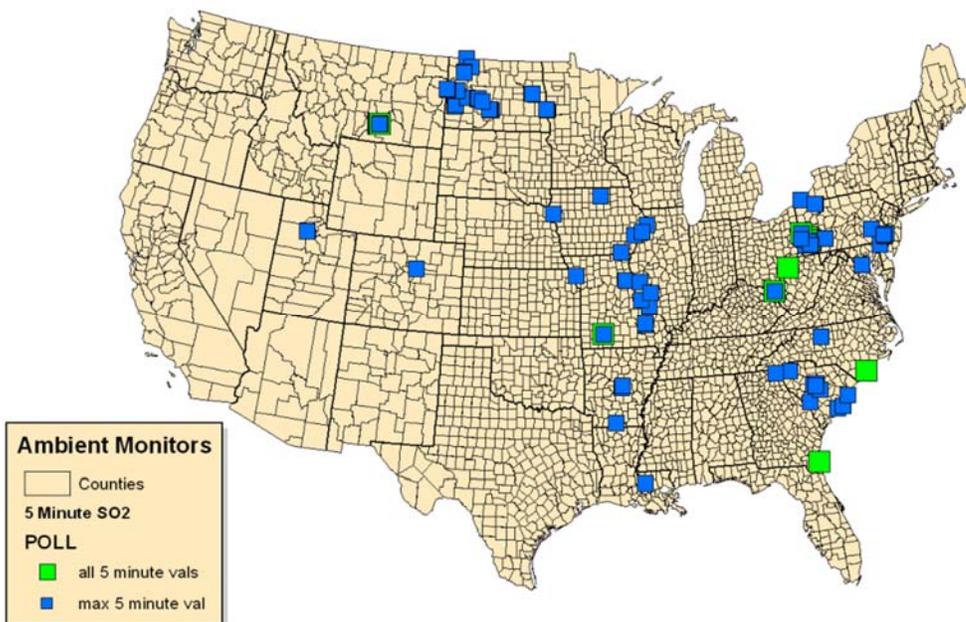
1 Although these 5-minute data meet AQS minimum quality assurance requirements, the  
 2 voluntary nature of this reporting and the high variability across space and time make these data  
 3 very difficult to use precisely.

**Table 2-6. Locations, counts, and sampling periods of monitors reporting 5-minute maximum SO<sub>2</sub> values, 1997–2006.**

STATE	NUMBER OF COUNTIES	NUMBER OF MONITORS	NUMBER OF YEARS	YEARS OPERATING
Arkansas	2	3	10	1997-2006
Colorado	1	1	10	1997-2006
Delaware	1	1	2	1997-1998
D.C.	1	1	5	2000-2004
Iowa	6	9	5	2001-2005
Louisiana	1	1	4	1997-2000
Missouri	7	14	10	1997-2006
Montana	1	7	10	1997-2006
North Carolina	1	1	8	1997-2004
North Dakota	11	19	10	1997-2006
Pennsylvania	8	23	7	1997-2003

**Table 2-7. Locations, counts, and sampling periods of monitors reporting all 12 5-minute SO<sub>2</sub> values in each hour, 1997–2006.**

STATE	NUMBER OF COUNTIES	NUMBER OF MONITORS	NUMBER OF YEARS	YEARS OPERATING
D.C.	1	1	1	2007
Florida	1	1	4	2002-2005
Missouri	1	2	4	2003-2006
Montana	1	4	1	2002
North Carolina	1	1	4	1999-2002
Pennsylvania	2	5	5	2002-2006
West Virginia	2	2	5	2001-2005



**Figure 2-17. SO<sub>2</sub> monitors reporting maximum or continuous 5-minute average values for any period, 1997–2006.**

#### 2.4.6. Policy Relevant Background Contributions to SO<sub>2</sub> Concentrations

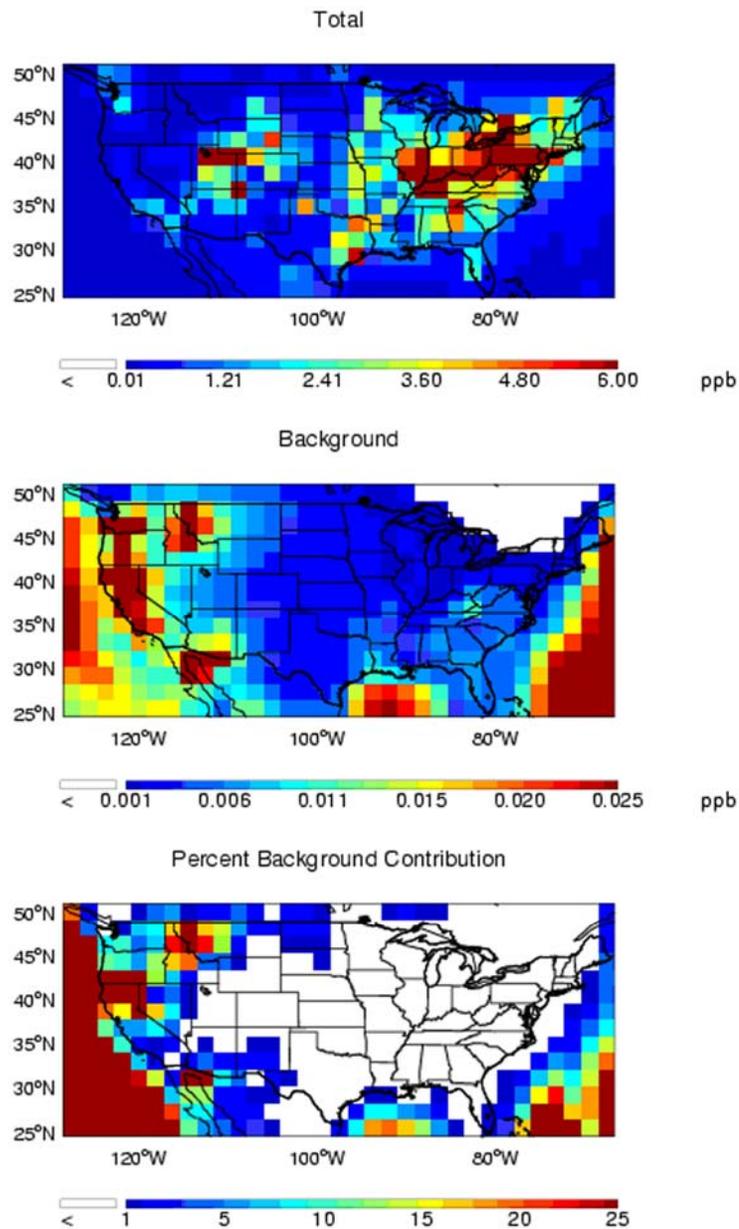
1 Background concentrations used for purposes of informing decisions about the NAAQS  
 2 are referred to as Policy Relevant Background (PRB) concentrations. PRB concentrations are  
 3 those concentrations that would occur in the United States in the absence of anthropogenic  
 4 emissions in continental North America (defined here as the United States, Canada, and Mexico).  
 5 PRB concentrations include contributions from natural sources everywhere in the world, and  
 6 from anthropogenic sources outside these three countries. Background levels so defined facilitate  
 7 separation of cases where pollution levels can be controlled by U.S. regulations (or through  
 8 international agreements with neighboring countries), from cases where pollution is generally  
 9 uncontrollable by the United States. EPA assesses risks to human health and environmental  
 10 effects from SO<sub>2</sub> levels in excess of PRB concentrations.

11 Contributions to PRB concentrations include natural emissions of SO<sub>2</sub> and photochemical  
 12 reactions involving reduced sulfur compounds of natural origin, as well as their long-range  
 13 transport from outside of North America from any source. As an example, transport of SO<sub>2</sub> from  
 14 Eurasia across the Pacific Ocean or the Arctic Ocean would carry PRB SO<sub>2</sub> into the U.S.

1 Annex B contains a schematic diagram showing the major photochemical processes involved in  
2 the sulfur cycle, including natural sources of reduced sulfur species from anaerobic microbial  
3 activity in wetlands and volcanic activity. Volcanoes and wildfires are the major natural source of  
4 SO<sub>2</sub>. Biogenic emissions from agricultural activities are not considered in the formation of PRB  
5 concentrations. Discussions of the sources and estimates of emissions are given in Annex  
6 Section B.6.

7 The MOZART-2 global model of tropospheric chemistry (Horowitz et al., 2003) is used to  
8 estimate the PRB contribution to SO<sub>2</sub> concentrations. The model setup for the present-day  
9 simulation, i.e., including all sources in the U.S. Canada and Mexico, was published in a series  
10 of papers from a recent model intercomparison (Dentener et al., 2006; van Noije et al., 2006).  
11 MOZART-2 is driven by the National Oceanic and Atmospheric Administration's National  
12 Center for Environmental Prediction (NOAA/NCEP) meteorological fields and the International  
13 Institute for Applied Systems Analysis (IIASA) 2000 emissions at a resolution of 1.9° × 1.9°  
14 with 28 σ (sigma) levels in the vertical, and includes gas- and aerosol-phase chemistry. Results  
15 shown in Figure 2-18 are for the meteorological year 2001. An additional PRB simulation was  
16 conducted in which continental North American anthropogenic emissions were set to zero.

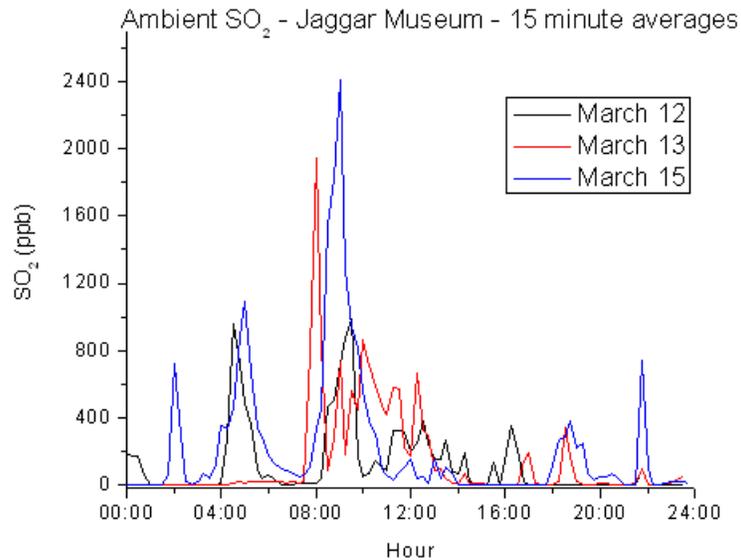
17 The role of PRB in contributing to SO<sub>2</sub> concentrations in surface air is examined first.  
18 Figure 2-18 shows the annual mean predicted SO<sub>2</sub> concentrations in surface air in the simulation  
19 including all sources, or the "base case" (top panel); the PRB simulation (middle panel); and the  
20 percentage contribution of the background to the total base case SO<sub>2</sub> (bottom panel). Maximum  
21 concentrations in the base case simulation, > 5 ppb, occur along the Ohio River Valley (upper  
22 panel). Background SO<sub>2</sub> concentrations are orders of magnitude smaller, below 10 parts per  
23 trillion (ppt) over much of the United States (middle panel). Maximum PRB concentrations of  
24 SO<sub>2</sub> are 30 ppt. In the Northwest where there are geothermal sources of SO<sub>2</sub>, the contribution of  
25 PRB to total SO<sub>2</sub> is 70 to 80%; however absolute SO<sub>2</sub> concentrations are still of the order of a  
26 couple of ppb or less. With the exception of the West Coast where volcanic SO<sub>2</sub> emissions cause  
27 high PRB concentrations, PRB contributes < 1% to present-day SO<sub>2</sub> concentrations in surface air  
28 (bottom panel).



**Figure 2-18. Annual mean model-predicted concentrations of SO<sub>2</sub> (ppb).**

1           When estimating background concentrations it is instructive to consider measurements of  
 2           SO<sub>2</sub> at relatively remote monitoring sites, i.e., sites located in sparsely populated areas not  
 3           subject to obvious local sources of pollution. Berresheim et al. (1993) used a type of atmospheric  
 4           pressure ionization mass spectrometer (APIMS) at Cheeka Peak, WA (48.30°N 124.62°W,  
 5           480 m asl), in April 1991 during a field study for DMS oxidation products. SO<sub>2</sub> concentrations  
 6           ranged between 20 and 40 ppt. Thornton et al. (2002) have also used an APIMS with an

1 isotopically labeled internal standard to determine background SO<sub>2</sub> levels. SO<sub>2</sub> concentrations of  
2 25 to 40 ppt were observed in northwestern Nebraska in October, 1999 at 150 m above ground  
3 using the National Center for Atmospheric Research (NCAR)'s C-130 research aircraft. These  
4 data are comparable to remote central South Pacific convective boundary layer SO<sub>2</sub> data  
5 (Thornton, 1999).

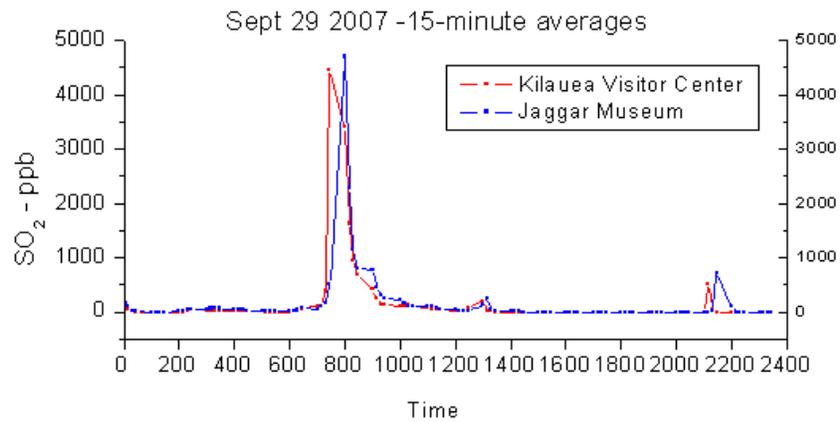


**Figure 2-19. 15-minute average ambient SO<sub>2</sub> concentrations measured at Hawaii Volcanoes National Park monitoring sites, March 12, 13, and 15, 2007.**

Source: National Park Service

6 As noted earlier, volcanic sources of SO<sub>2</sub> in the United States are found in the Pacific  
7 Northwest, Alaska, and Hawaii. The greatest potential domestic effects from volcanic SO<sub>2</sub> occurs  
8 on the island of Hawaii. Nearly continuous venting of SO<sub>2</sub> from Mauna Loa and Kilauea  
9 produces SO<sub>2</sub> in high concentrations (see Figure 2-19 and Figure 2-20) at two National Park sites  
10 near the Kilauea caldera and the nearby east rift zone. The latter emits several times as much SO<sub>2</sub>  
11 as the Kilauea caldera. The two measurement sites within the National Park are < 3 km from the  
12 summit emission source and ~10 km from the east rift source and are affected by the two sources  
13 during southerly and easterly winds. A number of communities and population centers are within  
14 the same distance from the east rift gas source that affects these two monitoring sites. When the

1 normal trade wind flows are disrupted, emissions from the sources can be brought directly to  
2 these various communities. Since these communities are located at a similar distance from the  
3 large east rift emission source as the Park monitoring stations, it is probable that these  
4 communities experience SO<sub>2</sub> concentrations as high as those measured within Hawaii Volcanoes  
5 National Park.



**Figure 2-20. 15-minute average ambient SO<sub>2</sub> concentrations measured at the two National Park monitoring sites at Hawaii Volcanoes NP, Hawaii on September 29, 2007.**

Source: National Park Service

6 Since 1980, the Mount St. Helens volcano (46.20°N, 122.18°W, summit 2549 m asl) in the  
7 Washington Cascade range has been a variable source of SO<sub>2</sub>. Its major effects came in the  
8 explosive eruptions of 1980, which primarily affected the northwestern United States. The  
9 Augustine volcano near the mouth of the Cook Inlet in southwestern Alaska (59.363°N,  
10 153.43°W, summit 1252 m asl) has emitted variable quantities of SO<sub>2</sub> since its last major  
11 eruptions in 1986. Volcanoes in the Kamchatka peninsula in far eastern Siberia do not  
12 particularly affect the surface concentrations in northwestern North America.

13 Overall, the background contribution to SO<sub>2</sub> over the United States is relatively small, with  
14 a max PRB of 0.030 ppb SO<sub>2</sub>, except for areas with volcanic activity.

## 2.5. Issues Associated with Evaluating $\text{SO}_2$ Exposure

### 2.5.1. General Considerations for Personal Exposure

1 Human exposure to an airborne pollutant consists of contact between the human and the  
2 pollutant at a specific concentration for a specified period of time. People spend various amounts  
3 of time in different microenvironments characterized by different pollutant concentrations. The  
4 integrated exposure of a person to a given pollutant is the sum of the exposures over all time  
5 intervals for all microenvironments. Figure 2-21 represents a composite average of activity  
6 patterns across all age groups in the United States, based on data collected in the National  
7 Human Activity Pattern Survey (NHAPS) (Klepeis et al., 2001). The demographic distribution of  
8 the respondents was designed to be similar to that of overall U.S. Census data. Different cohorts,  
9 e.g., the elderly, young and middle-aged working adults, and children exhibit different activity  
10 patterns.

11 A person's exposure to a pollutant, such as  $\text{SO}_2$ , can be represented by:

$$E_T = \sum_{i=1}^n C_i t_i \quad (2-7)$$

12 where  $E_T$  is an individual's total personal exposure for a specific time period,  $n$  is the total  
13 number of microenvironments encountered,  $C_i$  is the average concentration, and  $t_i$  is the time  
14 spent in the  $i$ th microenvironment. The exposure a person experiences can be characterized as: an  
15 instantaneous exposure; a peak exposure such as might occur during cooking; an average  
16 exposure; or an integrated exposure over all environments encountered. These distinctions are  
17 important because health effects caused by long-term low-level exposures may differ from those  
18 caused by short-term peak exposures.

19 An individual's total exposure ( $E_T$ ) can also be represented by:

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

20 subject to the constraint

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

1 where  $E_a$  is the ambient component of personal exposure,  $E_{na}$  is the nonambient component of  
2 personal exposure,  $y_o$  is the fraction of time spent outdoors, and  $y_i$  is the fraction of time spent in  
3 microenvironment  $i$ .  $F_{inf_i}$ ,  $P_i$ ,  $a_i$ , and  $k_i$  are the infiltration factor, penetration coefficient, air  
4 exchange rate, and decay rate, respectively for microenvironment  $i$ . In the case where an  
5 exposure occurs mainly in one microenvironment, Equation 2-8 may be approximated by  
6 Equation 2-10 where  $y$  is the fraction of time spent outdoors, and  $\alpha$  is the ratio of personal  
7 exposure from a pollutant of ambient origin to the pollutant's ambient concentration (or the  
8 ambient exposure factor). Other symbols have the same definitions as in Equations 2-8 and 2-9.

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

9 If concentrations in a single microenvironment are considered, then Equation 2-10 can be recast  
10 as

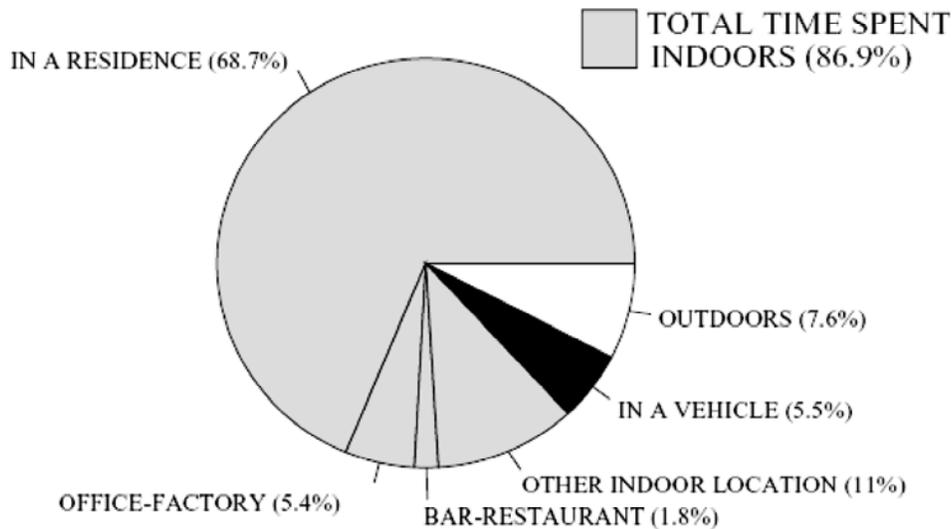
$$C_{me} = C_a + C_{na} = [Pa/(a + k)]C_a + S/[V(a + k)] \quad (2-11)$$

11 where  $C_{me}$  is the concentration in a microenvironment,  $C_a$  and  $C_{na}$  are the contributions to  $C_{me}$   
12 from ambient and nonambient sources,  $S$  is the microenvironmental source strength, and  $V$  is the  
13 volume of the microenvironment. (Bracketed symbols are same as Equation 2-8.) In this  
14 equation, it is assumed that microenvironments do not exchange air with each other, but only  
15 with the ambient environment.

16 Microenvironments in which people are exposed to air pollutants such as  $SO_2$  typically  
17 include residential indoor environments, other indoor locations, near-traffic outdoor  
18 environments, other outdoor locations, and in vehicles, as shown in Figure 2-21. Indoor  
19 combustion sources such as gas stoves and space heaters need to be considered when evaluating  
20 exposures to  $SO_2$ . Exposure misclassification may result when total human exposure is not  
21 disaggregated between various microenvironments, and this may obscure the true relationship  
22 between ambient air pollutant exposures and health outcomes.

## NHAPS - Nation, Percentage Time Spent

Total n = 9,196



**Figure 2-21. Percentage of time spent in various environments in the United States.<sup>1</sup>**

Source: Klepeis et al. (2001).

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

- 3 ■ ambient concentration  $C_a$
- 4 ■ air exchange rate  $a_i$
- 5 ■ pollutant specific penetration coefficient  $P_i$
- 6 ■ pollutant specific decay rate  $k_i$
- 7 ■ fraction of time an individual spends in the microenvironment  $y_i$

8 These factors are in turn affected by the following exposure factors:

- 9 ■ environmental conditions, such as weather and season

<sup>1</sup> For example, the cohort of working adults between the ages of 18 and 65 represents ~50% of the population. Of this total, about 60% work outside the home, spending ~24% (40 h/168 h) of their time in factory/office environments. Thus, this cohort is likely to spend considerably more time in offices and factories than shown in the figure (5.4%), which reflects the entire population, and is also likely to spend less time in a residence than small children or the elderly.

- 1       ▪ dwelling conditions, such as the location of the house which determines proximity to
- 2       sources and geographical features that can modify transport from sources, the amount of
- 3       natural ventilation (e.g., open windows and doors, and the “draftiness” of the dwelling)
- 4       and ventilation system (e.g., removal efficiency and operation cycle)
- 5       ▪ personal activities (e.g., the time spent cooking or commuting)
- 6       ▪ indoor sources and sinks of a pollutant

7 Microenvironmental exposures can also be influenced by the individual-specific factors such as  
8 age, gender, health or socioeconomic status.

9       Time-activity diaries, completed by study participants, are used to compile activity patterns  
10 for input to exposure models and assessments. The EPA’s National Exposure Research  
11 Laboratory (NERL) has consolidated the majority of the most significant human activity  
12 databases into one comprehensive database called the Consolidated Human Activity Database  
13 (CHAD). Eleven different human activity pattern studies were evaluated to obtain over 22,000  
14 person-days of 24-h human activities in CHAD (McCurdy et al., 2000). These data can be useful  
15 in assembling population cohorts to be used in exposure modeling and analysis.

16       In general, the relationship between personal exposures and ambient concentrations can be  
17 modified by microenvironments. During infiltration, ambient pollutants can be lost through  
18 chemical and physical loss processes, and therefore, the ambient component of a pollutant’s  
19 concentration in a microenvironment is not the same as its ambient concentration but the product  
20 of the ambient concentration and the infiltration factor ( $F_{inf}$  or  $\alpha$  if people spend 100% of their  
21 time indoors). In addition, exposure to nonambient, microenvironmental sources modifies the  
22 relationship between personal exposures and ambient concentrations.

23       In practice, it is extremely difficult to characterize community exposures by measurements  
24 of each individual’s personal exposures. Instead, the distribution of personal exposures in a  
25 community, or the population exposure, is simulated by extrapolating measurements of personal  
26 exposure using various techniques or by stochastic, deterministic or hybrid exposure modeling  
27 approaches such as APEX, SHEDS, and MENTOR (see Annex Section C.2 for a description of  
28 modeling methods). Variations in community-level personal exposures are determined by cross-  
29 community variations in ambient pollutant concentrations and the physical and exposure factors  
30 mentioned above. These factors also determine the strength of the association between  
31 population exposure to SO<sub>2</sub> of ambient origin and ambient SO<sub>2</sub> concentrations.

1           Of major concern is the ability of SO<sub>2</sub>, measured by ambient monitors, to serve as a  
2 reliable indicator of personal exposure to SO<sub>2</sub> of ambient origin. The key question is what errors  
3 are associated with using SO<sub>2</sub> measured by ambient monitors as a surrogate for personal  
4 exposure to ambient SO<sub>2</sub> and/or its oxidation products in epidemiological studies. There are three  
5 aspects to this issue: (1) ambient and personal sampling issues; (2) the spatial variability of  
6 ambient SO<sub>2</sub> concentrations; (3) the associations between ambient concentrations and personal  
7 exposures as influenced by exposure factors, e.g., indoor sources and time spent indoors and  
8 outdoors. Items (1) and (3) are treated individually in the following sections; item (2) was treated  
9 previously in Section 2.4.2.

### **2.5.2. Methods Used for Monitoring Personal Exposure**

10           Three basic methods of analysis have been used as personal exposure monitors (PEMs) to  
11 measure personal exposure to SO<sub>2</sub>. The Harvard-EPA annular denuder system (HEADS) was  
12 initially developed to measure particles and acid gases simultaneously (Brauer et al., 1999;  
13 Koutrakis et al., 1988). The aerosol is initially sampled at 10 L/min through an impactor that is  
14 attached to an annular denuder to remove particles. Subsequently, the aerosol is sampled through  
15 an annular denuder coated with sodium carbonate (Na<sub>2</sub>CO<sub>3</sub>). This denuder is used to trap SO<sub>2</sub>,  
16 nitric acid (HNO<sub>3</sub>), and nitrous acid (HNO<sub>2</sub>). Following sampling, the denuder is extracted with  
17 ultrapure water and analyzed by ion chromatography. Collection efficiencies of SO<sub>2</sub> in the  
18 denuder are typically around 0.993, which compares well with predicted values.

19           For a study conducted in Baltimore, MD, Chang et al. (2000) developed and employed a  
20 personal roll-around system (RAS, an active sampling system designed to measure short-term  
21 exposure) to measure personal exposure concentrations of several atmospherically relevant  
22 species, including SO<sub>2</sub>. For the measurement of SO<sub>2</sub>, the RAS employed an NO<sub>2</sub>/SO<sub>2</sub> sorbent  
23 denuder worn on a vest by the study participant. The hollow glass denuder, encased in an  
24 aluminum jacket, is coated with triethanolamine (TEA) for the collection of SO<sub>2</sub> and NO<sub>2</sub>, and  
25 aerosol is sampled through the denuder at 100 cc/min. Following sampling, the denuder can be  
26 extracted and analyzed for SO<sub>2</sub> concentrations by ion chromatography. The detection limit for  
27 1-h sampling of SO<sub>2</sub> was reported to be 62 ppb, which resulted in many of the 1-h samples being  
28 below the LOD.

1           The most commonly employed SO<sub>2</sub> PEM method for personal exposure studies is the  
2 passive badge sampler. A personal multipollutant sampler has been developed to measure  
3 particulate and gaseous pollutants simultaneously (Demokritou et al., 2001). A single elutriator,  
4 operating at 5.2 L/min, is employed to sample particulate pollutants. A passive SO<sub>2</sub> badge is  
5 attached diametrically to the elutriator, which has been coated with Teflon to minimize reactive  
6 gas losses. The passive badge sample is coated with TEA for the collection of SO<sub>2</sub> and NO<sub>2</sub>.  
7 Because wind speed can affect the collection rate of the passive badge sampler, this system  
8 employs a constant face velocity across the passive badge sampler. For 24-h sampling times, the  
9 estimated limit of detection (LOD) for SO<sub>2</sub> is 5 ppb.

10           Currently, limits exist for using PEM systems to measure personal exposure to SO<sub>2</sub>.  
11 Because SO<sub>2</sub> concentrations have been declining annually in the United States, little focus has  
12 been placed on improving the methods of analysis. LODs for SO<sub>2</sub> PEMs (~5-10 ppb for 24 hr  
13 sampling) are often greater than the concentrations of SO<sub>2</sub> that are typically observed in urban  
14 ambient environments. However, much lower detection limits can be achieved by extending the  
15 sampling time (Kasper-Giebl et al., 1999). Personal exposure monitoring studies often suffer  
16 from having many of the daily SO<sub>2</sub> samples (e.g., 30 to 70%) collected below the sampler's LOD  
17 (see Tables 2-10 and 2-11). Because of these issues, current methods can not characterize hourly  
18 or shorter exposures unless these values are in the range of several tens to hundreds of ppb.

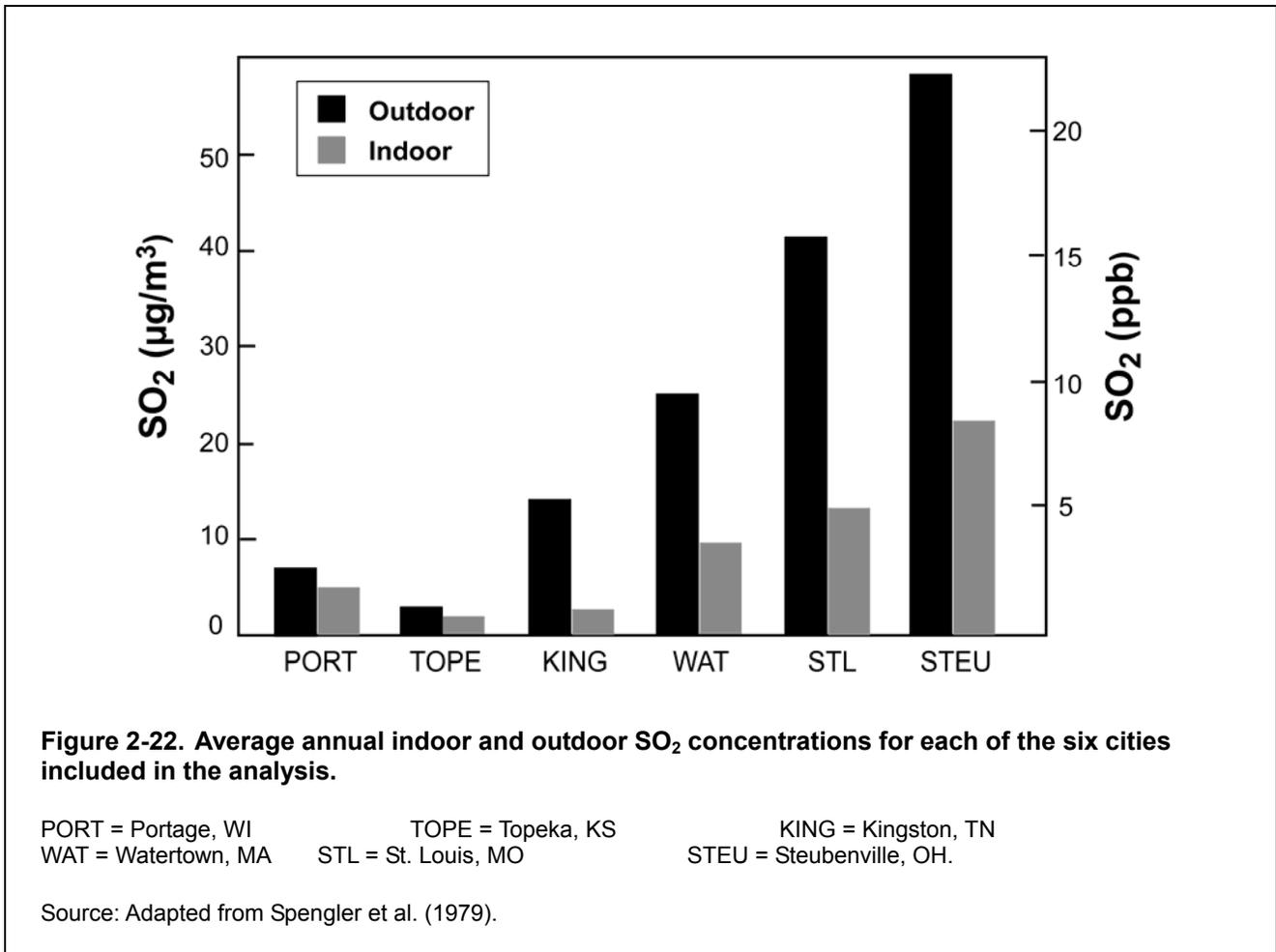
### **2.5.3. Relationship between Personal Exposure and Ambient Concentration**

19           Because SO<sub>2</sub> concentrations have declined markedly over the past few decades, relatively  
20 few studies have focused on SO<sub>2</sub>. Another consideration is that current indoor and outdoor levels  
21 in many areas are often beneath detection limits for passive personal SO<sub>2</sub> monitors.

#### **2.5.3.1. Indoor Versus Outdoor SO<sub>2</sub> Concentrations**

22           Several studies in the United States, Canada, Europe, and Asia have examined the  
23 relationships of indoor, outdoor, and personal concentrations of SO<sub>2</sub> to ambient SO<sub>2</sub>  
24 concentrations. Perhaps the most comprehensive set of indoor-outdoor data was obtained by  
25 Spengler et al. (1979) during the Harvard Six Cities Study. These data are shown in Figure 2-22.

- 1 Twenty-four-hour ambient and indoor SO<sub>2</sub> concentrations were measured every sixth day for
- 2 1 year in a minimum of 10 homes or public facilities for each of the cities studied.



3            As can be seen from Table 2-8, a wide range is found in the ratio of indoor to outdoor  
4 concentrations among the different studies. These differences among studies could be due in part  
5 to differences in building characteristics (e.g., residences versus schools or other public  
6 buildings), in activities affecting air exchange rates, and in analytical capabilities. In several  
7 studies, high values for R<sup>2</sup> were found, suggesting that indoor levels were largely driven by  
8 outdoor levels. A few studies found higher levels of SO<sub>2</sub> indoors than outdoors in some samples.  
9 This situation could have arisen if there were indoor sources or because of analytical  
10 measurement issues. One would expect to find lower concentrations indoors than outdoors,  
11 because SO<sub>2</sub> is consumed by reactions on indoor surfaces, especially those that are moist. Chao  
12 acknowledged this point but could not account for the findings of this study. It was noted that

1 two samples had unusually high indoor to outdoor ratios and that the mean ratios would have  
 2 been much lower otherwise. Winter-summer differences in the indoor:outdoor ratio are  
 3 consistent with seasonal differences in air exchange rates, as noted by Brauer et al. (1991).

**Table 2-8. Relationships of indoor to outdoor SO<sub>2</sub> concentrations.**

REFERENCE	LOCATION	INDOOR TO OUTDOOR RATIO V(# 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 <sup>2</sup> = 0.89	Summer, HEADS
		0.05 (geom. mean) (23), R <sup>2</sup> = 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 <sub>2</sub> = 0.56	Winter, PF
Patterson and Eatough (2000)	Lindon, UT	0.027 ± 0.0023, R <sup>2</sup> = 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)	
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  
 FRM = Federal Reference Method  
 ADS = Annular Denuder System

4 Indoor, or nonambient, sources of SO<sub>2</sub> could complicate the interpretation of associations  
 5 between personal exposure to ambient SO<sub>2</sub> in exposure studies. Possible sources of indoor SO<sub>2</sub>  
 6 are associated with the use of sulfur-containing fuels, with higher levels expected when  
 7 emissions are poorly vented. Brauer et al. (2002) noted that only one study (Biersteker et al.,  
 8 1965) conducted inferential analyses of potential determinants of exposure to indoor SO<sub>2</sub> levels.

1 In the Biersteker et al. study, conducted in the Netherlands, indoor levels increased with oil, coal,  
2 and gas heating, as well as smoking in homes and increased outdoor levels.

3 Triche et al. (2005) measured SO<sub>2</sub> levels in homes in which secondary heating sources  
4 (fireplaces, kerosene heaters, gas space heaters, and wood stoves) were used. They found  
5 elevated indoor levels of SO<sub>2</sub> when kerosene heaters were in use. Median levels of SO<sub>2</sub> when  
6 kerosene heaters were used (6.4 ppb) were much higher than when they were not in use  
7 (0.22 ppb). The maximum SO<sub>2</sub> level associated with kerosene heater use was 90.5 ppb. They did  
8 not find elevated SO<sub>2</sub> levels when the other secondary heating sources were in use.

### **2.5.3.2. Relationship of Personal Exposure to Ambient Concentration**

9 A few studies evaluated the association of personal exposure to SO<sub>2</sub> to ambient  
10 concentrations (Brauer et al., 1989; Chang et al., 2000; Sarnat et al., 2000; 2001; 2005; 2006).  
11 Some of these studies fall under the umbrella of the Health Effects Institute's Characterization of  
12 Particulate and Gas Exposures of Sensitive Subpopulations Living in Baltimore and Boston  
13 research plan (Koutrakis et al., 2005). However, the focus of many of these studies has been  
14 exposure to particles, with acid gases included to evaluate confounder or surrogate issues.

15 Table 2-9 summarizes the longitudinal correlation coefficients between personal SO<sub>2</sub>  
16 exposures and ambient concentrations of SO<sub>2</sub>, and Table 2-10 the pooled correlation coefficients.  
17 Most of the studies examined lack the ability to quantify 24-h averaged personal SO<sub>2</sub> exposures  
18 due to the low ambient SO<sub>2</sub> concentrations and the limitations of passive sampling, except two  
19 studies conducted by Brauer et al. (1989) and Sarnat et al (2006).

20 Brauer et al. (1989) determined the slope of the regression line between personal and  
21 ambient concentrations to be  $0.13 \pm 0.02$ ,  $R^2 = 0.43$ , based on 44 measurements made in Boston,  
22 MA during the summer of 1988. Most if not all of the data points obtained using the HEADS  
23 appeared to be above the working detection limits as defined by the authors in their publications  
24 (Brauer et al., 1989; Koutrakis et al., 1988). Note that calculating detection limits in this way  
25 could result in lower detection limits than if field blanks were used. The authors reported  
26 significance at the  $p < 0.001$  level, but the intercept was not significant at the  $p < 0.001$  level.  
27 Since the stationary monitoring site was located at an elevation of 250 m above street level, the  
28 use of data from this ambient monitoring site will overestimate personal exposure, as the  
29 concentration of SO<sub>2</sub> increases with height because it is emitted mainly by elevated point

1 sources. Indeed, the ambient concentrations are about a factor of two higher than the outdoor  
 2 concentrations. Sarnat et al. (2006) reported that ambient SO<sub>2</sub> was observed to be significantly  
 3 associated with personal SO<sub>2</sub> exposures during the fall (slope = 0.08 for overall population) in a  
 4 study in Steubenville, OH. The authors also observed the effect of ventilation on the association  
 5 between personal exposures and ambient concentrations (slope = 0.07 for subjects in buildings  
 6 with low ventilation rates, and 0.13 for subjects in buildings with high ventilation rates).

**Table 2-9. Association between personal exposure and ambient concentration (longitudinal correlations coefficients).**

REFERENCE	STUDY DESIGN	SEASON	MEAN CONC. (ppb)	SLOPE	INTERCEPT	r, R <sup>2</sup>	COMMENTS
Sarnat et al. (2000)	Longitudinal, Baltimore, 20 senior, healthy, nonsmoking people (average age 75), summer of 1998 and winter of 1999, 1 day averaged sample, for 12 consecutive days for each subject; four to six subjects were measured concurrently during each 12-day monitoring period.	Winter	Ambient: 6.6 – 10.2 Personal: -0.8 – 1.2	NR	NR	-0.75 to 0.65 (r) with a median of 0.02 (14 subjects)	The LOD for 24-h sampling was 6.5 ppb. All personal samples were below LOD.
Sarnat et al. (2001)	Longitudinal, Baltimore, 56 seniors, schoolchildren, and people with COPD, summer of 1998 and winter of 1999, 14 of 56 subjects participated in both sampling seasons; all subjects were monitored for 12 consecutive days (24-h avg samples) in each of the one or two seasons, with the exception of children who were measured for 8 consecutive days during the summer.	Winter	Ambient: 4 – 17 Personal: -2 – 3	-0.05* (N = 487 with 45 subjects)	0.54* (N = 487 with 45 subjects)	-0.75 to 0.6 (r) with a median of -0.1 (44 subjects)	1) Concentrations are estimated from Figure 1 in the paper. 2) Correlation coefficients are estimated from Figure 2 in the paper. 3) LOD was referred to Sarnat et al (2000), which was 6.5 ppb. Therefore, all personal samples were below LOD.
Sarnat et al. (2005)	Longitudinal, Boston, 43 seniors and schoolchildren, summer of 1999 and winter of 2000. Similar study design as Sarnat et al. (2001).	Summer	Ambient: 2.8 – 4.5 Personal: 0.3 – 0.5	0.00 (N = 335)	NR	-0.60 to 0.70 (r) with a median of 0.00 (Sample size NR)	1) Correlation coefficients are estimated from Figure 1 in the paper. 2) LOD was 2.3 ppb, and 96.5% of personal samples were below LOD.
		Winter	Ambient: 4.9 – 10.7 Personal: -0.3 – 1.9	-0.02 (N = 299)	NR	-0.55 to 0.60 (r) with a median of 0.10 (Sample size NR)	1) Correlation coefficients are estimated from Figure 1 in the paper. 2) LOD was 3.2 ppb, and 95.4% of personal samples were below LOD.

\* significant at  $\alpha = 0.05$  level

7 The associations between personal exposure and ambient concentration cannot be exam-  
 8 ined in the other studies because almost all the personal exposure concentrations were beneath

1 detection limits. For example, Chang et al. (2000) tested a new personal active sampling device  
 2 (a RAS with a TEA-based denuder) on volunteer participants to measure hourly personal  
 3 exposure to SO<sub>2</sub>. However, the method detection limit was too high for SO<sub>2</sub> (62 ppb for 1-h  
 4 sampling) to generate a robust SO<sub>2</sub> exposure dataset to perform further analysis, and so the  
 5 authors did not use the SO<sub>2</sub> data.

**Table 2-10. Association between personal exposure and ambient concentration (pooled correlations coefficients).**

REFERENCE	STUDY DESIGN	SEASON	MEAN CONC. (ppb)	SLOPE	INTERCEPT	r, R <sup>2</sup>	COMMENTS
Brauer et al. (1989)	Pooled, Boston, study population was NR, the number of participants was estimated to be 48, July and August of 1988 for 24 days, 1 day averaged sample, two subjects were monitored each day.	Summer	Ambient: 2.5 – 9.5 Personal: 0.4 – 1.8	0.13* (N = 44)	Not significant	0.43 (R <sup>2</sup> )	1) Concentrations estimated from Figure 2 in the paper. 2) Central site monitor was 250 m above the ground level. 3) LOD for personal samples was ~0.19 ppb based on the way to determine the LOD for an active sampling system.
Sarnat et al. (2006)	Steubenville, 15 senior subjects, summer and fall of 2000, two consecutive 24-h samples were collected for each subject for each wk, 23 wks total. Correlation coefficients were calculated in the pooled data set.	Summer	Ambient: 2.7 ± 3.9 Personal: 1.5 ± 3.3	0.03 (N = 106)	NR	0.00 (R <sup>2</sup> )	LOD was 5.5 ppb; 53.5% of personal samples were below LOD.
		Fall	Ambient: 5.4 ± 9.6 Personal: 0.7 ± 1.9	0.08* (N = 152)	NR	0.15 (R <sup>2</sup> )	LOD was 3.8 ppb, and 31.6% of personal samples were below LOD.

\* significant at  $\alpha = 0.05$  level

6 In the context of determining the effects of ambient pollutants on human health, the  
 7 association between the ambient component of personal exposures and ambient concentrations is  
 8 more relevant than the association between personal total exposures (ambient component +  
 9 nonambient component) and ambient concentrations. As described in Equations 2-8 and 2-10,  
 10 personal total exposure can be decomposed into two parts; an ambient and a nonambient  
 11 component. Usually, the ambient component of personal exposure is not directly measureable,  
 12 but it can be estimated by exposure models, or the personal total exposure can be regarded as the  
 13 personal exposure of ambient origin if there are no indoor or nonambient sources. It is expected  
 14 that the association between ambient concentrations and the ambient component of personal  
 15 exposures would be stronger than the association between ambient concentrations and personal  
 16 total exposures as long as the ambient and nonambient component of personal total exposure are  
 17 independent. None of the studies examined indoor sources, however, indoor sources are not

1 expected to be present. The correlation coefficients between personal ambient SO<sub>2</sub> exposures and  
2 ambient SO<sub>2</sub> concentrations in different types of exposure studies are relevant to different types  
3 of epidemiologic studies.

4 There are three types of correlations generated from different study designs and ways to  
5 analyze the data from exposure studies: longitudinal, “pooled,” and daily-average correlations  
6 (EPA, 2004). Longitudinal correlations<sup>1</sup> are calculated when data from a study includes  
7 measurements over multiple days for each subject (longitudinal study design). Longitudinal  
8 correlations describe the temporal relationship between daily personal SO<sub>2</sub> exposure or  
9 microenvironment concentration and daily ambient SO<sub>2</sub> concentration for the same subject. The  
10 longitudinal correlation coefficient can differ between subjects (i.e., each person may have a  
11 different correlation coefficient). The distribution of correlations for each subject across a  
12 population could be obtained with this type of data (e.g., Sarnat et al., 2000; 2001; 2005). A  
13 longitudinal correlation coefficient between the ambient component of personal exposures and  
14 ambient concentrations is relevant to the panel epidemiological study design. In Table 2-9, most  
15 longitudinal studies reported the association between personal total exposures and ambient  
16 concentrations for each subject; for some subjects the associations were strong and for some  
17 subjects the associations were weak. The weak personal and ambient associations do not  
18 necessarily mean that ambient concentrations are not a good surrogate for personal exposures,  
19 because the weak associations could have resulted from the day-to-day variation in the  
20 nonambient component of total personal exposure. The type of correlation analysis can have a  
21 substantial effect on the value of the resultant correlation coefficient.

22 Mage (1999) showed that very low correlations between personal exposure and ambient  
23 concentrations could be obtained when people with very different nonambient exposures are  
24 pooled, even though their individual longitudinal correlations are high.

---

$$r_{ax_i} = \frac{\sum_j (x_{ij} - \bar{x}_i)(a_j - \bar{a})}{(n-1)s_{x_i}s_a}$$

<sup>1</sup> where “r” is the longitudinal correlation coefficient between personal exposure and ambient concentration, “a” represents the ambient concentration, “x” represents exposure, “i” represents the ith subject, “j” represents the jth measurement (with the averaging time ranging from two days to two weeks for SO<sub>2</sub> measurement), “s” represents the standard deviation, and “n” in the longitudinal studies is the number of measurements for each subject. The ambient concentration a<sub>j</sub> could be measured by one ambient monitor or the average of several ambient monitors.

1 Pooled correlations<sup>1</sup> are calculated when a study involves one or only a few measurements  
 2 per subject and when different subjects are studied on subsequent days. Pooled correlations  
 3 combine individual-subject/individual-day data for the calculation of correlations. Pooled  
 4 correlations describe the relationship between daily personal NO<sub>2</sub> exposure and daily ambient  
 5 SO<sub>2</sub> concentration across all subjects in the study (e.g., Brauer et al., 1989; Sarnat et al., 2006).

6 Daily-average correlations<sup>2</sup> are calculated by averaging exposure across subjects for each  
 7 day. Daily-average correlations then describe the relationship between the daily average  
 8 exposure and daily ambient pollutant concentration. This type of correlation (i.e., the association  
 9 between community average exposures (ambient component) and ambient concentrations) is  
 10 more directly relevant to community time-series and long-term cohort epidemiologic studies, in  
 11 which ambient concentrations are used as a surrogate for community average exposure to  
 12 pollutants of ambient origin. However, exposure of the population to SO<sub>2</sub> of ambient origin has  
 13 not been reported in any of the studies examined.

14 Not only does the exposure study design determine the meaning of the correlation  
 15 coefficients in the context of exposure assessment in epidemiologic studies, but it also affects the  
 16 strength of the association between personal exposures and ambient concentrations. The strength  
 17 of the association between personal exposures and ambient and/or outdoor concentrations for a  
 18 population is determined by variations in several physical factors: indoor or other local sources,  
 19 air exchange rate, penetration, and decay rate of the pollutant in different microenvironments and  
 20 the time people spend in different microenvironments with different pollutant concentrations. For  
 21 different types of correlation coefficients, the components of the variance of these physical  
 22 factors are different, and therefore the strength of different types of correlation coefficients is  
 23 different. Longitudinal correlation coefficients reflect the *inter-personal* variations of these  
 24 physical factors; pooled correlation coefficient reflect both *inter-* and *intra-* personal variations  
 25 of these physical factors; and for the association between community average exposures and  
 26 ambient concentrations, *inter-personal* variations of these physical factors are reduced by

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$$1 \quad r_{ax} = \frac{\sum_{i,j} (x_{ij} - \bar{x})(a_j - \bar{a})}{(n-1)s_x s_a}$$

where "n" is the number of paired measurements of exposure and ambient concentration, and all other symbols are defined the same way as those in the longitudinal correlation coefficient.

$$2 \quad r_{ax} = \frac{\sum_j (\bar{x}_j - \bar{x})(a_j - \bar{a})}{(n-1)s_{\bar{x}} s_a}$$

where n is the number of measurement period, during each of which the exposure for all subjects are measured, and all other symbols are defined the same way as those in the longitudinal correlation coefficient.

1 averaging personal exposures across a community. Therefore, the strength of the associations  
2 between personal exposures and ambient concentrations may not be comparable directly,  
3 although these associations are determined by the same set of physical factors (but affected in  
4 different ways).

5 Since correlations are standardized quantities that depend on multiple features of the data,  
6 in a correlation, not only is the linear “relatedness” (covariance) of the two quantities important,  
7 but so is the variability of each, which can be affected by exposure factors in various ways. In the  
8 following assessments, the effects of these physical factors on the strength of correlation  
9 coefficients are primarily examined *within* a study, and the purpose of the inter-study comparison  
10 is to examine the consistency of the effects across different types of studies.

11 The strength of the associations between personal exposures and ambient concentrations  
12 could also be affected by the quality of the data collected during the exposure studies. There are  
13 at least six aspects associated with the quality of the data: method precision, method accuracy  
14 (compared with FRM), percent of data above method detection limits (based on field blanks),  
15 completeness of the data collection, sample size, and soundness of the quality assurance/quality  
16 control procedures. Unfortunately, not all studies reported the SIX aspects of the data quality  
17 issue. The fraction of data below the detection limit might be a concern for some studies (see  
18 Sarnat et al., 2000; 2001; 2005). Correlation coefficients would be biased low if data used in  
19 their calculation are below detection limits. Sampling interferences associated with both ambient  
20 (see Section 2.3) and personal sampling (see Section 2.5.2) could also affect data quality.

21 Therefore, caution must be exercised when interpreting the results in Table 2-9 and Table 2-10.  
22 Sarnat et al. (2001; 2005; 2006) examined the associations between ambient SO<sub>2</sub> concentrations  
23 and ambient or personal co-pollutant concentrations. Sarnat et al. (2001) reported that during the  
24 winter of 1999, ambient SO<sub>2</sub> was significantly associated (at 5% significance level) with personal  
25 exposure to fine particulate matter (PM<sub>2.5</sub>) (slope = - 0.24), personal exposure to SO<sub>4</sub><sup>2-</sup>  
26 (slope = - 0.03), and personal exposure to PM<sub>2.5</sub> of ambient origin (slope = - 0.16). However, it  
27 should be noted that all the slopes are negative perhaps as the result of measurement error. Sarnat  
28 et al. (2005) reported that significant associations between ambient SO<sub>2</sub> and either personal  
29 exposures or ambient concentrations of other pollutants were found for personal SO<sub>4</sub><sup>2-</sup> (winter,  
30 slope = 0.06), personal SO<sub>4</sub><sup>2-</sup> (summer, slope = 0.39), personal PM<sub>2.5</sub> (summer, slope = 1.68),  
31 ambient SO<sub>4</sub><sup>2-</sup> (winter, slope = 0.19), and ambient PM<sub>2.5</sub> (winter, slope = 0.80). In Sarnat et al.

1 (2006), ambient SO<sub>2</sub> was observed to be significantly associated with ambient PM<sub>2.5</sub>, ambient  
2 SO<sub>4</sub><sup>2-</sup> and ambient EC during the fall (R<sup>2</sup> = 0.22, 0.33, and 0.34 respectively), and was  
3 significantly associated with personal PM<sub>2.5</sub> during the summer, personal SO<sub>4</sub><sup>2-</sup> and personal EC  
4 during the fall (R<sup>2</sup> = 0.07, 0.06, and 0.05 respectively).

5 Of significant concern is the ability of currently available techniques for monitoring either  
6 personal exposures or ambient concentrations to measure SO<sub>2</sub> concentrations that are typically  
7 found in most urban environments. In some studies, most data, especially data for monitoring  
8 personal exposure and indoor concentrations, might be beneath detection limits. Indeed, in one  
9 study (Chang et al., 2000), the investigators had to discard data for SO<sub>2</sub>, because the values were  
10 mostly beneath detection limits. In the study of Kindzierski and Ranganathan (2006), all indoor  
11 concentration data were beneath detection limits. In Sarnat et al. (2000), ~70% of personal  
12 measurements were beneath detection limits, and ~33% of personal measurements returned  
13 apparent negative concentration values. In such situations, associations between ambient  
14 concentrations and personal exposure are inadequately characterized. When personal exposure  
15 concentrations are above detection limits, a reasonably strong association is observed between  
16 personal exposures and ambient concentrations.

#### **2.5.4. Exposure Measurement Errors in Epidemiological Studies**

17 For the purposes of this draft, the effects of exposure error on epidemiological study results  
18 refers to changes in the health effects estimate expressed as the relative risk factor,  $\beta$ , and in the  
19 related standard error that results from using the ambient concentration of an air pollutant as an  
20 exposure indicator rather than using the actual personal exposure in the epidemiological  
21 statistical analysis. There are many assumptions made in going from the available measurement  
22 of a pollution indicator to an estimate of the personal exposure. The importance of these  
23 assumptions and their effect on  $\beta$  depend on the type of epidemiological study.

24 The considerations of exposure error for SO<sub>2</sub> are simplified compared to those for NO<sub>2</sub> and  
25 PM. The only experimental measure available is the ambient concentration of SO<sub>2</sub>. In addition,  
26 indoor and other non-ambient sources of SO<sub>2</sub> are not thought to be important in population  
27 studies, lessening concerns about the possible influence of exposures other than to ambient SO<sub>2</sub>.

### **2.5.4.1. Community Time-Series Studies**

1           This section applies primarily to studies on the association of daily average SO<sub>2</sub>  
2 concentrations with daily measures of mortality or morbidity in a community. The following  
3 three exposure issues are of primary concern with respect to SO<sub>2</sub> time-series epidemiological  
4 analysis: (1) the relationship of the measured concentration of SO<sub>2</sub> to the true concentration; (2)  
5 the relationship of day-to-day variations in the concentrations of SO<sub>2</sub>, as measured at a central  
6 monitoring site, with the corresponding variations in the average concentration of SO<sub>2</sub> over the  
7 geographic area from which the health measurements are drawn; and (3) the relationship of the  
8 community average concentration of SO<sub>2</sub> to the average personal exposure to ambient SO<sub>2</sub>. These  
9 three issues are described below.

#### **2.5.4.1.1. Relationship of Measured SO<sub>2</sub> to the True Concentration**

10           Since there is always a random component to instrumental measurement error, the  
11 correlation of the measured SO<sub>2</sub> with the true SO<sub>2</sub>, on either a 24-h or 1-h basis, will be less  
12 than 1. Sheppard et al. (2005) indicate that instrument error in the individual or daily average  
13 concentrations have “the effect of attenuating the estimate of  $\alpha$ .” Zeger et al. (2000) suggest that  
14 instrument error has both Berkson and non-Berkson error components; however, the authors state  
15 that the “instrument error in the ambient levels is close to the Berkson type,” and in order for this  
16 error to cause substantial bias in  $\beta$ , the error term (the difference between the true concentrations  
17 and the measured concentrations) must be strongly correlated with the measured concentrations.  
18 Zeger et al. (2000) suggest that, “further investigations of this correlation in cities with many  
19 monitors are warranted.” Averaging across multiple unbiased ambient monitors in a region  
20 should reduce the instrument measurement error (Sheppard et al., 2005; Wilson and Brauer,  
21 2006; Zeger et al., 2000). There are concerns about the precision and accuracy of the ambient  
22 concentration measurements, because SO<sub>2</sub> concentrations are much lower now than when the SO<sub>2</sub>  
23 standards were first promulgated. Typical ambient concentrations of SO<sub>2</sub> in the contiguous  
24 United States are nearly all at or beneath the detection limit of the monitors currently used in the  
25 regulatory network. Thus, greater relative error is most often observed at the lower ambient  
26 concentrations compared to the less frequent higher concentration exposures, as might occur  
27 because of plume downwash near local point sources or entrainment of plumes downwind from

1 large power plants or smelters. It is unclear how uncertainties in the true concentrations of SO<sub>2</sub>,  
2 i.e., instrument measurement error, will change  $\beta$ .

#### **2.5.4.1.2. Relationship of Day-to-day Variations in the Ambient Concentration of SO<sub>2</sub> to Variations in the Community Average**

3 There has been little analysis of the spatial variation of SO<sub>2</sub> across communities. SO<sub>2</sub>  
4 emissions arise mainly from coal fired power plants (see Annex Table B-4). Newer power plants  
5 and smelters in the United States are no longer located within urban areas. However, some older  
6 power plants and industrial facilities are located in many urban areas, especially in the Midwest  
7 and Northeast. Downwash from the plumes emitted from these facilities can contribute to  
8 elevated levels of SO<sub>2</sub> at the surface in these cities. However, it is anticipated that SO<sub>2</sub> will  
9 behave largely as a regional pollutant in most areas. Site-to-site correlations of SO<sub>2</sub>  
10 concentrations, as shown for several cities in Table 2-3 vary from very low to very high values.  
11 This suggests the concentration of SO<sub>2</sub>, measured at any given monitoring site, may not be highly  
12 correlated with the average community concentration in some areas. There are a number of  
13 possible reasons for these findings: local sources that cause the SO<sub>2</sub> to be unevenly distributed  
14 spatially; a monitoring site being chosen to represent a nearby source; terrain features that divide  
15 the community into several sub-communities that differ in the temporal pattern of pollution; and  
16 errors in the measurement of the low concentrations of SO<sub>2</sub> present at most sites. To the extent  
17 that the correlation of the ambient concentration with the community average concentration is  
18  $< 1$ ,  $\beta$  will be reduced. Similarly,  $\beta$  will be reduced if there are subareas of the community where  
19 the correlation of the subarea average concentrations with the concentrations measured at the  
20 ambient monitoring site is  $< 1$ . If concentrations in an area of a community impacted by plumes  
21 from local SO<sub>2</sub> sources might be higher than, and not well-correlated with, the concentrations at  
22 the ambient monitor, and if such high concentrations affected a sizable portion of the population  
23 affected by a local source, that community might not be suitable for time-series epidemiological  
24 analyses. On the other hand, if the plume impacts the ambient monitor, the high concentration of  
25 SO<sub>2</sub> not accompanied by a corresponding high effect in the entire community will bias  $\beta$  toward  
26 the null.

### 2.5.4.1.3. Relationship of Community Average Concentration of SO<sub>2</sub> to Average Personal Exposure to Ambient SO<sub>2</sub>

1 People spend much of their time indoors and, in the absence of indoor sources, indoor  
2 concentrations are lower than outdoor concentrations. This is very likely the case with SO<sub>2</sub>, since  
3 the only known significant indoor source of SO<sub>2</sub> in the United States is the use of kerosene  
4 heaters, not thought to be widespread enough to influence population studies. Differences in  
5 infiltration factors among homes can also result in differences among individuals' personal  
6 exposures. It is necessary to consider how this difference between the ambient concentration,  
7 which is used in epidemiological analyses, and the personal ambient source exposure  
8 concentration (which includes exposure to the full outdoor concentration while outdoors, and  
9 exposure of only a fraction of the outdoor concentrations while indoors) will affect the calculated  
10  $\beta$ . The contribution of the ambient concentration of SO<sub>2</sub> to the personal exposure to ambient SO<sub>2</sub>  
11 is given by  $Ea = \alpha \cdot Ca$  where  $Ea$  is exposure to ambient SO<sub>2</sub>,  $\alpha$  is the ambient exposure factor  
12 with values between 0 and 1, and  $Ca$  is the ambient SO<sub>2</sub> concentration as measured at a  
13 community monitoring site. Zeger et al. (2000) noted that for community time-series  
14 epidemiology, which analyzes the association between health effects and potential causal factors  
15 at the community scale rather than the individual scale, it is the correlation of the daily average  
16 ambient concentrations with the daily *community average* personal exposures that is important,  
17 not the correlation between the daily average ambient concentrations and *the individual* personal  
18 exposures. Thus, as mentioned in Section 2.5.3, the low correlation between daily average  
19 ambient concentrations and individual personal exposures, as frequently found in pooled panel  
20 exposure studies, is not relevant to community time-series epidemiological analysis.  
21 Unfortunately, no studies provide adequate information about the community average personal  
22 exposure to SO<sub>2</sub>.

23 There has also been concern with the variation of  $\alpha$ . Zeger et al. (2000) suggested (for PM)  
24 that variations in the individual daily values of  $\alpha$  would be a Berkson error and would not change  
25 the point estimate of  $\beta$ . Sheppard et al. (2005) used simulations to confirm this for nonreactive  
26 pollutants. However, such variations increase the standard error. Day-to-day variations in the  
27 population average fraction of ambient exposure will not change the point estimate of  $\beta$  unless  
28 the population average fraction of ambient exposure is correlated with seasonal trends in ambient  
29 concentration, according to Sheppard et al.

1 Both Zeger et al. (2000) and Sheppard et al. (2005) show that if  $\beta_A$  is the health effect  
2 parameter that would be obtained with a time-series analysis using the ambient exposure and  $\beta_C$   
3 is the health effect parameter that would be obtained with a time-series analysis using the  
4 ambient concentration, then  $\beta_C = \alpha \cdot \beta_A$ . Thus, time-series studies yield different parameters  
5 depending on whether they use concentration or exposure. However, the two parameters are  
6 related by  $\alpha$ . Overestimation of exposure by substitution of the ambient concentration for the  
7 ambient exposure leads to underestimation of the effect estimate, or generally bias toward the  
8 null.

#### 2.5.4.2. Short-Term Panel Studies

9 Panel epidemiology refers to time series studies that follow a relatively smaller number of  
10 subjects for a relatively short time. Each subject must be considered individually. Panel studies  
11 typically examine the association between symptoms or health outcomes and either ambient  
12 concentrations or personal exposures. Personal exposures to  $\text{SO}_2$  are not measured; rather,  
13 ambient concentrations are used in panel studies. Similar types of exposure error as discussed for  
14 community time series apply to panel studies.

15 The ambient exposure factor ( $\alpha$ ) may differ for each person and each day leading to error  
16 in the exposure estimate. If a panel is composed of subjects who live in similar housing and have  
17 similar activity pattern, and the study is limited to a single season, the variation in  $\alpha$  over time  
18 and individual subjects may be small. However, if the panels are composed of more diverse  
19 subjects or extend or more than one season, values of  $\alpha$  may be quite variable. Such variability  
20 will cause error in the estimate of exposure for each subject.

#### 2.5.4.3. Long-Term Cohort Studies

21 For long-term exposure epidemiological studies, concentrations are integrated over time  
22 periods of a year or more, and usually for spatial areas the size of a city, county, or metropolitan  
23 statistical area (MSA), although integration over smaller areas may be feasible. Health effects are  
24 then regressed, in a statistical model, against the average concentrations in the series of cities (or  
25 other areas). In time-series studies, a constant difference between the measured and the true  
26 concentration (instrument offset) will not affect  $\beta$ , nor will variations in the daily average  $\alpha$  or

1 the daily average nonambient exposure, unless the variations are correlated with the daily  
2 variations in concentrations. However, in long-term exposure epidemiological studies, if  
3 instrument measurement errors, long-term average values of  $\alpha$ , or long-term averages of  
4 nonambient exposure differ for different cities (or other areas used in the analysis), the city-to-  
5 city long-term ambient SO<sub>2</sub> concentrations will not be perfectly correlated with the long-term  
6 average exposure to either ambient or total SO<sub>2</sub>. This lack of correlation would be expected to  
7 bias the point estimate of  $\beta$ .

#### **2.5.4.4. Summary of Evaluation of Exposure Measurement Error in Epidemiological Studies**

8 Exposure error caused by using ambient concentrations of SO<sub>2</sub> as a surrogate for exposure  
9 to ambient SO<sub>2</sub> affect  $\beta$  in different ways, dependent upon the type of epidemiological study. In  
10 community time-series and short-term panel epidemiological studies, in general, the nonambient  
11 source component of personal exposure and the variation in the ambient exposure factor caused  
12 by building ventilation practices and personal behaviors, will not change the estimate of  $\beta$ ; but  
13 the spatial variation of SO<sub>2</sub> or the representativeness of the ambient monitor might bias the  
14 estimate of  $\beta$  toward null. Therefore,  $\beta$  observed in SO<sub>2</sub> community time-series or panel  
15 epidemiological studies would be stronger and less uncertain if exposure errors had been  
16 adjusted and/or controlled for. In long-term cohort epidemiological studies, instrument  
17 measurement errors, factors that influence exposure to ambient SO<sub>2</sub>, or long-term averages of  
18 nonambient exposure may differ for different cities, which may bias the estimate of  $\beta$ , but the  
19 extent and direction of this bias is unclear.

## **2.6. Dosimetry of Inhaled Sulfur Oxides**

20 This section is intended to present an overview of general concepts related to the dosimetry  
21 of SO<sub>2</sub> in the respiratory tract. Dosimetry of SO<sub>2</sub> refers to the measurement or estimation of the  
22 amount of SO<sub>2</sub> or its reaction products reaching and persisting at specific respiratory tract and  
23 systemic sites after exposure. One of the principal effects of inhaled SO<sub>2</sub> is that it stimulates  
24 bronchial epithelial irritant receptors and initiates a reflexive contraction of smooth muscles in  
25 the bronchial airway. The compound most directly responsible for health effects may be the  
26 inhaled SO<sub>2</sub>, or perhaps its chemical reaction products. Complete identification of the causative

1 agents and their integration into SO<sub>2</sub> dosimetry is a complex issue that has not been thoroughly  
2 evaluated. Few studies have investigated SO<sub>2</sub> dosimetry in the interval since the 1982 AQCD and  
3 the 1986 Second Addendum.

### 2.6.1. Gas Deposition

4 The major factors affecting the transport and fate of gases and aerosols in the respiratory  
5 tract are: the morphology of the respiratory tract; the physicochemical properties of the mucous  
6 and surfactant layers; respiratory functional parameters such as tidal volume, flow rate, and route  
7 of breathing; physicochemical properties of the gas; and the physical processes that govern gas  
8 transport. Physicochemical properties of SO<sub>2</sub> relevant to respiratory tract uptake include its  
9 solubility and diffusivity in epithelial lining fluid (ELF), as well as its reaction-rate with ELF  
10 constituents. Henry's law relates the gas phase and liquid phase interfacial concentrations at  
11 equilibrium, and is a function of temperature and pressure. Henry's law shows that the amount of  
12 SO<sub>2</sub> in the aqueous phase is directly proportional to the partial pressure or concentration of SO<sub>2</sub> in  
13 the gas phase. Although the solubility of most gases in mucus and surfactant is not known, the  
14 Henry's law constant is known for many gases in water. The Henry's law constant for SO<sub>2</sub> is  
15 0.048 (mole/liter) air / (mole/liter) water at 37° C and 1 atm; for comparison, the value for O<sub>3</sub> is  
16 6.4 under the same conditions (Kimbell and Miller, 1999). In general, the more soluble a gas is in  
17 biological fluids, the more rapid, and proximal its absorption will be in the respiratory tract.  
18 When the partial pressure of SO<sub>2</sub> on mucosal surfaces exceeds that of the gas phase, such as  
19 during expiration, some desorption of SO<sub>2</sub> from the ELF may be expected.

20 Because SO<sub>2</sub> is highly soluble in water, it is expected to be almost completely absorbed in  
21 the nasal passages of both humans and laboratory animals under resting conditions. The  
22 dosimetry of SO<sub>2</sub> can be contrasted with the lower solubility gas, O<sub>3</sub>, for which the predicted  
23 tissue doses (O<sub>3</sub> flux to liquid-tissue interface) are very low in the trachea and increase to a  
24 maximum in the terminal bronchioles or first airway generation in the pulmonary region (see  
25 Chapter 4, EPA, 2006c). Similar to O<sub>3</sub>, the nasal passages remove SO<sub>2</sub> more efficiently than the  
26 oral pathway (Brain, 1970). With exercise, the pattern of SO<sub>2</sub> absorption shifts from the upper  
27 airway to the tracheobronchial airway in conjunction with a shift from nasal to oronasal  
28 breathing and increased ventilatory rates. Due to its effect on delivery and uptake, mode of  
29 breathing is also recognized as an important determinant of the severity of SO<sub>2</sub>-induced

1 bronchoconstriction, with the greatest responses occurring during oral breathing followed by  
2 oronasal breathing and the smallest responses observed during nasal breathing.

3 Melville (1970) measured the absorption of SO<sub>2</sub> (1.5 to 3.4 ppm) during nasal and oral  
4 breathing in 12 healthy volunteers. Total respiratory tract absorption of SO<sub>2</sub> was significantly  
5 greater ( $p < 0.01$ ) during nasal than oral breathing (85 versus 70%, respectively) and was  
6 independent of the inspired concentration. Respired flows were NR. Andersen et al. (1974)  
7 measured the nasal absorption of SO<sub>2</sub> (25 ppm) in 7 volunteers at an average inspired flow of 23  
8 L/min (i.e., eucapnic hyperpnea [presumably] to simulate light exertion). These investigators  
9 reported that the oropharyngeal SO<sub>2</sub> concentration was below their limit of detection (0.25 ppm),  
10 implying that at least 99% of SO<sub>2</sub> was absorbed in the nose of subjects during inspiration.  
11 Speizer and Frank (1966) also measured the absorption of SO<sub>2</sub> (16.1 ppm) in 7 healthy subjects  
12 at an average ventilation of 8.5 L/min (i.e., at rest). They reported that 14% of the inhaled SO<sub>2</sub>  
13 was absorbed within the first 2 cm into nose. The concentration of SO<sub>2</sub> reaching the pharynx was  
14 below the limit of detection, suggesting that at least 99% was absorbed during inspiration.

15 Frank et al. (1969) and Brain (1970) investigated the oral and nasal absorption of SO<sub>2</sub> in  
16 the surgically isolated upper respiratory tract of anesthetized dogs. Radiolabeled SO<sub>2</sub> (<sup>35</sup>SO<sub>2</sub>) at  
17 the concentrations of 1, 10, and 50 ppm was passed separately through the nose and mouth at the  
18 steady flows of 3.5 and 35 L/min for 5 min. The nasal absorption of SO<sub>2</sub> (1 ppm) was 99.9% at  
19 3.5 L/min and 96.8% at 35 L/min. The oral absorption of SO<sub>2</sub> (1 ppm) was 99.56% at 3.5 L/min,  
20 but only 34% at 35 L/min. The nasal absorption of SO<sub>2</sub> at 3.5 L/min increased with concentration  
21 at 1, 10, and 50 ppm and was reported to be 99.9, 99.99, and 99.999%, respectively. This  
22 increase in absorption with concentration was hypothesized to be due to increased mucous  
23 secretion and increased nasal resistance at the higher SO<sub>2</sub> concentrations. The increased mucus  
24 was thought to provide a larger reservoir for SO<sub>2</sub> uptake. The increased nasal resistance may  
25 increase turbulence in the airflow and, thereby, decrease the boundary layer between the gas and  
26 liquid phases. Dissimilar to the nose, SO<sub>2</sub> absorption in the mouth decreased from 99.56 to  
27 96.3% when the concentration was increased from 1 to 10 ppm at 3.5 L/min. Frank et al. (1969)  
28 noted that the aperture of the mouth may vary considerably, and that this variation may affect  
29 SO<sub>2</sub> uptake in the mouth. Although SO<sub>2</sub> absorption was dependent on inhaled concentration, the  
30 rate and route of flow had a greater effect on the magnitude of SO<sub>2</sub> absorption in the upper  
31 airway.

1 Strandberg (1964) studied the uptake of SO<sub>2</sub> in the respiratory tract of rabbits. A tracheal  
2 cannula with two outlets was utilized to allow sampling of inspired and expired air, and SO<sub>2</sub>  
3 absorption was observed to depend on inhaled concentration. The absorption during maximal  
4 inspiration was 95% at high concentrations (100 to 700 ppm), reflecting an increased SO<sub>2</sub>  
5 removal in the extrathoracic (ET) airway, whereas it was only 40% at low concentrations (0.05 to  
6 0.1 ppm). On expiration, the total SO<sub>2</sub> absorbed (i.e., inspiratory removal in the ET airway plus  
7 removal in the lower airway) was 98% at high concentrations and only 80% at the lower  
8 concentrations.

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

19 More recently, Ben-Jebria et al. (1990) investigated the absorption of SO<sub>2</sub> in excised  
20 porcine tracheae. Absorption was monitored over a 30-min period following the introduction of  
21 SO<sub>2</sub> (0.1 to 0.6 ppm, inlet concentration) at a constant flow (2.7 to 11 L/min). The data were  
22 analyzed using diffusion-reactor theory. An overall mass transfer coefficient (KSO<sub>2</sub>) was  
23 determined and separated into its contributions due to gas (convection and diffusion) and tissue  
24 phase (diffusivity, solubility, and reaction rates) resistances. SO<sub>2</sub> in the liquid phase was assumed  
25 to form HSO<sub>3</sub><sup>-</sup> rapidly, in proportion with the gas phase SO<sub>2</sub> concentration, HSO<sub>3</sub><sup>-</sup> then diffused  
26 down the concentration gradient into the tissues where it reacted irreversibly with biochemical  
27 substrates. Initially, KSO<sub>2</sub> was limited only by gas phase resistance, but decreased exponentially  
28 over the first 5 to 10 min of SO<sub>2</sub> exposure to a smaller steady-state value because of tissue  
29 resistance to SO<sub>2</sub> absorption. The initial and steady-state KSO<sub>2</sub> values were found to be  
30 independent of inlet SO<sub>2</sub> concentration, i.e., for a given flow, the fractional absorption of SO<sub>2</sub> did  
31 not depend on SO<sub>2</sub> concentration. An increased KSO<sub>2</sub> (initial and steady-state) was observed with

1 an increasing flow that was thought to be due to a decrease in the boundary layer near the walls  
2 of the trachea for radial SO<sub>2</sub> transport. This is in agreement with Aharonson et al. (1974), who  
3 also reported that the transfer rate coefficient for SO<sub>2</sub> increases with increasing flow. However,  
4 the initial molar flux of SO<sub>2</sub> across the gas-tissue interface appears to increase purely as a  
5 function of the increase in mass transport occurring with increasing flow (see Figure 5 in Ben-  
6 Jebria et al., 1990). Given that the steady-state KSO<sub>2</sub> remained stable during the 10 to 30 min of  
7 exposure and that no SO<sub>2</sub> leakage through the tissue was identified, the authors concluded that  
8 there was an irreversible sink for SO<sub>2</sub> within the tissue.

9 Mathematical modeling specific to the regional respiratory uptake of SO<sub>2</sub> is unavailable for  
10 humans and laboratory animals. More generally, the influence of age on gas dosimetry in humans  
11 during light activity (on average) was examined by Ginsberg et al. (2005) using the U.S. EPA  
12 reference concentration methodology (EPA, 1994a). For a highly soluble gas, such as SO<sub>2</sub>, they  
13 predicted that the majority of gas uptake would occur in the extrathoracic airway and that uptake  
14 in these airways would be modestly greater in a 3-month-old infant than an adult. The rate of gas  
15 uptake per surface, however, in the extrathoracic airway and large bronchial airway was not  
16 markedly different between infants and adults. The smaller bronchial airway of adults were  
17 predicted to receive a greater dose (i.e., uptake per unit time and surface area) relative to infants,  
18 although the majority of the inhaled SO<sub>2</sub> would be removed proximal to these airways.

19 In summary, inhaled SO<sub>2</sub> is readily absorbed in the upper airway of both humans and  
20 laboratory animals. During nasal breathing, the majority of available data suggests 95% or  
21 greater SO<sub>2</sub> absorption occurs in the nasal passages, even under ventilation levels comparable to  
22 exercise. Somewhat less SO<sub>2</sub> is absorbed in the oral passage than in the nasal passages. The  
23 difference in SO<sub>2</sub> absorption between the mouth and the nose is highly dependent on respired  
24 flow rates. With an increase in flow from 3.5 to 35 L/min, nasal absorption is relatively  
25 unaffected, whereas, oral absorption is reduced from 100 to 34%. Thus, the rate and route of  
26 breathing have a great effect on the magnitude of SO<sub>2</sub> absorption in the upper airway and so the  
27 penetration of SO<sub>2</sub> to the lower airway. Overall, the available data clearly show that the pattern of  
28 SO<sub>2</sub> absorption which shifts from the upper airway to the tracheobronchial airway in conjunction  
29 a shift from nasal to oronasal breathing and associated increased ventilatory rates in exercising  
30 humans. Mode of breathing is also recognized as an important determinant of the severity of

1 SO<sub>2</sub>-induced bronchoconstriction, with the greatest responses occurring during oral breathing  
2 followed by oronasal breathing and the smallest responses observed during nasal breathing.

### 2.6.2. Particles and Sulfur Oxide Mixtures

3 As already discussed, inhaled SO<sub>2</sub> is readily absorbed in the upper airway, particularly  
4 during nasal breathing. It has been suggested that sulfur oxides may become absorbed to  
5 particles and subsequently transported to more distal lung regions. Depending on atmospheric  
6 conditions, SO<sub>2</sub> can be transformed to secondary sulfate particles and acid aerosols (H<sub>2</sub>SO<sub>4</sub>) and  
7 can adsorb onto particulate matter. Jakab et al. (1996) observed that the conversion of SO<sub>2</sub> to  
8 SO<sub>4</sub><sup>2-</sup> on the surface of carbon black aerosols was dependent on high relative humidity (85%)  
9 and SO<sub>2</sub> concentration. These investigators suggested that fine carbon black particles can be an  
10 effective vector for delivery of SO<sub>4</sub><sup>2-</sup> to the peripheral lung. Other studies investigating the  
11 effects of SO<sub>2</sub> coated aerosols are briefly discussed in Section 3.1.5.

12 Sulfate aerosols are hygroscopic and grow in the respiratory tract. The implications of  
13 hygroscopic growth on deposition have been reviewed extensively by Morrow (1986) and Hiller  
14 (1991). In general, compared to nonhygroscopic particles of the same initial size, the deposition  
15 of hygroscopic aerosols in different regions of the lung may be higher or lower, depending on the  
16 initial size. For particles with initial sizes larger than 0.5 μm (aerodynamic diameter), the  
17 influence of hygroscopicity would be to increase total deposition with a shift in regional  
18 deposition from the distal to larger proximal airway; for smaller particles deposition would tend  
19 to be decreased. A thorough review of respiratory deposition and clearance of particulate matter  
20 is available elsewhere (EPA, 2004; 2006b). The intent herein was to briefly mention some issues  
21 specific to sulfur oxides.

### 2.6.3. Distribution and Elimination of Sulfur Oxides

22 When SO<sub>2</sub> contacts the fluids lining the airway, it dissolves into the aqueous fluid and  
23 forms hydrogen (H<sup>+</sup>) ions and bisulfite (HSO<sub>3</sub><sup>-</sup>) and sulfite (SO<sub>3</sub><sup>2-</sup>) anions (Bascom et al., 1996).  
24 The majority of anions are expected to be present as HSO<sub>3</sub><sup>-</sup> at a concentration proportional to the  
25 gas phase concentration of SO<sub>2</sub> (Ben-Jebria et al., 1990). Because of the chemical reactivity of  
26 these anions, various reactions are possible, leading to the oxidation of SO<sub>3</sub><sup>2-</sup> to SO<sub>4</sub><sup>2-</sup> (see  
27 Section 12.2.1, EPA, 1982). Clearance of SO<sub>3</sub><sup>2-</sup> from the respiratory tract may involve several

1 intermediate chemical reactions and transformations. Gunnison and Benton (1971) identified *S*-  
2 sulfonate in blood as a reaction product of inhaled SO<sub>2</sub>. Following inhalation of SO<sub>2</sub>, the  
3 clearance half-time of 4.1 days for *S*-sulfonate in rabbits has been reported (Gunnison and  
4 Palmes, 1973).

5         Some SO<sub>2</sub> is also removed by desorption of from the respiratory tract. Desorption is  
6 expected when the partial pressure of SO<sub>2</sub> in airway lining fluids exceeds that of the air. Speizer  
7 and Frank (1966) found that on expiration, 12% of the SO<sub>2</sub> absorbed during inspiration was  
8 desorbed into the expired air. During the first 15 min after the 25- to 30-min SO<sub>2</sub> exposure,  
9 another 3% was desorbed. In total, 15% of the amount originally inspired and absorbed SO<sub>2</sub> was  
10 desorbed from the nasal mucosa. Frank et al. (1969) reported that up to 18% of the SO<sub>2</sub> was  
11 desorbed within ~10 min after exposure.

## Chapter 3. Integrated Health Effects

1           This integrated discussion is structured to provide a coherent framework for the assessment  
2 of health risks associated with human exposure to ambient SO<sub>2</sub> in the United States. The main  
3 goals of this chapter are: (1) to integrate newly available epidemiological, human clinical, and  
4 animal toxicological evidence with consideration of key findings and conclusions from the 1982  
5 AQCD for Sulfur Oxides and First Addendum (EPA, 1982), 1986 Second Addendum (EPA,  
6 1986c), and 1994 Supplement to the Second Addendum, (EPA, 1994c); and (2) to draw  
7 conclusions about the causal nature of SO<sub>2</sub> in relation to a variety of health effects. These causal  
8 determinations utilize the framework outlined in Chapter 1.

9           This chapter is organized to present morbidity and mortality associated with short-term  
10 exposures to SO<sub>2</sub>, followed by morbidity and mortality associated with long-term exposures.  
11 Human clinical studies examining the effect of peak exposures (less than 1-h, generally 5-10  
12 min) of SO<sub>2</sub> on respiratory symptoms and lung function are discussed first. Later sections  
13 describe the findings of epidemiological studies that examine the association between short-term  
14 (generally 24-h avg) and long-term (generally months to years) ambient SO<sub>2</sub> exposure and health  
15 outcomes, such as respiratory symptoms in children and asthmatics, emergency department (ED)  
16 visits and hospital admissions for respiratory and cardiovascular diseases, and premature  
17 mortality. The human clinical and epidemiological evidence are presented with relevant animal  
18 toxicological data, when available.

### Considerations in the Interpretation of Health Evidence

19           Human clinical studies are conducted in a controlled laboratory setting using fixed  
20 concentrations of air pollutants under carefully regulated environmental conditions and subject  
21 activity levels. Results of human clinical studies provide evidence of potential mechanisms for  
22 observed effects and a direct quantitative assessment of the SO<sub>2</sub> exposure-health response  
23 relationship among asthmatic individuals. Observed effects in these studies may underestimate  
24 the response in certain sensitive subpopulations for a number of reasons. First, study subjects  
25 must either be healthy, or have a level of illness which does not preclude them from participating  
26 in the study. Second, asthmatics who are unable to withhold the use of bronchodilators for at

1 least 6 hours prior to exposure and subjects with a recent history of upper respiratory tract  
2 infections are typically excluded from clinical studies of exposure to SO<sub>2</sub>. While human clinical  
3 studies provide important information on the biological plausibility of associations observed  
4 between SO<sub>2</sub> exposure and health outcomes in epidemiological studies, the concentration-  
5 response relationships cannot necessarily be directly extrapolated to concentrations below those  
6 administered in the laboratory. Further, human clinical studies are normally conducted on a  
7 relatively small number of subjects, which reduces the power of the study to detect significant  
8 differences in the health outcomes of interest between exposure to varying concentrations of SO<sub>2</sub>  
9 and clean air.

10 Epidemiological studies provide important information on the associations between health  
11 effects and exposure of human populations to ambient levels of SO<sub>2</sub>. These studies also help to  
12 identify susceptible subgroups and associated risk factors. However, associations observed  
13 between specific air pollutants and health outcomes in epidemiological studies may be  
14 confounded by copollutants or meteorological conditions, and influenced by model  
15 specifications in the analytical methods. Extensive discussion of these issues is provided in the  
16 2004 AQCD for PM (EPA, 2004) and the 2006 AQCD for O<sub>3</sub> and Related Photochemical  
17 Oxidants (EPA, 2006c), and therefore presented only briefly below.

18 The use of multipollutant regression models has been the prevailing approach for  
19 controlling potential confounding by copollutants in air pollution health effects studies. Finding  
20 the likely causal pollutant from multipollutant regression models is made difficult by the  
21 possibility that one or more air pollutants may be acting as a surrogate for an unmeasured or  
22 poorly-measured pollutant or for a particular mixture of pollutants. SO<sub>2</sub> presents an especially  
23 interesting test of multipollutant effects models: correlations with sulfate, the principal  
24 atmospheric oxidation product of SO<sub>2</sub>, show temporal and spatial incongruities that can  
25 influence exposures and health effects. Short-term, mostly time-series epidemiological studies  
26 generally use intracity ambient concentration data which show very little or no correlation  
27 between emitted SO<sub>2</sub> and transformed sulfate. In contrast, long-term epidemiological studies  
28 using intercity data can show correlations between SO<sub>2</sub> and sulfate on the order of 0.8 or higher.  
29 In these studies the fine-scale spatiotemporal variations in the intracity data are significantly  
30 reduced, since sulfate has sufficient time for production from SO<sub>2</sub>, dispersed over a wide spatial  
31 area, and mixed down to ground level. Layered over these spatial and fine-scale temporal

1 differences are seasonal and regional dissimilarities driven by cities' various SO<sub>2</sub> emissions  
2 profiles and differing available time and sunlight conditions for oxidation. Thus, attempts to  
3 distinguish gaseous and particle effects related to SO<sub>2</sub> using multipollutant epidemiological  
4 models must be interpreted with caution. Despite these limitations, the use of multipollutant  
5 models is still the prevailing approach employed in most studies of SO<sub>2</sub> and health effects, and  
6 may provide some insight into the potential for confounding or interaction among pollutants.

7 Model specification and model selection also need to be considered in the interpretation of  
8 the epidemiological evidence. The studies presented in this chapter investigated the association  
9 between various measures of SO<sub>2</sub> (e.g., multiple lags and different exposure metrics) and various  
10 health outcomes using different model specifications. The summary of health effects in this  
11 chapter is vulnerable to the errors of publication bias and multiple testing. Efforts have been  
12 made to reduce the impact of multiple testing errors. For example, although many studies  
13 examined multiple single-day lag models, priority was given to effects observed at 0- or 1-day  
14 lags, rather than at longer lags. Additional focus was placed on results from distributed and  
15 moving average lags as they are able to take into consideration multiday effects. Both single- and  
16 multiple-pollutant models were considered and examined for robustness of results. Additional  
17 analyses of multiple model specifications for adjustment of temporal or meteorological trends are  
18 considered to be sensitivity analyses.

19 In addition to issues related to confounding by copollutants and model selection, the  
20 evaluation of the epidemiological evidence also considers study population and sample size, with  
21 particular emphasis placed on multicity studies. Other factors considered are study location  
22 (North America versus other regions), meaningfulness and reliability of the health endpoint  
23 measurements, and appropriateness of the statistical analyses methods used. These  
24 considerations in the interpretation of the epidemiological evidence lead to emphasis of certain  
25 studies in the chapter text, tables, and figures.

26 Animal toxicological studies may provide further evidence for the potential mechanism of  
27 an observed effect; however, most of these studies have been conducted at concentrations vastly  
28 exceeding current ambient conditions. In discussing the mechanisms of SO<sub>x</sub> toxicity, studies  
29 conducted under atmospherically relevant conditions are emphasized whenever possible; studies  
30 at higher levels are also considered, due to species-to-species differences and potential  
31 differences in sensitivity between study subjects and especially susceptible human populations.

1 This chapter focuses on important new scientific studies, with emphasis on those  
2 conducted at or near current ambient concentrations. Given their respective strengths and  
3 limitations, evidence from human clinical, epidemiological and animal toxicological studies are  
4 considered in order to evaluate the causality of SO<sub>x</sub>–health effects associations. The annexes  
5 supplement the information included here by presenting a more details of the literature.

## 3.1. Respiratory Morbidity Associated with Short-Term Exposure

### 3.1.1. Summary of Findings from the Previous Review

6 The majority of the SO<sub>2</sub> human clinical studies in the 1982 AQCD for Sulfur Oxides  
7 evaluated respiratory effects of SO<sub>2</sub> exposure in healthy adults, with some limited data from  
8 clinical studies of adults with asthma. SO<sub>2</sub>-related respiratory effects such as increased airway  
9 resistance and decreased forced expiratory volume in 1 s (FEV<sub>1</sub>) were observed in healthy  
10 individuals at concentrations > 1.0-5.0 ppm, and in asthmatics at concentrations < 1.0 ppm. The  
11 1986 Second Addendum (EPA) and 1994 Supplement to the Second Addendum (EPA) reviewed  
12 several additional controlled studies involving both healthy and asthmatic individuals. In general,  
13 these studies found no pulmonary effects of SO<sub>2</sub> exposure in healthy subjects exposed to  
14 concentrations < 1.0 ppm (Bedi et al., 1984; Folinsbee et al., 1985; Kulle et al., 1984; Stacy et  
15 al., 1983). However, in exposures of asthmatic adults, respiratory effects were observed  
16 following short-term exposures (5-10 min) to levels < 1.0 ppm (Balmes et al., 1987; Horstman et  
17 al., 1988; Linn et al., 1987).

18 Only a few epidemiological studies reviewed in the 1982 AQCD were useful in  
19 determining the concentration-response relationship of respiratory health effects from short-term  
20 exposure to SO<sub>2</sub>. The most notable study was by Lawther (1970), which examined the  
21 association between air pollution and worsening health status in bronchitic patients residing in  
22 London, England. It was concluded in the 1982 AQCD that worsening of health status among  
23 chronic bronchitic patients was associated with daily black smoke (BS) levels of 250-500 µg/m<sup>3</sup>  
24 in the presence of SO<sub>2</sub> levels in the range of 191-229 ppb. In the 1986 Second Addendum,  
25 additional studies investigated morbidity associated with short-term exposure to SO<sub>2</sub>. The most  
26 relevant study was by Dockery (1982), which examined pulmonary function in school children in

1 Steubenville, OH, as part of the Harvard Six Cities Study. This study found that small but  
2 statistically significant reversible decrements in forced vital capacity (FVC) and forced  
3 expiratory volume in 0.75 s (FEV<sub>0.75</sub>) were associated with increases in 24-h avg concentrations  
4 of total suspended particles (TSP) at levels ranging up to 220-420 µg/m<sup>3</sup> and SO<sub>2</sub> at levels  
5 ranging up to 107-176 ppb. However, it was impossible to separate the relative contributions of  
6 TSP and SO<sub>2</sub>, and no threshold level for the observed effects could be discerned from the wide  
7 range of exposure levels.

8 Epidemiological evidence for an association between SO<sub>2</sub> and respiratory morbidity, as  
9 indicated by increased use of ED facilities or increased hospital admissions for respiratory  
10 diseases, was also reported in the 1982 AQCD. Overall, these results suggested increased upper  
11 respiratory tract morbidity during episodic marked elevations of PM or SO<sub>2</sub> (400-500 ppb),  
12 especially among older adults. The 1982 AQCD further concluded that the studies reviewed  
13 provided essentially no evidence for an association between asthma attacks and acute exposures  
14 at typical ambient PM or SO<sub>2</sub> levels in the United States (the mean annual average SO<sub>2</sub>  
15 concentrations from 1972 to 1977 was approximately 6 ppb, with 90th percentile values ranging  
16 from 15 to 20 ppb).

17 The 1982 AQCD for Sulfur Oxides (EPA, 1982) reported numerous effects on the  
18 respiratory system in animals exposed to SO<sub>2</sub>. Effects were generally observed at levels  
19 exceeding those found in the ambient environment, and included morphological changes, altered  
20 pulmonary function, lipid peroxidation, and changes in host lung defenses. The immediate effect  
21 of acute SO<sub>2</sub> exposure in animals was increased pulmonary resistance to airflow, a measure of  
22 bronchoconstriction. Bronchoconstriction was reported to be the most sensitive indicator of lung  
23 function effects in acute SO<sub>2</sub> exposure.

24 Collectively, the human clinical, epidemiological and animal toxicological, studies  
25 provided biological plausibility and coherent evidence of an adverse effect of ambient SO<sub>2</sub> on  
26 respiratory health. Since the 1982 AQCD, 1986 Second Addendum, and 1994 Supplement to the  
27 Second Addendum, additional studies have been conducted to determine the relationship  
28 between short-term exposures to ambient SO<sub>2</sub> and adverse respiratory health effects, including  
29 respiratory symptoms, lung function, airway inflammation, airway hyperresponsiveness, lung  
30 host defenses, and ED visits and hospitalizations for respiratory causes. The epidemiological,  
31 human clinical, and animal toxicological evidence on the effects of SO<sub>2</sub> on these various

1 endpoints are discussed below. The finding of the previous review are integrated below with the  
2 current literature.

### 3.1.2. Potential Mode of Action for Respiratory Health Effects

3 The 1982 AQCD (EPA, 1982) gave background information on the biochemistry of SO<sub>2</sub>,  
4 chemical reactions of bisulfite (HSO<sub>3</sub><sup>-</sup>), metabolism of SO<sub>2</sub>, and the activating or inhibiting  
5 effects of bisulfite on various enzymes. SO<sub>2</sub> readily dissolves in water, rapidly becoming  
6 hydrated to form sulfurous acid, which at physiological pH substantially dissociates to form  
7 bisulfite and sulfite (SO<sub>3</sub><sup>2-</sup>) ions. Studies in vitro have shown that SO<sub>2</sub> and/or bisulfite readily  
8 react with nucleic acids, proteins, lipids, and other classes of biomolecules. Bisulfite participates  
9 in three important types of reactions with biomolecules: sulfonation (sulfitolysis), autooxidation  
10 with generation of free radicals, and addition to cytosine. Products of sulfonation reactions have  
11 been shown to be long-lived in vivo and may be highly reactive. Products of autooxidation may  
12 be responsible for the initiation of lipid peroxidation, which, among other effects, could damage  
13 plasma membranes. In contrast, studies have shown that bisulfite can react with nucleic acids to  
14 convert cytosine to uracil, thus resulting in mutational events. A principal mechanism of  
15 detoxification of SO<sub>2</sub> (and sulfite/bisulfite) occurs through the enzymatic activity of sulfite  
16 oxidase, resulting in the production of sulfate. Sulfite oxidase is a molybdenum-containing  
17 enzyme, and the 1982 AQCD noted that depleting its activity through a low-molybdenum diet  
18 supplemented with the competitive inhibitor tungsten resulted in a significant lowering of the  
19 LD<sub>50</sub> for intraperitoneally injected bisulfite. It was also noted that while in vitro exposure to SO<sub>2</sub>  
20 or sulfite/bisulfite had been shown to either activate or inhibit a variety of enzymes, no such  
21 effects had yet been demonstrated for in vivo exposure.

22 As discussed in the 1982 AQCD, the immediate effect of acute SO<sub>2</sub> exposure in animals  
23 was bronchoconstriction. Reactions of SO<sub>2</sub> with respiratory tract fluids can result in the  
24 production of bisulfite, sulfite, and a lowering of the pH, which may be involved in the  
25 bronchoconstrictive response. It is now widely appreciated that bronchoconstriction following  
26 SO<sub>2</sub> exposure is mediated by chemosensitive receptors in the tracheobronchial tree. Rapidly  
27 activating receptors (RARs) and sensory C-fiber receptors found at all levels of the respiratory  
28 tract are sensitive to irritant gases such as SO<sub>2</sub> (Coleridge and Coleridge, 1994; Widdicombe,  
29 2006). Activation of these vagal afferents causes central nervous system reflexes resulting in

1 bronchoconstriction, mucus secretion, mucosal vasodilation, cough, or apnea, followed by rapid  
2 shallow breathing and effects on the cardiovascular system such as bradycardia and hypotension  
3 or hypertension (Coleridge and Coleridge, 1994; Widdicombe and Lee, 2001; Widdicombe,  
4 2003).

5 Early experiments demonstrated that SO<sub>2</sub>-induced reflexes were mediated by cholinergic  
6 parasympathetic pathways involving the vagus nerve and inhibited by atropine (Grunstein et al.,  
7 1977; Nadel et al., 1965a; 1965b). Bronchoconstriction was found to involve smooth muscle  
8 contraction since  $\beta$ -adrenergic agonists such as isoproterenol reversed the effects (Nadel et al.,  
9 1965a; 1965b). Acetylcholine and histamine were also thought to be involved in SO<sub>2</sub>-induced  
10 bronchoconstriction (EPA, 1982).

11 More recent experiments in animal models conducted since 1982 have demonstrated that  
12 both cholinergic and noncholinergic mechanisms may be involved in SO<sub>2</sub>-induced effects. In two  
13 studies utilizing bilateral vagotomy, vagal afferents were found to mediate the immediate  
14 ventilatory responses to SO<sub>2</sub> (Wang et al., 1996), but not the prolonged bronchoconstrictor  
15 response (Barthelemy et al., 1988). Other studies showed that atropine failed to block SO<sub>2</sub>-  
16 induced bronchoconstriction, and that a local axon reflex resulting in C-fiber secretion of  
17 neuropeptides (i.e., neurogenic inflammation) was responsible for the effect (Atzori et al.,  
18 1992a; Hajj et al., 1996). Neurogenic inflammation has been shown to play a key role in animal  
19 models of airway inflammatory disease (Groneberg et al., 2004).

20 In humans, the mechanisms responsible for SO<sub>2</sub>-induced bronchoconstriction are not fully  
21 understood. In non-asthmatics, near complete attenuation of bronchoconstriction has been  
22 demonstrated using the anticholinergic agents atropine and ipratropium bromide (Snashall and  
23 Baldwin, 1982; Tan et al., 1982; Yildirim et al., 2005). However, in asthmatics, these same  
24 anticholinergic agents (Field et al., 1996; Myers et al., 1986a), as well as short- and long-acting  
25  $\beta$ 2-adrenergic agonists (Gong et al., 1996; Linn et al., 1988), theophylline (Koenig et al., 1992),  
26 cromolyn sodium (Myers et al., 1986), nedocromil sodium (Bigby and Boushey, 1993) and  
27 leukotriene receptor antagonists (Gong et al., 2001; Lazarus et al., 1997) only partially blocked  
28 SO<sub>2</sub>-induced bronchoconstriction. That none of these therapies have been shown to completely  
29 attenuate the effects of SO<sub>2</sub> implies the involvement of both parasympathetic pathways and  
30 inflammatory mediators in asthmatics. Strong evidence of this is borne out in a study by Myers  
31 et al. (1986), in which asthmatic adults were exposed to SO<sub>2</sub> following pretreatment with

1 cromolyn sodium (a mast cell stabilizer), atropine (a muscarinic receptor antagonist), and the two  
2 medications together. While both treatments individually provided some protection against the  
3 bronchoconstrictive effects of SO<sub>2</sub>, there was a much stronger and statistically significant effect  
4 following concurrent administration of the two medications.

5 It has been proposed that inflammation contributes to the enhanced sensitivity to SO<sub>2</sub> seen  
6 in asthmatics by altering autonomic responses (Tunnicliffe et al., 2001), enhancing mediator  
7 release (Tan et al., 1982) and/or sensitizing C-fibers and RARs (Widdicombe and Lee, 2001).  
8 Whether local axon reflexes also play a role in SO<sub>2</sub>-induced bronchoconstriction in asthmatics is  
9 not known (Widdicombe and Lee, 2001; Widdicombe, 2003; Groneberg et al., 2004). However,  
10 differences in respiratory tract innervation between rodents and humans suggest that C-fiber  
11 mediated neurogenic inflammation may be unimportant in humans (Groneberg et al., 2004;  
12 Widdicombe and Lee, 2001; Widdicombe, 2003).

### **3.1.3. Respiratory Effects Associated with Peak Exposure**

13 SO<sub>2</sub>-induced respiratory effects among exercising asthmatics are well-documented, and  
14 have been consistently observed following peak exposures (defined here as 5-10 min exposures  
15 to relatively higher concentrations, e.g., 0.4-1.0 ppm) (Balmes et al., 1987; Bethel et al., 1985;  
16 Horstman et al., 1986; 1988; Linn et al., 1984b; 1987; 1990; Schachter et al., 1984; Sheppard et  
17 al., 1981). Similar respiratory effects have been observed in some sensitive asthmatics at  
18 concentrations as low as 0.2-0.3 ppm; however, these effects have not reached statistical  
19 significance (Horstman et al., 1986; Linn et al., 1987; 1988; 1990). Since the publication of the  
20 1994 Supplement, several additional human clinical studies have been published that provide  
21 supportive evidence of SO<sub>2</sub>-induced decrements in lung function and increases in respiratory  
22 symptoms among exercising asthmatics (see Annex Table D-2). Descriptions of older studies are  
23 presented in the 1994 Supplement, and will not be described in great detail in this document.  
24 However, based on recent guidance from the American Thoracic Society (ATS) regarding what  
25 constitutes an adverse health effect of air pollution (ATS, 2000a), some key older studies were  
26 reviewed and analyzed along with studies published since 1994. In its official statement, the ATS  
27 recommended that transient loss in lung function with accompanying respiratory symptoms  
28 attributable to air pollution should be considered adverse. In addition, ATS concluded that a  
29 decrease in health-related quality of life, which refers to an individual's perception of well being,

1 should also be considered to represent an adverse effect of air pollution. Therefore, whereas the  
2 conclusions in the 1994 Supplement were based on SO<sub>2</sub> exposure concentrations which resulted  
3 in large decrements in lung function along with moderate to severe respiratory symptoms, the  
4 current review of data from human clinical studies focuses on moderate to large SO<sub>2</sub>-induced  
5 decrements in lung function combined with respiratory symptoms ranging from mild (perceptible  
6 wheeze or chest tightness) to severe (breathing distress requiring the use of a bronchodilator).

### 3.1.3.1. Respiratory Symptoms

7 The 1994 Supplement to the Second Addendum described in detail several studies that  
8 evaluated respiratory symptoms following controlled human exposures to SO<sub>2</sub>. Briefly, following  
9 5-min exposures to 0, 0.2, 0.4, and 0.6 ppm SO<sub>2</sub> during moderate to heavy levels of exercise (48  
10 L/min), Linn et al. (1983) reported that the severity of respiratory symptoms (i.e., cough, chest  
11 tightness, throat irritation) among asthmatics increased with increasing SO<sub>2</sub> concentration.  
12 Relative to clean air exposures, exposures to SO<sub>2</sub> resulted in statistically significant increases in  
13 respiratory symptoms at concentrations of 0.4 and 0.6 ppm. In a subsequent study, Linn et al.  
14 (1987) observed a significant effect of SO<sub>2</sub> on respiratory symptoms in asthmatics who were  
15 engaged in slightly lower levels of exercise (40 L/min) for a duration of 10 min. Clear increases  
16 in respiratory symptoms were observed at concentrations of 0.6 ppm, with 43% of subjects  
17 experiencing SO<sub>2</sub>-induced symptoms. Some evidence of SO<sub>2</sub>-induced increases in respiratory  
18 symptoms was also demonstrated at concentrations as low as 0.4 ppm, with 15% of subjects  
19 experiencing symptoms (Smith, 1994). It was also observed that these symptoms abated < 1 h  
20 after exposure. Balmes et al. reported that 7 out of 8 asthmatic adults developed respiratory  
21 symptoms, including wheezing and chest tightness, following 3-min exposures to 0.5 ppm SO<sub>2</sub>  
22 during eucapnic hyperpnea ( $\dot{V}_E = 60$  L/min).

23 Additional human clinical studies published since the 1994 Supplement to the Second  
24 Addendum have provided support for previous conclusions regarding the effect of peak  
25 exposures to SO<sub>2</sub> on respiratory symptoms. In a human clinical study with SO<sub>2</sub>-sensitive  
26 asthmatics, Gong et al. (1995) reported that respiratory symptoms (i.e., shortness of breath,  
27 wheeze, and chest tightness) increased with increasing SO<sub>2</sub> concentration (0, 0.5, and 1.0 ppm  
28 SO<sub>2</sub>) following exposures of 10 min with varying levels of exercise. It was also observed that  
29 exposure to 0.5 ppm SO<sub>2</sub> during light exercise evoked a more severe symptomatic response than

1 heavy exercise in clean air. Trenga et al. (1999) observed a significant correlation between  
2 decreases in FEV<sub>1</sub> and increases in respiratory symptoms following 10 min exposures to  
3 0.5 ppm SO<sub>2</sub>.

### 3.1.3.2. Lung Function

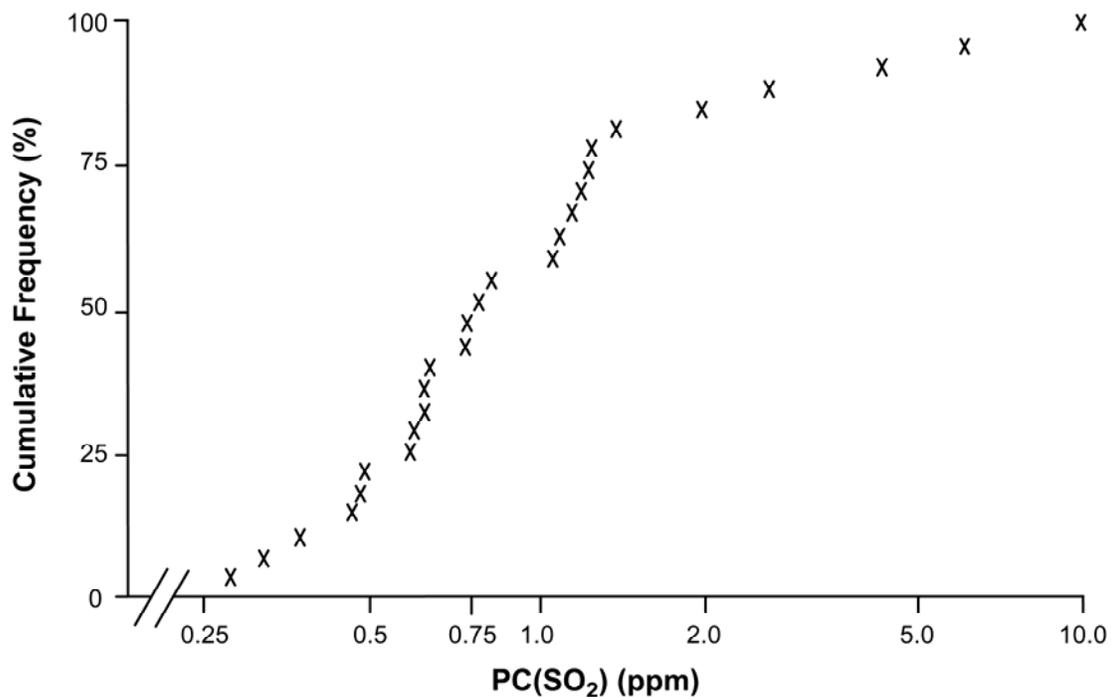
4 In controlled exposures of healthy human subjects to SO<sub>2</sub>, respiratory effects including  
5 increased respiration rates, decrements in peak flow, bronchoconstriction, and increased airway  
6 resistance have been observed at concentrations > 1 ppm (Abe, 1967; Amdur et al., 1953;  
7 Andersen et al., 1974; Frank et al., 1962; Lawther, 1955; Lawther et al., 1975; Sim and Pattle,  
8 1957; Snell and Luchsinger, 1969). SO<sub>2</sub>-induced decrements in lung function can be potentiated  
9 by increasing ventilation rate, either through eucapnic hyperpnea or by performing exercise  
10 during exposure. This effect is likely due to an increased uptake of SO<sub>2</sub> resulting from both the  
11 increase in  $\dot{V}_E$  as well as a shift from nasal breathing to oronasal breathing.

12 It has been clearly established that subjects with asthma are more sensitive to the  
13 respiratory effects of SO<sub>2</sub> exposure than healthy individuals without asthma. Asthmatic  
14 individuals exposed to SO<sub>2</sub> concentrations as low as 0.4-0.6 ppm for 5-10 min during exercise  
15 have been shown to experience moderate or greater bronchoconstriction, measured as an increase  
16 in sRaw ( $\geq 100\%$ ) or decrease in FEV<sub>1</sub> ( $\geq 15\%$ ) after correction for exercise-induced responses  
17 in clean air (Linn et al., 1983; 1984; 1987; 1988; 1990; Magnussen et al., 1990; Roger et al.,  
18 1985). Asthmatic subjects who are most sensitive to the respiratory effects of SO<sub>2</sub> have been  
19 observed to experience significant decrements in lung function following exposure to SO<sub>2</sub> at  
20 concentrations  $\leq 0.3$  ppm (Horstman et al., 1986; Sheppard et al., 1981). In some cases,  
21 bronchoconstrictive responses to SO<sub>2</sub> can occur in as little as 2 min after the start of exposure  
22 (Balmes et al., 1987; Horstman et al., 1988). Gong et al. (1995) demonstrated an exposure-  
23 response relationship between SO<sub>2</sub> and lung function by exposing 14 unmedicated, SO<sub>2</sub>-sensitive  
24 asthmatics to 0, 0.5, and 1 ppm SO<sub>2</sub> under 3 different levels of exercise. It was shown that  
25 increasing SO<sub>2</sub> concentration had a greater effect on sRaw and FEV<sub>1</sub> than increasing exercise  
26 level. Trenga et al. (1999) observed that 25 out of 47 adult asthmatics experienced a drop in  
27 FEV<sub>1</sub> versus baseline of between 8 and 44% (mean = 17.2%) following a 10 min exposure to 0.5  
28 ppm SO<sub>2</sub> during moderate exercise.

1 Since some of the studies involving asthmatic subjects have used change in sRaw as the  
2 endpoint of interest while others measured changes in FEV<sub>1</sub> or both, a comparison of FEV<sub>1</sub> and  
3 sRaw based on data from Linn et al. (1987; 1990) was provided in the 1994 Supplement to the  
4 Second Addendum. Based on simple linear interpolation of the data from these two studies, a  
5 100% increase in sRaw corresponded to a 12 to 15% decrease in FEV<sub>1</sub> and a 200% increase in  
6 sRaw corresponded to a 25 to 30% decrease in FEV<sub>1</sub>.

7 One of the aims of the Linn et al. (1987) study was to determine how the intensity of  
8 response varied with asthma severity or status. In this study, 24 normal, 21 atopic (but not  
9 asthmatic), 16 mild asthmatic, and 24 moderate/severe asthmatic subjects were exposed to SO<sub>2</sub>  
10 concentrations between 0 and 0.6 ppm. While the moderate/severe asthmatics were more  
11 responsive than mild asthmatics following exposure to clean air during exercise, their increases  
12 in response to increasing SO<sub>2</sub> concentrations were similar to those of the mild asthmatic group.  
13 Thus, it was concluded that SO<sub>2</sub> response was not strongly dependent on the clinical severity of  
14 asthma. However, the apparent lack of correlation between SO<sub>2</sub> response and asthma severity  
15 should be interpreted with caution, since the SO<sub>2</sub> response may have been attenuated by  
16 medication usage or its persistence. Three of the moderate/severe asthmatics were unable to  
17 withhold medication usage during the exposure period. Conversely, a few of the asthmatics,  
18 including some in the moderate/severe group, did not react to 0.6 ppm SO<sub>2</sub>.

19 One of the key studies discussed in the 1994 Supplement to the Second Addendum was by  
20 Horstman et al. (1986). In this study, 27 asthmatic subjects were exposed to concentrations of  
21 SO<sub>2</sub> between 0- and 2 ppm SO<sub>2</sub> for 10 min on different days under exercising conditions ( $\dot{V}_E =$   
22 42 L/min). The authors reported that for 22% of the subjects, the concentration of SO<sub>2</sub> needed to  
23 produce a doubling of sRaw compared to clean air exposure [PC(SO<sub>2</sub>)] was < 0.5 ppm, with 2  
24 subjects (7.4%) experiencing moderate decrements in lung function following exposure to  
25 concentrations of SO<sub>2</sub> at or below 0.3 ppm (see Figure 3-1). For approximately 15% of the  
26 subjects, the PC(SO<sub>2</sub>) was > 2 ppm, with approximately 35% of asthmatic subjects experiencing  
27 a doubling in sRaw versus clean air at ≤ 0.6-ppm SO<sub>2</sub>.



**Figure 3-1. Distribution of individual airway sensitivity to SO<sub>2</sub>. Each data point represents the value of PC(SO<sub>2</sub>) for an individual subject. PC(SO<sub>2</sub>) is defined as the concentration of SO<sub>2</sub> which resulted in a doubling of sRaw compared to clean air exposure.**

Source: Horstman et al. (1986).

1 It is important to note that a transient decrement in lung function following exposure to an  
 2 air pollutant is not automatically considered to represent an adverse effect. However,  
 3 SO<sub>2</sub>-induced decrements in lung function (increased sRaw and decreased FEV<sub>1</sub>) have frequently  
 4 been associated with increases in respiratory symptoms among asthmatics (Balmes et al., 1987;  
 5 Gong et al., 1995; Linn et al., 1987; 1988; 1990; 1983; Roger et al., 1985), which together does  
 6 constitute an adverse effect under the ATS guidelines. Linn et al. (1987) exposed 40 mild and  
 7 moderate asthmatics during 10 min periods of exercise to 0, 0.2, 0.4, and 0.6 ppm SO<sub>2</sub>. The  
 8 effect of SO<sub>2</sub> on lung function and respiratory symptoms was assessed immediately following  
 9 exposure, and the individual-specific results have been made available to the U.S. EPA by the  
 10 study authors (Smith, 1994). Following exposure to 0.6 ppm SO<sub>2</sub> and after adjusting for effects  
 11 of exercise in clean air, 21 of the 40 subjects demonstrated moderate or greater decrements in  
 12 lung function, defined as a ≥15% decrease in FEV<sub>1</sub>, a ≥100% increase in sRaw, or both. Of these

1 21 responders, 14 (67%) also experienced mild to severe respiratory symptoms (6 mild, 6  
2 moderate, and 2 severe). In the same study, 14 asthmatics experienced moderate or greater  
3 decrements in lung function at 0.4 ppm SO<sub>2</sub>, 5 of whom (36%) also experienced mild to  
4 moderate respiratory symptoms (2 mild, 3 moderate). Five asthmatics experienced moderate or  
5 greater decrements in lung function at the lowest SO<sub>2</sub> concentration tested (0.2 ppm), with 1 of  
6 the 5 (20%) also experiencing mild respiratory symptoms.

7 It has been proposed that, as in asthmatics, individuals with COPD may also be more  
8 susceptible to SO<sub>2</sub>-induced respiratory health effects. However, this group has not been  
9 extensively studied in human clinical studies. Among a group of older adults with physician-  
10 diagnosed COPD, Linn et al. (1985) reported no significant effect on lung function following 15  
11 min exposures to SO<sub>2</sub> at concentrations of 0.4 and 0.8 ppm. While it was concluded that older  
12 adults with COPD appear to be less sensitive to SO<sub>2</sub> when compared with younger adult  
13 asthmatics, the authors suggested that the lack of response may have been due in part to the very  
14 low levels of exercise used in the study ( $\dot{V}_E = 18$  L/min), which would result in a lower dose of  
15 SO<sub>2</sub> reaching the lower airway. In contrast to studies with asthmatics, most of the subjects in this  
16 study regularly used bronchodilators and were permitted their use up to 4 h prior to the study.

17 In summary, SO<sub>2</sub>-induced decrements in lung function have been observed following peak  
18 exposures in humans. These effects are particularly evident in exercising asthmatic individuals,  
19 with significant decreases in sRaw and increases in FEV<sub>1</sub> consistently demonstrated following  
20 5-10 min exposures to 0.4-0.6 ppm SO<sub>2</sub>. SO<sub>2</sub>-induced decrements in lung function have  
21 frequently been associated with respiratory symptoms, and with increasing SO<sub>2</sub> exposure  
22 concentration from 0.2-1.0 ppm, both the magnitude of response among asthmatics and the  
23 percentage of asthmatics significantly affected have been shown to increase.

### **3.1.3.3. Airway Inflammation**

24 A very limited number of human clinical studies have investigated the role of airway  
25 inflammation in the asthmatic response following peak exposure to SO<sub>2</sub>. Gong et al. (2001)  
26 observed an SO<sub>2</sub>-induced increase in sputum eosinophil counts in exercising asthmatics 2 h after  
27 a 10 min exposure to 0.75 ppm SO<sub>2</sub>. The results of this study provide some evidence that SO<sub>2</sub>  
28 may elicit an allergic inflammatory response in the airways of asthmatics which extends beyond  
29 the short time period typically associated with SO<sub>2</sub> effects.

### 3.1.3.4. Evidence of the Effect of Peak Exposure from Animal Studies

1 In addition to the findings of human clinical studies involving asthmatics, SO<sub>2</sub>-induced  
2 decrements in lung function have been demonstrated following peak exposures to SO<sub>2</sub> in  
3 laboratory animals. The 1982 AQCD reported bronchoconstriction, as indicated by increased  
4 pulmonary resistance, as the most sensitive indicator of lung function effects of acute SO<sub>2</sub>  
5 exposure based on the observations of increased pulmonary resistance in guinea pigs that were  
6 acutely exposed to 0.16 ppm SO<sub>2</sub>. Since 1982, a few new animal toxicological studies have  
7 demonstrated acute changes in lung function following SO<sub>2</sub> exposures of 45 min or less. These  
8 studies are summarized below and in Annex Table E-1.

9 Lewis and Kirchner (1984) measured lung function in dogs exposed for 5 min to two doses  
10 of SO<sub>2</sub> via an endotracheal tube. Increased pulmonary resistance and decreased compliance were  
11 observed in conscious dogs exposed to 30 ppm SO<sub>2</sub>, but not to 10 ppm SO<sub>2</sub>.

12 All other studies focused on the role of local nervous system reflexes and/or C-fiber  
13 receptors in mediating responses to SO<sub>2</sub>. Barthelemy et al. (1988) measured lung function in  
14 anesthetized rabbits exposed for 45 min by endotracheal tube to two doses of SO<sub>2</sub>. Airway  
15 resistance increased 16% and 50% following 0.5 and 5 ppm SO<sub>2</sub>, respectively. Bivagal vagotomy  
16 had little effect on the response to 5 ppm, indicating that the prolonged bronchoconstriction  
17 response did not result from a vagal reflex. This study did not rule out the possibility that vagal  
18 reflexes were involved in immediate bronchoconstriction following SO<sub>2</sub> exposure.

19 In another study, Atzori et al. (1992a) demonstrated bronchoconstriction, as measured by  
20 changes in dynamic lung compliance and airway conductance, within the first 5 min following  
21 exposure of isolated and perfused guinea pig lungs to 100 and 250 ppm SO<sub>2</sub> via an endotracheal  
22 tube. This response was found to be due to a local nervous system reflex. However, this result  
23 does not preclude involvement of central nervous system reflexes in SO<sub>2</sub>-induced  
24 bronchoconstriction under conditions of an intact vagus nerve. Furthermore, the formation of  
25 sulfite was observed in perfusate following SO<sub>2</sub> exposure. Using the same model, Atzori et al.  
26 (1992b) found that SO<sub>2</sub>-induced bronchoconstriction was associated with the release of a sensory  
27 neuropeptide and was inhibited when C-fiber receptors were blocked.

28 Other animal toxicological studies examined immediate respiratory effects from exposure  
29 to very high SO<sub>2</sub> concentrations. Hajj et al. (1996) exposed anesthetized guinea pigs to six tidal  
30 breaths of 500–2,000 ppm SO<sub>2</sub>. Increased total pulmonary resistance, decreased dynamic

1 compliance, and systemic hypotension were observed within seconds. Tachykinin antagonists  
2 blocked the changes in lung airway function, but not the changes in blood pressure in this model  
3 system. Atropine failed to block the airway response. These results suggest that a local nervous  
4 system reflex involving tachykinin release is an important mediator of bronchoconstriction  
5 following high concentrations of SO<sub>2</sub>. Wang et al. (1996) exposed anesthetized rats to two tidal  
6 breaths of 0.5% SO<sub>2</sub> via an endotracheal tube. Immediate and transient bradypnea and  
7 bradycardia were observed. Selective block of the C-fiber receptors and bilateral vagotomy  
8 eliminated the SO<sub>2</sub>-mediated effect on ventilation.

### **3.1.3.5. Summary of Evidence on the Effect of Peak Exposure on Respiratory Health**

9 Collectively, evidence from earlier studies considered in the previous review, along with a  
10 limited number of new human clinical studies, consistently indicates that with elevated  
11 ventilation rates, asthmatic individuals experience moderate or greater decrements in lung  
12 function, as well as increased respiratory symptoms, following peak exposures to SO<sub>2</sub> at  
13 concentrations as low as 0.4-0.6 ppm (Balmes et al., 1987; Gong et al., 1995; Horstman et al.,  
14 1986; Linn et al., 1987; Linn et al., 1983). These findings are consistent with our understanding  
15 of the potential modes of action for respiratory health as described in Section 3.1.2. Some  
16 sensitive asthmatics have been shown to experience moderate decrements in lung function at  
17 concentrations below 0.3 ppm (Balmes et al., 1987; Linn et al., 1987; Sheppard et al., 1981),  
18 although there is limited evidence of a significant increase in respiratory symptoms at these  
19 exposure concentrations. Among asthmatics, both the magnitude of SO<sub>2</sub>-induced decrements in  
20 lung function and the percent of individuals affected have consistently been shown to increase  
21 with increasing exposure to SO<sub>2</sub> concentrations between 0.2 and 1.0 ppm. This is summarized in  
22 Table 3-1 along with supporting evidence of SO<sub>2</sub>-induced increases in respiratory symptoms at  
23 various exposure concentrations. The table includes data from all studies where individual data  
24 are presented or have been made available by the authors (Smith, 1994). Although the vast  
25 majority of human clinical studies involving controlled exposure to SO<sub>2</sub> have been conducted in  
26 adult asthmatics, there is a relatively strong body of evidence to suggest that adolescents may  
27 experience many of the same respiratory effects at similar SO<sub>2</sub> exposure concentrations (Koenig  
28 et al., 1981; 1983; 1987; 1988; 1990; 1992). It should be noted, however, that in all of these

1 studies involving adolescents, SO<sub>2</sub> was administered via inhalation through a mouthpiece rather  
 2 than an exposure chamber. This exposure technique bypasses nasal absorption of SO<sub>2</sub>, likely  
 3 resulting in a relative increase of pulmonary SO<sub>2</sub> uptake (see Section 2.6.1).

**Table 3-1. Percentage of asthmatic individuals in controlled human exposures experiencing SO<sub>2</sub>-induced decrements in lung function.**

SO <sub>2</sub> CONC (ppm)	EXPOSURE DURATION	NO. SUBJ	VENTILATION (L/MIN)	LUNG FUNCT	CUMULATIVE PERCENTAGE OF RESPONDERS (NUMBER OF SUBJECTS) <sup>1</sup>			REFERENCE	RESPIRATORY SYMPTOMS: SUPPORTING STUDIES
					≥ 100% ↑	sRaw ≥ 200% ↑	≥ 300% ↑		
					≥ 15% ↓	FEV <sub>1</sub> ≥ 20% ↓	≥ 30% ↓		
0.2	10 min	40	~40	sRaw	5% (2)	0	0	Linn et al. (1987) <sup>2</sup>	Some evidence of SO <sub>2</sub> -induced increases in respiratory symptoms in the most sensitive individuals: Linn et al. (1987; 1988; 1990; 1984; 1983), Schacter et al. (1984)
	10 min	40	~40	FEV <sub>1</sub>	13% (5)	5% (2)	3% (1)	Linn et al. (1987)	
0.25	5 min	19	~50-60	sRaw	32% (6)	16% (3)	0	Bethel et al. (1985)	
	5 min	9	~80-90	sRaw	22% (2)	0	0		
	10 min	28	~40	sRaw	4% (1)	0	0	Roger et al. (1985)	
0.3	10 min	20	~50	sRaw	10% (2)	5% (1)	5% (1)	Linn et al. (1988) <sup>3</sup>	
	10 min	21	~50	sRaw	33% (7)	10% (2)	0	Linn et al. (1990) <sup>3</sup>	
	10 min	20	~50	FEV <sub>1</sub>	15% (3)	0	0	Linn et al. (1988)	
	10 min	21	~50	FEV <sub>1</sub>	24% (5)	14% (3)	10% (2)	Linn et al. (1990)	
0.4	10 min	40	~40	sRaw	23% (9)	8% (3)	3% (1)	Linn et al. (1987)	
	10 min	40	~40	FEV <sub>1</sub>	30% (12)	23% (9)	13% (5)	Linn et al. (1987)	
0.5	5 min	10	~50-60	sRaw	60% (6)	40% (4)	20% (2)	Bethel et al. (1983)	(1987) <sup>4</sup> , Gong et al. (1995), Linn et al. (1987; 1983), Roger et al. (1985)
	10 min	28	~40	sRaw	21% (6)	4% (1)	4% (1)	Roger et al. (1985)	
	10 min	45	~30	sRaw	36% (16)	16% (7)	13% (6)	Magnussen et al. (1990) <sup>4</sup>	
0.6	10 min	40	~40	sRaw	35% (14)	28% (11)	18% (7)	Linn et al. (1987)	Clear and consistent increases in SO <sub>2</sub> -induced respiratory symptoms: Linn et al. (1987; 1988; 1984; 1990), Gong et al. (1995), Horstman et al. (1988)
	10 min	20	~50	sRaw	60% (12)	35% (7)	10% (2)	Linn et al. (1988)	
	10 min	21	~50	sRaw	57% (12)	33% (7)	14% (3)	Linn et al. (1990)	
	10 min	40	~40	FEV <sub>1</sub>	53% (21)	45% (18)	20% (8)	Linn et al. (1987)	
	10 min	20	~50	FEV <sub>1</sub>	55% (11)	55% (11)	5% (1)	Linn et al. (1988)	
	10 min	21	~50	FEV <sub>1</sub>	45% (9)	35% (7)	19% (4)	Linn et al. (1990)	
1.0	10 min	28	~40	sRaw	54% (15)	25% (7)	14% (4)	Roger et al. (1985)	
	10 min	10	~40	sRaw	60% (6)	20% (2)	0	Kehrl et al. (1987)	

<sup>1</sup>Data presented from all references from which individual data were available. Percentage of individuals who experienced greater than or equal to a 100, 200, or 300% increase in specific airway resistance (sRaw), or a 15, 20, or 30% decrease in FEV<sub>1</sub>. Lung function decrements are adjusted for effects of exercise in clean air.

<sup>2</sup>Responses of mild and moderate asthmatics reported in Linn et al. (1987) have been combined.

<sup>3</sup>Analysis includes data from only mild (1988) and moderate (1990) asthmatics who were not receiving supplemental medication.

<sup>4</sup>Indicates studies in which exposures were conducted using a mouthpiece rather than a chamber.

1 In laboratory animals, SO<sub>2</sub>-induced decrements in lung function were observed following  
2 peak exposures in several studies conducted since the last review. Most of these experiments  
3 were designed to evaluate the mode of action underlying SO<sub>2</sub>-mediated bronchoconstriction.  
4 They used high concentrations of administered SO<sub>2</sub>, which in many cases were delivered using  
5 an endotracheal tube. As a result, these studies are of limited usefulness in understanding the  
6 effects of SO<sub>2</sub> at or near ambient levels or under conditions of nasal breathing.

### **3.1.4. Respiratory Effects Associated with Short-Term (≥ 1 h) Exposure**

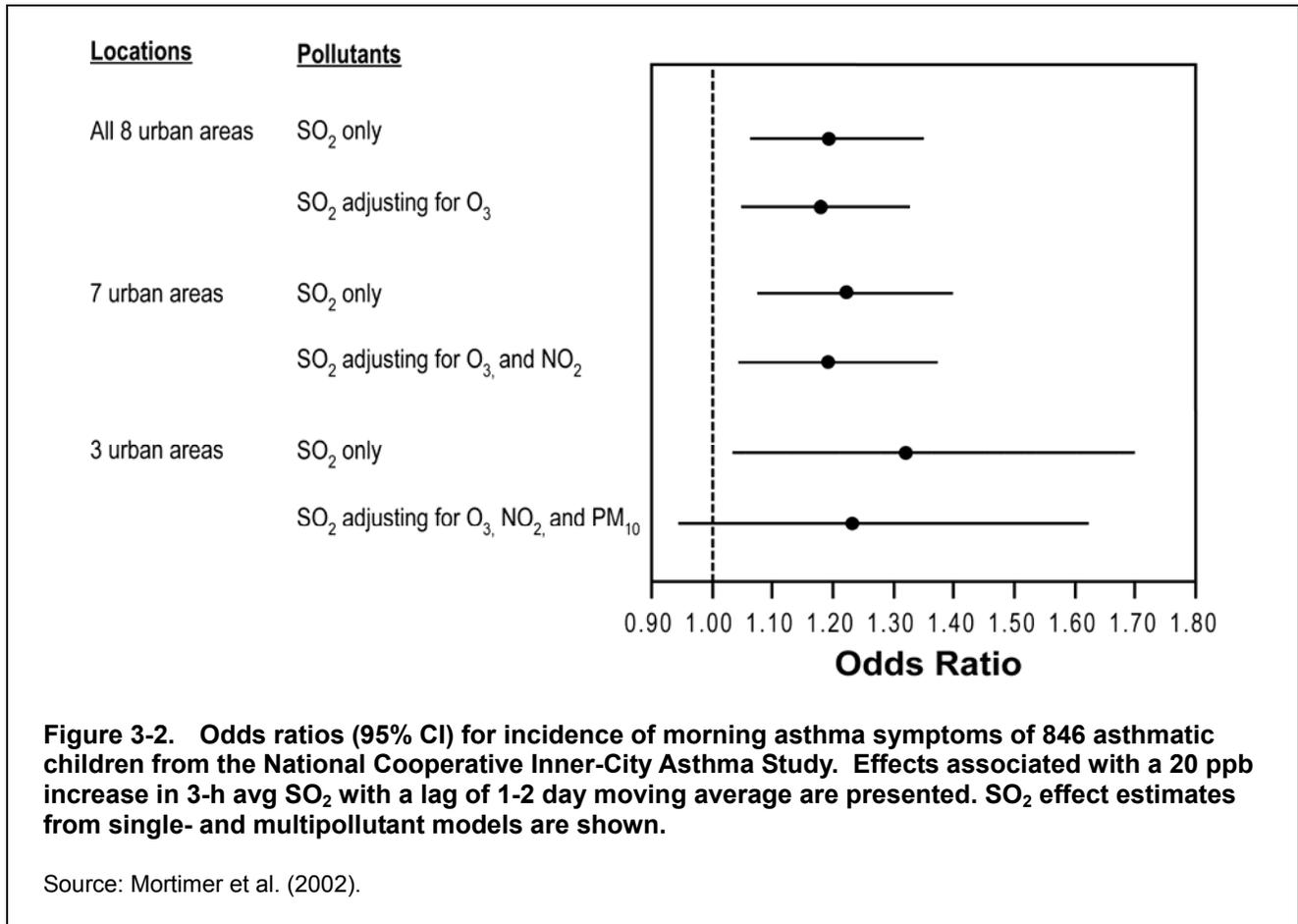
#### **3.1.4.1. Respiratory Symptoms**

7 Consideration of the mode of action suggests that SO<sub>2</sub> may contribute to respiratory  
8 symptoms by stimulating mucus secretion and cough through activating central nervous system  
9 reflexes. Recent studies in vitro have demonstrated increased expression of a gene encoding  
10 mucin protein, MUC5AC, in human bronchial epithelial cells following exposure to the SO<sub>2</sub>  
11 derivatives sulfite and bisulfite at concentrations of 1-10 μM (Li and Meng, 2007). Increased  
12 levels of MUC5AC protein were also reported. Sulfite and bisulfite were used, since SO<sub>2</sub>  
13 dissolves into the aqueous fluid and forms hydrogen ions and bisulfite and sulfite anions when it  
14 contacts the fluids lining the airway. These same investigators conducted a related in vivo study  
15 in which rats were exposed by inhalation to 2 ppm SO<sub>2</sub> for 1 h per day for 7 days. Rats which  
16 were sensitized and challenged with ovalbumin, as well as exposed to SO<sub>2</sub>, had increased  
17 MUC5AC mRNA and protein levels compared with animals treated with ovalbumin or SO<sub>2</sub>  
18 alone (Li et al., 2007b). Further studies are required to determine the relevance of mucin gene  
19 expression to mucous secretion and respiratory symptoms in allergic and non-allergic animals at  
20 ambient levels of SO<sub>2</sub>. However, evidence from toxicological studies such as these may provide  
21 biological plausibility for the effects of SO<sub>2</sub> on respiratory symptoms in humans.

22 Epidemiological studies have examined the association between ambient SO<sub>2</sub>  
23 concentrations and respiratory symptoms in both adults and children. In air pollution field  
24 studies, respiratory symptoms are usually assessed using questionnaire forms (or “daily diaries”)  
25 completed by study subjects. Questions address the daily experience of coughing, wheezing,  
26 shortness of breath (or difficulty breathing), production of phlegm, and others.

### 3.1.4.1.1. Children

1 Epidemiological studies on respiratory symptoms published since the last review are  
 2 summarized in Annex Table F-1; key studies are discussed in detail below.



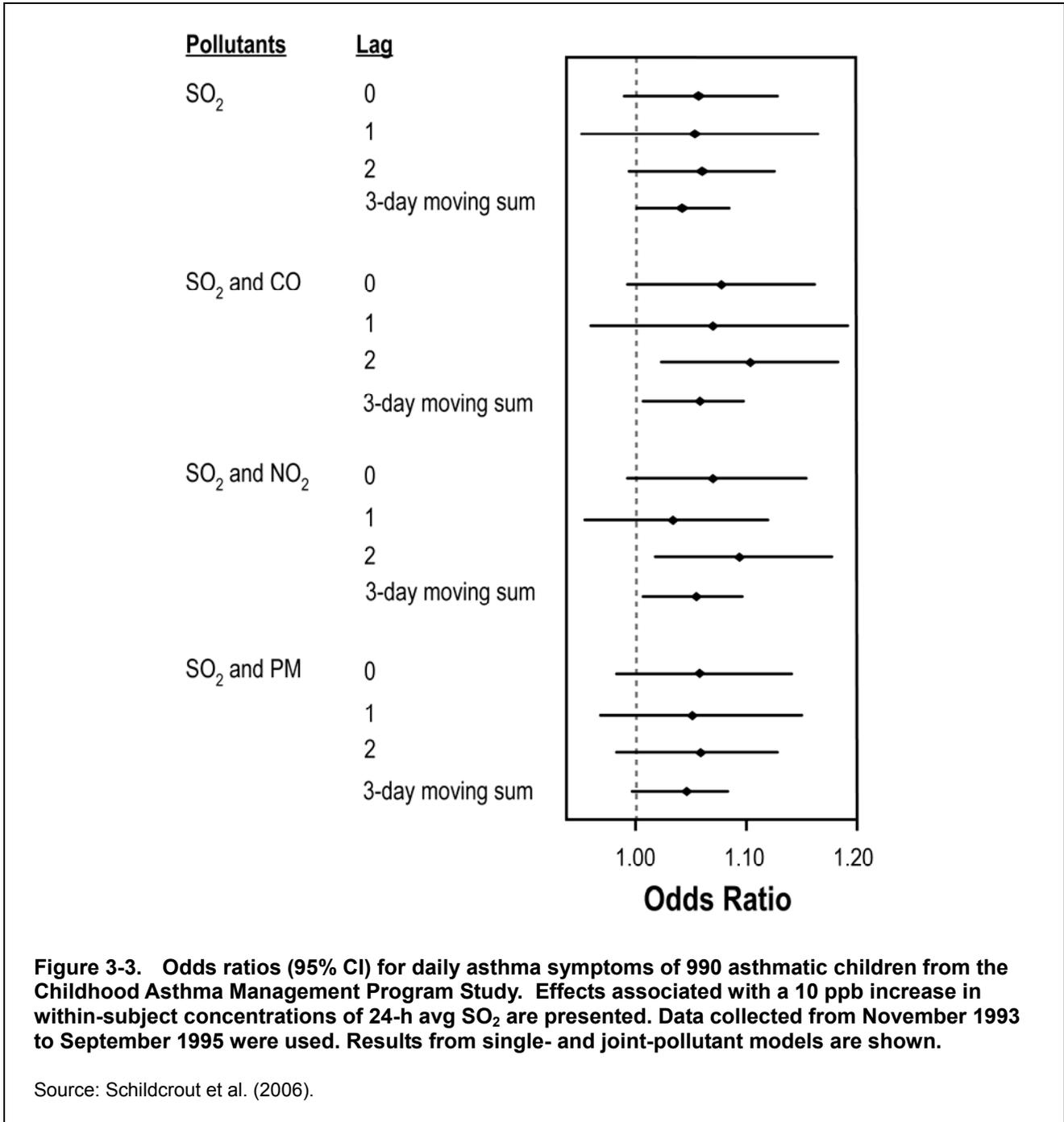
3 The strongest epidemiological evidence for an association between respiratory symptoms  
 4 and exposure to ambient SO<sub>2</sub> comes from two large U.S. multicity studies (Mortimer et al., 2002;  
 5 Schildcrout et al., 2006). Mortimer et al. examined 846 asthmatic children from eight U.S. urban  
 6 areas in the National Cooperative Inner-City Asthma Study (NCICAS) for summertime air  
 7 pollution-related respiratory symptoms. Median 3-h avg SO<sub>2</sub> (8 to 11 a.m.) levels ranged from 17  
 8 ppb in Detroit, MI to 37 ppb in East Harlem, NY. Morning symptoms were found to be most  
 9 strongly associated with an average of a 1- to 2-day lag of SO<sub>2</sub> concentrations. In multipollutant  
 10 models with O<sub>3</sub> and NO<sub>2</sub> (measured in seven cities), the SO<sub>2</sub> association remained robust (see

1 Figure 3-2). When particulate matter with an aerodynamic diameter of  $\leq 10 \mu\text{m}$  ( $\text{PM}_{10}$ ) was also  
2 included in the multipollutant models, the  $\text{SO}_2$  effect estimate decreased only slightly; however,  
3 it became nonsignificant, possibly due to reduced statistical power (only three of eight cities  
4 were included in this analysis) or collinearity resulting from adjustment of multiple pollutants. A  
5 similar decline was observed in the effect estimate for  $\text{PM}_{10}$  in the multipollutant model  
6 compared to the single-pollutant model.

7 In the Childhood Asthma Management Program (CAMP) study, the association between  
8 ambient air pollution and asthma exacerbations in children ( $n = 990$ ) from eight North American  
9 cities was investigated (Schildcrout et al., 2006).  $\text{SO}_2$  measurements were available in seven of  
10 the eight cities. The median 24-h avg  $\text{SO}_2$  concentrations ranged from 2.2 ppb (interquartile  
11 range [IQR]: 1.7, 3.1) in San Diego, CA to 7.4 ppb (IQR: 5.3, 10.7) in St. Louis, MO. Results for  
12 the associations between asthma symptoms and all pollutants are shown in Figure 3-3. Analyses  
13 indicate that although  $\text{SO}_2$  was positively related to increased risk of asthma symptoms at all  
14 lags, only the 3-day moving average was statistically significant. No associations were observed  
15 between  $\text{SO}_2$  and rescue inhaler use. Stronger associations were observed for CO and  $\text{NO}_2$ . The  
16 effect estimates appear to be slightly larger in joint-pollutant models with CO or  $\text{NO}_2$ ,  
17 particularly at a 2-d lag, but did not change much when  $\text{PM}_{10}$  was jointly considered.

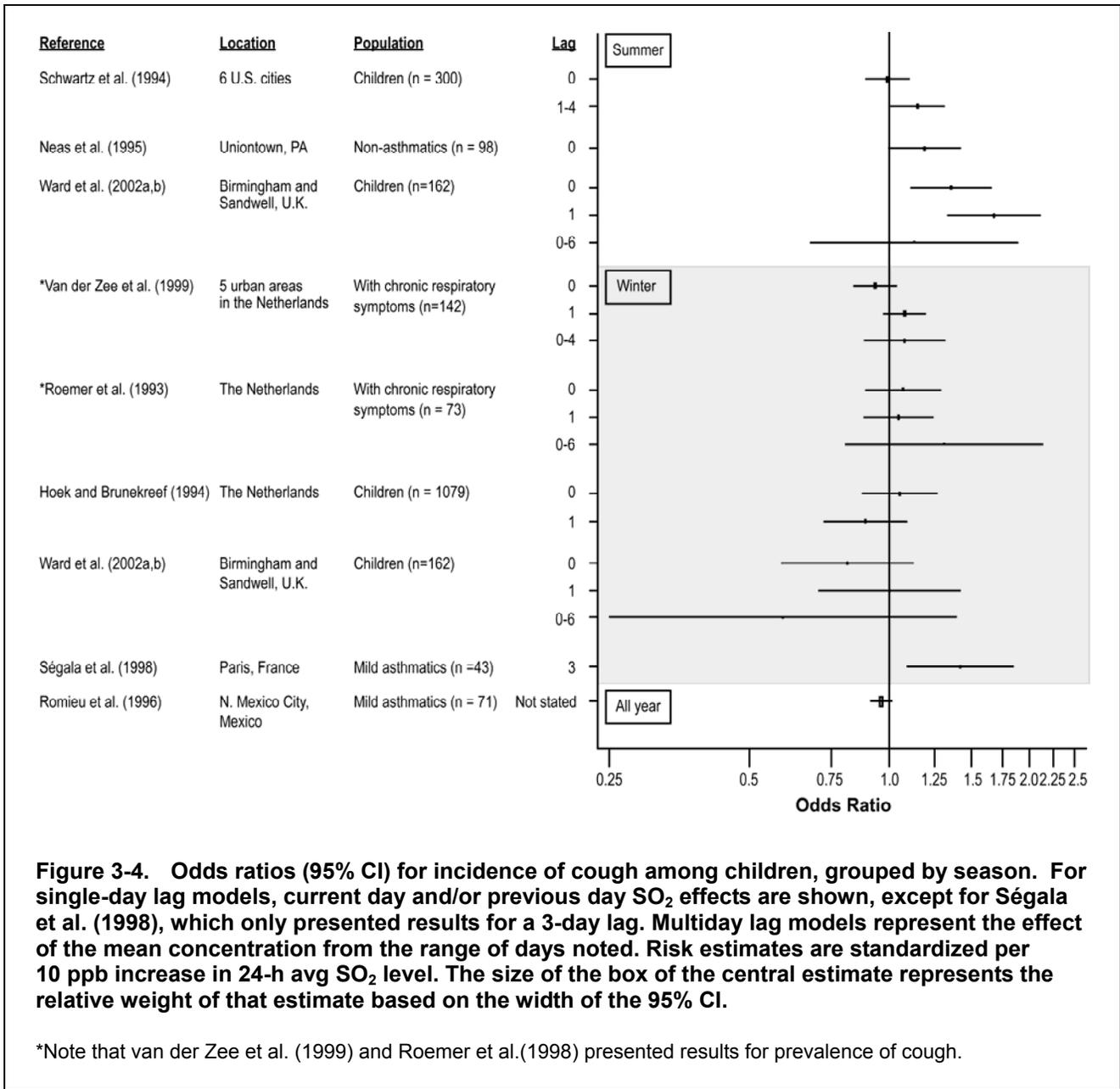
18 A longitudinal study of 1,844 schoolchildren during the summer from the Harvard Six  
19 Cities Study suggested that the association between  $\text{SO}_2$  and respiratory symptoms could be  
20 confounded by  $\text{PM}_{10}$  (Schwartz et al., 1994). The median 24-h avg  $\text{SO}_2$  concentration during this  
21 period was 4.1 ppb (10th–90th percentile: 0.8, 17.9; max 81.9).  $\text{SO}_2$  concentrations were found  
22 to be associated with cough incidence and lower respiratory tract symptoms. Of the pollutants  
23 examined,  $\text{PM}_{10}$  had the strongest associations with respiratory symptoms. In two-pollutant  
24 models, the effect of  $\text{PM}_{10}$  was found to be robust to adjustment for other copollutants, while the  
25 effect of  $\text{SO}_2$  was substantially reduced after adjustment for  $\text{PM}_{10}$ . Because the  $\text{PM}_{10}$   
26 concentrations were correlated strongly to  $\text{SO}_2$ -derived sulfate particles ( $r = 0.80$ ), the diminution  
27 of the  $\text{SO}_2$  effect estimate may indicate that for  $\text{PM}_{10}$  dominated by fine sulfate particles,  $\text{PM}_{10}$   
28 has a slightly stronger association than  $\text{SO}_2$ . This study further investigated the concentration-  
29 response function and observed a nonlinear relationship between  $\text{SO}_2$  concentrations and  
30 respiratory symptoms. Though an increasing trend was observed at concentrations as low as

- 1 10 ppb, no statistically significant increase in the incidence of lower respiratory tract symptoms
- 2 was seen until concentration exceeded a 24-h avg SO<sub>2</sub> of 22 ppb.



1 In the Pollution Effects on Asthmatic Children in Europe (PEACE) study, a multicenter  
2 study of 14 cities across Europe, the effects of acute exposure to various pollutants including SO<sub>2</sub>  
3 on the respiratory health of children with chronic respiratory symptoms (n = 2,010) was  
4 examined during the winter of 1993–1994 (Roemer et al., 1998). Mean 24-h avg SO<sub>2</sub>  
5 concentrations ranged from 1 ppb in the urban area of Umeå, Sweden, to 43 ppb in the urban  
6 area of Prague, Czech Republic. No associations were observed between SO<sub>2</sub> and daily  
7 prevalence of respiratory symptoms or bronchodilator use at any of the single- and multiday lags  
8 considered. In addition, no associations were observed for any of the other pollutants examined.  
9 It should be noted that during the study period, there were only two major air pollution episodes,  
10 at the beginning and end of the study period. In the epidemiological model, the control for time  
11 trend was accomplished through the use of linear and quadratic terms. Given the timing of the air  
12 pollution episodes, the quadratic trend term would have removed most of the air pollution effect.  
13 Other studies that participated in the PEACE study and analyzed results for longer periods of  
14 time have observed statistically significant associations between SO<sub>2</sub> and respiratory symptoms  
15 in children (van der Zee et al., 1999, presented below).

16 Additional studies have examined the relationship between respiratory symptoms and  
17 ambient SO<sub>2</sub> concentrations and generally found positive associations, including two U.S. studies  
18 (Delfino et al., 2003; Neas et al., 1995) and several European studies (Hoek and Brunekreef,  
19 1994; Peters et al., 1996; Roemer et al., 1993; Segala et al., 1998; Timonen and Pekkanen, 1997;  
20 van der Zee et al., 1999). However, some did not find a consistent association between  
21 respiratory symptoms and SO<sub>2</sub> concentrations (e.g., Hoek and Brunekreef, 1993; 1995; Romieu  
22 et al., 1996). Only one of these studies examined possible confounding of the SO<sub>2</sub> effect by  
23 copollutants. Van der Zee et al. (1999) looked at the association between respiratory symptoms  
24 and SO<sub>2</sub> in 7- to 11-year-old children (n = 633) with and without chronic respiratory symptoms  
25 in the Netherlands. Significant associations with lower respiratory tract symptoms and increased  
26 bronchodilator use were observed for SO<sub>2</sub>, as well as PM<sub>10</sub>, BS, and sulfate, in symptomatic  
27 children living in urban areas (n = 142). In a two-pollutant model with PM<sub>10</sub>, the results were  
28 robust for bronchodilator use, but slightly reduced for lower respiratory tract symptoms. A  
29 subgroup analysis of this cohort examining SO<sub>2</sub>-related respiratory symptoms in children with  
30 airway hyperresponsiveness and atopy (Boezen et al., 1999) is discussed in Section 3.1.4.4.

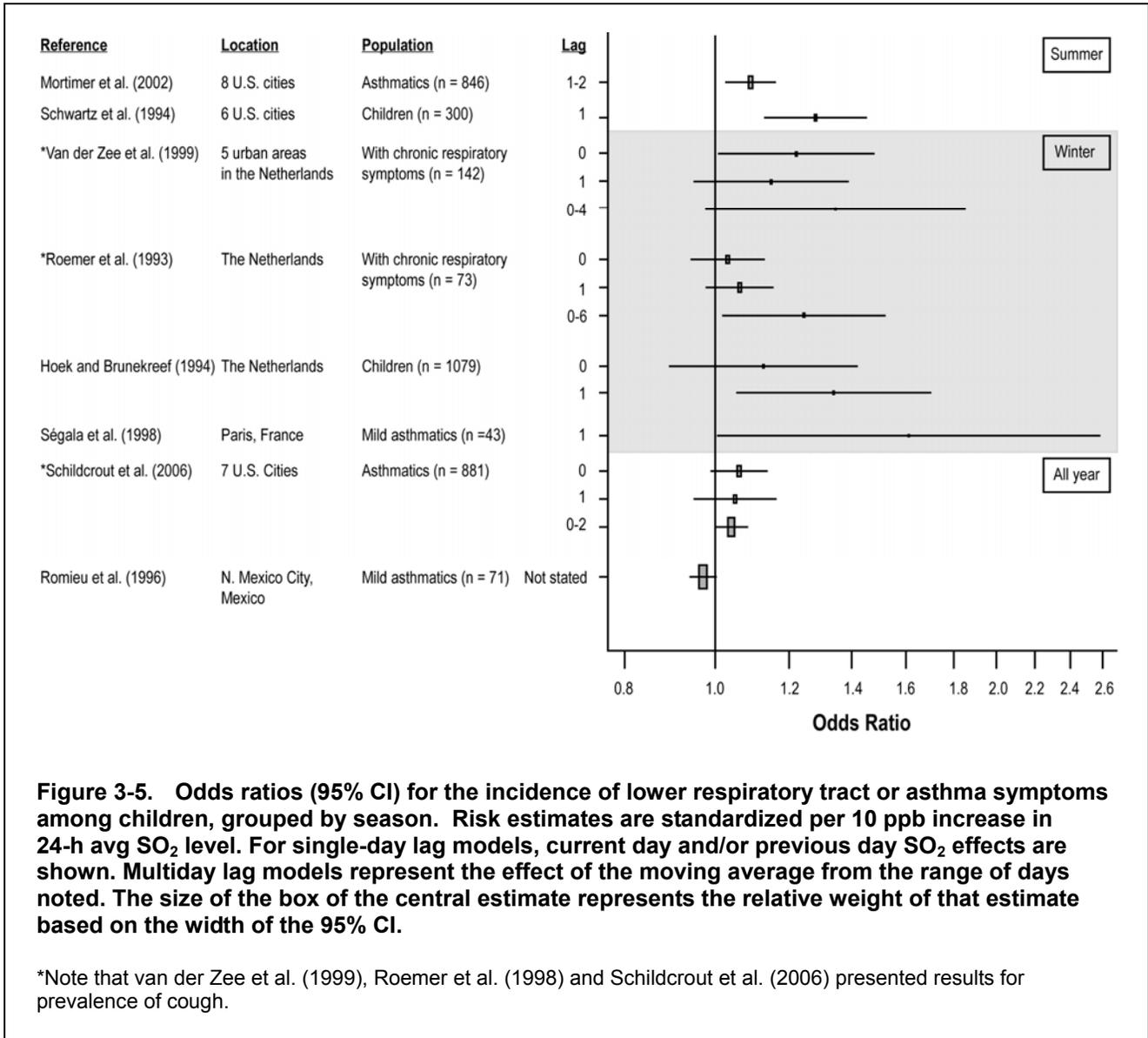


**Figure 3-4. Odds ratios (95% CI) for incidence of cough among children, grouped by season. For single-day lag models, current day and/or previous day SO<sub>2</sub> effects are shown, except for Ségala et al. (1998), which only presented results for a 3-day lag. Multiday lag models represent the effect of the mean concentration from the range of days noted. Risk estimates are standardized per 10 ppb increase in 24-h avg SO<sub>2</sub> 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.(1998) presented results for prevalence of cough.

1            Figure 3-4 and Figure 3-5 present the odds ratios for SO<sub>2</sub>-related cough and lower  
2 respiratory tract or asthma symptoms, respectively, from several epidemiological studies with  
3 relevant data. The results for cough are somewhat variable with wide confidence intervals, as  
4 shown in Figure 3-4. The studies conducted in the summer generally indicate increased risk of  
5 cough from exposure to SO<sub>2</sub>. A more consistent effect of SO<sub>2</sub> is observed on lower respiratory  
6 tract or asthma symptoms (Figure 3-5). Although there is some variability in the individual effect  
7 estimates, the majority of the odds ratios appear to be greater than one. As was the case with

1 cough, stronger associations with lower respiratory tract or asthma symptoms were observed in  
 2 the summer, as opposed to the winter. There was some variability among the different lags of  
 3 exposure; however, effects were generally observed with current day or previous day exposure  
 4 and, in some cases, with a distributed lag of 2 to 3 days.



5 Overall, recent epidemiological studies provide evidence for an association between  
 6 ambient SO<sub>2</sub> exposures and increased respiratory symptoms in children, particularly those with  
 7 asthma or chronic respiratory symptoms. Recent U.S. multicity studies observed significant

1 associations between SO<sub>2</sub> and respiratory symptoms at a median range of 17 to 37 ppb (75th  
2 percentile: ~25 to 50) across cities for 3-h avg SO<sub>2</sub> (NCICAS, Mortimer et al., 2002) and 2.2 to  
3 7.4 ppb (90th percentile: 4.4 to 14.2) for 24-h avg SO<sub>2</sub> (CAMP, Schildcrout et al., 2006).  
4 However, an earlier study that examined the concentration-response function found that a  
5 statistically significant increase in the incidence of lower respiratory tract symptoms was not  
6 observed until concentrations exceeded a 24-h avg SO<sub>2</sub> of 22 ppb, though an increasing trend  
7 was observed at concentrations as low as 10 ppb (Harvard Six Cities Study, Schwartz et al.,  
8 1994). In the limited number of studies that examined potential confounding by copollutants  
9 through multipollutant models, the SO<sub>2</sub> effect was generally found to be robust after adjusting  
10 for PM and other copollutants. More details of the literature published since the last review are  
11 found in Annex Table F-1.

#### **3.1.4.1.2. Adults**

12 Compared to the number of studies conducted with children, fewer epidemiological studies  
13 were performed that examined the effect of ambient SO<sub>2</sub> exposure on respiratory symptoms in  
14 adults. Most of these studies focused on potentially susceptible populations, i.e., those with  
15 asthma or COPD. One of the larger studies was conducted by van der Zee et al. (2000) in 50- to  
16 70-year-old adults, with (n = 266) and without (n = 223) chronic respiratory symptoms in the  
17 Netherlands. In adults both with and without chronic respiratory symptoms, no consistent  
18 associations were observed between SO<sub>2</sub> levels and respiratory symptoms or medication use. A  
19 subgroup analysis of this cohort examining SO<sub>2</sub>-related respiratory symptoms in individuals with  
20 airway hyperresponsiveness and atopy (Boezen et al., 2005) is discussed in Section 3.1.4.4.

21 Studies by Desqueyroux et al. (2002b; 2002a) examined the association between air  
22 pollution and respiratory symptoms in other potentially susceptible populations, i.e., those with  
23 severe asthma (n = 60, mean age 55 years) and COPD (n = 39, mean age 67 years), in Paris,  
24 France. The mean 24-h avg SO<sub>2</sub> concentration was 3 ppb (range: 1, 10) in the summer and 7 ppb  
25 (range: 1, 31) in the winter. No associations were observed between SO<sub>2</sub> concentrations and the  
26 incidence of asthma attacks or episodes of symptom exacerbation in severe asthmatics or  
27 individuals with COPD. O<sub>3</sub> was found to have the strongest effect in these studies.

28 Several other European studies did observe an association between ambient SO<sub>2</sub>  
29 concentrations and respiratory symptoms in adults with asthma or chronic bronchitis (Higgins et

1 al., 1995; Neukirch et al., 1998; Peters et al., 1996; Taggart et al., 1996). Only one of these  
2 studies examined possible confounding of the association by copollutants. Higgins et al.  
3 examined the effect of summertime air pollutant exposure on respiratory symptoms in 62 adults  
4 with either asthma, COPD, or both. The max 24-h avg SO<sub>2</sub> level was 45 ppb. An association was  
5 observed between SO<sub>2</sub> and symptoms of wheeze, and it remained robust after adjustment for O<sub>3</sub>  
6 and NO<sub>2</sub>. The effects of PM were not examined in this study.

7 Results from the epidemiological studies examining the association between SO<sub>2</sub> and  
8 respiratory symptoms in adults are generally mixed, with some showing positive associations  
9 and others finding no relationship at current ambient levels. The overall epidemiological  
10 evidence that 24-h avg SO<sub>2</sub> exposures at or near ambient concentrations has an effect on adults is  
11 inconclusive. However, as discussed in Section 3.1.3.1, human clinical studies have observed an  
12 effect of peak exposures to SO<sub>2</sub> on respiratory symptoms, particularly among SO<sub>2</sub>-sensitive  
13 asthmatics, with 10 min exposures to SO<sub>2</sub> concentrations as low as 0.4-0.6 ppm under exercise  
14 conditions. These effects in clinical studies are at levels that have sometimes been measured in  
15 ambient air for similarly short-time durations.

### 3.1.4.2. Lung Function

16 The 1982 AQCD reported bronchoconstriction, indicated by increased pulmonary  
17 resistance, as the most sensitive indicator of lung function effects of acute SO<sub>2</sub> exposure, based  
18 on the observations of increased pulmonary resistance in guinea pigs that were acutely exposed  
19 to 0.16 ppm SO<sub>2</sub>. Since then, only a few new animal toxicological studies have measured lung  
20 function at or near ambient levels of SO<sub>2</sub>. These studies, and those using higher concentrations of  
21 SO<sub>2</sub>, are summarized in Annex Table E-4. Increased pulmonary resistance and decreased  
22 dynamic compliance were observed in conscious guinea pigs exposed to 1 ppm SO<sub>2</sub> for 1 h  
23 (Amdur et al., 1983). Effects were seen immediately after exposure and were not present 1 h  
24 post-exposure. No changes in tidal volume, minute volume or breathing frequency were found.  
25 These same investigators also exposed guinea pigs to 1 ppm SO<sub>2</sub> for 3 h/day for 6 days (Conner  
26 et al., 1985). No changes were observed in pulmonary function or respiratory parameters, i.e.,  
27 diffusing capacity for carbon monoxide, functional reserve capacity, vital capacity, total lung  
28 capacity, respiratory frequency, tidal volume, pulmonary resistance or pulmonary compliance. In  
29 another study, Barthelemy et al. (1988) demonstrated a 16% increase in airway resistance

1 following a 45-min exposure of anesthetized rabbits to 0.5 ppm SO<sub>2</sub> via an endotracheal tube.  
2 This latter exposure is more relevant to oronasal than nasal breathing.

### 3.1.4.2.1. Children

3 Most epidemiological studies discussed in the previous section on respiratory symptoms  
4 also examined lung function. In these studies self-administered PEF meters were primarily used  
5 to assess lung function. PEF follows a circadian rhythm, with the highest values found during the  
6 afternoon and lowest values during the night and early morning (Borsboom et al., 1999).  
7 Therefore, these studies generally analyze PEF data stratified by time of day. The  
8 epidemiological studies on lung function are summarized in Annex Table F-1.

9 Mortimer et al. (2002) examined 846 asthmatic children from eight U.S. urban areas in the  
10 NCICAS for changes in PEF related to air pollution. The mean 3-h avg SO<sub>2</sub> was 22 ppb across  
11 the eight cities during the study period of June through August, 1993. No associations were  
12 observed between SO<sub>2</sub> concentrations and morning or evening PEF. Of all the pollutants  
13 examined, including PM<sub>10</sub>, O<sub>3</sub>, and NO<sub>2</sub>, only O<sub>3</sub> was associated with changes in morning PEF.

14 In another U.S. study (Neas et al., 1995), 83 children from Uniontown, PA reported twice-  
15 daily PEF measurements during the summer of 1990. The mean daytime 12-h avg SO<sub>2</sub>  
16 concentration was 14.5 ppb (max 44.9). No associations were observed between daytime 12-h  
17 avg SO<sub>2</sub> concentrations and mean deviation in evening PEF, even after concentrations were  
18 weighted by the proportion of hours spent outdoors during the prior 12-h. Statistically significant  
19 associations were observed for O<sub>3</sub>, total sulfate particles, and particle-strong acidity.

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

26 Multipollutant analyses also were conducted in a study by Chen et al. (1999), which  
27 examined the effects of short-term exposure to air pollution on the pulmonary function of  
28 895 children, ages 8 to 13 years, in three communities in Taiwan. The daytime 1-h max SO<sub>2</sub> the  
29 day before spirometry ranged from 0 to 72.4 ppb. In a single-pollutant model, 1-h max SO<sub>2</sub>

1 concentration at a 2-day lag was significantly associated with FVC, -50.80 mL (95% CI: -97.06,  
2 -4.54), or a 2.6% decline, per 40 ppb 1-h max SO<sub>2</sub>. However, in multipollutant models, authors  
3 noted that only O<sub>3</sub> remained significantly associated with FVC and FEV<sub>1</sub>. Effect estimates for  
4 SO<sub>2</sub> in multipollutant models were not provided.

5 While additional studies have observed associations between ambient SO<sub>2</sub> concentrations  
6 and changes in lung function in children (Hoek and Brunekreef, 1993; Roemer et al., 1993;  
7 Peters et al., 1996; Segala et al., 1998; Timonen and Pekkanen, 1997), several other studies did  
8 not find a significant association between SO<sub>2</sub> and lung function parameters. In addition, in  
9 studies that did observe an association, the correlations between SO<sub>2</sub> and other pollutants,  
10 particularly PM indices, were high [for example,  $r = 0.8-0.9$  in Peters et al. (1996), making it  
11 difficult to separate the contributions of individual pollutants.

12 In conclusion, while some epidemiological studies observed a positive association between  
13 short-term SO<sub>2</sub> exposure and lung function in children, several others, including a large U.S.  
14 multicity study, did not observe such an association. The limited evaluation of potential  
15 confounding by copollutants also indicated mixed results. Overall, the evidence is insufficient to  
16 conclude that short-term exposure to ambient SO<sub>2</sub> has an independent effect on lung function in  
17 children.

#### **3.1.4.2.2. Adults**

18 Only a limited number of epidemiological studies have been conducted examining the  
19 association between ambient SO<sub>2</sub> concentrations and lung function in adults, as in the case of  
20 respiratory symptoms. In a cross-sectional survey, Xu et al. (1991) investigated the effects of  
21 indoor and outdoor air pollutants on the respiratory health of 1,140 adults (aged 40 to 69 years)  
22 living in residential, industrial, and suburban areas of Beijing, China. The annual mean  
23 concentrations of SO<sub>2</sub> in residential, industrial, and suburban areas from 1981 to 1985 were 49  
24 ppb, 22 ppb, and 7 ppb, respectively. Log-transformed SO<sub>2</sub> and TSP were significantly  
25 associated with reductions in FEV<sub>1</sub> and FVC. The authors cautioned that since SO<sub>2</sub> and TSP  
26 concentrations were strongly correlated, the effect of SO<sub>2</sub> could not be separated.

27 Van der Zee et al. (2000) observed an association between SO<sub>2</sub> and morning PEF in 50- to  
28 70-year-old adults ( $n = 138$ ) with chronic respiratory symptoms living in urban areas of the  
29 Netherlands. No associations were observed with evening PEF. The OR for a > 20% decrement

1 in PEF was 1.21 (95% CI: 0.76, 1.92) per 10 ppb increase in 24-h avg SO<sub>2</sub> with same-day  
2 exposure and 1.56 (95% CI: 1.02, 2.39) at a 1-day lag. No associations were observed for a  
3 > 10% decrement in PEF. The authors hypothesized that while SO<sub>2</sub> level did not have much  
4 effect on PEF in most subjects, a small subgroup of individuals experienced fairly large PEF  
5 decrements when SO<sub>2</sub> levels were high. No multipollutant analyses were conducted.

6 Higgins et al. (1995) examined the association between pulmonary function and air  
7 pollution in 75 adults with either asthma, COPD, or both. Exposure to SO<sub>2</sub> was associated with  
8 increased variation in PEF, but not with mean or minimum PEF. The SO<sub>2</sub> effects on PEF  
9 variation were robust to adjustment for O<sub>3</sub> and NO<sub>2</sub>. Effects of PM were not considered.  
10 Neukirch et al. (1998) also observed associations between lung function and SO<sub>2</sub> concentrations  
11 in a study of asthmatic adults in Paris, France; however, significant associations were found for  
12 all pollutants examined, including BS, PM<sub>13</sub>, and NO<sub>2</sub>. Other epidemiological studies observed  
13 only weak relationships between ambient SO<sub>2</sub> concentrations and lung function in adults (Peters  
14 et al., 1996; Taggart et al., 1996).

15 Evidence from human clinical studies clearly indicates that asthmatic individuals  
16 experience moderate or greater decrements in lung function, as well as increased respiratory  
17 symptoms, following peak exposure (5-10 min) to SO<sub>2</sub> (Balmes et al., 1987; Gong et al., 1995;  
18 Horstman et al., 1986; Linn et al., 1987; 1983) These effects were seen at peak concentrations as  
19 low as 0.4-0.6 ppm. However, in a human clinical study by Tunnicliffe et al. (2003) that  
20 evaluated the effect of 1-h exposures to 0.2 ppm SO<sub>2</sub> in resting healthy and asthmatic subjects,  
21 no significant changes were observed in lung function as measured by FEV<sub>1</sub>, FVC, and maximal  
22 midexpiratory flow (MMEF).

23 In summary, the epidemiological studies examining adults do not provide strong evidence  
24 for an association between short-term exposure to ambient SO<sub>2</sub> and lung function. While some  
25 studies did observe associations between SO<sub>2</sub> exposure and decrements in lung function  
26 parameters, the strong correlation between SO<sub>2</sub> and various copollutants in most studies, and the  
27 lack of evidence evaluating potential confounding by copollutants, limit interpretation of  
28 independent effects of SO<sub>2</sub> on lung function.

### 3.1.4.3. Airway Inflammation

1           The animal toxicological studies on airway inflammation are summarized in Annex Table  
2 E-1. In one study, guinea pigs were exposed to 1 ppm SO<sub>2</sub> for 3 h/day for 5 days and  
3 bronchoalveolar lavage was performed daily (Conner et al., 1985) No change in numbers of total  
4 cells or neutrophils was observed. However, in two models of allergic sensitization, SO<sub>2</sub>  
5 exposure increased airway inflammation. In one study (Park et al., 2001), guinea pigs were  
6 exposed to 0.1 ppm SO<sub>2</sub> for 5 h/day for 5 days and sensitized with 0.1% ovalbumin aerosols for  
7 45 min on days 3-5. One week later, animals were subjected to bronchial challenge with 1.0%  
8 ovalbumin and bronchoalveolar lavage and histopathologic examination were performed 24 h  
9 later. Results demonstrated increased numbers of eosinophils in lavage fluid, and an infiltration  
10 of inflammatory cells, bronchiolar epithelial cell damage and plugging of the airway lumen with  
11 mucus and cells in the bronchial tissues of animals treated with both SO<sub>2</sub> and ovalbumin, but not  
12 in animals treated with ovalbumin or SO<sub>2</sub> alone.

13           In a second study, rats which were sensitized and challenged with ovalbumin and exposed  
14 to 2 ppm SO<sub>2</sub> for 1 h/day for 7 days had an increased number of inflammatory cells in  
15 bronchoalveolar lavage fluid and an enhanced histopathological response compared with those  
16 treated with ovalbumin or SO<sub>2</sub> alone (Li et al., 2007a). Similar responses were noted for ICAM-  
17 1, a protein involved in regulating inflammation. Further experiments are required to determine  
18 whether near ambient SO<sub>2</sub> also enhance inflammatory responses in non-allergic and allergic rats.  
19 Taken together, these animal experiments suggest that near-ambient levels of SO<sub>2</sub> may play a  
20 role in exacerbating allergic responses.

21           In a human clinical study, Tunnicliffe et al. (2003) measured levels of exhaled NO (eNO)  
22 in asthmatic and healthy adult subjects, before and after 1-h exposure to 0.2 ppm SO<sub>2</sub> under  
23 resting conditions. While eNO concentrations were higher in the asthmatic than in healthy  
24 subjects, no significant difference was observed between pre- and postexposure in either group.

25           One epidemiological study by Adamkiewicz et al. (2004) examined eNO as a biological  
26 marker for inflammation in 29 older adults (median age 70.7 years) in Steubenville, OH. The  
27 mean 24-h avg SO<sub>2</sub> concentration was 12.5 ppb (IQR 11.5). The authors reported that, while  
28 significant and robust associations were observed between increased daily levels of fine PM  
29 (PM<sub>2.5</sub>) and increased eNO, no associations were observed with any of the other pollutants  
30 examined, including SO<sub>2</sub>, NO<sub>2</sub>, and O<sub>3</sub>.

1 Overall, the very limited human clinical and epidemiological evidence does not indicate  
2 that exposure to SO<sub>2</sub> at current ambient concentrations is associated with inflammation in the  
3 airway. However, toxicological studies suggest that repeated exposures to SO<sub>2</sub>, at concentrations  
4 as low as 0.1 ppm in guinea pigs, may exacerbate inflammatory responses in allergic animals.

#### **3.1.4.4. Airway Hyperresponsiveness and Allergy**

5 The toxicological studies describing SO<sub>2</sub>-induced effects on airway obstruction,  
6 hypersensitivity and/or allergy in guinea pigs and sheep are summarized in Annex Table E-3. In  
7 one study, Amdur et al. (1988) exposed guinea pigs for 1 h to 1 ppm SO<sub>2</sub> and measured airway  
8 responsiveness to acetylcholine 2 h later. No airway hyperresponsiveness (AHR) was observed.  
9 In a second study, Douglas et al., (1994) found no AHR following a histamine challenge 24 h  
10 after exposure of rabbits to 5 ppm SO<sub>2</sub> for 2 h. In a third study, exposure of sheep for 4 h to 5  
11 ppm SO<sub>2</sub> failed to result in AHR following carbachol (Gong et al., 2001). In a fourth study, a 5  
12 min exposure to 30 ppm but not to 10 ppm SO<sub>2</sub> resulted in AHR in horses challenged with  
13 methacholine (Lewis and Kirchner, 1984). Collectively, these results show that a single exposure  
14 to SO<sub>2</sub> at a concentration of 10 ppm or less failed to induce AHR following challenge in 4  
15 different animal models.

16 However, two other studies demonstrated increased airway responsiveness in guinea pigs  
17 exposed repeatedly to SO<sub>2</sub> and allergen. Riedel et al. (1988) studied the effect of SO<sub>2</sub> exposure  
18 on local bronchial sensitization to inhaled antigen. Guinea pigs were exposed by inhalation to  
19 0.1, 4.3 and 16.6 ppm SO<sub>2</sub> for 8 h/d for 5 days. During the last 3 days, SO<sub>2</sub> exposure was  
20 followed by exposure to nebulized ovalbumin for 45 min. Following bronchial provocation with  
21 inhaled ovalbumin (0.1%) one week later, airway obstruction was measured by whole body  
22 plethysmography. In addition, specific antibodies against ovalbumin were measured in serum  
23 and bronchoalveolar fluids. Results show significantly higher bronchial obstruction in animals  
24 exposed to SO<sub>2</sub> (at all concentration levels) with ovalbumin compared with animals exposed  
25 only to ovalbumin. In addition, significant increases in anti-ovalbumin IgG antibodies were  
26 detected in bronchoalveolar lavage fluid of animals exposed to 0.1, 4.3 and 16.6 ppm SO<sub>2</sub> and in  
27 serum from animals exposed to 4.3 and 16.6 ppm SO<sub>2</sub> compared with controls exposed only to  
28 ovalbumin. These results demonstrate that repeated exposure to SO<sub>2</sub> can enhance allergic  
29 sensitization in the guinea pig at a concentration as low as 0.1 ppm. In a second study, guinea

1 pigs were exposed to 0.1 ppm SO<sub>2</sub> for 5 h/day for 5 days and sensitized with 0.1% ovalbumin  
2 aerosols for 45 min on days 3 to 5 (Park et al., 2001). One week later, animals were subjected to  
3 bronchial challenge with 1.0% ovalbumin and lung function was evaluated 24 h later by whole  
4 body plethysmography. Results demonstrated a significant increase in enhanced pause (P<sub>enh</sub>), a  
5 measure of airway obstruction, in animals exposed to SO<sub>2</sub> with ovalbumin but not in animals  
6 treated with ovalbumin or SO<sub>2</sub> alone. These experiments also indicate that near ambient levels of  
7 SO<sub>2</sub> may play a role in exacerbating allergic responses in the guinea pig.

8 In a human clinical study evaluating SO<sub>2</sub>-induced AHR to an inhaled allergen (house dust  
9 mite), Devalia et al. (1994) found that neither SO<sub>2</sub> (0.2 ppm) nor NO<sub>2</sub> (0.4 ppm) enhanced  
10 sensitization to the allergen in asthmatic individuals. However, following concurrent exposure  
11 (6 h) to SO<sub>2</sub> and NO<sub>2</sub> while at rest, subjects did exhibit increased sensitivity to the inhaled  
12 allergen. In a subsequent study, Rusznak et al. (1996) confirmed these findings and observed that  
13 the combination of SO<sub>2</sub> and NO<sub>2</sub> enhanced sensitization to house dust mite antigen up to 48  
14 hours post-exposure.

15 A limited number of epidemiological studies also examined the association between SO<sub>2</sub>  
16 and AHR. Other studies considered individuals with AHR and atopy as a subgroup potentially  
17 susceptible to SO<sub>2</sub>-related health effects. These studies are summarized in Annex Table F-1.  
18 Søyseth et al. (1995) investigated the effect of short-term exposure to SO<sub>2</sub> and fluoride on the  
19 number of capillary blood eosinophils, and the prevalence of AHR in schoolchildren, ages 7 to  
20 13 years, (n = 620) from two regions in Norway, a valley containing an SO<sub>2</sub>-emitting aluminum  
21 smelter and a similar but nonindustrialized valley. The median 24-h avg SO<sub>2</sub> concentration was  
22 8 ppb (10th–90th percentile: 1, 33) in the exposed area and 1 ppb (10th–90th percentile: 0, 4) in  
23 the nonindustrialized valley. The mean number of eosinophils was significantly greater in  
24 children living near the aluminum smelter compared to the nonindustrialized area. However,  
25 within children in the exposed area, a negative concentration-response relationship was observed  
26 between mean eosinophils and previous-day 24-h avg SO<sub>2</sub>. The observed association between  
27 SO<sub>2</sub> and eosinophils was limited to atopic children. In children living in the exposed area, a  
28 statistically significant positive association was observed between prevalence of AHR and  
29 previous-day 24-h avg SO<sub>2</sub> concentrations. Similar associations were observed for fluoride. The  
30 authors hypothesized that recent exposure to SO<sub>2</sub> may have induced changes in the airway

1 leading to AHR, in addition to recruitment of eosinophils to the airways in atopic subjects.  
2 Exposure to PM was not assessed in this study.

3 A study by Taggart et al. (1996) examined the effect of summertime air pollution levels in  
4 northwestern England on AHR in nonsmoking, asthmatic subjects (n = 38) aged 18 to 80 years  
5 who were determined to be methacholine (MCh) reactors. Subjects were tested multiple times,  
6 for a total of 109 evaluable challenge tests, with a range of two to four tests per subject. The max  
7 24-h avg SO<sub>2</sub> concentration during the study period was 40 ppb. This study reported that  
8 24-h avg SO<sub>2</sub> levels were marginally associated with a decreased dose of MCh required for a  
9 20% drop in the postsaline FEV<sub>1</sub> (PD20FEV<sub>1</sub>).

10 Other epidemiological studies investigated the effect of exposure to SO<sub>2</sub> on children and  
11 adults with AHR and atopy. Boezen et al. (1999) examined 7- to 11-year-old children (n = 459)  
12 in the Netherlands and tested them for AHR and atopy. These children were a subset of a larger  
13 cohort examined in van der Zee et al. (1999). It was hypothesized that children with AHR, as  
14 measured using a MCh challenge, and atopy, indicated by raised serum total IgE (> 60 kU/L, the  
15 median value), may be susceptible to the effects of air pollution. One of the strengths of this  
16 study was the use of AHR and serum IgE concentration to indicate susceptibility; these  
17 measurements would be less prone to error than self-reported chronic respiratory symptoms. A  
18 total of 121 children were found to have AHR and relatively high serum total IgE; 67 had AHR  
19 and relatively low serum total IgE, 104 had no AHR but had a relatively high serum total IgE  
20 concentration, and 167 were found to have neither AHR nor relatively high serum total IgE. For  
21 the subset of children with relatively low serum total IgE with or without AHR, no associations  
22 were observed between SO<sub>2</sub> and any respiratory symptoms. However, for children with relatively  
23 high serum total IgE either with or without AHR, the prevalence of lower respiratory tract  
24 symptoms increased with increasing SO<sub>2</sub> concentrations. For children with AHR and relatively  
25 high serum total IgE, the OR for the prevalence of lower respiratory tract symptoms was 1.70  
26 (95% CI: 1.26, 2.29) with a 5-day moving average for every 10 ppb increase in SO<sub>2</sub>. For children  
27 without AHR but with relatively high serum total IgE, the OR was 1.82 (95% CI: 1.33, 2.50)  
28 with a 5-day moving average.

29 Boezen et al. (2005) conducted a similar study in 50- to 70-year-old adults (n = 327) in the  
30 Netherlands. The subgroup of individuals with elevated serum total IgE, both with (n = 48) and  
31 without (n = 112) AHR, were found to be more susceptible to air pollutants when contrasted with

1 those who did not have elevated serum total IgE (n = 167). Significant associations were ob-  
2 served between previous-day 24-h avg SO<sub>2</sub> concentrations and the prevalence of upper respira-  
3 tory tract symptoms in those with elevated serum total IgE. Stratified analyses by gender indi-  
4 cated that, among those with AHR and elevated IgE, only males (n = 25) were at a higher risk for  
5 respiratory symptoms. The OR for these males was 3.54 (95% CI: 1.79, 7.07) increase in  
6 24-h avg SO<sub>2</sub> for a 5-day moving average, compared with 1.05 (95% CI: 0.59, 1.91) for the  
7 females.

8 In summary, the animal toxicological evidence suggests that repeated exposures to SO<sub>2</sub> at  
9 concentrations as low as 0.1 ppm in guinea pigs can exacerbate airway responsiveness following  
10 allergic sensitization. Two new human clinical studies have demonstrated an increase in sensitiv-  
11 ity to an inhaled allergen in asthmatic subjects following exposures to a combination of 0.2-ppm  
12 SO<sub>2</sub> and 0.4-ppm NO<sub>2</sub>. These findings are consistent with the very limited epidemiological evi-  
13 dence that suggests that exposure to SO<sub>2</sub> may lead to AHR in atopic individuals.

#### **3.1.4.5. Respiratory Illness-Related Absences**

14 An additional concern has been the potential for SO<sub>2</sub> exposure to enhance susceptibility to,  
15 or the severity of illness resulting from respiratory infections, especially in children. School  
16 absenteeism is an indicator of morbidity in children caused by acute conditions. Respiratory  
17 conditions are the most frequent cause, particularly influenza and the common childhood infec-  
18 tious diseases. Park et al. (2002) examined the association between air pollution and school  
19 absenteeism in 1,264 first- to sixth-grade students attending school in Seoul, Korea. The study  
20 period extended from March 1996 to December 1999, with a mean 24-h avg SO<sub>2</sub> concentration  
21 of 9.19 ppb (SD 4.61). Note that analyses were performed using Poisson Generalized Additive  
22 Model (GAM) with default convergence criteria. Same-day SO<sub>2</sub> concentrations were positively  
23 associated with illness-related absences (16% excess risk [95% CI: 13, 22] per 10 ppb increase in  
24 24-h avg SO<sub>2</sub>), but inversely associated with non-illness-related absences (9% decrease [95%  
25 CI: 2, 15]). PM<sub>10</sub> and O<sub>3</sub> concentrations also were positively associated with illness-related ab-  
26 sences. In two-pollutant models containing SO<sub>2</sub> and either PM<sub>10</sub> or O<sub>3</sub>, the SO<sub>2</sub> estimates were  
27 robust.

28 A study by Pönka (1990) observed results that were consistent with those from the Park et  
29 al. (2002) study. Pönka found that absenteeism due to febrile illnesses among children in day

1 care centers and schools and in adults was significantly higher on days of higher SO<sub>2</sub> concentra-  
2 tions (> 8.1 ppb weekly mean of 1-h avg), compared to days of lower SO<sub>2</sub> concentrations. In  
3 addition, on days of higher SO<sub>2</sub> concentrations, the mean weekly number of cases of upper  
4 respiratory tract infections and tonsillitis reported from health centers increased. Temperature,  
5 but not NO<sub>2</sub>, was also found to be associated with febrile illnesses and respiratory tract infec-  
6 tions. From these epidemiological studies, it is unknown whether SO<sub>2</sub> increases susceptibility to  
7 infection or whether its presence exacerbates preexisting morbidity following infection.

8 Pino et al. (2004) examined the association between air pollution and respiratory illnesses  
9 in a cohort of 504 infants recruited at 4 months of age from primary health care units in  
10 southeastern Santiago, Chile. The infants were followed through the first year of life. The mean  
11 24-h avg SO<sub>2</sub> concentration was 11.6 ppb (5th–95th percentile: 3.0, 29.0). The most frequent  
12 diagnosis during follow-up was wheezing bronchitis. No associations were observed between  
13 current-day or previous-day SO<sub>2</sub> and wheezing bronchitis, but with a 7-day lag, a 21% (95% CI:  
14 8, 39) excess risk in wheezing bronchitis was observed per 10 ppb increase in 24-h avg SO<sub>2</sub>.  
15 However, it should be noted that stronger associations were observed with PM<sub>2.5</sub>, which was  
16 well-correlated with SO<sub>2</sub> (r = 0.73). These epidemiologic studies are summarized in Annex  
17 Table F-1.

18 To summarize, very few studies have examined the association between ambient SO<sub>2</sub>  
19 concentrations and absences from school or work as a result of respiratory illnesses. The limited  
20 evidence suggests a possible association between exposure to SO<sub>2</sub> concentrations and increased  
21 respiratory illnesses, particularly among young children; however, this association was also seen  
22 with PM, which was correlated with SO<sub>2</sub>.

#### **3.1.4.6. Emergency Department Visits and Hospitalizations for Respiratory Diseases**

23 Total respiratory causes for ED visits and hospital admissions typically include asthma,  
24 bronchitis and emphysema (collectively referred to as COPD), upper and lower respiratory tract  
25 infections, pneumonia, and other minor categories. Temporal associations between ED visits or  
26 hospital admissions for respiratory diseases and the ambient concentrations of SO<sub>2</sub> have been the  
27 subject of more than fifty peer-reviewed research publications since 1994. In addition to  
28 considerable statistical and analytical refinements, recent studies have examined responses of

1 morbidity in different age groups, the effect of seasons on ED and hospital usage, and  
2 multipollutant models to characterize the effects of copollutant mixtures. The epidemiological  
3 studies of ED visits and hospital admissions for respiratory causes are summarized in Annex  
4 Table F-2.

#### **3.1.4.6.1. All Respiratory Diseases**

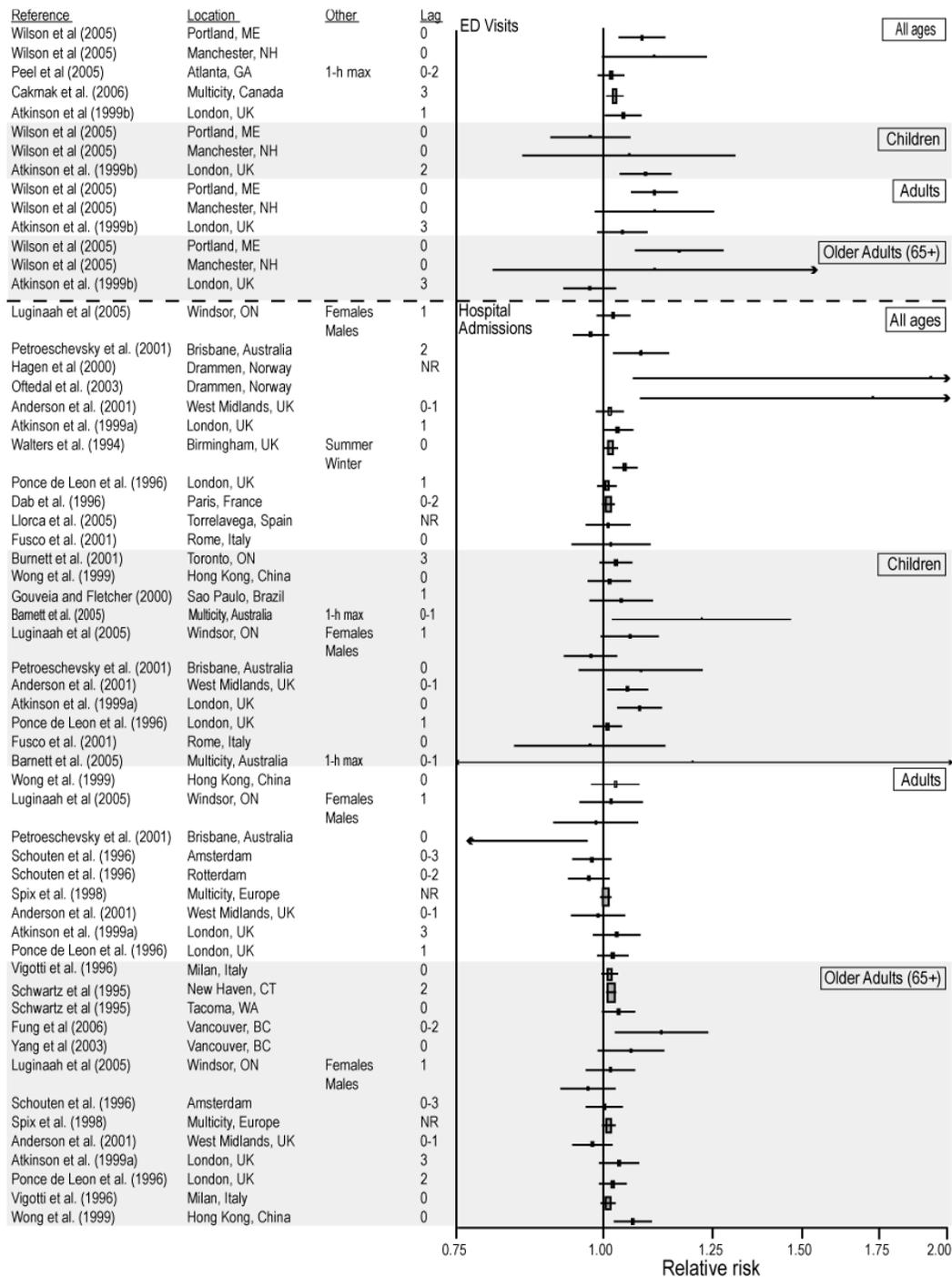
5 There are relatively few studies of ED visits for all respiratory causes in contrast to the  
6 quantity of studies that examine hospital admissions for all respiratory causes. Collectively,  
7 studies of ED visits and hospitalizations provide suggestive evidence of an association between  
8 ambient SO<sub>2</sub> levels and ED visits and hospitalizations for all respiratory causes. When analyses  
9 were restricted by age, the results among children (0-14 years) and older adults (65+ years) were  
10 mainly positive, though not all statistically significant. The studies that examined the association  
11 of these outcomes and SO<sub>2</sub> levels among adults (15-64 years) reported a mix of positive and  
12 negative results. When all age groups were combined, the results of ED and hospitalization  
13 studies were mainly positive; however, the excess risk estimates were generally smaller  
14 compared to the children and older adults groups. It is possible that the effects observed in the  
15 combined age groups were driven by increases in the very young or older adult subpopulations.  
16 The results from the hospitalization and ED studies, separated by analyses among all ages and  
17 age-specific analyses, are shown in Figure 3-6. Overall, the effect estimates in this figure range  
18 from a -5% to 20% excess risk in ED visits or hospital admissions for respiratory causes per 10  
19 ppb increase in 24-h avg SO<sub>2</sub>, with the large majority of studies suggesting an increase in risk.

20 Wilson et al. (2005) examined ED visits for all respiratory causes in Portland, ME from  
21 1996–2000 and in Manchester, NH from 1998–2000. The mean 1-h max SO<sub>2</sub> concentration in  
22 Portland was 11.1 ppb (SD 9.1), and was higher during the winter months (mean 17.1 ppb (SD  
23 12.0)) and lower in the summer (mean 9.1 ppb [SD 8.0]). In Manchester, the mean 1-h max SO<sub>2</sub>  
24 concentration was 16.5 ppb (SD 14.7 ppb), and was higher in the winter months (mean 25.7 ppb  
25 [SD 15.8]) as opposed to the summer months (mean 10.6 ppb [SD 15.1]). Though the authors  
26 reported the 1-h max SO<sub>2</sub> concentrations, they used the 24-h avg SO<sub>2</sub> concentrations in their  
27 analyses. When all ages were included in analyses, Wilson et al. found positive associations  
28 between ED visits and SO<sub>2</sub>, with an 8% (95% CI: 3.0, 11) and 11% (95% CI: 0.0, 20.0) excess

1 risk per 10 ppb increase in 24-h avg SO<sub>2</sub> at a 0-d lag in Portland, ME and Manchester, NH,  
2 respectively.

3 Peel et al. (2005) investigated ED visits for all respiratory causes in Atlanta, GA from  
4 1993–2000. This study included 484,830 ED visits. The mean 1-h max SO<sub>2</sub> concentration was  
5 16.5 ppb (SD 17.1). The researchers found a weak positive relationship between ED visits and  
6 SO<sub>2</sub>, though the increased risk was not statistically significant (1.6% [95% CI: -0.6, 3.8] excess  
7 risk per 40 ppb increase in 1-h max SO<sub>2</sub>). Tolbert et al. (2007) recently reanalyzed these data  
8 with four additional years of data and found similar results. An analysis by Dab et al. (1996)  
9 examined the association between SO<sub>2</sub> and hospital admissions for all respiratory causes in Paris,  
10 France, using both the 24-h avg and 1-h max. It should be noted that these researchers observed  
11 similar effect estimates for both exposure metrics; however, only the estimate using 24-h avg  
12 was statistically significant (1.1% [95% CI: 0.1, 2.0] excess risk per 10 ppb increase in 24-h avg  
13 SO<sub>2</sub> versus 1.9% [95% CI: -1.3, 5.0]) per 40 ppb increase in 1-h max SO<sub>2</sub>).

14 When analyses were stratified to include only children (0-14 years), evidence of a modest  
15 association between SO<sub>2</sub> and ED visits or hospitalizations for all respiratory causes in children  
16 was reported in several Australian (Barnett et al., 2005; Petroeshevsky et al., 2001) and  
17 European (Anderson et al., 2001; Atkinson et al., 1999a; 1999b) studies. Excess risks ranging  
18 from 3% to 22% per 10 ppb increase in 24-h avg SO<sub>2</sub> were reported by these studies. In a  
19 multicity study spanning Australia and New Zealand, Barnett et al. (2005) compared hospital  
20 admission data collected from 1998–2001 with ambient SO<sub>2</sub> concentrations, where the mean  
21 24-h avg SO<sub>2</sub> concentration ranged from 0.9 to 4.8 ppb. The authors found a 5% (95% CI: 1, 9)  
22 excess risk per 10 ppb increment in 24-h avg SO<sub>2</sub> among children (1-4 years) in these cities.  
23 However, some additional U.S. (Wilson et al., 2005), European (Fusco et al., 2001; Ponce de  
24 Leon et al., 1996), and Latin American (Braga et al., 1999; 2001) studies did not find statistically  
25 significant associations between ambient SO<sub>2</sub> concentrations and hospitalizations for all  
26 respiratory causes among children.



**Figure 3-6. Relative risks (95% CI) of SO<sub>2</sub>-associated emergency department visits and hospitalizations for all respiratory causes among all ages and separated by age group. Risk estimates are standardized per 10 ppb increase in 24-h avg SO<sub>2</sub> concentrations or 40 ppb increase in 1-h max SO<sub>2</sub>. The size of the box of the central estimate represents the relative weight of that estimate based on the width of the 95% CI.**

1 Wilson et al. (2005) found a positive association between ED visits and SO<sub>2</sub>, with a 16%  
2 (95% CI: 8.0, 25.0) excess risk per 10 ppb increase in 24-h avg SO<sub>2</sub> at a 0-d lag, and no  
3 association in Manchester, NH when only older adults (65+ years) were considered. In another  
4 two-city study, Schwartz (1995) compared 13,740 hospital admission in New Haven, CT and  
5 Tacoma, WA from 1988–1990 with ambient SO<sub>2</sub> concentrations. The mean 24-h avg SO<sub>2</sub>  
6 concentration was 29.8 ppb (90<sup>th</sup> percentile: 159) in New Haven and 16.8 ppb (90<sup>th</sup> percentile:  
7 74) in Tacoma. Schwartz found positive associations between hospitalizations and SO<sub>2</sub>, with a  
8 2% (95% CI: 1.0, 3.0) excess risk at a 2-d lag in New Haven and 3% (95% CI: 1.0, 6.0) excess  
9 risk at a 0-d lag in Tacoma per 10 ppb increase in 24-h avg SO<sub>2</sub>. In two-pollutant models, the  
10 SO<sub>2</sub> effect estimate from New Haven, but not Tacoma, was found to be robust to adjustment for  
11 PM<sub>10</sub>. Here, the term robust is used to indicate that there was little change in the magnitude of  
12 the central estimate, though statistical significance may have been lost. In Vancouver, BC, both  
13 Fung et al. (2006a) and Yang et al. (2003) also found positive associations between  
14 hospitalizations and SO<sub>2</sub>. In a multipollutant model including coefficient of haze (CoH), NO<sub>2</sub>,  
15 O<sub>3</sub>, and CO, the SO<sub>2</sub> effect estimate diminished slightly (Jaffe et al., 2003).

16 Additional evidence of a positive association between ED visits or hospitalizations for all  
17 respiratory causes among older adults and SO<sub>2</sub> comes from several European (Spix et al., 1998;  
18 Sunyer et al., 2003; Vigotti et al., 1996) and Australian (Petroeschevsky et al., 2001) studies.  
19 Excess risks ranging from 1% to 12% per 10 ppb increase in 24-h avg SO<sub>2</sub> were reported by  
20 these studies. Petroeschevsky et al. (2001) examined 33,710 hospital admissions in Brisbane,  
21 Australia from 1987–1994. The mean 24-h avg SO<sub>2</sub> concentration was 4.1 ppb, and was highest  
22 in the winter months (4.8 ppb) and lowest in the spring (3.7 ppb). Petroeschevsky et al. found a  
23 12% (95% CI: 2.0, 23.0) excess risk per 10 ppb increase in 24-h SO<sub>2</sub> at 0-d lag. Additional  
24 European studies did not find statistically significant associations between ambient SO<sub>2</sub>  
25 concentrations and hospitalizations for all respiratory causes among older adults (Anderson et al.,  
26 2001; Atkinson et al., 1999b; Ponce de Leon et al., 1996; Schouten et al., 1996).

27 In summary, many studies show a small, positive, though not statistically significant  
28 association between ambient SO<sub>2</sub> concentrations and ED visits and hospitalizations, particularly  
29 among children and older adults (65+ years). The positive evidence from these studies is  
30 supported by the results of panel, human clinical, and limited toxicological studies that also  
31 found a positive relationship between SO<sub>2</sub> levels and adverse respiratory outcomes.

### 3.1.4.6.2. Asthma

1 Studies of ED visits and hospitalizations provide suggestive evidence of an association  
2 between ambient SO<sub>2</sub> levels and ED visits and hospitalizations for asthma. The results from the  
3 hospitalization and ED studies, separated by analyses among all ages and age-specific analyses,  
4 are shown in Figure 3-7. Overall, central effect estimates in the figure range from a -10% to 40%  
5 excess risk in ED visits and hospitalizations for asthma per 10 ppb increase in 24-h avg SO<sub>2</sub>.  
6 Most of the effect estimates are positive (suggesting an association with SO<sub>2</sub> and ED visits and  
7 hospitalizations for asthma), though few are statistically significant at the 95% confidence level.  
8 When all ages were included in the analyses, Wilson et al. (2005) found a positive association  
9 between ED visits and SO<sub>2</sub>, with a 10% (95% CI: 2.0, 20.0) excess risk per 10 ppb increase in  
10 24-h avg SO<sub>2</sub> at a 0-d lag in Portland, ME and a positive, though not statistically significant  
11 association in Manchester, NH. Ito et al. (2003) found a 36% (95% CI: 1.23, 1.51) excess risk in  
12 asthma ED visits per 10 ppb increase in 24-h avg SO<sub>2</sub>, though this association was diminished  
13 once NO<sub>2</sub> was included in the model. A study conducted in (NY Dept of Health, 2006) found a  
14 11% (95% CI: 6, 17) excess risk in asthma hospital admissions per 10 ppb increase in 24-h avg  
15 SO<sub>2</sub> for Bronx residents, but a null association for the residents of Manhattan. A study conducted  
16 in Atlanta (Peel et al., 2005) found a null relationship between asthma ED visits and 1-h max  
17 SO<sub>2</sub>.

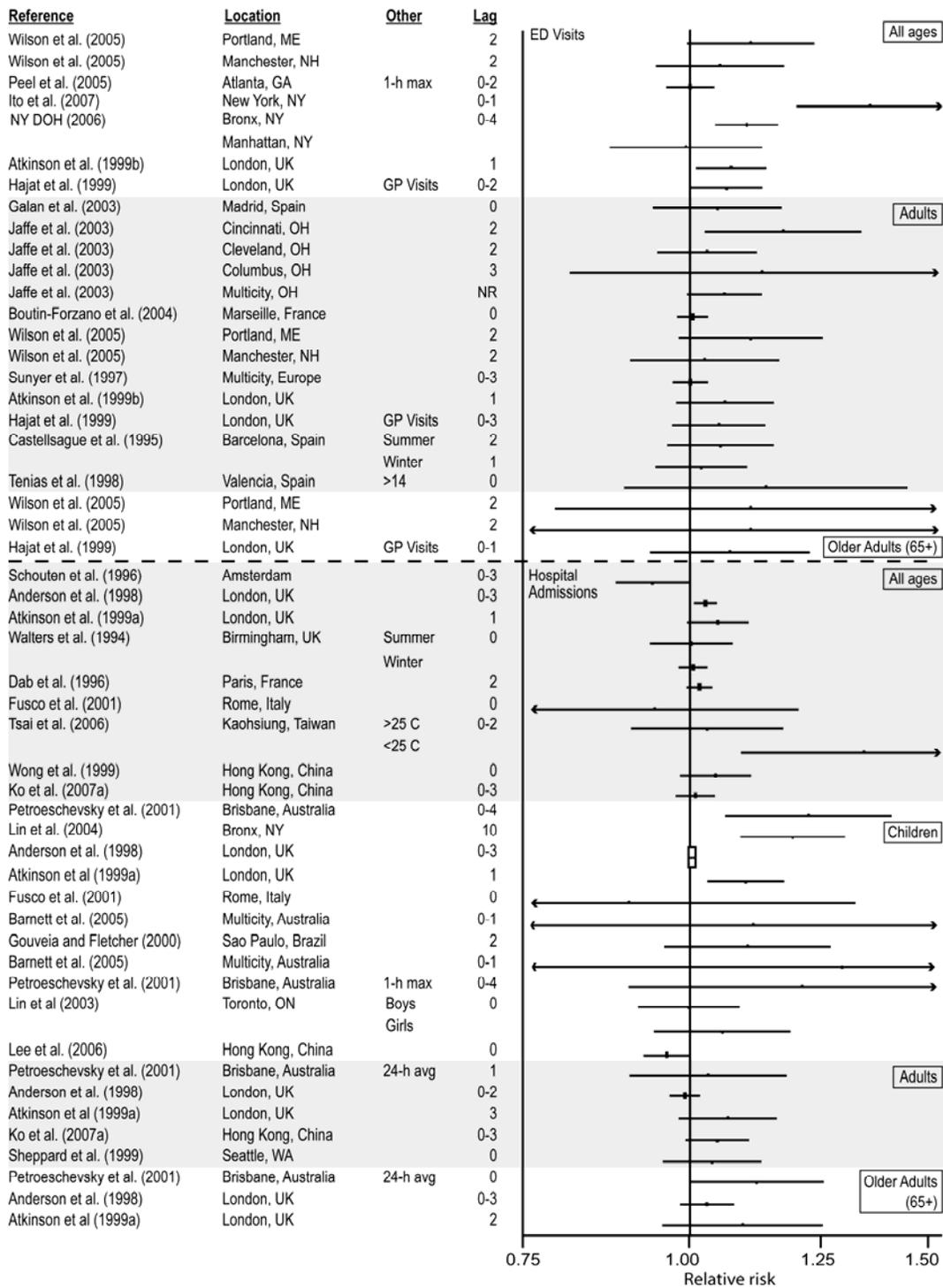
18 A study by Jaffe et al. (2003) examined the association between SO<sub>2</sub> and ED visits for  
19 asthma in three cities in Ohio – Cincinnati, Cleveland, and Columbus – in asthmatics aged 5 to  
20 34 years. The mean 24-h avg SO<sub>2</sub> concentrations were 14 ppb (range: 1–50) in Cincinnati,  
21 15 ppb (range: 1–64) in Cleveland, and 4 ppb (range: 0–22) in Columbus. A positive association  
22 was observed in the multicity analysis, with a 6.1% (95% CI: 0.5, 11.5) excess risk in asthma  
23 visits observed per 10 ppb increase in 24-h avg SO<sub>2</sub>. In the city-stratified analyses, significant  
24 associations were only observed for Cincinnati (17.0% [95% CI: 4.6, 30.8]).

25 When analyses were stratified to include children (0-14 years) only, Wilson et al. (2005)  
26 found positive, but not statistically significant associations between ED visits and SO<sub>2</sub> in  
27 Portland, ME or Manchester, NH. Similarly, Lin et al. (2005) observed a weak positive  
28 association between hospitalizations for asthma and SO<sub>2</sub> among girls, and a null association for  
29 boys (Toronto, ON; mean 24-h avg SO<sub>2</sub> of 5.36 ppb [SD 5.90]). Stronger evidence comes from a  
30 study of childhood asthma hospitalizations conducted in Bronx County, New York (Lin et al.,

1 2003b). In this study, the authors conducted a case-control study of children aged 0-14 years and  
2 examined the association of daily ambient SO<sub>2</sub> concentrations (categorized into quartiles of both  
3 average and max levels) and cases admitted to the hospital for asthma or controls who were  
4 admitted for reasons other than asthma. The mean 24-h avg SO<sub>2</sub> was below 17 ppb for both cases  
5 and controls across all lag days examined. The authors found that cases were exposed to higher  
6 24-h avg SO<sub>2</sub> than controls. When the highest exposure quartile was compared with the lowest,  
7 the ORs were strongest when a 3-day lag was employed (OR 2.16 [95% CI: 1.77, 2.65] for 24-h  
8 avg SO<sub>2</sub>; OR 1.86 [95% CI: 1.52, 2.27] for 1-h max SO<sub>2</sub>). The results were positive and  
9 statistically significant for all lag days examined. These results suggest a consistent positive  
10 association between SO<sub>2</sub> exposure and hospitalizations for childhood asthma.

11 Additional evidence of a positive association between ED visits or hospitalizations for  
12 asthma and SO<sub>2</sub> comes from several European (Anderson et al., 1998; Atkinson et al., 1999a;  
13 Hajat et al., 1999; Sunyer et al., 1997; 2003; Thompson et al., 2001) and Asian (Lee et al., 2002)  
14 studies. Excess risks ranging from 2% to 10% per 10 ppb increase in 24-h avg SO<sub>2</sub> were reported  
15 by these studies. Several of these studies observed that the SO<sub>2</sub> effect estimate was robust to  
16 adjustment for BS and NO<sub>2</sub> (Anderson et al., 1998; Sunyer et al., 1997), but one study observed  
17 that the SO<sub>2</sub> effect diminished considerably with adjustment for PM<sub>10</sub> and benzene (Thompson et  
18 al., 2001). Atkinson et al. (1999b) compared 165,032 hospital admissions in London from 1992–  
19 1994 with ambient SO<sub>2</sub> levels (mean 24-h avg of 7.2 ppb [SD 4.7]). They found a 10% (95% CI:  
20 4.0, 16.0) excess risk per 10 ppb increase in 24-h avg SO<sub>2</sub> at 1-d lag. Additional European (Fusco  
21 et al., 2001), Australian (Barnett et al., 2005; Petroschevsky et al., 2001), Asian (Ko et al., 2007;  
22 Lee et al., 2006) and Latin American (Gouveia and Fletcher, 2000) studies did not find  
23 statistically significant associations between ambient SO<sub>2</sub> concentrations and hospitalizations for  
24 all respiratory causes among children.

25 In summary, small, positive associations were observed between ambient SO<sub>2</sub>  
26 concentrations and ED visits and asthma hospitalizations. Evidence from these studies is further  
27 supported by the results of panel and human clinical studies that have also found SO<sub>2</sub>-related  
28 respiratory effects in asthmatics.



**Figure 3-7. Relative risks (95% CI) of SO<sub>2</sub>-associated emergency department visits and hospitalizations for asthma among all ages and age-specific groups. Risk estimates are standardized per 10 ppb increase in 24-h avg SO<sub>2</sub> concentrations or 40 ppb increase in 1-h max SO<sub>2</sub>. The size of the box of the central estimate represents the relative weight of that estimate based on the width of the 95% CI.**

### 3.1.4.6.3. Chronic Obstructive Pulmonary Disease

1           There are relatively few studies that have examined the association of ED visits and  
2 hospitalizations for COPD and ambient SO<sub>2</sub> levels, and very little evidence that an association  
3 exists. A recent study (Ko et al., 2007) found a significant association between hospital  
4 admissions for COPD (not including asthma) in Hong Kong (1.8% [95% CI: 0.3, 3.8]) excess  
5 risk per 10 ppb increase in 24-h avg SO<sub>2</sub> concentration). Three additional studies reported  
6 positive and statistically significant results for COPD and SO<sub>2</sub>; all three studies included asthma  
7 in their diagnostic definition of COPD (Anderson et al., 2001; Moolgavkar, 2003; Sunyer et al.,  
8 2003). Anderson et al. (2001) reported a 12% (95% CI: 5.0, 20.0) excess risk per 10 ppb increase  
9 in 24-h avg SO<sub>2</sub> among children, while Moolgavkar (2003) and Sunyer et al. (2003) found 5%  
10 and 2% excess risks per 10 ppb increase in 24-h avg SO<sub>2</sub> among older adults populations,  
11 respectively. Other studies examining COPD did not find statistically significant results  
12 (Atkinson et al., 1999b; Burnett et al., 1999; Michaud et al., 2004).

13           Overall, this limited and inconsistent evidence does not support a relationship between ED  
14 visits and hospitalizations for COPD and ambient SO<sub>2</sub> levels.

### 3.1.4.6.4. Respiratory Diseases Other than Asthma or COPD

15           Studies of ED visits or hospital admissions for other respiratory diseases looked at several  
16 other specific outcomes. There are limited studies with mixed results for upper respiratory tract  
17 infections (Burnett et al., 1999; Hajat et al., 2002; Lin et al., 2005; Peel et al., 2005), pneumonia  
18 (Barnett et al., 2005; Moolgavkar et al., 1997; Peel et al., 2005), bronchitis (Barnett et al., 2005;  
19 Michaud et al., 2004), and allergic rhinitis (Hajat et al., 1999; Villeneuve et al., 2006). The  
20 limited evidence is suggestive of an association between SO<sub>2</sub> levels and ED visits for lower  
21 respiratory tract diseases (Atkinson et al., 1999b; Farhat et al., 2005; Hajat et al., 1999; Lin et al.,  
22 1999; Martins et al., 2002). All of the studies that characterized this relationship found a positive  
23 and statistically significant excess risk associated with increases in SO<sub>2</sub>. Excess risks ranging  
24 from 3% to 33% per 10 ppb increase in 24-h avg SO<sub>2</sub> were reported by these studies.

25           In summary, few studies provide results with mixed respiratory health outcomes other than  
26 asthma and COPD. This makes it difficult to draw conclusions about the effects of SO<sub>2</sub> on these  
27 diseases. Limited evidence does exist to support a suggestive association between ambient SO<sub>2</sub>  
28 levels and ED visits for lower respiratory tract diseases.

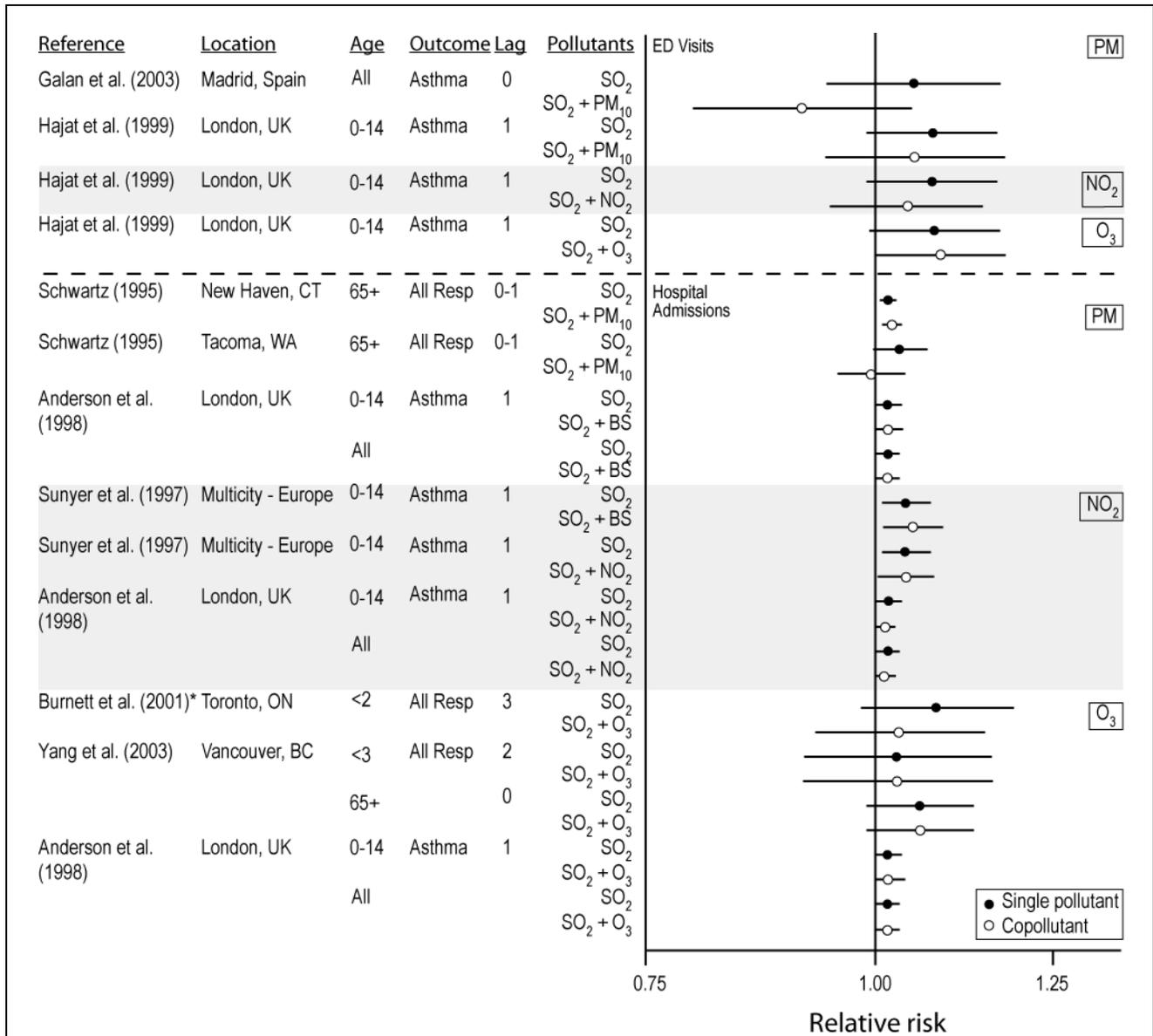
### 3.1.4.6.5. Summary of Evidence on Emergency Department Visits and Hospitalizations for Respiratory Diseases

1 Small, positive associations exist between ambient SO<sub>2</sub> concentrations and ED visits and  
2 hospitalizations for all respiratory causes, particularly among children and older adults (65+  
3 years), and for asthma, though not always statistically significant. The SO<sub>2</sub>-related changes in  
4 ED visits or hospital admissions for respiratory causes ranged from -5% to 20% excess risk, with  
5 the large majority of studies suggesting an increase in risk. No association was observed between  
6 SO<sub>2</sub> levels and ED visits and hospitalizations for COPD. Given the limited number of studies  
7 with mixed results, it is difficult to draw conclusions about the effect of SO<sub>2</sub> on other respiratory  
8 diseases, though studies of lower respiratory tract diseases are somewhat suggestive of an  
9 association.

10 Multipollutant regression analyses indicate that SO<sub>2</sub> risk estimates, in general, are not  
11 sensitive to the inclusion of copollutants, including O<sub>3</sub> (Anderson et al., 1998; Hajat et al., 1999;  
12 Yang et al., 2003; 2005), PM (Hagen et al., 2000; Lin et al., 2003; 2005; Schwartz, 1995) CO  
13 (Farhat et al., 2005) and NO<sub>2</sub> (Anderson et al., 1998; Lin et al., 2004; Sunyer et al., 1997). Figure  
14 3-8 presents SO<sub>2</sub> excess risk estimates with and without adjustment for various copollutants. PM  
15 and NO<sub>2</sub> are the main foci, since these pollutants have been found to be highly-correlated with  
16 SO<sub>2</sub> in epidemiological studies and have known respiratory health effects. Although the studies  
17 showed that copollutant adjustment had varying degrees of influence on the SO<sub>2</sub> effect estimates,  
18 the effect of SO<sub>2</sub> on respiratory health outcomes appears to be generally robust and independent  
19 of the effects of ambient particles or other gaseous copollutants.

20 The results of several studies (Anderson et al., 1998; Hajat et al., 1999; Schouten et al.,  
21 1996; Spix et al., 1998; Wong et al., 1999) have demonstrated a greater increase in ED visits and  
22 hospitalizations for respiratory illnesses during the summer months, despite the fact that the  
23 average concentrations for SO<sub>2</sub> in some of areas studied were greatest in winter. In contrast,  
24 some studies found the associations between ED visits and hospital admissions and respiratory  
25 disease with similar increases in SO<sub>2</sub> to be greater in winter than summer (Vigotti et al., 1996;  
26 Walters et al., 1994). Other studies were unable to discern a seasonal difference in ED visits and  
27 hospitalizations for respiratory causes (Castellsague et al., 1995; Tenias et al., 1998; Wong et al.,  
28 2002). These effects were not consistent across age groups. Warmer months were more likely to  
29 show evidence of an association with adverse respiratory outcomes in children, while older

- 1 adults appeared more likely to be affected during the cooler months. These seasonal associations
- 2 remain somewhat uncertain and require additional investigation.



**Figure 3-8. Relative risks (95% CI) of SO<sub>2</sub>-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 avg SO<sub>2</sub> concentrations or 40 ppb increase in 1-h max SO<sub>2</sub>. In Burnett et al. (2001), analyses were performed using default convergence criteria for Poisson GAM with a nonparametric LOESS prefilter applied to air pollution and hospitalization data.**

1 In conclusion, a large number of epidemiologic studies provide evidence of an association  
2 between ambient SO<sub>2</sub> concentrations and ED visits and hospitalizations for all respiratory causes,  
3 in particular among children and older adults (65+ years), and for asthma. The findings are  
4 generally robust when additional copollutants are included in the model. These associations are  
5 supported by panel studies that observed SO<sub>2</sub>-related increases in asthma and other respiratory  
6 symptoms in children, and human clinical and animal toxicological studies that found a positive  
7 relationship between SO<sub>2</sub> exposure and various respiratory outcomes.

#### **3.1.4.7. Summary of Evidence on the Effect of Short-Term (≥ 1 h) Exposure on Respiratory Health**

8 Numerous epidemiological studies have observed associations between short-term (≥ 1-h,  
9 generally 24-h avg) exposure to SO<sub>2</sub> and respiratory health effects, ranging from respiratory  
10 symptoms to ED visits and hospital admissions for respiratory causes. The associations between  
11 ambient SO<sub>2</sub> concentrations and several respiratory outcomes were generally consistent, with the  
12 large majority of studies showing positive associations, and multicity studies, as well as several  
13 single-city studies, indicating statistically significant findings. The respiratory effects related to  
14 short-term exposure to SO<sub>2</sub> found in animal toxicological studies, and to a more limited extent  
15 the human clinical studies, provide coherence and biological plausibility for the observed  
16 epidemiological associations. The causal effects of peak exposure to SO<sub>2</sub> on respiratory health  
17 found in the human clinical studies (see Section 3.1.3.5) provide further evidence of biological  
18 plausibility for the effects associated with short-term exposure to SO<sub>2</sub>.

19 Two recent multicity studies (Mortimer et al., 2002; Schildcrout et al., 2006) and several  
20 other studies (Delfino et al., 2003; Neas et al., 1995; van der Zee et al., 1999) have found an  
21 association between short-term ambient SO<sub>2</sub> concentrations and respiratory symptoms in  
22 children. In the limited number of studies that assessed potential confounding by copollutants  
23 using multipollutant models, the SO<sub>2</sub> effect on respiratory symptoms was generally found to be  
24 robust to adjustment for copollutants. These findings provide supportive evidence for an  
25 association between short-term exposure to ambient SO<sub>2</sub> exposure and respiratory symptoms in  
26 children, particularly those with asthma. Several recent studies (Desqueyroux et al., 2002a;  
27 2002b; van der Zee et al., 2000) found no association between ambient SO<sub>2</sub> levels and  
28 respiratory symptoms in adults, though there was limited epidemiological evidence which

1 suggested that atopic adults as well as children may be at increased risk for SO<sub>2</sub>-induced  
2 respiratory symptoms (Boezen et al., 1999; 2005).

3 Animal toxicological studies in guinea pigs showed changes in lung function immediately  
4 following 1 ppm SO<sub>2</sub> exposure (Amdur et al., 1983). Guinea pigs, as a species, are typically more  
5 sensitive to air pollution than other laboratory animals and, thus, may provide a better model for  
6 characterizing the effects of air pollutants on lung function. Epidemiological studies do not  
7 provide strong evidence of an association between short-term ambient SO<sub>2</sub> exposure and lung  
8 function in either children (Mortimer et al., 2002; Roemer et al., 1998) or adults (e.g., Peters et  
9 al., 1996; Taggart et al., 1996). Several other studies reported positive results; however, the  
10 generally mixed findings, as well as the relative lack of evidence available to evaluate potential  
11 confounding by copollutants, limits the causal interpretation of ambient SO<sub>2</sub> on lung function.

12 Only one epidemiological study (Adamkiewicz et al., 2004) evaluated inflammation, as  
13 indexed by eNO, and found no association with SO<sub>2</sub> exposure. Animal toxicological studies  
14 found that repeated exposure to near ambient levels of SO<sub>2</sub> leads to increased airway  
15 inflammation in two models involving animals which were sensitized to an antigen (Park et al.,  
16 2001; Li et al., 2007). Studies of other ambient pollutants indicate that influx of macrophages  
17 and other inflammatory cells, with the related release of inflammatory cytokines, is a common  
18 response to — and may further contribute to — injury.

19 Effects of short-term exposure to SO<sub>2</sub> on AHR have been observed. In two animal  
20 toxicological studies, repeated exposure to 0.1 ppm SO<sub>2</sub> led to AHR in guinea pigs sensitized to  
21 an antigen (Riedel et al., 1988; Park et al., 2001). Human clinical studies by Devalia et al. (1994)  
22 and Rusznak et al. (1996) demonstrated increased sensitivity to an inhaled allergen in asthmatic  
23 subjects following exposure to a combination of SO<sub>2</sub> (0.2 ppm) and NO<sub>2</sub> (0.4 ppm). This effect  
24 was not observed following exposure to either SO<sub>2</sub> or NO<sub>2</sub> alone. These findings of increased  
25 pulmonary resistance are in concordance with the limited epidemiological findings of  
26 SO<sub>2</sub>-induced AHR (Taggart et al., 1996).

27 Epidemiological studies provide suggestive evidence for an association between ambient  
28 SO<sub>2</sub> levels and ED visits and hospitalizations for all respiratory diseases in two susceptible  
29 populations: children (Dab et al., 1996; Petroschevsky et al., 2001; Walters et al., 1994) and  
30 older adults (65+ years) (Fung et al., 2006; Schwartz, 1995; Spix et al., 1998; Wong et al., 1999).  
31 Evidence for an association between ambient SO<sub>2</sub> levels and these outcomes in adults was less

1 consistent. A modest association between ambient SO<sub>2</sub> and ED visits and hospitalizations for  
2 asthma was also suggested. SO<sub>2</sub> effect estimates were generally robust to the inclusion of  
3 copollutants, including PM, O<sub>3</sub>, CO and NO<sub>2</sub>, indicating that the observed effects of SO<sub>2</sub> on  
4 respiratory endpoints is independent of the effects of other ambient air pollutants.

### 3.1.5. Mixtures and Interactive Effects

#### 3.1.5.1. Evidence from Human Clinical Studies

5 The interaction of SO<sub>2</sub> with other common air pollutants or the sequential exposure of SO<sub>2</sub>  
6 after prior exposure to another pollutant can potentially modify SO<sub>2</sub>-induced respiratory effects.  
7 However, only a few human clinical studies have looked at the interactive effects of coexisting  
8 ambient air pollutants. In a human clinical study designed to simulate an ambient “acid summer  
9 haze,” Linn et al. (1997) exposed healthy and asthmatic children (9–12 years of age) for 4 h with  
10 intermittent exercise to a mixture of SO<sub>2</sub> (0.1 ppm), H<sub>2</sub>SO<sub>4</sub> (100 µg/m<sup>3</sup>), and O<sub>3</sub> (0.1 ppm).  
11 Compared with exposure to filtered air, exposure to the air pollution mixture did not result in  
12 significant changes in lung function or respiratory symptoms. These findings are in agreement  
13 with a series of similar studies conducted by Kleinman et al. (1981; 1984; 1985).

14 In a human clinical study of asthmatic adolescents (12- to 16-years-old), Koenig et al.  
15 (1983) evaluated changes in FEV<sub>1</sub> following a 10-min exposure during moderate exercise to  
16 1-mg/m<sup>3</sup> NaCl alone and in combination with 0.5 and 1.0 ppm SO<sub>2</sub>. Significant decreases of 15  
17 and 23% were reported in FEV<sub>1</sub> following exposure to 1 mg/m<sup>3</sup> NaCl in combination with 0.5-  
18 and 1.0-ppm SO<sub>2</sub>, respectively. No significant changes in FEV<sub>1</sub> were observed between pre- and  
19 post-exposure to 1-mg/m<sup>3</sup> NaCl without SO<sub>2</sub>. The effect observed in this study may be the result  
20 of the presence of hygroscopic particles that can carry SO<sub>2</sub> deeper into the lung.

21 Koenig et al. (1990) also examined the effect of 15-min exposures to 0.1 ppm SO<sub>2</sub> in  
22 adolescent asthmatics engaged in moderate levels of exercise. Immediately preceding this  
23 exposure, subjects were exposed for 45 min to 0.12 ppm O<sub>3</sub> during intermittent moderate  
24 exercise. Subjects also underwent two additional exposure sequences with the same exercise  
25 regimen: 15-min exposure to 0.1 ppm SO<sub>2</sub> following a 45-min exposure to clean air, and 15-min  
26 exposure to 0.12 ppm O<sub>3</sub> following a 45-min exposure to 0.12 ppm O<sub>3</sub>. The authors found that  
27 the change in FEV<sub>1</sub> compared to baseline was significantly different following the O<sub>3</sub>-SO<sub>2</sub>

1 exposure (8% decrease) when compared to the change following the air-SO<sub>2</sub> or O<sub>3</sub>-O<sub>3</sub> exposures  
2 (decreases of 3 and 2%, respectively). In a more recent study, Trenga et al. (2001) reported that  
3 among adult asthmatics, exposure to O<sub>3</sub> (0.12 ppm for 45 min) resulted in a slight increase in  
4 bronchial responsiveness to SO<sub>2</sub> at a concentration of 0.25 ppm (6.5% decrease in FEV<sub>1</sub> with  
5 pre-exposure to O<sub>3</sub>, compared with a 3.4% decrease in FEV<sub>1</sub> with pre-exposure to filtered air).  
6 Hazucha and Bates (1975) demonstrated a synergistic effect of concurrent exposure to SO<sub>2</sub>  
7 (0.37 ppm) and O<sub>3</sub> (0.37 ppm) on lung function in healthy asthmatics; however, no such effect  
8 was observed in a similar study conducted by Bedi et al. (1979).

9 Jörres and Magnussen (1990) and Rubinstein et al. (1990) investigated the effects of a  
10 prior NO<sub>2</sub> exposure on SO<sub>2</sub>-induced bronchoconstriction in asthmatic adults. While Jörres and  
11 Magnussen suggested that prior exposure to NO<sub>2</sub> increased the responsiveness to SO<sub>2</sub>,  
12 Rubinstein et al. did not find that NO<sub>2</sub> exacerbated the effects of SO<sub>2</sub>. Linn et al. (1980) reported  
13 no difference in lung function or respiratory symptoms among a group of exercising asthmatics  
14 exposed to both clean air and a combination of NO<sub>2</sub> (0.5 ppm) and SO<sub>2</sub> (0.3 ppm).

15 In summary, although findings from some human clinical studies suggest that respiratory  
16 effects of exposure to SO<sub>2</sub> may be enhanced when preceded by, or occurring concomitant with  
17 exposure to other air pollutants, this evidence is quite limited and inconsistent.

### **3.1.5.2. Evidence from Animal Toxicological Studies**

18 As discussed earlier, SO<sub>2</sub> is a component of complex air pollution mixtures that vary  
19 geographically and temporally (e.g., by hour, week, and season). Depending on atmospheric  
20 conditions, SO<sub>2</sub> can be transformed to secondary sulfate particles and acid aerosols (H<sub>2</sub>SO<sub>4</sub>) and  
21 can adsorb onto particulate matter. Since SO<sub>2</sub>, H<sub>2</sub>SO<sub>4</sub> and PM share a common source—fossil  
22 fuels—health effects of fossil-fuel derived air pollution mixtures may be determined by  
23 interactions among individual components. Although epidemiological studies provide  
24 information on real-world exposure, it is difficult to evaluate causative factors and quantitative  
25 relationships from such studies. Animal studies are therefore useful in evaluating health effects  
26 of mixtures. The studies discussed below demonstrate important interactions between SO<sub>2</sub> and  
27 other air pollution components.

28 An informative study of complex air pollutants was conducted in dogs and addressed in the  
29 1982 AQCD (EPA, 1982). In dogs that were exposed to SO<sub>2</sub> and H<sub>2</sub>SO<sub>4</sub>, with or without

1 irradiated or non-irradiated auto exhaust concentrations relevant to urban exposures, functional  
2 lung changes were observed at 61 months of exposure and at 2 years after exposures ended.  
3 Morphological and biochemical changes were observed at 2.5–3 years after exposure.

4 Since then, studies have demonstrated respiratory responses following inhalation of SO<sub>2</sub>  
5 which had been layered onto metal or carbon particles. The resulting particles were submicron in  
6 size; they would be expected to deposit in the lower respiratory tract. As discussed in Section  
7 3.2.2, chemosensitive receptors are present at all levels of the respiratory tract and are known to  
8 activate reflexes involving the respiratory and cardiovascular systems. It has been postulated that  
9 bronchial C-fiber receptors are more sensitive to chemical irritants than pulmonary C-fibers  
10 receptors, but that more intense cardiovascular responses are triggered by the pulmonary  
11 receptors (Coleridge and Coleridge, 1994; Widdicombe and Lee, 2001). Some of the work  
12 involving SO<sub>2</sub> layered onto particles has been reviewed in the PM AQCD (EPA, 1996; 2004).  
13 Important studies are described briefly to show biological plausibility for the health effects of  
14 SO<sub>2</sub> which rarely, if at all, exists in nature in the absence of PM. This work is summarized in  
15 Annex Tables F-15 through 5-1.

#### **3.1.5.2.1. Effects of SO<sub>2</sub> Layered on Metallic Particles**

16 Studies examining interactions between SO<sub>2</sub> and metallic or carbonaceous particles are  
17 summarized in Annex Table E-14. Metal oxides may be released into the atmosphere with SO<sub>2</sub>  
18 during combustion of fossil fuels or by smelting operations (Lam et al., 1982). The 1982 AQCD  
19 noted that sorption of SO<sub>2</sub> onto liquid or solid particles, which may act as carriers, tended to  
20 increase its potency, but the mechanism for the effect was not known. The studies discussed  
21 below strongly suggest that SO<sub>2</sub> adsorbed to particles penetrates to more distal regions of the  
22 lung, compared with gaseous SO<sub>2</sub>. In addition, SO<sub>2</sub> which is adsorbed to particles can transform  
23 to sulfite, sulfate, H<sub>2</sub>SO<sub>4</sub> and sulfur trioxide.

24 In an early study, guinea pigs were exposed to submicron zinc oxide aerosols alone or to  
25 0.8-6 mg/m<sup>3</sup> zinc oxide in combination with 1–2 ppm SO<sub>2</sub> for 3 h (Lam et al., 1982). The higher  
26 concentrations of zinc oxide served to carry more sulfur in the aerosol (Amdur et al., 1988).  
27 Animal exposure to zinc oxide alone resulted in a decrease in functional residual capacity;  
28 animal exposure to the combination of zinc oxide and SO<sub>2</sub> resulted in dose-dependent decreases  
29 in total lung capacity, vital capacity, functional residual capacity, residual volume, diffusion

1 capacity for carbon monoxide and alveolar volume (Amdur et al., 1988; Lam et al., 1982).  
2 Another study exposed guinea pigs to ~1 ppm SO<sub>2</sub> and 1–2 mg/m<sup>3</sup> zinc oxide for 1 h (Amdur et  
3 al., 1983). Results demonstrated the formation of sulfite, sulfate, and sulfur trioxide under  
4 conditions of high humidity and temperature, and greater than additive decrements in pulmonary  
5 function, compared with exposures to SO<sub>2</sub> or zinc oxide alone or with a mixture of SO<sub>2</sub> and zinc  
6 oxide where no transformation had taken place. Additional studies in guinea pigs involved 1 h  
7 exposures to ~1 ppm SO<sub>2</sub> and 1-3 mg/m<sup>3</sup> copper oxide (Chen et al., 1991) and ~1ppm SO<sub>2</sub> and  
8 1-3 mg/m<sup>3</sup> zinc oxide (Chen et al., 1992). In the copper oxide-SO<sub>2</sub> study, components were  
9 mixed at either 37°C or 1,411°C prior to exposure (Chen et al., 1991). Results demonstrated  
10 increased pulmonary resistance when the compounds were mixed at low temperature, leading to  
11 the formation of sulfite; when components were mixed at high temperature, leading to the  
12 formation of sulfate, no increase was found. This suggested that sulfite has greater biological  
13 effect than sulfate. The zinc oxide-SO<sub>2</sub> study found a synergistic interaction between zinc oxide  
14 and SO<sub>2</sub>. Co-exposure, but not exposure to either component alone, led to airway  
15 hyperresponsiveness following an acetylcholine challenge (Chen et al., 1991). A further study by  
16 these same investigators determined that H<sub>2</sub>SO<sub>4</sub> was the predominant species of sulfur associated  
17 with the zinc oxide particles mixed with SO<sub>2</sub> under high temperature and humidity conditions  
18 (Amdur et al., 1988). H<sub>2</sub>SO<sub>4</sub> has a valence of S(VI), unlike that of SO<sub>2</sub> and sulfite, which have a  
19 valence of S(IV). This study also correlated increased bronchial sensitivity to acetylcholine with  
20 the formation of H<sub>2</sub>SO<sub>4</sub> at 21 and 30 µg/m<sup>3</sup> in animals exposed for 1 h to this mixture. The  
21 authors concluded that the response might have been enhanced by H<sub>2</sub>SO<sub>4</sub> being carried on the  
22 metal particles. Furthermore, the H<sub>2</sub>SO<sub>4</sub>-coated zinc oxide particle was five- to tenfold more  
23 potent in eliciting a response than H<sub>2</sub>SO<sub>4</sub> alone.

24 Several subacute studies were also conducted. One involved the exposure of guinea pigs  
25 for 3 h/day for 6 consecutive days to 6 mg/m<sup>3</sup> submicron zinc oxide particles generated in a  
26 humid furnace mixed with 1 ppm SO<sub>2</sub> or to SO<sub>2</sub> alone (Conner et al., 1985). Exposure to the zinc  
27 oxide/SO<sub>2</sub> particles resulted in significant decreases in total lung capacity, vital capacity and  
28 functional residual capacity compared with controls or exposure to SO<sub>2</sub> alone. These decreases  
29 were maintained for at least 72 h following the last exposure. Decreases in diffusing capacity for  
30 carbon monoxide and alveolar volume, as well as increased alveolar-duct inflammation, were  
31 observed in response to zinc oxide-SO<sub>2</sub> but not to SO<sub>2</sub> alone. Because the changes noted in

1 response to zinc oxide-SO<sub>2</sub> were identical to those seen in a previous study using zinc oxide, the  
2 authors concluded that SO<sub>2</sub> played a minor role in these responses. Subsequent studies employed  
3 a lower concentration of zinc oxide (1 and 2.5 mg/m<sup>3</sup>) in order to unmask the effects of the  
4 SO<sub>2</sub>-zinc oxide interaction (Amdur et al., 1988; Conner et al., 1989). In one of these, significant  
5 changes were observed in numbers of cells and other lavage fluid components in guinea pigs  
6 exposed for 3 h/day for 5 days to SO<sub>2</sub>-zinc oxide compared with those exposed only to SO<sub>2</sub> or  
7 zinc oxide. As previously described, it was determined that the mixture of zinc oxide and SO<sub>2</sub> in  
8 a high temperature furnace with sufficient humidity resulted in the formation of a zinc oxide/  
9 H<sub>2</sub>SO<sub>4</sub> aerosol. Exposure of guinea pigs for 3 h/day for 5 days to this H<sub>2</sub>SO<sub>4</sub>-coated ultrafine  
10 aerosol at a concentration of 7-11 µg/m<sup>3</sup> S(VI) resulted in a significant decrease in diffusing  
11 capacity for carbon monoxide, an effect not seen with exposure to zinc oxide or SO<sub>2</sub> alone. The  
12 authors concluded that the response was due to the H<sub>2</sub>SO<sub>4</sub> associated with the aerosol and  
13 delivered to the lower respiratory tract (Amdur et al., 1988).

#### **3.1.5.2.2. Effects of SO<sub>2</sub> Layered on Carbon Particles**

14 Effects of SO<sub>2</sub>-containing mixtures on host defenses were examined in several studies.  
15 Host defense results will not be discussed since high concentrations (10 ppm) of SO<sub>2</sub> were used.  
16 However, these experiments were important since they demonstrated that mixing SO<sub>2</sub> and  
17 submicron particles of carbon black in the presence of 85% relative humidity led to significant  
18 adsorption of SO<sub>2</sub> onto the carbon black and oxidation of SO<sub>2</sub> to acid sulfate. No high  
19 temperature furnace was employed in these studies (Jakab et al., 1996; Clarke et al., 2000).

#### **3.1.5.2.3. Effects of Sulfite Aerosols**

20 Several studies used sulfite particles as a surrogate for SO<sub>2</sub> adsorbed onto carbonaceous or  
21 metallic particulates. These are discussed below and in Annex Table E-15. Sulfite and SO<sub>2</sub>, both  
22 S(IV) species, were expected to have similar chemical reactivities. An acute 1-h exposure of  
23 guinea pigs to submicron aerosols of sodium sulfite (204-1,152 µg/m<sup>3</sup> of sulfite) resulted in  
24 significant effects on pulmonary function (Chen et al., 1987). A 50% increase in resistance and  
25 19% decrease in compliance were observed using 972 µg/m<sup>3</sup> of sulfite, while dose-dependent  
26 decreases in total lung capacity, vital capacity, functional residual capacity, residual volume,  
27 diffusion capacity for carbon monoxide and increases in lung wet weight at concentrations of

1 204  $\mu\text{g}/\text{m}^3$  and above. The authors noted that aerosols of S(IV) were 6 times more potent than  
2 gaseous S(IV) in terms of bronchoconstriction and attributed these effects to greater pulmonary  
3 deposition of the S(IV) aerosol. An earlier study by the same group found that 1-h exposure of  
4 rabbits to greater than 1,200  $\mu\text{g}/\text{m}^3$  of sulfite led to accelerated clearance of a tracer aerosol from  
5 the bronchial tree (Chen and Schlesinger, 1983). Chronic studies involving sulfite aerosols are  
6 discussed in Section 3.4.2.5.

#### **3.1.5.2.4. Other Mixtures**

7 In addition to examining the interaction of  $\text{SO}_2$  and particles, animal studies performed  
8 since the publication of the 1982 AQCD evaluated the effects of binary mixtures, laboratory-  
9 generated complex mixtures (e.g., simulation of regional air pollution), or actual ambient air  
10 mixtures. Annex Tables E-17 through E-20 summarize results from short-term studies on  
11 possible toxicity relationships between  $\text{SO}_2$  and  $\text{O}_3$ , and between  $\text{SO}_2$  and sulfates as well as the  
12 effects of complex air pollution mixtures in healthy animals and disease models. Possible  
13 interactions between  $\text{SO}_2$  and cold air were also examined (Annex Table E-20). Generally, most  
14 studies with ambient or laboratory-generated complex mixtures did not include a  $\text{SO}_2$ -only  
15 exposure group, making it difficult to determine the contribution of  $\text{SO}_x$ . No definitive  
16 conclusions can be made from these studies.

#### **3.1.5.2.5. Summary of Evidence on $\text{SO}_2$ Interactions with PM and Other Mixtures**

17 The key findings by Amdur and others discussed above demonstrate that the effects of  $\text{SO}_2$   
18 may be enhanced when aerosol particles act as carriers and deliver  $\text{SO}_2$  to the lower respiratory  
19 tract. Interaction of  $\text{SO}_2$  and PM may also lead to transformation of  $\text{SO}_2$  to other forms of  $\text{SO}_x$   
20 which may have more potent biological effects than  $\text{SO}_2$ . Studies discussed above reported  
21 transformation of  $\text{SO}_2$  adsorbed onto metal oxide or carbon particles to sulfite, sulfate, sulfur  
22 trioxide, and  $\text{H}_2\text{SO}_4$  depending on conditions of temperature and relative humidity.

#### **3.1.6. Evidence of the Effect of $\text{SO}_2$ on Respiratory Morbidity from Intervention Studies**

23 Many epidemiological studies have examined the association of short-term  $\text{SO}_2$   
24 concentrations and various respiratory morbidity outcomes. These studies collectively suggest

1 that increased ambient SO<sub>2</sub> concentrations are associated with increased risk of respiratory  
2 outcomes, ranging from respiratory symptoms to ED visits and hospitalizations. Further  
3 contributing to the evidence base are intervention studies that reported decreases in respiratory  
4 morbidity following improvements in air quality, particularly reductions in SO<sub>2</sub> concentrations.

5 In Hong Kong, a sudden change in regulation in July 1990 required all power plants and  
6 road vehicles to use fuel oil with a sulfur content of  $\leq 0.5\%$  by weight. These regulations were  
7 enforced quickly, and provided opportunities to observe changes in morbidity before and after  
8 the intervention. Peters et al. (1996) followed 3,521 children (mean age 9.5 years) residing in  
9 two districts with good and poor air quality before the intervention from 1989 to 1991. The  
10 intervention resulted in large reductions in SO<sub>2</sub> (up to 80% in polluted district), along with a  
11 modest reduction in sulfate (38% in polluted district). Only a small change in TSP levels was  
12 observed after the intervention (15% decline in polluted district). In 1989 and 1990, an excess  
13 risk of respiratory symptoms was observed in the polluted district. After the intervention, there  
14 was a greater decline in reported symptoms of cough, sore throat, phlegm, and wheezing in the  
15 polluted compared with the unpolluted district. For example, the OR for cough, comparing the  
16 polluted to the unpolluted district, was 1.22 (95% CI: 1.05, 1.42) in 1989 and 1990, and  
17 decreased to 0.92 (95% CI: 0.73, 1.15) in 1991.

18 A study by Keles et al. (1999) evaluated the prevalence of chronic rhinitis among high  
19 school students before and after installation of a natural gas network for domestic heating and  
20 industrial works, in a polluted area of Istanbul, Turkey. Concentrations of CO, NO<sub>2</sub>, and  
21 hydrocarbons were relatively low compared to SO<sub>2</sub> and TSP in this area. After the intervention,  
22 the annual mean TSP concentration declined by 23% from 89.7  $\mu\text{g}/\text{m}^3$  to 68.8  $\mu\text{g}/\text{m}^3$ . An even  
23 greater decline (46%) was observed for SO<sub>2</sub>, from an annual mean of 70.8 ppb to 38.2 ppb. The  
24 prevalence of rhinitis decreased significantly from 62.5% to 51% of the student population ( $p <$   
25  $0.05$ ) following the installation of the natural gas network. Symptoms of rhinitis were associated  
26 with air pollution levels, but not with any of the other factors considered, including sex,  
27 household crowding, heating source, and smoking status. Although the effects from TSP could  
28 not be separated from SO<sub>2</sub> effects, this study demonstrated that reductions in both pollutants  
29 (with greater declines in SO<sub>2</sub>) resulted in significant reductions in the prevalence of chronic  
30 rhinitis in a highly polluted area.

1 Another study in Germany observed that reductions in air pollutant levels were associated  
2 with improvement in reported respiratory symptoms. Heinrich et al. (2002) examined the  
3 influence of reduced air pollution levels on respiratory symptoms in children aged 5 to 14 years  
4 (n = 7,632). Questionnaires were collected from the children during 1992–1993, 1995–1996, and  
5 1998–1999 in three study areas. During the study period, SO<sub>2</sub> concentrations decreased by more  
6 than 90% and TSP concentrations decreased by approximately 60%. Concentrations of  
7 nucleation-mode particles (10-30 nm) increased during this time period. For most respiratory  
8 outcomes, the prevalence continued to decline in each of the three surveys. The temporal  
9 changes followed similar trends in all three study areas. Stronger effects between SO<sub>2</sub> and  
10 prevalence of respiratory symptoms were observed among children without indoor exposures.  
11 For those without indoor exposures, ORs of 1.21 (95% CI: 1.11, 1.32) were observed for  
12 prevalence of bronchitis and 1.11 (95% CI: 1.02, 1.22) for frequent colds per 5-ppb increase in  
13 the annual mean of SO<sub>2</sub>. Frye et al. (2003) reported changes in lung function parameters  
14 associated with declines in SO<sub>2</sub> concentrations in 2,493 children during this period as well. The  
15 researchers observed a 0.6% (95% CI: 0.1, 1.2) increase in FVC and a 0.4% (95% CI: -0.1, 0.9)  
16 increase in FEV<sub>1</sub> per 5-ppb decrease in the annual mean of SO<sub>2</sub>. They concluded that the  
17 decreasing prevalence of respiratory symptoms and the increase in lung function following  
18 decreases in air pollution levels might indicate the reversibility of adverse health effects in  
19 children.

20 In summary, these studies observed that improvements in air quality, in particular large  
21 decreases in SO<sub>2</sub> concentrations, were associated with improvements in respiratory symptoms  
22 and lung function. However, the decreased respiratory morbidity following large reductions in  
23 ambient SO<sub>2</sub> concentrations does not preclude the possibility that other constituents of the  
24 pollution mixture that share the same source as SO<sub>2</sub> are also responsible for adverse effects. In  
25 the German and Turkey studies, both SO<sub>2</sub> and TSP concentrations decreased dramatically.  
26 Although PM<sub>10</sub> levels before and after the intervention were stable in Hong Kong, large  
27 reductions in ambient nickel and vanadium were observed concomitantly with reductions of  
28 sulfur after the intervention (Hedley et al., 2006). As discussed in Section 3.1.5, interactions of  
29 SO<sub>2</sub> and PM may lead to transformation of SO<sub>2</sub> to other forms of SO<sub>x</sub> which have more potent  
30 biological effects; thus the improvements in respiratory health may also be attributable to both  
31 declines in SO<sub>2</sub> and PM. Nonetheless, considered collectively with the larger body of evidence

1 from epidemiological, human clinical, and animal toxicological studies, these studies are  
2 supportive of SO<sub>2</sub>-related effects on respiratory morbidity.

### 3.1.7. Summary of Evidence of the Effect of Short-Term SO<sub>2</sub> Exposure on Respiratory Health

3 Evaluation of the health evidence led to the conclusion that it is *sufficient to infer a causal*  
4 *relationship between respiratory morbidity and short-term exposure to SO<sub>2</sub>*. This conclusion is  
5 supported by the consistency, coherence, and plausibility of findings observed in human clinical  
6 studies with 5-10 min exposures, epidemiological studies using largely 24-h avg exposures and  
7 animal toxicological studies using exposures of minutes to hours.

8 The strongest evidence for this causal relationship comes from human clinical studies  
9 reporting respiratory symptoms and decreased lung function following peak exposures of 5-10  
10 min duration to SO<sub>2</sub>. These effects have been observed consistently across studies involving  
11 exercising mild to moderate asthmatics. Statistically significant decrements in lung function  
12 accompanied by respiratory symptoms including wheeze and chest tightness have been clearly  
13 demonstrated following exposure to 0.4-0.6 ppm SO<sub>2</sub>. Although studies have not reported  
14 statistically significant respiratory effects following exposure to 0.2-0.3 ppm SO<sub>2</sub>, some  
15 asthmatic subjects (5-20%) have been shown to experience moderate to large decrements in lung  
16 function at these exposure concentrations. A larger body of evidence supporting this  
17 determination of causality comes from numerous epidemiological studies reporting associations  
18 with respiratory symptoms, ED visits, and hospital admissions with short-term SO<sub>2</sub> exposures,  
19 generally of 24-h avg. Important new multicity studies and several other studies have found an  
20 association between 24-h avg ambient SO<sub>2</sub> concentrations and respiratory symptoms in children,  
21 particularly those with asthma. Furthermore, limited epidemiological evidence indicates that  
22 atopic children and adults may be at increased risk for SO<sub>2</sub>-induced respiratory symptoms.  
23 Generally consistent and robust associations also were observed between ambient SO<sub>2</sub>  
24 concentrations and ED visits and hospitalizations for all respiratory causes, particularly among  
25 children and older adults (65+ years), and for asthma. Results of experiments in laboratory  
26 animals support these observations; studies in animals sensitized with antigen demonstrate that  
27 repeated exposure to near ambient SO<sub>2</sub> levels (as low as 0.1 ppm in guinea pigs) can exacerbate

1 allergic responses including mucin production, airway inflammation and airway  
2 hyperresponsiveness.

## **3.2. Other Morbidity Associated with Short-Term SO<sub>2</sub> Exposure**

### **3.2.1. Summary of Findings from the Previous Review**

3 The studies reviewed in the 1982 AQCD primarily investigated respiratory health  
4 outcomes. There were no key animal toxicological or human clinical studies available at the last  
5 review to address effects of SO<sub>2</sub> exposure on the cardiovascular system. The only report was a  
6 study in dogs exposed to air pollutant mixtures (SO<sub>2</sub> + H<sub>2</sub>SO<sub>4</sub> with or without nonirradiated or  
7 irradiated auto exhaust). No changes were observed in cardiovascular function at the end of 3  
8 years of exposure and 3 years after exposure. No epidemiological studies linking exposure to  
9 SO<sub>2</sub> with cardiovascular physiological endpoints or ED visits or hospital admissions for  
10 cardiovascular causes were examined in the last review. Other organ systems in addition to  
11 cardiovascular were not addressed in the 1982 AQCD.

### **3.2.2. Cardiovascular Effects Associated with Short-Term Exposure**

12 The biological basis for SO<sub>2</sub>-related cardiovascular health effects may lie in the stimulation  
13 of chemosensitive receptors found in the respiratory tract which respond to irritants like SO<sub>2</sub>.  
14 Vagally-mediated responses may affect the cardiovascular system by inducing bradycardia and  
15 either hypotension or hypertension, as discussed in Section 3.1.2. Alternatively oxidation  
16 reactions mediated by the SO<sub>2</sub> metabolites sulfite and bisulfite which have been absorbed into  
17 the systemic circulation may potentially alter cardiovascular function. In general, vagally-  
18 mediated responses have been observed at lower concentrations of SO<sub>2</sub> than oxidative injury.

19 Since 1982, several animal toxicological studies have addressed the effects of SO<sub>2</sub> on  
20 cardiovascular endpoints. These are summarized below and in Annex Table E-5. In addition,  
21 there is one noteworthy study examining the hematological effects of short-term SO<sub>2</sub> exposure  
22 (Annex Table E-8). Acute exposure of rats to 0.87 ppm SO<sub>2</sub> for 24 h resulted in increased  
23 hematocrit, sulfhemoglobin and osmotic fragility as well as decreased whole blood and packed  
24 cell viscosities (Baskurt, 1988). These results indicate a systemic effect of inhaled SO<sub>2</sub> at

1 concentrations near ambient levels and are consistent with an oxidative injury to red blood cells.  
2 Only one study since 1982 measured systemic levels of sulfite or bisulfite following SO<sub>2</sub>  
3 inhalation (Gunnison et al., 1987; Annex Table E-22). Further studies are required to confirm that  
4 inhalation exposures of SO<sub>2</sub> at or near ambient levels increase blood sulfite and bisulfite levels  
5 sufficient for oxidative injury to blood cells or other tissues.

6 Recent epidemiological studies have examined the association between air pollution and  
7 cardiovascular effects, including increased heart rate (HR), reduced heart rate variability (HRV),  
8 incidence of ventricular arrhythmias, changes in blood pressure, incidence of myocardial  
9 infarctions (MI), and ED visits and hospitalizations due to cardiovascular causes. The results of  
10 these cardiovascular studies are summarized in Annex Tables F-3 and F-4.

### **3.2.2.1. Heart Rate and Heart Rate Variability**

11 Heart rate variability (HRV) is generally determined by analyses of time (e.g., standard  
12 deviation of normal R-R intervals [SDNN]) and frequency domains (e.g., low frequency [LF] /  
13 high frequency [HF] ratio by power spectral analysis, reflecting autonomic balance) measured  
14 during 24 h of electrocardiography (ECG). Brook et al. (2004) stated that HRV, resting heart rate,  
15 and blood pressure are modulated by a balance between the two determinants of autonomic tone  
16 (the sympathetic and parasympathetic nervous systems). An imbalance of cardiac autonomic  
17 control may predispose susceptible people to greater risk of ventricular arrhythmias and  
18 consequent cardiac deaths (Brook et al., 2004; Liao et al., 2004).

19 A limited number of human clinical studies examined the effect of SO<sub>2</sub> on HRV. During a  
20 controlled exposure of 12 healthy subjects and 12 subjects with asthma to 0.2 ppm SO<sub>2</sub> for 1 h  
21 under resting conditions, Tunnicliffe et al. (2001) reported that HF power, LF power, and total  
22 power were higher with SO<sub>2</sub> exposures compared to air exposure in the healthy subjects, but that  
23 these indices were reduced during SO<sub>2</sub> exposure in the subjects with asthma. The LF/HF ratios  
24 were unchanged in both groups. The authors postulated two autonomic pathways for SO<sub>2</sub>-  
25 mediated bronchoconstriction. In healthy subjects, the dominant pathway was proposed to be the  
26 rapidly adapting receptor/C-fiber route, which results in a central nervous system reflex with an  
27 increase in vagal tone. In the asthmatic subjects, proximal airway narrowing was proposed as the  
28 dominant response, possibly through neurogenic inflammation. This likely causes a  
29 compensatory central nervous system-mediated reduction in vagal tone, resulting in

1 bronchodilation of the distal airway. While there were no detectable changes in symptoms or  
2 lung function in either of the groups, this study provides some evidence that exposure to SO<sub>2</sub>  
3 may elicit systemic responses at these low levels (0.2 ppm).

4 In a similar study, Routledge et al. (2006) exposed patients with stable angina as well as  
5 healthy subjects to 50 µg/m<sup>3</sup> carbon particles, 0.2 ppm SO<sub>2</sub>, alone and in combination, for 1 h  
6 under resting conditions. HRV, C-reactive protein, and coagulation markers were measured. The  
7 authors reported that for the healthy subjects, SO<sub>2</sub> exposure was associated with a decrease in  
8 HRV markers of cardiac vagal control 4 h after exposure. However, it should be noted that there  
9 was no apparent difference in the absolute value of the root mean square of successive RR  
10 interval differences (r-MSSD) at 4 h postexposure between the control, SO<sub>2</sub>, carbon, and  
11 carbon/SO<sub>2</sub> groups. The significant difference reported in the change in r-MSSD from baseline to  
12 4 h postexposure with SO<sub>2</sub> appears to be due to a higher baseline value of r-MSSD preceding the  
13 SO<sub>2</sub> exposure compared to the baseline value of r-MSSD preceding the air exposure. There were  
14 no changes in HRV among the patients with stable angina. The authors noted that this lack of  
15 response in the heart patients may be due to a drug treatment effect rather than decreased  
16 susceptibility; a large portion of the angina patients were taking beta blockers, which are known  
17 to increase indices of cardiac vagal control.

18 In an epidemiological study, Liao et al. (2004) investigated short-term associations  
19 between ambient pollutants and cardiac autonomic control from the fourth cohort examination  
20 (1996 through 1998) of the population-based Atherosclerosis Risk in Communities (ARIC) study  
21 using a cross-sectional study design. Men and women aged 45 to 64 years (n = 6,784) from three  
22 U.S. study centers in North Carolina, Minnesota, and Mississippi were examined. Resting,  
23 supine, and 5-min beat-to-beat R-R interval data were collected. The mean 24-h avg SO<sub>2</sub> level  
24 measured 1 day prior to the HRV measurement was 4 ppb (SD 4). In addition to SO<sub>2</sub>, the  
25 potential effects of PM<sub>10</sub>, O<sub>3</sub>, CO, and NO<sub>2</sub> were evaluated. Previous-day SO<sub>2</sub> concentrations  
26 were positively associated with HR and inversely associated with SDNN and LF power.  
27 Consistently more pronounced associations were suggested between SO<sub>2</sub> and HRV among  
28 persons with a history of coronary heart disease. Significant associations with HRV indices also  
29 were observed for PM<sub>10</sub> and the other gaseous pollutants. When the regression coefficients for  
30 each individual pollutant model were compared, the effects of PM<sub>10</sub> on HRV were considerably

1 larger than the effects for the gaseous pollutants, including SO<sub>2</sub>. No multipollutant analyses were  
2 conducted.

3 Gold et al. (2000; reanalysis 2003) examined the effect of short-term changes in air  
4 pollution on HRV in a panel study of 21 older adults (aged 53 to 87 years) in Boston, MA. The  
5 study participants were observed up to 12 times from June to September 1997. The mean  
6 24-h avg SO<sub>2</sub> concentration was 3.2 ppb (range: 0, 12.6). The 24-h avg SO<sub>2</sub> concentration was  
7 associated with decreased HR in the first 5-min rest period, but not in the overall 25-min study  
8 protocol. The effect estimate for SO<sub>2</sub> slightly diminished but remained marginally significant in a  
9 two-pollutant model with PM<sub>2.5</sub>. The inverse association between SO<sub>2</sub> and HR observed in this  
10 study are in contrast to the SO<sub>2</sub>-related increases in HR observed by Liao et al. (2004) and Peters  
11 et al. (1999). No associations were observed between HRV and SO<sub>2</sub>. The strongest associations  
12 with HRV were observed for PM<sub>2.5</sub> and O<sub>3</sub>.

13 Another study of air pollutants and HRV was conducted in Boston, MA on 497 men from  
14 the Normative Aging Study (Park et al., 2005). The best 4-consecutive-min interval from a 7-min  
15 sample was used for the HRV calculations. For the exposure variable, 4-, 24-, and 48 h moving  
16 averages matched on the time of the ECG measurement for each subject were considered. The  
17 mean 24-h avg SO<sub>2</sub> concentration was 4.9 ppb (range: 0.95, 24.7). Associations with measures of  
18 HRV were reported for PM<sub>2.5</sub> and O<sub>3</sub>, but not with SO<sub>2</sub> for any of the averaging periods. In  
19 another study conducted in Boston, MA, Schwartz et al. (2005) found significant effects of  
20 increases in PM<sub>2.5</sub> on measures of HRV, while no associations with SO<sub>2</sub> were observed. Other  
21 studies examined the relationship of SO<sub>2</sub> with HRV (Chan et al., 2005; de Paula Santos et al.,  
22 2005; Holguin et al., 2003; Luttmann-Gibson et al., 2006). Most of these studies, with the  
23 exception of de Paula Santos et al., did not observe associations with SO<sub>2</sub>.

24 In the limited number of epidemiological studies that examined a possible effect of SO<sub>2</sub> on  
25 HRV, there were some suggestive findings; however, results reported from the human clinical  
26 studies were inconsistent. The overall evidence does not support the conclusion that SO<sub>2</sub> affects  
27 cardiac autonomic control.

### 3.2.2.2. Repolarization Changes

1 In addition to the role played by the autonomic nervous system in arrhythmogenic  
2 conditions, myocardial vulnerability and repolarization abnormalities are believed to be key  
3 factors contributing to the mechanism of such diseases.

4 Two in vitro studies (Nie and Meng, 2005) conducted with a 1:3 molar:molar mixture of  
5 the SO<sub>2</sub> derivatives bisulfite and sulfite demonstrated effects of a 10-μm bisulfite:sulfite mixture  
6 on sodium and L-type calcium currents (which included changes in inactivation and/or  
7 activation, recovery from inactivation, and inactivation/activation time constants) in ventricular  
8 myocytes. These in vitro observations suggested a potential role for L-type calcium current in  
9 cardiac injury following SO<sub>2</sub> exposure. However, in vivo cardiovascular effects were observed  
10 only at high SO<sub>2</sub> concentrations (10 ppm and higher). Additional toxicological studies are  
11 necessary to evaluate repolarization changes at ambient levels of SO<sub>2</sub>.

12 In an epidemiological study, Henneberger et al. (2005) examined the association of  
13 repolarization parameters (QT duration, T-wave complexity, variability of T-wave complexity,  
14 and T-wave amplitude) with air pollutants in patients with preexisting coronary heart disease (n =  
15 56, all males) in East Germany. The patients were examined repeatedly once every 2 weeks for 6  
16 months, for a total of 12 ECG recordings. The mean 24-h avg SO<sub>2</sub> concentration was 2 ppb  
17 (range: 1, 4). Ambient SO<sub>2</sub> concentrations during the 24-h preceding the ECG were associated  
18 with the QT interval duration, but not with any other repolarization parameters. Stronger  
19 associations were observed between PM indices and QT interval duration, T-wave amplitude,  
20 and T-wave complexity.

21 To summarize, the evidence, while suggestive, is too limited to draw conclusions on the  
22 association of SO<sub>2</sub> exposure and repolarization changes at this time.

### 3.2.2.3. Cardiac Arrhythmias

23 One toxicological study examined the effects of PM, ultrafine carbon, and SO<sub>2</sub> on  
24 spontaneous arrhythmia frequency in 18-month-old rats (Nadziejko et al., 2004). The rats were  
25 exposed to 1 ppm SO<sub>2</sub> for 4 h. No significant change in the frequency of spontaneous  
26 arrhythmias was found with SO<sub>2</sub> and ultrafine carbon exposure. However, rats exposed to

1 concentrated ambient PM had a significantly greater increase in the frequency of delayed beats  
2 than rats exposed to air.

3 In a panel study of 100 patients with implanted cardioverter defibrillators (ICDs) in  
4 Eastern Massachusetts, Peters et al (2000) tested the hypothesis that patients with ICDs would  
5 experience life-threatening arrhythmias after an air pollution episode. The mean 24-h avg SO<sub>2</sub>  
6 concentration measured at two sites in Boston during the study period was 7 ppb (5th–95th  
7 percentile: 1, 19). ICDs monitor ECG abnormalities, and treat ventricular fibrillation or  
8 ventricular tachycardias by administering shock therapy to restore the normal cardiac rhythm.  
9 The ICD device also stores information on each tachyarrhythmia and shock. There was no  
10 association between SO<sub>2</sub> and defibrillator discharges in the 33 subjects who had any defibrillator  
11 discharges during the follow-up period or in the 6 subjects who had at least 10 discharges. There  
12 was some evidence that NO<sub>2</sub> was associated with increased defibrillatory interventions in the  
13 subjects with any defibrillator discharges. Among the patients with at least 10 events, NO<sub>2</sub>, CO,  
14 and PM<sub>2.5</sub> were found to be associated with defibrillator discharges.

15 In a follow-up study designed to confirm the findings of Peters et al. (2000), Dockery et al.  
16 (2005) used a larger sample of ICD patients in Boston (n = 203) with a longer follow-up period.  
17 The median concentration of 48-h avg SO<sub>2</sub> averaged across multiple sites in Boston was 4.9 ppb  
18 (IQR 4.1). No significant associations were found between ventricular arrhythmic episode days  
19 and any of the air pollutants. However, when the analysis was stratified by recent arrhythmias  
20 (i.e., within 3 days), there was evidence of an excess risk of ventricular arrhythmia with SO<sub>2</sub>,  
21 PM<sub>2.5</sub>, black carbon, NO<sub>2</sub>, and CO. Since PM<sub>2.5</sub>, black carbon, NO<sub>2</sub>, and CO were correlated with  
22 each other and with SO<sub>2</sub>, the authors noted that differentiating the independent effects of the  
23 pollutants would be difficult. A case-crossover analysis of the same data by Rich et al. (2005)  
24 also observed associations with 48-h avg SO<sub>2</sub>, but the SO<sub>2</sub> effect was not found to be robust to  
25 adjustment by PM<sub>2.5</sub>. In a similar study conducted in St. Louis, MO, an excess risk was  
26 associated with SO<sub>2</sub> concentrations in the 24 h prior to an arrhythmia, but not with PM<sub>2.5</sub> and O<sub>3</sub>  
27 (Rich et al., 2006). In this study, none of the other measured pollutants (PM, elemental carbon,  
28 O<sub>3</sub>, CO, NO<sub>2</sub>) were correlated with SO<sub>2</sub>. The authors suggested that the different effects observed  
29 in St. Louis and Boston may be due to differences in the source or mix of air pollutants in these  
30 cities. Finally, findings from a time series study of tachyarrhythmic events among 518 patients

1 over a 10 year period in Atlanta do not indicate an association with SO<sub>2</sub>, nor with the other  
2 pollutants studied including PM<sub>2.5</sub> and its components (Metzger et al., 2007).

3 Additional studies have examined the relationship of SO<sub>2</sub> with arrhythmias in Vancouver,  
4 and observed associations at very low ambient SO<sub>2</sub> concentrations (mean 24-h avg SO<sub>2</sub> of ~2.5  
5 ppb with a max of 8.1 ppb). Vedal et al. (2004) stated that of all pollutants examined, the only  
6 one with somewhat consistent positive associations with arrhythmia events was SO<sub>2</sub>. In season-  
7 stratified analyses, SO<sub>2</sub> was positively associated with arrhythmias in the winter, while in the  
8 summer the association was negative. On the other hand, in the Rich et al. (2004) study, positive  
9 associations were observed in the summer but not in the winter. The authors stated that it was  
10 difficult to interpret these findings.

11 Collectively, the epidemiological evidence for an association between short-term exposure  
12 to SO<sub>2</sub> and arrhythmias is inconsistent. The limited toxicological evidence does not provide  
13 biological plausibility for an effect.

#### **3.2.2.4. Blood Pressure**

14 Two animal toxicological studies examined the effect of SO<sub>2</sub> on blood pressure (Annex  
15 Table E-5). Hälinen et al. (2000) examined blood pressure changes in guinea pigs. The animals  
16 were hyperventilated to simulate exercise, and exposed to 1-, 2.5-, and 5 ppm SO<sub>2</sub> in cold, dry  
17 air. After 10-min exposures to each SO<sub>2</sub> concentration, separated by 15-min exposures to clean,  
18 warm, humid air, a transient increase in blood pressure was observed during 5 ppm SO<sub>2</sub> exposure  
19 in cold, dry air. In a second study (Halinen et al., 2000b), hyperventilated guinea pigs were  
20 exposed to cold, dry air alone or to 1 ppm SO<sub>2</sub> in cold, dry air for 60 min. The study reported  
21 similar increases in blood pressure and HR with exposure to cold, dry air or to SO<sub>2</sub> in cold, dry  
22 air. The increase in HR was gradual, while increases in blood pressure generally occurred during  
23 the first 10 to 20 min of exposure. Similar effects were observed with exposure to cold, dry air or  
24 to SO<sub>2</sub> in cold, dry air, suggesting that effects were associated with cold, dry air rather than with  
25 SO<sub>2</sub>.

26 Ibalid-Mulli et al. (2001) examined the association between blood pressure and SO<sub>2</sub> using  
27 survey data from the MONICA (Monitoring Trends and Determinants in Cardiovascular Disease)  
28 Project. Blood pressure measurements were taken from 2,607 men and women. The mean  
29 24-h avg SO<sub>2</sub> concentration was 23 ppb (range: 5, 91). An increase in systolic blood pressure was

1 associated with 24-h avg SO<sub>2</sub> and TSP. However, in a two-pollutant model with TSP, the effect of  
2 SO<sub>2</sub> on blood pressure was substantially reduced and became nonsignificant while the effect of  
3 TSP was robust.

4 In a study by de Paula Santos et al. (2005), changes in blood pressure in association with  
5 SO<sub>2</sub> were investigated in vehicular traffic controllers (n = 48) aged 31 to 55 years living in São  
6 Paulo, Brazil, where vehicles are the primary source of air pollution. The mean 24-h avg SO<sub>2</sub>  
7 level, measured at six different stations around the city, was 7 ppb (SD 3). Blood pressure was  
8 measured every 10 min when subjects were awake (6 a.m. to 11 p.m.) and every 20 min during  
9 sleep (11 p.m. to 6 a.m.). Results indicated that SO<sub>2</sub>, as well as CO, were associated with  
10 increases in systolic and diastolic blood pressure. However, when a two-pollutant model was  
11 used to test the robustness of the associations, only the CO effect remained statistically  
12 significant.

13 Very few studies have examined the effects of short-term SO<sub>2</sub> exposure on blood pressure.  
14 Collectively, the limited toxicological and epidemiological evidence does not suggest that  
15 exposure to SO<sub>2</sub> has effects on blood pressure.

### **3.2.2.5. Blood Markers of Cardiovascular Risk**

16 Folsom et al. (1997) demonstrated that elevated levels of fibrinogen, white blood cell  
17 count, factor VIII coagulant activity (factor VIII-C), and von Willebrand factor were associated  
18 with risk of cardiovascular disease. Schwartz (2001) investigated the association between various  
19 blood markers of cardiovascular risk and air pollution among subjects in the Third National  
20 Health and Nutrition Examination Survey (NHANES III) in the United States conducted between  
21 1989 and 1994 across 44 counties. The NHANES III is a random sample of the U.S. population  
22 with oversampling for minorities (30% of NHANES sample) and the elderly (20% of the  
23 sample). The mean SO<sub>2</sub> concentration was 17.2 ppb (IQR 17) across the 25 counties where data  
24 were available. This study looked at fibrinogen levels, platelet counts, and white blood cell  
25 counts. After controlling for age, ethnicity, gender, body mass index, and smoking status and  
26 number of cigarettes per day, SO<sub>2</sub> was found to be positively associated with white blood cell  
27 counts. PM<sub>10</sub> was associated with all blood markers. In two-pollutant models, PM<sub>10</sub> remained a  
28 significant predictor of white blood cell counts after controlling for SO<sub>2</sub>, but not vice versa.

1 A recent cross-sectional study by (Liao et al., 2005) investigated the effects of air pollution  
2 on plasma hemostatic and inflammatory markers in the ARIC study (n = 10,208). The authors  
3 hypothesized that short-term exposure to air pollutants was associated with increased levels of  
4 inflammatory markers and lower levels of albumin, as serum albumin is inversely associated  
5 with inflammation. The mean 24-h avg SO<sub>2</sub> concentration was 5 ppb (SD 4). Significant  
6 curvilinear relationships were observed between SO<sub>2</sub> and factor VIII-C, white blood cell counts,  
7 and serum albumin. The authors noted that since no biological explanation could be offered for  
8 the “U”-shaped curve between SO<sub>2</sub> and factor VIII-C and the “inverse U”-shape between SO<sub>2</sub>  
9 and albumin, generalization of the association should be exercised with caution. No associations  
10 were observed between SO<sub>2</sub> and fibrinogen or von Willebrand factor.

11 In another large cross-sectional study of 7,205 office workers in London, Pekkanen et al  
12 (2000) examined the association between plasma fibrinogen and ambient air pollutants. The  
13 mean 24-h avg SO<sub>2</sub> was 9 ppb (10th–90th percentile: 5, 19). Associations with fibrinogen were  
14 observed for all pollutants examined, either in all-year or summer-only analyses, except for SO<sub>2</sub>  
15 and O<sub>3</sub>.

16 Taken together, results from the limited number of studies do not suggest that SO<sub>2</sub> is  
17 associated with various blood markers of cardiovascular risk.

### **3.2.2.6. Acute Myocardial Infarction**

18 The association between air pollution and the incidence of MI was examined in a small  
19 number of studies. As part of the Determinants of Myocardial Infarction Onset Study, Peters  
20 et al. (2001) examined 772 patients with MI living in greater Boston, MA. A case-crossover  
21 design was used to assess changes in the risk of acute MI after exposure to potential triggers. The  
22 mean 24-h avg SO<sub>2</sub> was 7 ppb (range: 1, 20) during the study period. Similarly, the mean 1-h avg  
23 SO<sub>2</sub> was 7 ppb (range: 0, 23). In an analysis that considered both the 2-h avg (between 60 and  
24 180 min before the onset of symptoms) and 24-h avg (between 24 and 48 h before the onset)  
25 concentrations jointly, the study found no significant association between risk of MI and SO<sub>2</sub>. Of  
26 all the pollutants considered, only PM<sub>2.5</sub> and PM<sub>10</sub> were found to be associated with an excess  
27 risk of MI. In a study of 5793 confirmed cases of acute MI in King County Washington, Sullivan  
28 et al. (2005) also used a case-crossover design to investigate the association of ambient levels of

1 several air pollutants 1, 2, 4 and 24 h before the MI onset. No association with SO<sub>2</sub> (or with  
2 PM<sub>2.5</sub>) was observed. The mean SO<sub>2</sub> level was 9 ppb (range: 0-39 ppb) at the time of the study.

3 In the MONICA Project, the effect of air pollution on acute MI was studied in Toulouse,  
4 France, using a case-crossover study design (Ruidavets et al., 2005). The mean 24-h avg SO<sub>2</sub>  
5 level was 3 ppb (5th–95th percentile: 1, 5). A total of 399 cases of acute MI were recorded during  
6 the study period. O<sub>3</sub>, but not SO<sub>2</sub> or NO<sub>2</sub>, was found to be associated with the incidence of acute  
7 MI. Exposure to PM was not considered in this study.

8 Only a limited number of studies examined the association between ambient SO<sub>2</sub>  
9 concentrations and incidence of acute MI. These studies provide no evidence that exposure to  
10 SO<sub>2</sub> increases the risk of MI.

### **3.2.2.7. Emergency Department Visits and Hospitalizations for Cardiovascular Diseases**

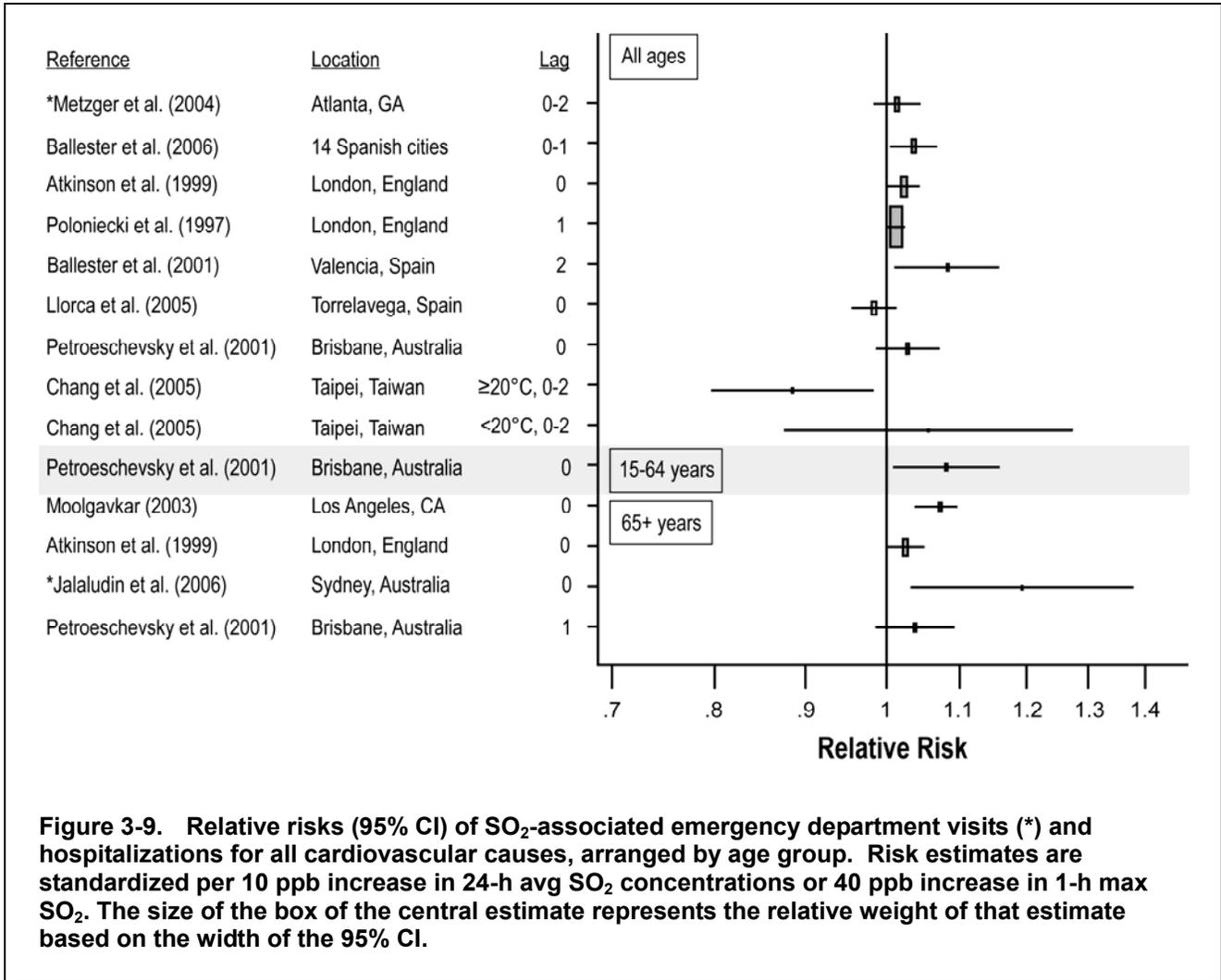
11 The current review includes more than 30 peer-reviewed studies that address the effect of  
12 SO<sub>2</sub> exposure on ED visits or hospitalizations for cardiovascular diseases. These studies are  
13 discussed briefly in this section and further summarized in Annex Table F-4.

#### **3.2.2.7.1. All Cardiovascular Diseases**

14 The disease grouping of all cardiovascular diseases typically includes all diseases of the  
15 circulatory system (e.g., heart diseases and cerebrovascular diseases, ICD9 Codes 390-459). A  
16 summary of the associations reported for ambient SO<sub>2</sub> concentrations with all cardiovascular  
17 diseases are presented in Figure 3-9.

18 In a study of 11 cities in Spain, an excess risk of 3.6% (95% CI: 0.6, 6.7) per 10 ppb  
19 increase in 24-h avg SO<sub>2</sub> at a 0-1 day lag was observed for all cardiovascular disease admissions  
20 (Ballester et al., 2006). The mean 24-h avg SO<sub>2</sub> level in the cities studied was 6.6 ppb. In  
21 addition, time-series data linking SO<sub>2</sub> with hospital admissions for cardiovascular diseases in  
22 three metropolitan areas in the United States (i.e., Cook, Maricopa, Los Angeles Counties) was  
23 conducted (Moolgavkar, 2000; reanalysis, 2003). Among older adults (65+ years) in Los Angeles  
24 County, a 13.7% (95% CI: 11.3, 16.1) excess risk in admissions was observed per 10 ppb  
25 increase in 24-h avg SO<sub>2</sub> at lag 0 day, using a Generalized Linear Model (GLM) and natural  
26 splines to adjust for temporal trends rather than GAM. The median 24-h avg SO<sub>2</sub> level for Los

- 1 Angeles County was 2 ppb during the study period. Results for Maricopa and Cook counties
- 2 were not presented in the reanalysis.



**Figure 3-9. Relative risks (95% CI) of SO<sub>2</sub>-associated emergency department visits (\*) and hospitalizations for all cardiovascular causes, arranged by age group. Risk estimates are standardized per 10 ppb increase in 24-h avg SO<sub>2</sub> concentrations or 40 ppb increase in 1-h max SO<sub>2</sub>. The size of the box of the central estimate represents the relative weight of that estimate based on the width of the 95% CI.**

- 3 In a large single city study Metzger et al. (2004) examined approximately 4.4 million
- 4 hospital visits to 31 hospitals from 1993 to 2000 in Atlanta, GA and reported a 1.4% (95% CI: 1.5, 4.4)
- 5 excess risk in ED visits for cardiovascular causes per 40-ppb increase in 1-h max SO<sub>2</sub>.
- 6 Peel et al. (2006) conducted analyses using the same dataset to compare results obtained with a
- 7 case-crossover design to the Metzger et al. (2007) results, which were obtained using a time
- 8 series approach. Peel et al. and Metzger et al. report similar findings. The median 1-h max SO<sub>2</sub>
- 9 level in Atlanta during the study period was 11 ppb (10th–90th percentile: 2–39). Results from
- 10 several single-city studies in Europe, Australia, and Taiwan indicated positive associations with

1 SO<sub>2</sub> (Atkinson et al., 1999a; Ballester et al., 2001; Jalaludin et al., 2006; Petroeschevsky et al.,  
2 2001; Poloniecki et al., 1997), though others observed negative associations (Chang et al., 2005;  
3 Llorca et al., 2005) (see Figure 3-9).

### 3.2.2.7.2. Specific Cardiovascular Diseases

4 Several studies examined the effect of ambient SO<sub>2</sub> on hospital admissions for cardiac  
5 disease (ICD9 Codes 390-429), ischemic heart disease (IHD, ICD9 Codes 410-414),  
6 dysrhythmia (ICD9 Code 427), congestive heart failure (CHF, ICD9 Code 428), MI (410) or  
7 cerebrovascular diseases (ICD9 Codes 430-438). A European multicity study reported  
8 statistically significant positive associations with cardiac disease admissions (Ballester et al.,  
9 2006). However, adjustment for PM<sub>10</sub> and CO in two-pollutant models diminished the  
10 association reported by Ballester et al. by approximately 50%. Findings for cardiac disease  
11 admissions reported in several additional single city studies conducted in the United States,  
12 Canada, Australia and Europe were inconsistent (Fung et al., 2005; Jalaludin et al., 2006; Llorca  
13 et al., 2005; Michaud et al., 2004).

14 Analyses restricted to diagnoses of IHD (Jalaludin et al., 2006; Lee et al., 2003; Lin et al.,  
15 2003a; Metzger et al., 2004; Peel et al., 2007), CHF (Koken et al., 2003; Metzger et al., 2004;  
16 Morris et al., 1995; Peel et al., 2007; Wellenius et al., 2005b), dysrhythmia (Koken et al., 2003;  
17 Metzger et al., 2004; Peel et al., 2007), MI (Koken et al., 2003; Lin et al., 2003a), and angina  
18 pectoris (Hosseinpoor et al., 2005) were also conducted. Metzger et al. (2004) observed weak  
19 nonsignificant or negative associations of 1-h max SO<sub>2</sub> with IHD, CHF, and dysrhythmia. Using  
20 the same dataset, Peel et al. (2007) investigated effect modification of cardiovascular disease  
21 outcomes across comorbid disease status categories, including hypertension, diabetes, COPD,  
22 dysrhythmia, and CHF. Authors observed only weak nonsignificant or negative associations for  
23 IHD, CHF, and dysrhythmia with ambient 1-h max SO<sub>2</sub> level in any comorbid disease category.  
24 Both increases in admissions or ED visits (Jalaludin et al., 2006; Koken et al., 2003; Wellenius et  
25 al., 2005a) and weak or negative associations (Hosseinpoor et al., 2005; Lee et al., 2003b; Lin et  
26 al., 2003a) were reported in other studies.

27 Studies of the effect of SO<sub>2</sub> on cerebrovascular admissions were also considered. Positive  
28 associations were reported for ischemic stroke (Villeneuve et al., 2006; Wellenius et al., 2005b;  
29 Wellenius et al., 2005a). However Wellenius et al. (2005b) reported stronger associations for

1 NO<sub>2</sub> and CO than SO<sub>2</sub>, and the association reported by Villeneuve et al. (2006) was diminished  
2 in two-pollutant models. No meaningful positive associations of ambient SO<sub>2</sub> with  
3 cerebrovascular diseases were observed in several other studies (Henrotin et al., 2007; Jalaludin  
4 et al., 2006; Metzger et al., 2004; Peel et al., 2007; Tsai et al., 2003).

### **3.2.2.7.3. Summary of Evidence on Emergency Department Visits and Hospitalizations from Cardiovascular Diseases**

5 Several studies have observed positive associations between ambient SO<sub>2</sub> concentrations  
6 and ED visits or hospital admissions for cardiovascular diseases (e.g., all cardiovascular diseases,  
7 cardiac diseases, cerebrovascular diseases) particularly among individuals 65+ years of age, but  
8 results are not consistent across studies. The strongest evidence comes from a large multicity  
9 study conducted in Spain (Ballester et al., 2006) that observed statistically significant positive  
10 associations between ambient SO<sub>2</sub> and cardiovascular disease admissions; however, the SO<sub>2</sub>  
11 effect was found to diminish by half with PM<sub>10</sub> and CO adjustment. Only a limited number of  
12 studies assessed potential confounding by copollutants despite the moderate to strong correlation  
13 between SO<sub>2</sub> and various copollutants in most studies. While some studies suggest that the  
14 association of SO<sub>2</sub> with cardiovascular hospitalizations were generally robust to adjustment for  
15 BS and PM<sub>10</sub> (Ballester et al., 2001; Fung et al., 2005), several other studies, including that by  
16 Ballester et al. (2006), observed that the effect of SO<sub>2</sub> on cardiovascular ED visits and  
17 hospitalizations may be confounded by copollutant exposures. Jalaludin et al. (2006) reported a  
18 3% excess risk in cardiovascular disease hospital admissions per 0.75 ppb incremental change in  
19 24-h avg SO<sub>2</sub> in single-pollutant models, which was reduced to null when CO was included.  
20 Chang et al. (2005) noted that the observed negative association of SO<sub>2</sub> with all cardiovascular  
21 disease hospitalizations they observed was strengthened after adjusting for NO<sub>2</sub>, PM<sub>10</sub>, and CO  
22 in two-pollutant models. The authors attributed this finding to possible collinearity problems  
23 between SO<sub>2</sub> and copollutants. None of the epidemiological studies examined effects of possible  
24 interactions among copollutants.

### **3.2.2.8. Summary of Evidence on the Effect of Short-Term SO<sub>2</sub> Exposure on Cardiovascular Health**

25 The overall evidence on the effect of short-term exposure to SO<sub>2</sub> on cardiovascular health  
26 effects is *inadequate to infer the presence or absence of a causal relationship*. Epidemiological

1 studies of HRV, cardiac repolarization changes, and cardiac rhythm disorders provide limited  
2 evidence of associations with short-term exposure to SO<sub>2</sub>. There was some suggestive evidence  
3 of an association between SO<sub>2</sub> exposure and HRV in the epidemiological studies, but the  
4 evidence from two human clinical studies were weak and inconsistent. Similarly, several studies  
5 observed positive associations between ambient SO<sub>2</sub> concentrations and ED visits or hospital  
6 admissions for cardiovascular diseases, but results were not consistent across studies and specific  
7 cardiovascular disease outcomes. In general, most epidemiological studies observed that these  
8 cardiac outcomes were associated more strongly with PM compared to SO<sub>2</sub>. In the limited  
9 studies that examined potential confounding by copollutants using multipollutant models, the  
10 SO<sub>2</sub> effect was generally found to diminish with adjustment for PM indices or CO.

11         Given the lack of coherence among the cardiovascular outcomes examined and the limited  
12 evidence available to evaluate potential confounding and interaction by copollutants, the overall  
13 evidence for cardiovascular health effects following exposure to ambient SO<sub>2</sub> is weak and  
14 insufficient to make a causal determination.

### **3.2.3. Other Effects Associated with Short-Term SO<sub>2</sub> Exposure**

15         The short-term effects of SO<sub>2</sub> on other organ systems were not examined in the previous  
16 review. A review of animal toxicological studies published since the 1982 AQCD indicates a  
17 limited number of research inquiries addressing the systemic effects of short-term SO<sub>2</sub> exposure  
18 in various other organs. The most recent studies on these are summarized in Annex Tables E-6  
19 through E-9 and E-22 through E-24.

20         Of note are three ex vivo acute exposure studies using SO<sub>2</sub> derivatives (sulfite and  
21 bisulfite) on hippocampal or dorsal root ganglion neurons isolated from Wistar rats (Du and  
22 Meng, 2004a; b; 2006). Perturbations were observed in potassium-, sodium-, and calcium-gated  
23 channels at concentrations of 0.01-100 μM. These authors speculated that such effects might  
24 correlate with the neurotoxicity that has been associated with SO<sub>2</sub> inhalation. However effects on  
25 the nervous system have generally been studied using chronic exposures ≥ 5 ppm SO<sub>2</sub>. Effects  
26 observed at these levels are of questionable significance in evaluating the health effects at  
27 ambient levels. These studies are summarized in Annex Table E-6.

## 3.3. Mortality Associated with Short-Term SO<sub>2</sub> Exposure

### 3.3.1. Summary of Findings from the Previous Review

1           The studies available to review in the 1982 AQCD were mostly from historical data  
2 including London, England, and New York City air pollution episodes. Effects of SO<sub>x</sub> (mainly  
3 SO<sub>2</sub>) were investigated along with PM indices because they shared a common source, coal  
4 burning, and separating their associations with mortality was a challenge that many of the earlier  
5 episodic studies could not resolve. The SO<sub>2</sub> levels observed in these air pollution episodes were  
6 several orders of magnitude higher than the current average levels observed in U.S. cities (e.g., in  
7 the 1962 New York City episode, SO<sub>2</sub> in Manhattan peaked at 400 to 500 ppb). Some of these  
8 London and New York City studies suggested that PM, not SO<sub>2</sub>, was associated with observed  
9 mortality, but the 1982 AQCD could not resolve the relative roles of these two pollutants and  
10 suggested that the clearest mortality associations were seen when both pollutants were at high  
11 levels (24-h avg values of both BS and SO<sub>2</sub> exceeding 1000 µg/m<sup>3</sup> [~400 ppb for SO<sub>2</sub>]) and less  
12 so at lower ranges although the review of the studies and reanalyses found no clear evidence of a  
13 threshold for SO<sub>2</sub>.

14           The 1986 Second Addendum to the 1982 AQCD reviewed more reanalyses of the London  
15 data and analyses of New York City, Pittsburgh, and Athens data. While these reanalyses and  
16 some new analyses confirmed earlier findings (and suggested stronger evidence of BS effects  
17 than of the SO<sub>2</sub> effects), given the remaining uncertainties with exposure error and statistical  
18 modeling, there was not sufficient information to quantitatively determine concentration-  
19 response relationships at lower concentrations of either PM or SO<sub>2</sub>.

20           A series of short-term mortality effects studies in the late 1980s and early 1990s (Pope,  
21 1989; Fairley, 1990; Dockery et al., 1992; Pope et al., 1992; Schwartz and Dockery, 1992)  
22 showed associations between mortality and PM indices at relatively low levels. Since then, a  
23 large number of epidemiological studies have investigated the adverse health effects of air  
24 pollution with hypotheses mainly focused on PM, and SO<sub>2</sub> was often analyzed as one of the  
25 potential confounders in these studies.

### **3.3.2. Associations of Mortality and Short-Term SO<sub>2</sub> Exposure in Multicity Studies and Meta-Analyses**

1 In reviewing the range of SO<sub>2</sub> mortality effect estimates, multicity studies provide  
2 especially useful information because they analyze data from multiple cities using a consistent  
3 method, avoiding potential publication bias. There have been several multicity studies from the  
4 United States, Canada, and Europe, some of which will be discussed in the sections below. Meta-  
5 analysis studies also provide useful information on describing heterogeneity of effect estimates  
6 across studies; however, in contrast to multicity studies, the observed heterogeneity may reflect  
7 the variation in analytical approaches across studies. In addition, the effect estimate from a meta-  
8 analysis may be subject to publication bias, unless the analysis specifically examines such bias  
9 and adjusts for it. These studies, as well as many other single-city studies, are summarized in  
10 Annex Table F-5.

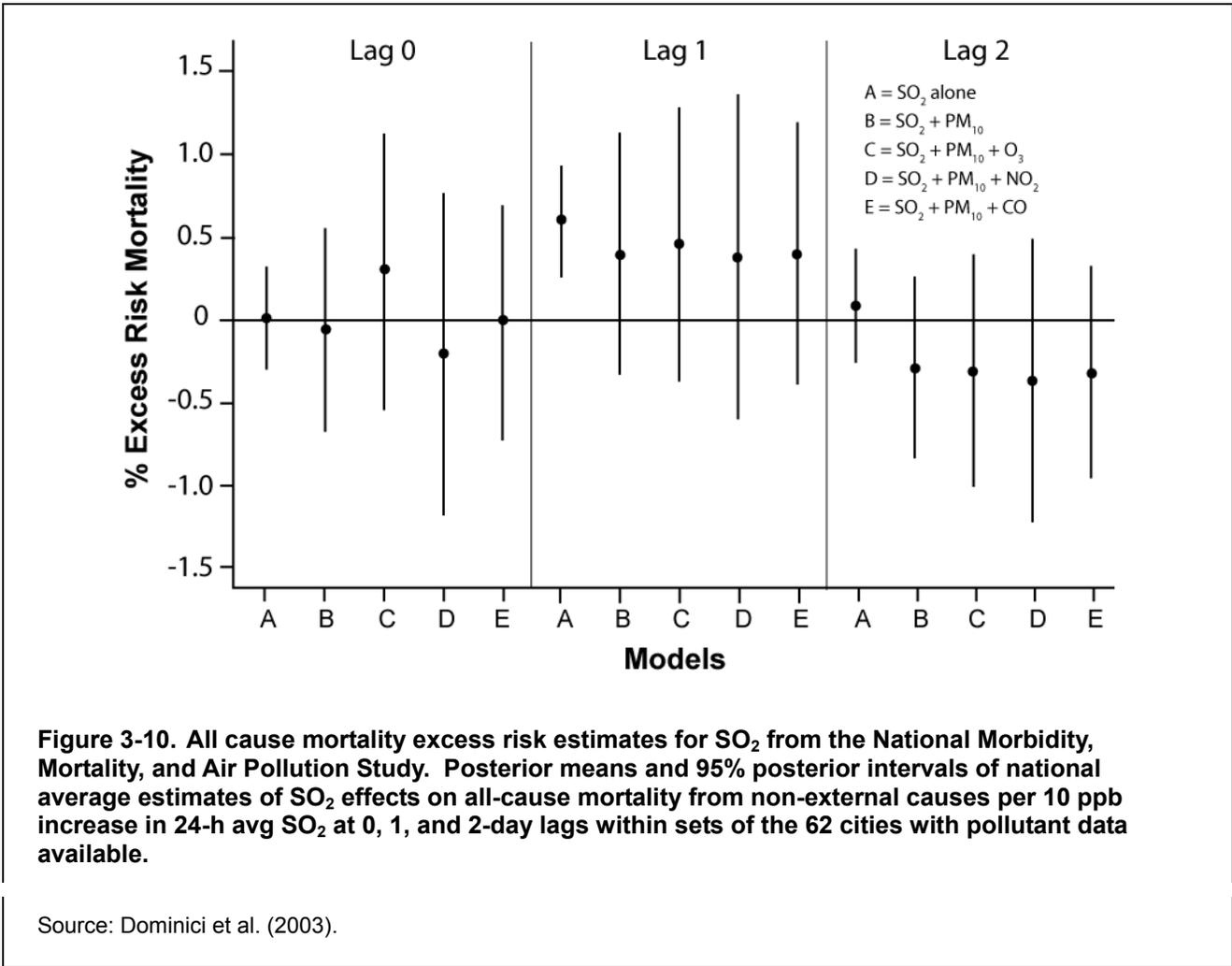
#### **3.3.2.1.1. Multicity Studies**

#### **3.3.2.1.2. National Morbidity, Mortality, and Air Pollution Study**

11 The time-series analysis of the largest 90 U.S. cities (Samet et al., 2000; reanalysis  
12 Dominici et al., 2003) in the National Morbidity, Mortality, and Air Pollution Study (NMMAPS)  
13 is by far the largest multicity study conducted to date to investigate the mortality effects of air  
14 pollution, but its primary focus was PM<sub>10</sub>. It should also be noted that, according to the table of  
15 mean pollution levels in the original report (Samet et al., 2000), SO<sub>2</sub> data were missing in 28 of  
16 90 cities. Annual 24-h avg mean SO<sub>2</sub> levels ranged from 0.4 ppb (Riverside, CA) to 14.2 ppb  
17 (Pittsburgh, PA), with a mean of 5.9 ppb during the study period of 1987 to 1994. The analysis in  
18 the original report used GAM models with default convergence criteria. Dominici et al. (2003)  
19 reanalyzed the data using GAM with stringent convergence criteria as well as using GLM. It  
20 should be noted that this model's adjustment for weather effects employs more terms than other  
21 time-series studies in the literature, suggesting that the model adjusts for potential confounders  
22 more aggressively than the models in other studies.

23 Figure 3-10 shows the all-cause mortality excess risk estimates for SO<sub>2</sub> from Dominici  
24 et al. (2003). The mortality excess risk estimate with a 1-day lag was 0.60% (95% CI: 0.26, 0.95)  
25 per 10 ppb increase in 24-h avg SO<sub>2</sub>. PM<sub>10</sub> and O<sub>3</sub> (in summer) appeared to be more strongly  
26 associated with mortality compared to the other gaseous pollutants. The model with PM<sub>10</sub> and

1 NO<sub>2</sub> resulted in an appreciably reduced SO<sub>2</sub> excess risk estimate, 0.38% (95% CI: -0.62, 1.38)  
 2 per 10 ppb increase in 24-h avg SO<sub>2</sub>. These results suggest that the observed SO<sub>2</sub>-mortality  
 3 association could be confounded by PM<sub>10</sub> and NO<sub>2</sub>. The authors stated that the results did not  
 4 indicate associations of SO<sub>2</sub>, NO<sub>2</sub>, and CO with all-cause mortality.



### 3.3.2.1.3. Canadian Multicity Studies

5 There have been three Canadian multicity studies conducted by the same group of  
 6 investigators examining the association between mortality and short-term exposure to air  
 7 pollutants (Burnett et al., 1998; 2000b; 2004). This section focuses on Burnett et al. (2004) as  
 8 this study is the most extensive Canadian multicity study, both in terms of the length and  
 9 coverage of cities. The discussion in this study focused on NO<sub>2</sub>, because NO<sub>2</sub> was the best

1 predictor of short-term mortality fluctuations among the pollutants. This was also the case in the  
2 Burnett et al. (1998) study of the gaseous pollutants in 11 Canadian cities. The mean 24-h avg  
3 SO<sub>2</sub> levels across the 12 cities was 5.8 ppb, with city means ranging from 1 ppb in Winnipeg to  
4 10 ppb in Halifax. The population-weighted average was 5 ppb. The mean SO<sub>2</sub> levels in this  
5 study were similar to those in the NMMAPS (mean 24-h avg SO<sub>2</sub> levels across the 62 NMMAPS  
6 cities was 5.9 ppb).

7 All-cause (nonaccidental), cardiovascular, and respiratory mortality were analyzed in  
8 Burnett et al. (2004). For SO<sub>2</sub>, PM<sub>2.5</sub>, PM<sub>10-2.5</sub>, PM<sub>10</sub> (arithmetic addition of PM<sub>2.5</sub> and PM<sub>10-2.5</sub>),  
9 CoH, and CO, the strongest mortality association was found at a 1-day lag, whereas for NO<sub>2</sub>, it  
10 was the 3-day moving average (i.e., average of 0, 1, and 2-day lags), and for O<sub>3</sub>, it was the 2-day  
11 moving average. The daily 24-h avg values showed stronger associations than the daily 1-h max  
12 values for all the gaseous pollutants and CoH except for O<sub>3</sub>. The SO<sub>2</sub> all-cause mortality excess  
13 risk estimate was 0.74% (95% CI: 0.29, 1.19) per 10 ppb increase in the 24-h avg SO<sub>2</sub> with a 1-  
14 day lag. After adjusting for NO<sub>2</sub>, the SO<sub>2</sub> effect estimate was reduced to 0.42% (95% CI: 0.01,  
15 0.84), while the NO<sub>2</sub> effect estimate was only slightly affected. In this analysis, no regression  
16 analysis using both SO<sub>2</sub> and PM was conducted. The Burnett et al. (2000) analysis observed that  
17 the simultaneous inclusion of SO<sub>2</sub> and PM<sub>2.5</sub> in the model reduced the SO<sub>2</sub> effect estimate by  
18 half, whereas the PM<sub>2.5</sub> estimate was only slightly reduced. Overall, these results suggest that  
19 SO<sub>2</sub> was not an important predictor of daily mortality in the Canadian cities and that its mortality  
20 associations could be confounded with NO<sub>2</sub> or PM.

#### **3.3.2.1.4. Air Pollution and Health: A European Approach**

21 Several Air Pollution and Health: a European Approach (APHEA) analyses have reported  
22 SO<sub>2</sub> mortality excess risk estimates. Katsouyanni et al. (1997) examined the association of PM<sub>10</sub>,  
23 BS, and SO<sub>2</sub> with all-cause mortality in 12 European cities using the standard APHEA (GLM)  
24 approach. The same data set was reanalyzed to adjust for the seasonal cycles (Samoli et al., 2001;  
25 2003). The reanalysis by Samoli et al. (2003) produced results that were similar to those in the  
26 original analysis by Katsouyanni et al. (1997). Since the original analysis presented more results,  
27 including multipollutant model results, discussion will focus on this analysis.

28 The study by Katsouyanni et al. includes seven western European cities (Athens,  
29 Barcelona, Cologne, London, Lyon, Milan, and Paris) and five central eastern European cities

1 (Bratislava, Krakow, Lodz, Poznan, and Wroclaw). The data covered at least 5 consecutive years  
2 for each city within the years 1980 through 1992. The SO<sub>2</sub> levels in these cities were generally  
3 higher than in the United States or Canada, with the median 24-h avg SO<sub>2</sub> ranging from 5 ppb in  
4 Bratislava to 28 ppb in Krakow. Analysis was restricted to days when PM and SO<sub>2</sub>  
5 concentrations did not exceed 200 µg/m<sup>3</sup> (76 ppb for SO<sub>2</sub>) to evaluate the effects of moderate to  
6 low exposures. The data were analyzed by each center separately following a standardized  
7 method, but the lag for the “best” model was allowed to vary in these cities from 0 to 3 days. The  
8 city-specific effect estimates were then examined in the second stage for source of heterogeneity  
9 using city-specific variables such as mean pollution and weather variables, accuracy of the air  
10 pollution measurements, health of the population, smoking prevalence, and geographical  
11 differences.

12 The city-specific estimates were found to be heterogeneous and, among the explanatory  
13 variables, only the separation between western and central eastern European cities resulted in  
14 more homogeneous groups. The all-cause mortality excess risk estimates were 1.14% (95% CI:  
15 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  
16 combined, western cities, and central eastern cities, respectively, per 10 ppb increase in the  
17 24-h avg SO<sub>2</sub> at variable single-day lags. Zmirou et al. (1998) analyzed cardiovascular and  
18 respiratory mortality in 10 of the 12 APHEA cities and observed that the cause-specific mortality  
19 excess risk estimates were higher than those for all-cause mortality. As in the analyses of all-  
20 cause mortality, SO<sub>2</sub> effect estimates for these cause specific deaths were higher in western  
21 European cities than in central eastern European cities.

22 Seasonal analyses indicated that the summer estimate was slightly higher than the winter  
23 estimate in the western cities, but the difference was not statistically significant. The results for  
24 the two-pollutant model with SO<sub>2</sub> and BS were presented for the western cities, with a similar  
25 extent (~30%) of reductions in the estimates of both pollutants (1.31% [95% CI: 0.40, 2.23] for  
26 SO<sub>2</sub>). Furthermore, for western cities, they estimated effects for SO<sub>2</sub> for days with high or low  
27 BS levels and the corresponding BS effects for days with high or low SO<sub>2</sub> levels and found that  
28 the effects were similar in the stratified data. From these results, Katsuoanni et al. (1997)  
29 suggested that the effects of the two pollutants were independent.

30 Overall, the APHEA studies provide some suggestive evidence that the effect of short-term  
31 exposure to SO<sub>2</sub> on mortality is independent of PM. This is somewhat in contrast to the U.S. and

1 Canadian studies. The SO<sub>2</sub> levels were much higher in the European cities, but the type of PM  
2 constituents also might be different.

### 3.3.2.1.5. The Netherlands Study

3 In the Netherlands studies by Hoek et al. (Hoek et al., 2000; 2001; reanalysis, Hoek, 2003),  
4 the association between air pollutants and mortality were examined in a large population (14.8  
5 million for the entire country) over the period of 1986 through 1994. The Netherlands were not  
6 part of the APHEA analysis. The median 24-h avg SO<sub>2</sub> level in the Netherlands was 4 ppb (6 ppb  
7 for the four major cities). All the pollutants examined, including PM<sub>10</sub>, BS, O<sub>3</sub>, NO<sub>2</sub>, SO<sub>2</sub>, CO,  
8 sulfate, and nitrate, were associated with all-cause mortality, and for single-day models, a 1-day  
9 lag showed the strongest associations for all the pollutants. The following effect estimates are all  
10 from the GLM models with natural splines for smoothing functions. The SO<sub>2</sub> excess risk  
11 estimate in a single-pollutant model was 1.31% (95% CI: 0.69, 1.93) per 10 ppb increase in  
12 24-h avg SO<sub>2</sub> at a 1-day lag and 1.78% (95% CI: 0.86, 2.70) at an average of 0- to 6-day lag.  
13 Seasonal analyses showed slightly greater effect estimates during the summer compared to the  
14 winter. SO<sub>2</sub> was most highly correlated with BS (r = 0.70). The simultaneous inclusion of SO<sub>2</sub>  
15 and BS reduced the effect estimates for both pollutants (SO<sub>2</sub> effect estimate was 1.07% [95% CI:  
16 -0.27, 2.42] per 10 ppb increase with an average of 0- to 6-day lag of 24-h avg SO<sub>2</sub>). PM<sub>10</sub> was  
17 less correlated with SO<sub>2</sub> (r = 0.65), and the simultaneous inclusion of these pollutants resulted in  
18 an increase in the SO<sub>2</sub> effect estimate. These results from the analysis of the Netherlands data  
19 suggested some indication of confounding between SO<sub>2</sub> and BS.

20 Cause specific analysis showed larger excess risk estimates for COPD (3.61% [95% CI: -  
21 0.29, 7.67] per 10 ppb increase in the average of 0- through 6-day lags of 24-h avg SO<sub>2</sub>) and  
22 pneumonia (6.56% [95% CI: 1.16, 12.24]) deaths compared to that from all causes, but because  
23 essentially all of the pollutants showed larger effect estimates for these sub-categories, it is  
24 difficult to interpret these estimates as effects of SO<sub>2</sub> alone. Similarly, the effect estimates for  
25 heart failure (7.1% [95% CI: 2.6, 11.7]) and thrombosis-related deaths (9.6% [95% CI: 3.1,  
26 16.6]) were larger than that for total cardiovascular (2.7% [95% CI: 1.3, 4.1]) causes. Since the  
27 same pattern was seen for other pollutants as well, it is difficult to interpret these cause-specific  
28 effect estimates due to SO<sub>2</sub> alone or any one of the pollutants analyzed.

### 3.3.2.1.6. Other European Multicity Studies

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

5 Biggeri et al. analyzed eight Italian cities (Turin, Milan, Verona, Ravenna, Bologna,  
6 Florence, Rome, and Palermo) for mortality and hospital admissions (mortality data were not  
7 available for Ravenna and Verona). The study period varied from city to city between 1990 and  
8 1999. Only single-pollutant models were examined in this study. The SO<sub>2</sub> excess risk estimates  
9 were 4.14% (95% CI: 1.05, 7.33), 4.94% (95% CI: 0.41, 9.67), and 7.37% (95% CI: -3.58,  
10 19.57) per 10 ppb increase with an average of 0- and 1-day lag of 24-h avg SO<sub>2</sub> for all-cause,  
11 cardiovascular, and respiratory deaths, respectively. Since all the pollutants showed positive  
12 associations with these mortality categories and the correlations among the pollutants were not  
13 presented, it is not clear how much of the observed associations are shared or confounded. The  
14 mortality excess risk estimates were not heterogeneous across cities for all the gaseous  
15 pollutants. It should be noted that in Turin, Milan, and Rome, the mean SO<sub>2</sub> values declined by  
16 50% from the first half to the second half of the study period, while the levels of other pollutants  
17 declined by smaller fractions. This also complicates the interpretation of SO<sub>2</sub> effect estimates in  
18 this study, which are much higher than those from the APHEA studies.

19 The Le Tertre et al. study of nine French cities examined BS, SO<sub>2</sub>, NO<sub>2</sub>, and O<sub>3</sub> by  
20 generally following the APHEA protocol, but using GAM with default convergence criteria and  
21 using the average of lags 0 and 1 day for combined estimates. SO<sub>2</sub> data were not available in one  
22 of the nine cities (Toulouse). All four pollutants were positively associated with mortality  
23 outcomes. The study did not report descriptions of correlation among the pollutants or conduct  
24 multipollutant models, and therefore, it is difficult to assess the potential extent of confounding  
25 among these pollutants. The SO<sub>2</sub> effect estimates were homogeneous across cities, with the  
26 exception of Bordeaux, which was the only city that used strong acidity as a proxy for SO<sub>2</sub>.

27 The Spanish Multicentre Study on Air Pollution and Mortality (EMECAM) examined the  
28 association of PM indices (i.e., PM<sub>10</sub>, TSP, BS) and SO<sub>2</sub> with mortality in 13 cities (Ballester et  
29 al., 2002). These studies followed the APHEA protocol, but using the GAM approach. The daily  
30 mean 24-h avg SO<sub>2</sub> concentrations ranged from 3 to 17 ppb. In the seven cities where 1-h max

1 SO<sub>2</sub> data were also available, mean concentrations ranged from 21 to 43 ppb. The combined  
2 effect estimates for all-cause and respiratory mortality were statistically significant for both  
3 24-h avg SO<sub>2</sub> and 1-h max SO<sub>2</sub>. Controlling for PM indices substantially diminished the effect  
4 estimates for 24-h avg SO<sub>2</sub>, but not for 1-h max SO<sub>2</sub>. The authors reported that these results  
5 could indicate an independent impact of peak values of SO<sub>2</sub> more than an effect due to a longer  
6 exposure.

### **3.3.2.2. Meta-Analyses of Air Pollution-Related Mortality Studies**

#### **3.3.2.2.1. Meta-Analysis of All Criteria Pollutants**

7 Stieb et al. (2002) reviewed time-series mortality studies published between 1985 and  
8 2000, and conducted a meta-analysis to estimate combined effects for PM<sub>10</sub>, CO, NO<sub>2</sub>, O<sub>3</sub>, and  
9 SO<sub>2</sub>. Since many of the studies reviewed in that analysis used GAM with default convergence  
10 parameters, Stieb et al. (2003) updated the estimates by separating the GAM versus non-GAM  
11 studies. In addition, separate combined estimates were presented for single- and multipollutant  
12 models. There were more GAM estimates than non-GAM estimates for all the pollutants except  
13 for SO<sub>2</sub>. For SO<sub>2</sub>, there were 29 non-GAM estimates from single-pollutant models and 10  
14 estimates from multipollutant models. The lags and multiday averaging used in these estimates  
15 varied. The combined estimate for all-cause mortality was 0.95% (95% CI: 0.64, 1.27) per  
16 10 ppb increase in 24-h avg SO<sub>2</sub> from the single-pollutant models and 0.85% (95% CI: 0.32,  
17 1.39) from the multipollutant models. Because these estimates are not from an identical set of  
18 studies, the difference (or lack of a difference, as in this case) between the two estimates may not  
19 necessarily be due to the effect of adding a copollutant in the model. Note that the data extraction  
20 procedure of this meta-analysis for the multipollutant models was to include from each study the  
21 multipollutant model that resulted in the greatest reduction in effect estimates compared with that  
22 observed in single-pollutant models. It should also be noted that all the multicity studies whose  
23 combined estimates have been discussed in the previous section were published after this meta-  
24 analysis.

#### **3.3.2.2.2. Health Effects Institute Review of Air Pollution Studies in Asia**

25 The Health Effects Institute (HEI) conducted a comprehensive review of air pollution  
26 health effects studies (HEI, 2004). They summarized the results from mortality and hospital

1 admission studies of the health effects of ambient air pollution in Asia (East, South, and  
2 Southeast) published in peer-reviewed scientific literature from 1980 through 2003. Of the 138  
3 papers the report identified, most were studies conducted in East Asia (mainland China, Taipei,  
4 Hong Kong, South Korea, and Japan). The levels of SO<sub>2</sub> in these Asian cities were generally  
5 higher than in U.S. or Canadian cities, with more than half of these studies reporting mean  
6 24-h avg SO<sub>2</sub> levels of > 10 ppb. Based on a comparison of the reported mean SO<sub>2</sub> levels from  
7 the same cities in different time periods, it is clear that the SO<sub>2</sub> levels declined significantly in  
8 the 1990s. The meta-analysis used the most recent estimate for each city to reflect recent  
9 pollution levels. Based on the criteria of having at least one year of data, model adjustment for  
10 major time-varying confounders, and reporting effect estimates per unit increase in air pollution,  
11 the meta-analysis included 28 time-series studies (11 from South Korea, 6 from mainland China,  
12 6 from Hong Kong, and 1 each from Taipei, India, Singapore, Thailand, and Japan). The lags  
13 selected to compute combined estimates were inevitably variable; a systematic approach was  
14 used to favor the a priori lag stated in the study, followed by the most significant lag, and then  
15 the largest effect estimate.

16 Among the health outcomes examined in the meta-analysis, all-cause mortality was  
17 addressed in the largest number of studies (13 studies) and SO<sub>2</sub> was the most frequently studied  
18 pollutant (11 studies). The report generally focused on the results of single-pollutant models, as  
19 there were too few studies with results of comparable multipollutant models to allow meaningful  
20 analysis. The SO<sub>2</sub> mortality effect estimates showed evidence of heterogeneity. The combined  
21 estimate for all-cause mortality was 1.49% (95% CI: 0.86, 2.13) per 10 ppb increase in 24-h avg  
22 SO<sub>2</sub>. One of the limitations noted in the report was that some degree of publication bias was  
23 present in these studies.

### **3.3.3. Evidence of the Effect of SO<sub>2</sub> on Mortality from an Intervention Study**

24 Many time-series studies provide estimates of excess risk of mortality, but a question  
25 remains as to the likelihood of a reduction in deaths when SO<sub>2</sub> levels are actually reduced. A  
26 sudden change in regulation in Hong Kong in July 1990 required the conversion to fuel oil with  
27 low sulfur content. The reduction in respiratory symptoms among children living in the polluted  
28 district in Hong Kong after the intervention were previously discussed in Section 3.1.6. Hedley

1 et al. (2002) examined changes in mortality rates following the intervention. The SO<sub>2</sub> levels after  
2 the intervention declined about 50% (from about 17 ppb to 8 ppb), but the levels for PM<sub>10</sub>, NO<sub>2</sub>,  
3 and sulfate did not change and O<sub>3</sub> levels slightly increased. The seasonal mortality analysis  
4 results showed that the apparent reduction in seasonal death rate occurred only during the first  
5 winter, and this was followed by a rebound (i.e., higher than expected death rate) in the  
6 following winter, then returned to the expected pattern three to five years after the intervention.  
7 Using Poisson regression of the monthly deaths, the average annual trend in death rate  
8 significantly declined after the intervention for all causes (2.1%), respiratory causes (3.9%), and  
9 cardiovascular causes (2.0%), but not from other causes. These results seem to suggest that a  
10 reduction in SO<sub>2</sub> leads to an immediate reduction in deaths and a continuing decline in the annual  
11 trend in death rates. Hedley et al. estimated that the expected average gain in life expectancy per  
12 year due to the lower SO<sub>2</sub> levels was 20 days for females and 41 days for males.

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

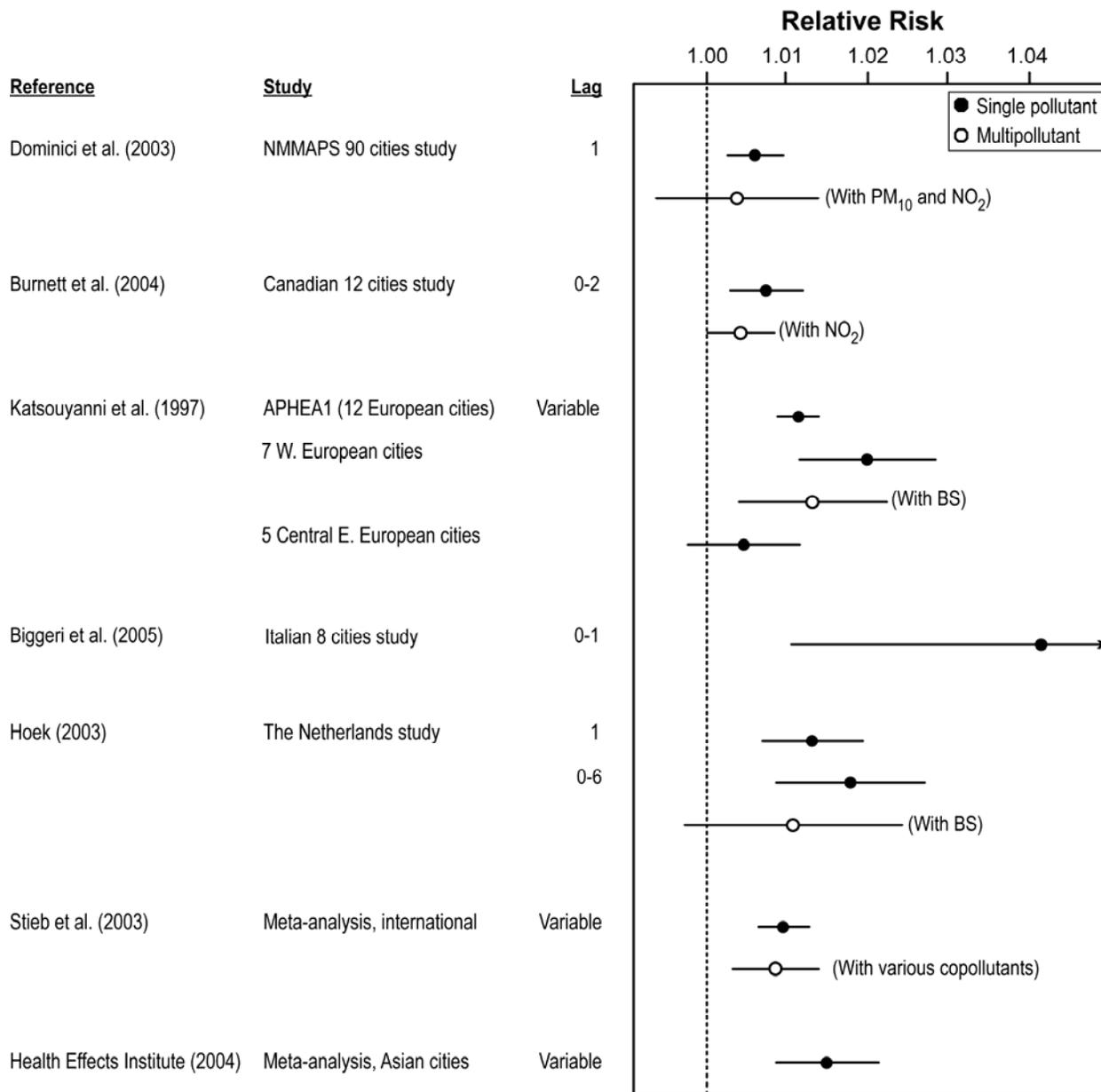
25         The decline in mortality following the intervention does not preclude the possibility that  
26 other constituents of the pollution mixture that share the same source as SO<sub>2</sub> are responsible for  
27 the adverse effects. Even though PM<sub>10</sub> levels before and after the intervention were stable in  
28 Hong Kong, it is possible that constituents that do not explain a major fraction of PM may have  
29 declined. As also noted previously in Section 3.1.6, Hedley et al. (2006) noted large reductions in  
30 ambient nickel and vanadium concomitantly with reductions of sulfur after the intervention. SO<sub>2</sub>  
31 also may be serving as a modifier of the effect of respirable particles. Thus, while the Hong

1 Kong data are supportive of SO<sub>2</sub>-mortality effects, the possibility remains that mortality effects  
2 may be caused by constituents of SO<sub>2</sub>-associated sources.

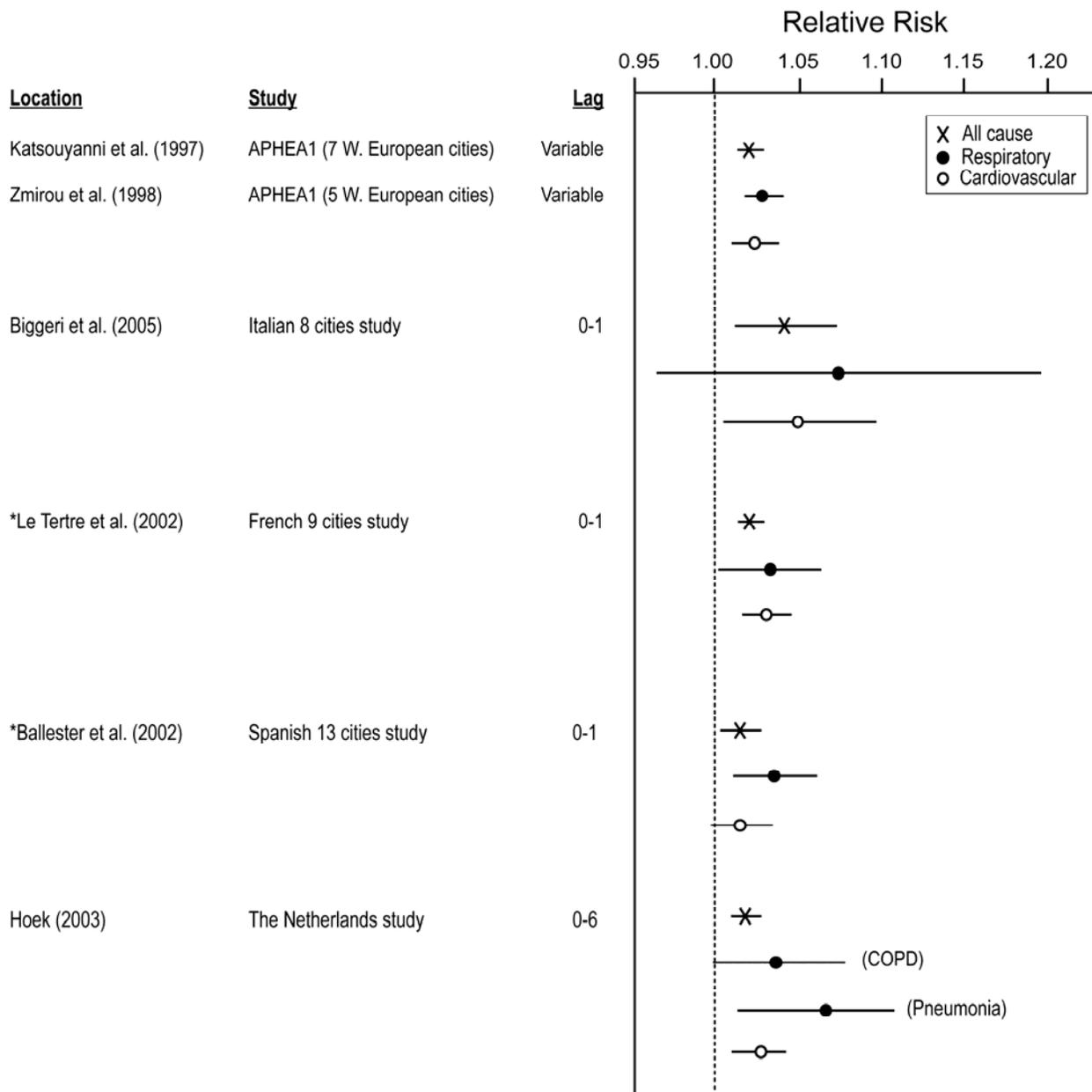
### 3.3.4. Summary of Evidence on the Effect of Short-Term SO<sub>2</sub> Exposure on Mortality

3 The epidemiological evidence on the effect of short-term exposure to SO<sub>2</sub> on all-cause  
4 (nonaccidental) and cardiopulmonary mortality is *suggestive but not sufficient to infer a causal*  
5 *relationship* at ambient concentrations. The epidemiological studies are generally consistent in  
6 reporting positive associations between SO<sub>2</sub> and mortality; however, there was a lack of  
7 robustness of the observed associations to adjustment for copollutants.

8 Figure 3-11 presents all-cause SO<sub>2</sub> mortality excess risk estimates from the multicity  
9 studies and meta-analyses. The mortality effect estimates from single-pollutant models range  
10 from 0.6% (NMMAPS) to 4.1% (Italian 8-cities study) per 10 ppb increase in 24-h avg SO<sub>2</sub>  
11 concentrations, but given the large confidence band in the Italian study, a more stable range may  
12 be 0.6 to 2%. It is noteworthy that the SO<sub>2</sub> effect estimates for the NMMAPS and Canadian 12-  
13 city studies are quite comparable (0.6 and 0.7%, respectively), considering the differences in the  
14 modeling approach. The heterogeneity of estimates in the multicity studies and meta-analyses  
15 may be due to several factors, including the differences in model specifications, averaging/lag  
16 time, SO<sub>2</sub> levels, and effect-modifying factors. Only the APHEA study examined possible  
17 sources of heterogeneity for SO<sub>2</sub>-related mortality. They examined several potential effect  
18 modifiers such as the mean levels of pollution and weather variables, accuracy of the air  
19 pollution measurements, health of the population, smoking prevalence, and geographical  
20 differences. The only variable that could explain the heterogeneity of city-specific effect  
21 estimates was the geographic separation (western versus central eastern European cities) for both  
22 SO<sub>2</sub> and BS, but heterogeneity in the SO<sub>2</sub> effect estimates remained within the western cities.



**Figure 3-11. Relative risks (95% CI) of SO<sub>2</sub>-associated all-cause (nonaccidental) mortality, with and without copollutant adjustment, from multicity and meta-analysis studies. Effect estimates are standardized per 10 ppb increase in 24-h avg SO<sub>2</sub> concentrations. For multipollutant models, results from the models that resulted in the greatest reduction in the SO<sub>2</sub> effects are shown. (NMMAPS = National Morbidity, Mortality, and Air Pollution Study; APHEA = Air Pollution and Health: a European Approach)**



**Figure 3-12. Relative risks (95% CI) of SO<sub>2</sub>-associated mortality for all (nonaccidental), respiratory, and cardiovascular causes from multicity studies. Effect estimates are standardized per 10 ppb increase in 24-h avg SO<sub>2</sub> concentrations. (APHEA = Air Pollution and Health: a European Approach)**

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

1 Several multicity studies provided effect estimates for broad cause-specific categories,  
2 typically respiratory and cardiovascular mortality. A summary of these effect estimates, along  
3 with the all-cause mortality estimates for comparison, are presented in Figure 3-12. These results  
4 from multicity studies suggest that the mortality effect estimates for cardiovascular and  
5 respiratory causes were generally larger than that for all-cause mortality, though in some cases  
6 the effects were not statistically significant, possibly because of reduced statistical power by  
7 which to examine cause-specific associations. In these studies, the effect estimates for respiratory  
8 mortality were also found to be larger than the cardiovascular mortality effect estimates,  
9 suggesting a stronger association of SO<sub>2</sub> with respiratory mortality compared to cardiovascular  
10 mortality. This suggestive finding is consistent with the observed greater effects of SO<sub>2</sub> on  
11 respiratory morbidity compared to cardiovascular morbidity.

12 As shown previously in Figure 3-11, the mortality effect estimates from the multipollutant  
13 models in the multicity studies suggest some extent of confounding between SO<sub>2</sub> and PM and/or  
14 results from multicity studies generally suggest some evidence of confounding, in the sense of  
15 instability of effect estimates in multipollutant models. It should be noted, however, that  
16 interpretation of the single- versus multipollutant model results are complicated by potential  
17 interaction among copollutants and differing degrees of measurement error for correlated  
18 pollutants.

19 Very few studies specifically examined possible interactions among the copollutants.  
20 Katsouyanni et al. (1997) examined the effect estimates for SO<sub>2</sub> and BS in seven western  
21 European cities for subsets stratified by high and low levels of the other pollutant and found that  
22 the estimates were similar for days with low or high levels of the other pollutant. From these  
23 results, Katsouyanni et al. suggested that the effects of SO<sub>2</sub> and BS were independent.

24 Other multi- or single-city studies did not consider examination of possible interaction  
25 effects between SO<sub>2</sub> and copollutants.

26 In summary, recent epidemiological studies have reported associations between mortality  
27 and SO<sub>2</sub>, often at mean 24-h avg levels of < 10 ppb. The range of the excess risk estimates for  
28 SO<sub>2</sub> on all-cause mortality is 0.4 to 2% per 10 ppb increase in 24-h avg SO<sub>2</sub> in several multicity  
29 studies and meta-analyses. The effect estimates for more specific categories may be larger. The  
30 larger European study suggests that the observed heterogeneity in SO<sub>2</sub> effect estimates is at least  
31 in part regional. The intervention study from Hong Kong supports the idea that a reduction in

1 SO<sub>2</sub> levels results in a reduction in deaths, but this does not preclude the possibility that the  
2 causal agent is not SO<sub>2</sub> but rather something else that is associated with SO<sub>2</sub> sources. Results  
3 from the multicity studies suggest that SO<sub>2</sub>-mortality excess risk estimates may be confounded to  
4 some extent by copollutants, making a definitive distribution of effects among the pollutants  
5 difficult. However, the interpretation of multipollutant model results also requires caution  
6 because of possible interaction among the copollutants and influence of varying measurement  
7 error. Very limited information was available to determine possible interaction effects between  
8 SO<sub>2</sub> and PM or other copollutants. Overall, the evidence that SO<sub>2</sub> is causally related to mortality  
9 at current ambient levels is suggestive, but limited by potential confounding and lack of  
10 understanding regarding the interaction of SO<sub>2</sub> with copollutants in the epidemiological data.

## **3.4. Morbidity Associated with Long-Term SO<sub>2</sub> Exposure**

### **3.4.1. Summary of Findings from the Previous Review**

11 The 1982 AQCD addressed some effects of long-term SO<sub>2</sub> exposure. It was reported that  
12 bronchoconstriction resulted from chronic exposure to 5.1 ppm SO<sub>2</sub> in dogs but not in monkeys.  
13 This increased pulmonary resistance was thought to occur as a result of morphological changes  
14 in the airway or hypersecretion of mucus leading to airway narrowing. However, there were no  
15 remarkable pulmonary pathological findings in monkeys and dogs in these studies. This could  
16 have been due to the conventional light microscopic examination applied, which could not detect  
17 alterations in surface membranes or subtle changes in cilia.

18 It was also noted that repeated exposures of rats  $\geq 50$  ppm SO<sub>2</sub> produced a chronic  
19 bronchitis similar to that seen in humans although there was no evidence to suggest that  
20 bronchitis developed in humans at ambient levels of SO<sub>2</sub>. Furthermore, nasal mucosal alterations  
21 were observed in mice exposed to 10 ppm SO<sub>2</sub> for 72 h by inhalation. Lack of data on  
22 morphological effects of SO<sub>2</sub> at near ambient concentrations was noted. In addition, some  
23 alterations in lung host defenses were discussed with chronic exposure to SO<sub>2</sub> at doses exceeding  
24 ambient concentrations.

25 In the 1982 AQCD, only a few epidemiological studies provided sufficient quantitative  
26 evidence relating respiratory symptoms or pulmonary functions changes to long-term exposure

1 to SO<sub>2</sub>. Briefly, a study by Lunn et al. (1967) in Sheffield, England, provided the strongest  
2 evidence of an association between pulmonary function decrements and increased frequency of  
3 lower respiratory tract symptoms in 5- to 6-year-old children chronically exposed to ambient BS  
4 (annual level of 230 to 301 µg/m<sup>3</sup>) and SO<sub>2</sub> levels (69 to 105 ppb). A follow-up study in 1968 by  
5 Lunn (1970) found no effect with much lower levels of BS (range: 48, 169 µg/m<sup>3</sup>) and SO<sub>2</sub>  
6 (range: 36, 97 ppb); it was suggested that this might be due to insufficient power to detect small  
7 health effect changes.

8 The 1986 Second Addendum presented three additional studies that examined the effects of  
9 long-term exposure on respiratory health. A study by Ware et al. (1986) reported that respiratory  
10 symptoms were associated with annual average TSP in the range of ~30 to 150 µg/m<sup>3</sup> in children  
11 (n = 8,380) from six U.S. studies. Only cough was found to be significantly associated with SO<sub>2</sub>.  
12 Although the increase in symptoms did not appear concomitantly with any decrements in lung  
13 function, this may indicate different mechanisms of effect. Other studies by Chapman et al.  
14 (1985) and Dodge et al. (1985) also observed increased prevalence of cough among children and  
15 young adults living in areas of higher SO<sub>2</sub> concentrations; however, it was noted that the  
16 observed effects might have been due to intermittent high SO<sub>2</sub> peak concentrations.

17 In addition to respiratory effects from long-term exposure to SO<sub>2</sub>, the potential  
18 carcinogenicity of SO<sub>2</sub> or other SO<sub>x</sub> was also examined in the previous review. The 1982 AQCD  
19 concluded that little or no clear epidemiological evidence substantiated the hypothesized links  
20 between SO<sub>2</sub> or other SO<sub>x</sub> and cancer, though there was some animal toxicological evidence that  
21 led to the conclusion that SO<sub>2</sub> may be considered a suspect carcinogen/cocarcinogen. There was  
22 very limited consideration of the effects of long-term exposure to SO<sub>2</sub> on other organ systems.

23 Since the 1982 AQCD and the 1986 Second Addendum, a number of animal toxicological  
24 and epidemiological studies have investigated the effect of long-term exposure to SO<sub>2</sub> on  
25 respiratory morbidity, including asthma, bronchitis and respiratory symptoms, lung  
26 function, morphological effects, and lung host defense. Additional studies have examined the  
27 effect of long-term SO<sub>2</sub> exposure on genotoxic and carcinogenic effects, cardiovascular effects,  
28 and prenatal and neonatal outcomes, which are also briefly discussed in this section.

## 3.4.2. Respiratory Effects Associated with Long-Term Exposure to SO<sub>2</sub>

### 3.4.2.1. Asthma, Bronchitis, and Respiratory Symptoms

1           Several epidemiological studies have examined the association between long-term  
2 exposure to SO<sub>2</sub> and other air pollutants on asthma, bronchitis, and a variety of respiratory  
3 symptoms. These studies are summarized in Annex Table F-1. In the Six Cities Study of Air  
4 Pollution and Health, cross-sectional associations between air pollutants and respiratory  
5 symptoms were examined in 5,422 white children aged 10 to 12 years old from Watertown, MA,  
6 St. Louis, MO, Portage, WI, Kingston-Harriman, TN, Steubenville, OH, and Topeka, KS  
7 (Dockery et al., 1989). Annual means of 24 h avg SO<sub>2</sub> concentrations ranged from 3.5 ppb in  
8 Topeka to 27.8 ppb in Steubenville. Except for O<sub>3</sub>, the correlations among pairs of pollution  
9 measures varied between 0.53 and 0.98. No associations were observed between SO<sub>2</sub> and a  
10 variety of respiratory symptoms, including bronchitis, chronic cough, chest illness, persistent  
11 wheeze, and asthma. Stronger associations were observed for PM indices.

12           Dockery et al. (1996) examined the respiratory health effects of acid aerosols in 13,369  
13 white children aged 8 to 12 years old from 24 communities in the United States and Canada  
14 between 1988 and 1991. The city-specific annual mean SO<sub>2</sub> concentration was 4.8 ppb, with a  
15 range of 0.2 to 12.9 ppb. With the exception of the gaseous acids, nitrous and nitric acid, none of  
16 the particulate or gaseous pollutants, including SO<sub>2</sub>, were associated with increased asthma or  
17 any asthmatic symptoms. Stronger associations with particulate pollutants were observed for  
18 bronchitis and bronchitic symptoms. For SO<sub>2</sub>, the only significant association found was with  
19 chronic phlegm, with an OR of 1.19 (95% CI: 1.00, 1.40) per 5 ppb increase in SO<sub>2</sub>.

20           Herbarth et al. (2001) performed a meta-analysis of three cross-sectional surveys  
21 conducted in East Germany investigating the relationship between lifetime exposure (from birth  
22 to completion of questionnaire survey) to SO<sub>2</sub> and TSP in children and the prevalence of chronic  
23 bronchitis. Using a logistic model that included variables on parental predisposition (mother or  
24 father with bronchitis) and environmental tobacco smoke exposure, the authors reported that the  
25 OR for bronchitis due to a lifetime exposure to SO<sub>2</sub> was 3.51 (95% CI: 2.56, 4.82) (the  
26 concentration change for which the OR was based was not presented). No associations were  
27 found between TSP and the prevalence of bronchitis in children.

1 As part of the international SAVIAH (Small-Area Variation in Air Pollution and Health)  
2 study, Pikhart et al. (2001) examined the respiratory health effects from long-term exposure to  
3 SO<sub>2</sub> in children (n = 6,959) from two central European cities with high pollution levels (Prague,  
4 Czech Republic, and Poznan, Poland). A novel technique was used to estimate the outdoor  
5 concentrations of SO<sub>2</sub> at a small-area level. Outdoor SO<sub>2</sub> was measured by passive samplers at  
6 130 sites in the two cities during 2-week periods. Concentrations of SO<sub>2</sub> at each location in the  
7 study areas were estimated from these data by modeling using a geographic information system  
8 (GIS). The estimated mean exposure to outdoor SO<sub>2</sub> was 32 ppb, (range: 25, 37) in Prague and  
9 31 ppb, (range: 17, 53) in Poznan. The prevalence of wheezing or whistling in the past 12  
10 months was associated with SO<sub>2</sub> (OR of 1.08 [95% CI: 1.03, 1.13] per 5 ppb increase in SO<sub>2</sub>).  
11 Moreover, the lifetime prevalence of wheezing or whistling (OR 1.03 [95% CI: 1.00, 1.07]) and  
12 lifetime prevalence of physician-diagnosed asthma (OR 1.09 [95% CI: 1.00, 1.19]) also were  
13 associated with SO<sub>2</sub> levels. In the SAVIAH study, the only other pollutant considered in relation  
14 to health outcomes was NO<sub>2</sub>. An earlier publication by Pikhart et al. (2000) presented  
15 preliminary results of the Prague data and indicated that the observed associations between NO<sub>2</sub>  
16 and respiratory symptoms were generally similar to that of SO<sub>2</sub>.

17 The International Study of Asthma and Allergies in Children (ISAAC) included thousands  
18 of children in several European countries and Taiwan (Hirsch et al., 1999; Hwang et al., 2005;  
19 Penard-Morand et al., 2005; Ramadour et al., 2000; Studnicka et al., 1997). Pénard-Morand et al.  
20 examined the effect of long-term exposures to air pollution and prevalence of exercise-induced  
21 bronchial reactivity (EIB), flexural dermatitis, asthma, allergic rhinitis, and atopic dermatitis in  
22 9,615 children aged 9 to 11 years in six French communities. Using 3-year averaged  
23 concentrations of SO<sub>2</sub>, the investigators reported that the prevalence of exercise-induced  
24 bronchial reactivity, lifetime asthma, and allergic rhinitis were significantly associated with  
25 increases in SO<sub>2</sub> exposure. The estimated 3-year averaged concentration of SO<sub>2</sub> was 2 ppb in the  
26 low-exposure schools and 4 ppb in the high-exposure schools. In a single-pollutant model, the  
27 ORs were 2.37 (95% CI: 1.44, 3.77) for EIB and 1.58 (95% CI: 1.00, 2.46) for lifetime asthma  
28 per 5 ppb increase in SO<sub>2</sub>. In this study, SO<sub>2</sub> was correlated with PM<sub>10</sub> (r = 0.76) but not with O<sub>3</sub>  
29 (r = -0.02). Using a two-pollutant model that included PM<sub>10</sub>, the associations of SO<sub>2</sub> with EIB  
30 and lifetime asthma were fairly robust (< 5% change).

1 In a German study of 5,421 children, the annual mean SO<sub>2</sub> concentration was associated  
2 with morning cough reported in the last 12 months, but not bronchitis (Hirsch et al., 1999). This  
3 study further observed that the association of SO<sub>2</sub> and other air pollutants with respiratory  
4 symptoms were stronger in nonatopic than in atopic children. The authors noted that these  
5 findings were in line with the hypothesis that these air pollutants induce nonspecific irritative  
6 rather than allergic inflammatory changes in the airway mucosa, as irritative effects would affect  
7 the clinical course in nonatopic children more strongly than in atopics whose symptoms are also  
8 determined by allergen exposure.

9 In contrast to the studies noted above, other studies using the ISAAC protocol did not  
10 observe an association between long-term exposure to SO<sub>2</sub> and respiratory symptoms. In France,  
11 (Ramadour et al., 2000) performed an epidemiological survey of 2,445 children aged 13 to 14  
12 years living in communities with contrasting levels of air pollution to determine the relationship  
13 between long-term exposure to gaseous air pollutants and prevalence rate of rhinitis, asthma, and  
14 asthma symptoms. The average SO<sub>2</sub> concentrations during the 2-month survey period ranged  
15 from 7 ppb to 22 ppb across the seven communities. This study found no relationship between  
16 the mean levels of SO<sub>2</sub>, NO<sub>2</sub>, or O<sub>3</sub> and the above-mentioned symptoms. Another study of 843  
17 children from eight nonurban communities in Austria did not observe consistent associations  
18 between SO<sub>2</sub> and prevalence of asthma and symptoms (Studnicka et al., 1997). Compared to the  
19 lowest SO<sub>2</sub> concentration category, the ORs in the higher SO<sub>2</sub> concentration categories (third and  
20 fourth quartiles) did not exceed one for any of the symptoms examined (wheeze, cough,  
21 bronchitis, and asthma).

22 A cohort study was conducted by (Goss et al., 2004) to examine the effect of air pollutants  
23 on a potentially susceptible population, patients with cystic fibrosis. Study participants included  
24 11,484 patients (mean age 18.4 years) enrolled in the Cystic Fibrosis Foundation National Patient  
25 Registry in 1999–2000. Exposure was assessed by linking air pollution values from ambient  
26 monitors with the patient's home ZIP code. During the study period, the mean SO<sub>2</sub> concentration  
27 was 4.9 ppb (SD 2.6, IQR: 2.7, 5.9). This study found no association between SO<sub>2</sub> and the odds  
28 of having two or more pulmonary exacerbations. One of the limitations addressed by the authors  
29 was the lack of information regarding tobacco use or environmental tobacco smoke, an important  
30 risk factor for pulmonary exacerbations.

1           Several studies examined the effects of long-term exposure to SO<sub>2</sub> on asthma, bronchitis,  
2 and respiratory symptoms. The studies reported positive associations in children; the notable  
3 exception was the Harvard Six Cities Study. However, there were inconsistencies in the results  
4 observed: some found effects on bronchitic but not asthmatic symptoms; others found the  
5 converse. A major limitation was that some subjects were asked to recall prevalence of  
6 symptoms in the last 12 months or in a lifetime; such long recall periods may have caused  
7 significant recall bias. Another concern is the high correlation of long-term average SO<sub>2</sub> and  
8 copollutant concentrations, particularly PM, and the very limited evaluation of potential  
9 confounding in these studies. Overall, while the evidence is suggestive, the variety of outcomes  
10 examined and the inconsistencies in the observed results make it difficult to assess the direct  
11 impact of long-term exposure of SO<sub>2</sub> on asthma, bronchitis, or respiratory symptoms.

#### **3.4.2.2. Lung Function**

12           Only a few new animal toxicological studies involving longer-term inhalation exposures to  
13 SO<sub>2</sub> were conducted since the last review. These studies are summarized here and in Annex Table  
14 E-1. Rabbits that were neonatally immunized to *Alternaria tenuis* and exposed to 5 ppm SO<sub>2</sub> for  
15 13 weeks beginning in the neonatal period (Douglas et al., 1994) did not demonstrate alterations  
16 in lung resistance, dynamic compliance, trans-pulmonary pressure, tidal volume, respiration rate  
17 or minute volume. Similarly, no changes in physiological function were noted in dogs exposed to  
18 15 ppm SO<sub>2</sub> for 2 h/day and 4-5 days/week for 5 months (Scanlon et al., 1987), although changes  
19 were noted at 50 ppm. However, Smith et al. (1989) found decreased residual volume and  
20 quasistatic compliance in rats at 4 months of exposure to 1 ppm SO<sub>2</sub> for 5 h/day and 5  
21 days/week.

22           Only a limited number of epidemiological studies examined the association between long-  
23 term exposure to SO<sub>2</sub> and changes in lung function. The Harvard Six Cities Study by Dockery  
24 et al. (1989) reported that no associations were observed between lung function and long-term  
25 exposure to air pollution, including SO<sub>2</sub>, in a cohort of more than 5,000 children. An analysis of  
26 NHANES II data by Schwartz (1989), which included information on children and youths from  
27 44 cities but was limited by a cross-sectional study design, also did not observe an association  
28 with SO<sub>2</sub>, though inverse associations of FVC and FEV<sub>1</sub> with annual concentrations of TSP, NO<sub>2</sub>  
29 and O<sub>3</sub> were found. Additional studies conducted in Europe observed mixed results.

1 In a longitudinal cohort study of 1,150 children in nine communities in Austria, Frischer  
2 et al. (1999) examined the effect of long-term exposure to air pollutants on lung function. Lung  
3 function was measured in the spring and fall over a 3-year period from 1994 through 1996.  
4 Annual mean SO<sub>2</sub> concentrations ranged from 2 to 6 ppb across the nine communities. The  
5 authors reported no consistent associations between SO<sub>2</sub>, PM<sub>10</sub>, or NO<sub>2</sub> and lung function. For  
6 SO<sub>2</sub>, a negative parameter estimate was observed during the summer, but a positive estimate was  
7 found during the winter period. Horak et al. (2002a; b) extended the study of Frischer et al.  
8 (1999) with an additional year of data. The mean SO<sub>2</sub> concentration was 6 ppb in the winter and  
9 3 ppb in the summer. This study found a positive association between wintertime SO<sub>2</sub>  
10 concentrations and changes in FVC, which became null with PM<sub>10</sub> in a two-pollutant model.

11 Jedrychowski et al. (1999) conducted a prospective cohort study of 1,001 preadolescent  
12 children from two areas of Krakow, Poland, that differed in ambient air pollutants. In the city  
13 center, which had higher pollution area, the mean annual level of SO<sub>2</sub> was 16.7 ppb (SD 12.5). In  
14 comparison, the mean annual SO<sub>2</sub> level in the control area was 12.1 ppb (SD 8.4). A similar  
15 difference in TSP levels was observed between the city center and control area. The adjusted  
16 ORs comparing the city center to the control area for the occurrence of slower lung function  
17 growth over a two-year period were 2.10 (95% CI: 1.27, 3.46) for FVC and 2.10 (95% CI: 1.27,  
18 3.48) for FEV<sub>1</sub> in boys. The adjusted ORs for girls were 1.54 (95% CI: 0.89, 2.64) for FVC and  
19 1.51 (95% CI: 0.90, 2.53) for FEV<sub>1</sub>. However, as both TSP and SO<sub>2</sub> levels were higher in the city  
20 center, the observed effects on lung function growth cannot be specifically attributable to SO<sub>2</sub>.

21 One notable study examined the potential effect of long-term exposure to air pollution on  
22 lung function in adults. The study by Ackermann-Lieblich et al. (1997) included 9,651 adults  
23 aged 18 to 60 years old residing in eight different areas in Switzerland (Study on Air Pollution  
24 and Lung Diseases in Adults [SAPALDIA]). They observed a 0.1% decrease in FEV<sub>1</sub> per 5 ppb  
25 increase in SO<sub>2</sub> for adults. Significant associations also were observed for PM<sub>10</sub> and NO<sub>2</sub>. The  
26 limited number of study areas and high intercorrelation between the pollutants made it difficult  
27 to assess the effect of an individual pollutant. The authors concluded that air pollution from fossil  
28 fuel combustion, which was the main source of air pollution for SO<sub>2</sub>, NO<sub>2</sub>, and PM<sub>10</sub> in  
29 Switzerland, was associated with decrements in lung function parameters in this study.

1 Collectively, the results from the limited number of animal toxicological and  
2 epidemiological studies do not give support to long-term exposure to ambient SO<sub>2</sub> having a  
3 detrimental effect on lung function.

### 3.4.2.3. Morphological Effects

4 Three animal toxicological studies of morphological effects resulting from subacute to  
5 chronic SO<sub>2</sub> exposures have been published since the 1982 AQCD. These studies are  
6 summarized in Annex Table E-11. No alveolar lesions (including electron microscopic  
7 evaluation) or changes in numbers of tracheal secretory cells were observed in guinea pigs  
8 exposed to 1 ppm SO<sub>2</sub> for 3 h/day for 6 days (Conner et al., 1985). No pulmonary or nasal  
9 lesions were observed in rats exposed to 5 ppm SO<sub>2</sub> for 5 days/week for 4 weeks (Wolff et al.,  
10 1989). A weakness of the latter study is that histopathological methods were not reported.  
11 However, a third study reported histopathological changes in the respiratory system involving  
12 lesions in the bronchioles. Smith et al. (1989) exposed rats for 4 to 8 months to 1 ppm SO<sub>2</sub> for  
13 5 h/day and 5 days/week and observed increased incidence of bronchiolar epithelial hyperplasia  
14 and a small increase (12%) in numbers of nonciliated epithelial cells in terminal respiratory  
15 bronchioles at 4 but not 8 months of exposure. A limitation of the study was the examination of a  
16 single concentration, which does not allow for concentration-response assessment or  
17 identification of a no-effect-level.

18 In summary, results from these animal toxicological studies do not support an association  
19 between long-term exposure to ambient SO<sub>2</sub> and prolonged effects on lung morphology.

### 3.4.2.4. Lung Host Defense

20 The 1982 AQCD reported some detrimental effects of SO<sub>2</sub> on lung host defenses that  
21 generally occurred at concentrations exceeding ambient exposure concentrations. In rats exposed  
22 to 0.1 ppm SO<sub>2</sub> for ~2 to 3 weeks, clearance of labeled particles from the lung was accelerated at  
23 10 and 23 days following exposure. In rats exposed to 1 ppm for ~2 to 3 weeks, clearance was  
24 accelerated at 10 days and slowed down at 25 days. Tracheal mucus flow was decreased with a  
25 1-year exposure of dogs to 1 ppm SO<sub>2</sub>, but was unaffected by a 30-minute exposure of donkeys  
26 to 25 ppm SO<sub>2</sub>. Studies in mice suggested no effect on susceptibility to bacterial infection with

1 exposure to SO<sub>2</sub> concentrations of ≤ 5 ppm for 3 months. Antiviral defenses were impaired in  
2 mice exposed to 7-10 ppm SO<sub>2</sub> for 7 days. No alterations in pulmonary immune system were  
3 reported with chronic exposure of mice to 2 ppm SO<sub>2</sub>.

4 Several studies on lung host defense have been conducted since the last review and are  
5 summarized in Annex Table E-4. Only one study published after the last review evaluated  
6 mucociliary clearance in rats after exposure to SO<sub>2</sub>. In this subchronic study, no effect on  
7 clearance of radiolabeled particles from the lung was observed in rats exposed to 5 ppm SO<sub>2</sub> for  
8 2 h/day for 4 weeks (Wolff et al., 1989). These findings are in contrast to the altered clearance  
9 reported in the 1982 AQCD. Three other recent studies were conducted evaluating the effects of  
10 10 ppm SO<sub>2</sub> on immune responses.

11 In summary, animal toxicological studies do not provide much evidence for long-term  
12 exposure to ambient SO<sub>2</sub> having detrimental effects on lung host defense.

#### **3.4.2.5. SO<sub>2</sub> Interactions with PM and Other Mixtures**

13 An elegant series of experiments was conducted in dogs exposed to 0.31 mg/m<sup>3</sup> neutral  
14 sulfite aerosol for 22.5 h/day for 290 days (Heyder et al., 1992). The aerosol particles were  
15 submicron in size. These studies are summarized in Annex Table E-14. Although sulfite particles  
16 are not usually found in nature, they were engineered and used in these studies for the purpose of  
17 delivering SO<sub>2</sub>-like reactivity to the lower respiratory tract. It should be noted that the reactivity  
18 of SO<sub>2</sub> is due to the IV-valent sulfur, a feature shared by sulfite but not sulfate which has VI-  
19 valent sulfur. The concentration of sulfite particles used in these studies was comparable to  
20 ambient levels of SO<sub>2</sub> on smog-alert days in Germany (i.e., 0.25 ppm). Important findings from  
21 these studies included a significant decrease in specific lung compliance and increase in alveolar-  
22 capillary permeability in sulfite-exposed dogs compared with controls (Maier et al., 1992; Schulz  
23 et al., 1992). In addition, macrophage respiratory burst activity and phagocytic capacity were  
24 significantly decreased while intrapulmonary particle transport to the larynx was increased  
25 (Maier et al., 1992; Kreyling et al., 1992). Morphological effects included hyperplastic changes  
26 in the respiratory mucosa of the nasal cavity and a moderate mononuclear cell infiltration. Loss  
27 of cilia in larynx and trachea was also noted. Some of the dogs also exhibited changes in the  
28 larynx and trachea (Takenaka et al., 1992). The authors concluded that chronic exposure to a low  
29 dose of sulfur (IV) aerosols can initiate a pathophysiological response.

1 A second set of studies was conducted by these same investigators in dogs exposed to  
2 sulfite and sulfate aerosols for 13 months (Heyder et al., 1999). These are summarized in Annex  
3 Table E-14. This protocol involved daily exposures of 16.5 h neutral sulfite aerosol at the same  
4 concentration used in the previous study followed by 6 hrs of an acidic sulfate aerosol at a  
5 concentration of 15.2  $\mu\text{mol}/\text{m}^3$  hydrogen ions. Both aerosols were about 1  $\mu\text{m}$  MMAD in size.  
6 The authors stated that the dose received by each dog in 13 months was equivalent to what a  
7 person living for 70 years in an urban environment would receive. Results of these experiments  
8 demonstrated no change in lung compliance or other measure of lung function in dogs exposed  
9 consecutively to sulfite and sulfate each day (Schulz et al., 1999). Alveolar-capillary  
10 permeability was no different than in controls (Maier et al., 1999). Intrapulmonary particle  
11 transport to the larynx was decreased while transport to the tracheobronchial lymph nodes was  
12 increased in dogs exposed to both sulfite and sulfate (Kreyling et al., 1999). No alteration in the  
13 surfactant system was observed (Griese et al., 1999). Slight morphological effects were observed  
14 in the proximal alveolar region but not in the nasal cavity, larynx or trachea (Takenaka et al.,  
15 1999). The authors attributed this milder response to a modulating effect of the acidic sulfate  
16 aerosol. They concluded that inhalation of low levels of sulfite and hydrogen ion is not likely to  
17 constitute a health risk. These results are somewhat surprising given the pathophysiologic  
18 response to sulfite alone found by these same authors in a similar model. Possibly they indicate  
19 an antagonistic interaction between sulfate and sulfite.

20 In addition to studies examining the interaction of  $\text{SO}_2$  and particles, other animal studies  
21 performed since the 1982 AQCD involved binary mixtures, laboratory-generated complex  
22 mixtures (e.g., simulation of regional air pollution), or actual ambient air mixtures (Annex Tables  
23 E-18 through E-20). Generally, most studies with ambient or laboratory-generated complex  
24 mixtures did not include an  $\text{SO}_2$ -only exposure group, making it difficult to determine the  
25 contribution of  $\text{SO}_x$ . No definitive conclusions can be made from these studies.

#### **3.4.2.6. Summary of Evidence on the Effect of Long-Term Exposure on Respiratory Health**

26 The overall epidemiological evidence on the respiratory effects of long-term exposure to  
27  $\text{SO}_2$  is *inadequate to infer the presence or absence of a causal relationship*. Studies that  
28 examined the effects of long-term exposure to  $\text{SO}_2$  on asthma, bronchitis, and respiratory

1 symptoms observed positive associations in children. However, the variety of outcomes  
2 examined and the inconsistencies in the observed results make it difficult to assess the impact of  
3 long-term exposure of SO<sub>2</sub> on respiratory symptoms. In the limited number of studies examining  
4 the SO<sub>2</sub> associations with lung function, results were generally mixed. A major consideration in  
5 evaluating SO<sub>2</sub>-related health effects in these epidemiological studies of long-term exposure is  
6 the high correlation among the pollutant levels observed, particularly between long-term average  
7 SO<sub>2</sub> and PM concentrations. The lack of evidence available to evaluate potential confounding by  
8 copollutants limits the ability to make a causal determination based on these studies.

9 A limited number of animal toxicological have examined the effect of long-term exposure  
10 to SO<sub>2</sub> on lung function. Results from these studies do not provide strong biological plausibility  
11 for effects of long-term exposure to SO<sub>2</sub> on respiratory morbidity. These studies observed no  
12 effects on physiological lung function at SO<sub>2</sub> concentrations ≤ 5 ppm in rabbits and dogs;  
13 however, one study found decreased residual volume and quasistatic compliance at 1 ppm SO<sub>2</sub> in  
14 rats. In addition, no morphological changes were found in guinea pigs exposed subacutely to  
15 1 ppm SO<sub>2</sub>, or in rats exposed subchronically to 5 ppm SO<sub>2</sub>. While mild, bronchiolar epithelial  
16 hyperplasia was observed in rats exposed to 1 ppm for 4 months, this change was not apparent at  
17 8 months. Furthermore, animal toxicological studies provide no evidence for decrements in lung  
18 host defense at or near ambient levels of SO<sub>2</sub>.

19 Overall, results from the generally limited number of epidemiological and animal  
20 toxicological studies do not give support to respiratory effects from long-term exposure to SO<sub>2</sub> at  
21 ambient concentrations. However, chronic studies in dogs exposed to sulfite particles at  
22 concentrations equivalent to near ambient levels of SO<sub>2</sub> demonstrated a mild pathophysiologic  
23 response, suggesting that deposition of SO<sub>x</sub> in the lower respiratory tract may lead to more  
24 profound effects on the respiratory system than those observed with gaseous SO<sub>2</sub> alone. These  
25 changes were modulated and in some cases reversed by sequential exposure to sulfate particles,  
26 suggesting an antagonistic interaction among the different PM in the mixture.

### **3.4.3. Carcinogenic Effects Associated with Long-Term Exposure**

27 The 1982 AQCD concluded that little or no clear epidemiological evidence substantiated  
28 the hypothesized links between SO<sub>2</sub> or other SO<sub>x</sub> and cancer. From the toxicological studies, it  
29 was noted that while there were some indications of carcinogenicity for both SO<sub>2</sub> and SO<sub>2</sub> +

1 benzo[*a*]pyrene (B[*a*]P), complex exposure regimens, problematic dose determinations, and/or  
2 inadequately reported experimental details led to the conclusion that SO<sub>2</sub> could only be  
3 considered a suspect carcinogen/cocarcinogen.

4 Since the last review, numerous studies have examined the genotoxic effects of SO<sub>2</sub>. These  
5 are summarized in Annex Table E-22. SO<sub>2</sub> and its metabolite sulfite were found not to be  
6 mutagenic or to induce DNA damage in vitro (Pool et al., 1988; Pool-Zobel et al., 1990).  
7 However, inhalation studies demonstrated increased mouse bone marrow micronucleated  
8 polychromatic erythrocytes and DNA damage in cells isolated from various organs when mice  
9 were exposed for 4-6 h/day for 7 days to 5-30 ppm SO<sub>2</sub> (Meng et al., 2002; 2005; Ruan et al.,  
10 2003). These in vivo studies suggest that inhaled SO<sub>2</sub> may have systemic effects at high  
11 concentrations, but they are of questionable significance in evaluating the effects of SO<sub>2</sub> at  
12 ambient levels.

13 The carcinogenic potential of SO<sub>2</sub> was examined in animal toxicological studies which are  
14 summarized in Annex Table E-11. Gunnison et al. (1988) conducted a two-part study in which  
15 rats were exposed either for 21 weeks (6 h/day, 5 days/week) by inhalation to 0, 10, or 30 ppm  
16 SO<sub>2</sub>, or for 21 weeks to two tungsten-supplemented, molybdenum-deficient diets. This latter  
17 regimen induced a condition of sulfite oxidase deficiency, resulting in elevated systemic levels of  
18 sulfite:bisulfite relative to control values (e.g., in plasma, from 0 to 44 μM; and in tracheal tissue,  
19 from 33 to 69 or 550 nmol/g wet weight). Beginning with week 4, some groups from each  
20 regimen received weekly tracheal installations of 1-mg B[*a*]P for 15 weeks. Overall results  
21 indicated that squamous cell carcinoma was not induced, or in the B[*a*]P groups coinduced or  
22 promoted, by SO<sub>2</sub> inhalation or elevated systemic sulfite:bisulfite. Researchers found a very high  
23 incidence of animals with tumors in the groups exposed to only B[*a*]P (128/144). As a result,  
24 carcinogenicity or cocarcinogenicity of SO<sub>2</sub> or sulfite:bisulfite could only have been detected as  
25 a shortening of tumor induction time or an increase in rate of tumor appearance, and neither was  
26 observed. As noted by the authors, these findings do not support the conclusion that SO<sub>2</sub>  
27 exposure enhances the carcinogenicity of B[*a*]P. It was proposed that SO<sub>2</sub> exposure, by  
28 elevating systemic sulfite:bisulfite, would generate glutathione-*S*-sulfonates, which in turn could  
29 inhibit glutathione *S*-transferase (GST) and reduce intracellular GSH and, thus, interfere with a  
30 major detoxication pathway for B[*a*]P. See Annex Table E-21 for further discussion from the  
31 work of Menzel et al., (1986).

1 Two similar studies were published that investigated the ability of 10 to 11 months of  
2 exposure (16 h/day) to 4 ppm SO<sub>2</sub>, 6 ppm NO<sub>2</sub>, or their combination to affect the carcinogenicity  
3 of either urban suspended PM (SPM) (Ito et al., 1997) or diesel exhaust particle (DEP) (Ohyama  
4 et al., 1999) extract-coated carbon particles. The former study found that, while exposure to SPM  
5 extract-coated carbon particles significantly increased pulmonary endocrine cell (PEC)  
6 hyperplasia, coexposure to SO<sub>2</sub>, NO<sub>2</sub>, or their combination was without additional affect. Also,  
7 irrespective of gas coexposure, SPM extract-coated carbon particles demonstrated a few PEC  
8 papillomas versus control frequencies of zero.

9 Using Syrian golden hamsters, Heinrich et al. (1989) investigated whether coexposure to  
10 10 ppm SO<sub>2</sub> and 5 ppm NO<sub>2</sub> for 6 to 8 months (5 days/week, 19 hours/day) could enhance  
11 tumorigenesis induced by a single subcutaneous injection of diethylnitrosamine (DEN) during  
12 week 2. The combined gas exposure did not affect body weight gain and only minimally  
13 shortened survival times. Compared to the DEN groups, serial sacrifices of gas-exposed animals  
14 demonstrated progressively increasing numbers of tracheal mucosal cells and aberrant tracheal  
15 cell cilia. In the lung, effects related to gas mixtures were largely limited to a progressive type of  
16 alveolar lesion that involved the lining of bronchiolar epithelium and the appearance of pigment-  
17 containing AM and to a mild, diffuse thickening of the alveolar septa. Exposure to the combined  
18 gases by itself did not induce tumors of the upper respiratory tract, nor did it enhance the  
19 induction of such tumors by DEN.

20 In addition to the animal toxicological studies that examined the genotoxic and  
21 carcinogenic potential of SO<sub>2</sub>, a limited number of recent epidemiologic studies have  
22 investigated the relationship between long-term exposure to SO<sub>2</sub> and lung cancer incidence and  
23 mortality. These studies are summarized in Annex Table F-7. Nyberg et al. (2000) conducted a  
24 case-control study of men aged 40 to 75 years with (n = 1,042) and without (n = 2,364) lung  
25 cancer in Stockholm County, Sweden. They mapped residence addresses to a GIS database to  
26 assign individual exposures to SO<sub>2</sub> from defined emission sources (mainly local oil-fueled  
27 residential heating). Available SO<sub>2</sub> measurement data were used to calibrate the model. In this  
28 study, SO<sub>2</sub> was considered an indicator of air pollution from residential heating. Exposure to  
29 NO<sub>2</sub>, considered to be a marker of traffic pollution, also was evaluated in this study. The 90th  
30 percentile 30-year average SO<sub>2</sub> level was 30 ppb. After adjusting for potential confounders (e.g.,  
31 smoking, occupational exposures), long-term average heating-related SO<sub>2</sub> exposure was not

1 associated with an increase in risk of lung cancer incidence. A weak association for the 30-year  
2 average traffic-related NO<sub>2</sub> exposure was observed.

3 Very similar results were reported in a Norwegian study by Nafstad et al. (2003). The study  
4 population is a cohort of 16,209 men who enrolled in a study of cardiovascular diseases in 1972.  
5 The Norwegian cancer registry identified 422 incident cases of lung cancer. SO<sub>2</sub> exposure data  
6 were modeled based on residence using data for observed concentrations and emission from  
7 point sources (e.g., industry and heating of buildings and private homes) and traffic. Once again,  
8 no association was observed between long-term exposure to SO<sub>2</sub> and lung cancer incidence.

9 Three additional European cohort studies examined the associations between long-term  
10 exposure to air pollution and lung cancer mortality (Beelen et al., 2008; Filleul et al., 2005;  
11 Nafstad et al., 2004) in cohorts ranging in size from 14,284 to 120,852 subjects, who were  
12 followed for 9 to > 20 years. Consistent with the results for lung cancer incidence, none of these  
13 studies observed an association between long-term SO<sub>2</sub> exposure and lung cancer mortality.  
14 These studies are discussed in further detail in Section 3.5.2.2.

15 Similar to the European cohort studies, studies conducted in the United States generally did  
16 not observe an association between long-term exposure to SO<sub>2</sub> and lung cancer mortality. In the  
17 reanalysis of the Harvard Six Cities study, Krewski et al. (2000) estimated a RR of 1.03 (95% CI:  
18 0.91, 1.16) per 5 ppb increase in average SO<sub>2</sub> over the study period, while Pope et al. observed a  
19 positive but not statistically significant (RR ~1.04 per 5 ppb increase in average SO<sub>2</sub> from 1982  
20 to 1998) association in the extended analysis of the American Cancer Society (ACS) cohort. The  
21 California Seventh-day Adventists study by Abbey et al. (1999) did observe a statistically  
22 significant association between lung cancer mortality and SO<sub>2</sub> (and most of the pollutants  
23 examined including PM<sub>10</sub>, sulfate, O<sub>3</sub>, and NO<sub>2</sub>), but the number of lung cancer deaths in this  
24 cohort was very small (12 for female, 18 for male) and, therefore, it is difficult to interpret these  
25 estimates. More detailed discussions of these studies are provided in Section 3.5.2.2.

26 In conclusion, the toxicological studies indicate that SO<sub>2</sub> at high concentrations may cause  
27 DNA damage but fails to induce carcinogenesis, cocarcinogenesis, or tumor promotion.  
28 Furthermore, the epidemiological studies did not provide evidence that long-term exposure to  
29 SO<sub>2</sub> is associated with an excess risk of lung cancer.

### 3.4.4. Cardiovascular Effects Associated with Long-Term Exposure

1 The effects of SO<sub>2</sub> on the cardiovascular system were not addressed in the 1982 AQCD.  
2 Since then, animal toxicological studies have reported oxidation (Meng et al., 2003) and  
3 glutathione (GSH) depletion (Langley-Evans et al., 1996; Meng et al., 2003; Wu and Meng,  
4 2003) in the hearts of rodents which were exposed by inhalation to SO<sub>2</sub>. However, as  
5 concentrations of SO<sub>2</sub> used in these studies were 5 ppm and above, the oxidative injury observed  
6 is probably not relevant to cardiovascular effects seen at ambient levels of SO<sub>2</sub>. These and other  
7 animal toxicology studies measuring cardiovascular endpoints are summarized in Annex Table  
8 E-5.

9 A recent epidemiological study examined the association between long-term exposure to  
10 air pollution, including SO<sub>2</sub>, and one or more fatal or nonfatal cardiovascular events. In the  
11 Women's Health Initiative cohort study, Miller et al. (2007) studied 65,893 postmenopausal  
12 women between the ages of 50 and 79 years without previous cardiovascular disease in 36 U.S.  
13 metropolitan areas from 1994 to 1998. Subjects' exposures to air pollution were estimated using  
14 residents' five-digit ZIP code, assigning the annual mean levels of air pollutants measured at the  
15 nearest monitor. A total of 1,816 women had one or more fatal or nonfatal cardiovascular events,  
16 including 261 deaths from cardiovascular causes. Hazard ratios for the first cardiovascular event  
17 were estimated. The results for models that only included subjects with non-missing exposure  
18 data for all pollutants (n = 28,402 subjects, resulting in 879 cardiovascular events) are described  
19 here. In the single-pollutant models, PM<sub>2.5</sub> showed the strongest associations with cardiovascular  
20 events among the pollutants (Hazard Ratios = 1.24 [95% CI: 1.04, 1.48] per 10 µg/m<sup>3</sup> increase in  
21 annual average), followed by SO<sub>2</sub> (1.07 [95% CI: 0.95, 1.20] per 5 ppb increase in the annual  
22 average). In the multipollutant model where all the pollutants (i.e., PM<sub>2.5</sub>, PM<sub>10-2.5</sub>, CO, SO<sub>2</sub>,  
23 NO<sub>2</sub>, O<sub>3</sub>) were included in the model, the PM<sub>2.5</sub> association with overall cardiovascular events  
24 was even stronger (1.53 [95% CI: 1.21, 1.94]). The association with SO<sub>2</sub> also became stronger  
25 (1.13 [95% CI: 0.98, 1.30]). Correlations among these pollutants were not described and,  
26 therefore, the extent of confounding among these pollutants in these associations could not be  
27 examined, but among all the air pollutants considered, PM<sub>2.5</sub> was clearly the best predictor of  
28 cardiovascular events.

29 The available toxicological and epidemiological evidence to assess the effect of long-term  
30 exposure to SO<sub>2</sub> on cardiovascular health is too limited to make any conclusions at this time.

### 3.4.5. Prenatal and Neonatal Outcomes Associated with Long-Term Exposure

1 Several animal toxicological studies examined developmental effects of SO<sub>2</sub> and are  
2 summarized in Annex Table E-7. No changes in birth weight or neurobehavioral development  
3 were noted in mouse pups prenatally exposed to 5-30 ppm SO<sub>2</sub> (1996), while some behavioral  
4 modifications were seen in adults exposed prenatally to these same levels (Fiore et al.). However,  
5 effects observed at such high concentrations of SO<sub>2</sub> are of questionable relevance.

6 In recent years, the effects of prenatal and neonatal exposure to air pollution have been  
7 examined in epidemiologic studies by several investigators. These studies are summarized in  
8 Annex Table F-8. The most common endpoints studied are low birth weight, preterm delivery,  
9 and measures of intrauterine growth. Preterm birth and low birth weight may result in serious  
10 long-term health outcomes for the infant. Preterm birth is the leading cause of infant mortality  
11 and is a major determinant of a variety of adverse neurodevelopmental outcomes and chronic  
12 adverse respiratory effects (Berkowitz and Papiernik, 1993). Low birth weight has also been  
13 linked with increased risk of infant mortality and morbidity. Other studies have examined  
14 associations between maternal exposure to ambient air pollution and sudden infant death  
15 syndrome (SIDS) and neonatal hospitalizations.

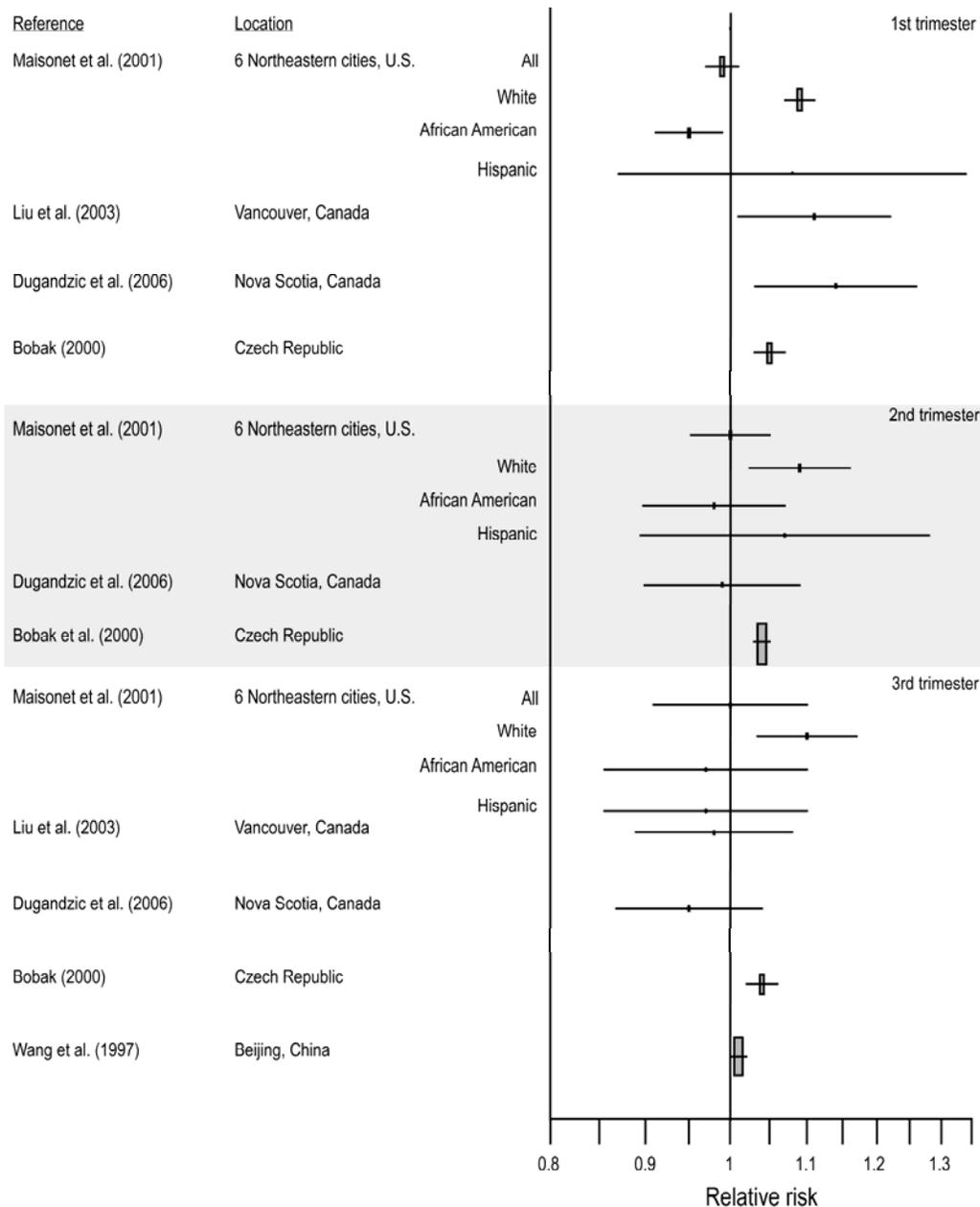
16 These studies analyzed air pollution data and birth certificates from a given area. In  
17 evaluating the results of these studies, it is important to consider the limitations of these data. For  
18 example, the reliability and validity of birth certificate data have been reviewed (Buescher et al.,  
19 1993; Piper et al., 1993) and have been found to vary in degrees of reliability by specific  
20 variables. The variables considered the most reliable include birth weight, maternal age, race,  
21 and insurance status. Whereas gestational age, parity and delivery type (vaginal vs. cesarean)  
22 were reasonably reliable, obstetrical complications and maternal lifestyle factors such as  
23 smoking and alcohol consumption were not reliable. Another concern in these studies regards  
24 adequate control for potential confounders. While most of these studies adequately controlled for  
25 maternal education, parity, age, and sex of child, many did not adjust for socioeconomic status,  
26 occupational exposures, indoor pollution levels, maternal smoking, alcohol use, prenatal care, or  
27 concurrent temperature exposures as fetal growth is associated with all of these factors. This  
28 makes overall comparisons across studies a difficult task.

1           While most studies analyzed average SO<sub>2</sub> exposure for the whole pregnancy, many also  
2 considered exposure during specific trimesters, or other time periods (e.g., first and last months  
3 of gestation). Different exposure periods have been examined because the biological mechanisms  
4 and timing of critical exposures that link air pollution to adverse birth outcomes are yet to be  
5 determined. For example, fetal growth is much more variable during the third trimester;  
6 therefore, exposure during the third trimester would have the greatest likelihood of an  
7 association. However, insufficient placentation during the first trimester may be associated with  
8 early environmental insult, whereby subsequent fetal growth is hindered. Similarly, it is possible  
9 that preterm delivery is associated with insufficient placentation resulting from early exposure.  
10 Furthermore, preterm delivery may be the result of acute exposures just prior to delivery.

11           Epidemiological studies examining the effects of air pollutants on low birth weight are  
12 summarized in Figure 3-13. Maisonet et al. (2001) examined the association between air  
13 pollution and low birth weight in six northeastern cities: Boston, MA; Hartford, CT;  
14 Philadelphia, PA; Pittsburgh, PA; Springfield, MA; and Washington, DC. The study population  
15 consisted of 89,557 singleton, full-term, live births (37-44 weeks of gestation) born between  
16 January 1994 and December 1996. Low birth weight was classified as < 2,500 g (5.5 lbs.). This  
17 study observed an association between low birth weight and SO<sub>2</sub> concentrations during each  
18 trimester among Caucasians; however, the association was not consistent in other races and  
19 ethnicities.

20           An excess risk for low birth weight associated with ambient SO<sub>2</sub> concentrations was  
21 reported by Dugandzic et al. (2006) in a large cohort study of 74,284 women with full-term,  
22 singleton births from 1988–2000 in Nova Scotia, Canada. The mean 24-h avg SO<sub>2</sub> concentration  
23 over the study period was 10 ppb (IQR 7). These investigators found that exposure only during  
24 the first trimester was associated with increased risk of low birth weight. The RR was 1.14 (95%  
25 CI: 1.04, 1.26) per 5 ppb increase in SO<sub>2</sub> level.

26



**Figure 3-13. Relative risks (95% CI) for low birth weight, grouped by trimester of SO<sub>2</sub> exposure. Risk estimates are standardized per 5 ppb increase in SO<sub>2</sub> 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.**

1 Liu et al. (2003) found similar results in a study of pregnancy outcomes and air pollution in  
 2 Vancouver, Canada. The mean 24-h avg SO<sub>2</sub> concentration was 4.9 ppb (IQR 7.7) from 1985 to  
 3 1998. Maternal exposure during the first month was associated with an increased risk of low

1 birth weight (OR 1.11 [95% CI: 1.01, 1.22]). Additional studies from the United States, Europe,  
2 Latin America and Asia have reported positive associations between low birth weight and  
3 maternal exposure to SO<sub>2</sub> during the first (Bell et al., 2007; Bobak, 2000; Ha et al., 2001;  
4 Mohorovic, 2004; Yang et al., 2003a), second (Bobak, 2000; Gouveia et al., 2003; Lee et al.,  
5 2003a) and third (Bobak, 2000; Lin et al., 2004; Wang et al., 1997) trimesters.

6 Preterm delivery, intrauterine growth retardation (IUGR), and birth defects are additional  
7 adverse birth outcomes that have been associated with ambient SO<sub>2</sub> levels. In a time-series  
8 analysis using data from four Pennsylvania counties, (Sagiv et al., 2005) reported that the mean  
9 6-week SO<sub>2</sub> exposure prior to birth was associated with increased risk of preterm birth, with a  
10 RR of 1.05 (95% CI: 1.00, 1.10) per 5 ppb increase in SO<sub>2</sub>. A 5 ppb increase in SO<sub>2</sub>  
11 concentrations three days before birth was associated with a RR of 1.02 (95% CI: 0.99, 1.05).  
12 The authors discussed two plausible mechanisms for the effects of air pollution on preterm birth:  
13 (1) changes in blood viscosity due to inflammation as a result of air pollution (citing Peters et al.,  
14 1997); and (2) maternal infection during pregnancy as a consequence of impaired immunity from  
15 air pollution exposure. Liu et al. (2003) reported that SO<sub>2</sub> exposure during the last month of  
16 pregnancy was associated with preterm birth, with an OR of 1.09 (95% CI: 1.01, 1.19) for a  
17 5 ppb increase in SO<sub>2</sub>, in Vancouver, Canada. Similar results were found for studies conducted in  
18 the Czech Republic (Bobak, 2000), Korea (Leem et al., 2006), and Beijing (Xu et al., 1995).

19 Liu et al. (2003) further reported that SO<sub>2</sub> exposure during the last month of pregnancy  
20 was associated with IUGR (OR 1.07 [95% CI: 1.01, 1.13]). However, in a later study in the  
21 Canadian cities of Calgary, Edmonton and Montreal, (Liu et al., 2007) did not observe  
22 associations between maternal exposure to SO<sub>2</sub> and increased risk of IUGR.

23 Two Brazilian studies examined exposure to SO<sub>2</sub> and neonatal deaths. Pereira et al. (1998)  
24 found a positive association between SO<sub>2</sub> and intrauterine mortality in São Paulo during a 2-year  
25 period, though the effect was sensitive to model specifications and did not support a  
26 concentration-response relationship. The most robust association was observed for an index of  
27 three gaseous pollutants (NO<sub>2</sub>, SO<sub>2</sub>, CO) with mortality. Lin et al. (2004) found that a 5 ppb  
28 increase in SO<sub>2</sub> was associated with an increase of 8.8% (95% CI: 5.8, 11.8). A similar  
29 relationship was found for PM<sub>10</sub>. The creation of an index containing both PM<sub>10</sub> and SO<sub>2</sub> allowed  
30 the observation of their cumulative effects on daily death counts. The result of this analysis was

1 similar in magnitude to the effect of SO<sub>2</sub> alone. An ecologic cohort study of infant mortality in  
2 the U.S. found no association with annual averages of SO<sub>2</sub> concentration (Lipfert et al., 2000a).

3 Gilboa et al. (2005) conducted a population-based case-control study to investigate the  
4 association between maternal exposure and air pollutant exposure during weeks 3-8 of  
5 pregnancy, the risk of selected cardiac birth defects and oral clefts in live births, and fetal deaths  
6 between 1997 and 2000 in seven Texas counties. When the highest quartile of exposure was  
7 compared to the lowest, the authors observed a positive association between SO<sub>2</sub> and isolated  
8 ventricular septal defects (OR 2.16 [95% CI: 1.51, 3.09]). Although this is the only study to have  
9 examined the effect of maternal exposure to SO<sub>2</sub> on birth defects, it supports the notion that the  
10 developing embryo and growing fetus is susceptible to maternal air pollution exposure.

11 Several studies examined adverse health outcomes in relation to SO<sub>2</sub> concentrations during  
12 the neonatal period. Dales et al. (2006) evaluated hospitalizations for respiratory disorders in  
13 neonates < 4 weeks of age from hospitals in 11 large Canadian cities during a 15-year study  
14 period (population-weighted average 24-h avg SO<sub>2</sub> of 4.3 ppb). The researchers observed a 5.5%  
15 (95% CI: 2.8, 8.3) excess risk in respiratory hospitalizations associated with a 10 ppb increase in  
16 24-h avg SO<sub>2</sub> concentrations with a 2-d lag. This effect was slightly attenuated after adjusting for  
17 PM<sub>10</sub> and gaseous copollutants. To investigate the influence of ambient SO<sub>2</sub> concentrations on  
18 SIDS, Dales et al. (2004) conducted a time-series analysis comparing daily rates of SIDS and  
19 daily SO<sub>2</sub> concentrations from 12 large, Canadian cities during a 16-year period. The mean  
20 24-h avg SO<sub>2</sub> level across the 12 cities was 5.51 ppb (IQR 4.92). There was an 18.0% (95% CI:  
21 4.4, 33.4) excess risk in SIDS incidence for a 10 ppb increase in 24-h avg SO<sub>2</sub> levels. The  
22 authors concluded that the effect of SO<sub>2</sub> was independent of sociodemographic factors, temporal  
23 trends, and weather.

24 In summary, epidemiological studies on birth outcomes have found suggestive positive  
25 associations between SO<sub>2</sub> exposure and low birth weight; however, toxicological studies provide  
26 very little biological plausibility for reproductive outcomes related to SO<sub>2</sub> exposure. The  
27 inconsistent results across trimesters of pregnancy and the lack of evidence regarding  
28 confounding by copollutants further limit the interpretation of these studies. The limited number  
29 of studies addressing preterm delivery, IUGR, birth defects, neonatal hospitalizations, and infant  
30 mortality make it difficult to draw conclusions regarding the effect of SO<sub>2</sub> on these outcomes.

### **3.4.6. Other Organ System Effects Associated with Long-Term Exposure**

1           The 1982 AQCD presented only one chronic exposure study which was relevant to nervous  
2 system effects. Dogs were exposed for 68 months to a mixture of SO<sub>2</sub> and H<sub>2</sub>SO<sub>4</sub>. No effects on  
3 visual evoked brain potentials during or immediately after exposure to the SO<sub>x</sub> mixture were  
4 observed. Since then, numerous studies have examined brain lipid content, lipid peroxidation and  
5 glutathione content and antioxidant enzymes following inhalation exposure of rodents to SO<sub>2</sub> at  
6 concentrations of 10 ppm or higher. Concentrations of 5 ppm or higher SO<sub>2</sub> were used in studies  
7 examining neurobehavior and neurodevelopment in mice. These studies are summarized in  
8 Annex Table E-6.

9           In the past 25 years, numerous animal toxicological studies have evaluated the effects of  
10 long-term SO<sub>2</sub> exposure on other organ systems such as reproductive, hematological,  
11 gastrointestinal, renal, lymphatic, and endocrine systems. Most of these studies used  
12 concentrations of SO<sub>2</sub> of 5 ppm or higher. Many of these studies examined alteration profiles of  
13 lipid peroxidation and antioxidant levels (Langley-Evans et al., 1996; Meng and Bai, 2004;  
14 Meng et al., 2003b) and are summarized in Annex Table E-7 through E-9 and E-22 through E-24.

## **3.5. Mortality Associated with Long-Term SO<sub>2</sub> Exposure**

### **3.5.1. Summary of Findings from the Previous Review**

15           At the time of the 1982 AQCD, the available studies on the effects of long-term exposure  
16 to SO<sub>2</sub> on mortality were all ecological cross-sectional studies. This study design could not take  
17 into consideration such confounders as cigarette smoking, occupational exposures, and social  
18 status. In addition, there were questions regarding how representative the aerometric data used  
19 were for community exposure. Therefore, it was concluded that the epidemiological studies did  
20 not provide valid quantitative data relating respiratory disease or other types of mortality to long-  
21 term (annual average) exposures to SO<sub>2</sub> or PM.

22           The 1986 Secondary Addendum reviewed more studies of this type, with information on  
23 more detailed components of PM (inhalable and fine particles, and particulate sulfate). While  
24 some studies suggested importance of the size of PM, the fundamental problem of the study

1 design made it difficult to interpret the effect estimates. The 1986 Secondary Addendum also  
2 reviewed a Japanese study in which the death rates from asthma and chronic bronchitis in a  
3 highly polluted section of Yokkaichi, an industrial city with large SO<sub>2</sub> emissions from the largest  
4 oil-fired power plant in Japan, were compared with those in a less polluted area of the same city.  
5 SO<sub>x</sub> levels (measured using the lead peroxide method) averaged across several monitoring sites  
6 in the polluted harbor area ranged from around 1.0 to 2.0 mg/day (annual average) during 1964  
7 through 1972 and then steadily declined to less than 0.5 mg/day in 1982. This is in contrast to  
8 levels consistently < 0.3 mg/day in the low pollution areas throughout 1967 through 1982.  
9 Annual average levels for other pollutants (i.e., NO<sub>2</sub>, TSP, oxidants) monitored in the high  
10 pollution area were consistently low from 1974 through 1982. The results indicated elevated  
11 rates of chronic bronchitis mortality in the highly polluted area compared to the less polluted  
12 area, but the 1986 Secondary Addendum could not conclude that this was due to SO<sub>2</sub> alone,  
13 because sulfate or other particulate SO<sub>x</sub> such as H<sub>2</sub>SO<sub>4</sub> could have been responsible.

14 Several, more recent studies have examined long-term exposure effects of air pollution,  
15 including SO<sub>2</sub>, on mortality. These studies are summarized in Annex Table F-9. As with short-  
16 term exposure studies, the focus of most of these studies was mainly on PM though some  
17 focused on traffic-related air pollution. They all used Cox proportional hazards regression  
18 models with adjustment for potential confounders. The designs of these studies were better than  
19 earlier cross-sectional studies as the outcome and most of the potential confounders (e.g.,  
20 smoking history, occupational exposure) were measured on an individual basis. However, the  
21 geographic scale and method for exposure estimates varied across these studies.

## **3.5.2. Associations of Mortality and Long-Term Exposure in Key Studies**

### **3.5.2.1. U.S. Cohort Studies**

#### **3.5.2.1.1. Harvard Six Cities Studies**

22 Dockery et al. (1993) conducted a prospective cohort study to study the effects of air  
23 pollution with the main focus on PM components in six U.S. cities. These cities were chosen  
24 based on levels of air pollution, with Portage, WI and Topeka, KS representing the least polluted  
25 cities and Steubenville, OH representing the most polluted city. Mean SO<sub>2</sub> levels ranged from

1 1.6 ppb in Topeka to 24.0 ppb in Steubenville from 1977 to 1985. Cox proportional hazards  
2 regression was conducted with data from a 14- to 16-year follow-up study of 8,111 adults in the  
3 six cities. Dockery et al. reported that lung cancer and cardiopulmonary mortality were more  
4 strongly associated with the concentrations of inhalable and fine PM, and sulfate particles, than  
5 with the levels of TSP, SO<sub>2</sub>, NO<sub>2</sub>, or acidity of the aerosol.

6 Krewski et al. (2000) conducted a sensitivity analysis of the Harvard Six Cities study and  
7 examined associations between gaseous pollutants (i.e., O<sub>3</sub>, NO<sub>2</sub>, SO<sub>2</sub>, and CO) and mortality.  
8 SO<sub>2</sub> showed positive associations with total mortality (RR = 1.05 [95% CI: 1.02, 1.09] per 5 ppb  
9 increase in average SO<sub>2</sub> over the study period) and cardiopulmonary deaths (1.05 [95% CI: 1.00,  
10 1.10]), but in this dataset SO<sub>2</sub> was highly correlated with PM<sub>2.5</sub> (r = 0.85), sulfate (r = 0.85), and  
11 NO<sub>2</sub> (r = 0.84).

### **3.5.2.1.2. American Cancer Society Cohort Studies**

12 Pope et al. (1995) investigated associations between long-term exposure to PM and the  
13 mortality outcomes in the ACS cohort. Ambient air pollution data from 151 U.S. metropolitan  
14 areas in 1981 were linked with individual risk factors in 552,138 adults who resided in these  
15 areas when enrolled in the prospective study in 1982. Death outcomes were ascertained through  
16 1989. PM<sub>2.5</sub> and sulfate were associated with total, cardiopulmonary, and lung cancer mortality,  
17 but not with mortality for all other causes. Gaseous pollutants were not analyzed in this study.

18 Krewski and co-investigators (Jerrett et al., 2003; Krewski et al., 2000) conducted an  
19 extensive sensitivity analysis of the Pope et al. (1995) ACS data, augmented with additional  
20 gaseous pollutants data. The mean SO<sub>2</sub> concentrations were 7.18 ppb in the warm season (April  
21 to September) and 11.24 ppb in the cool season (October to March). Among the gaseous  
22 pollutants examined, only SO<sub>2</sub> showed positive associations with mortality. The RR for total  
23 mortality was 1.06 (95% CI: 1.05, 1.07) per 5 ppb increase in the annual average SO<sub>2</sub>. Analysis  
24 using SO<sub>2</sub> measured in different seasons produced a somewhat higher estimate for the warm  
25 season than that for the cool season (7% compared to 5% excess risk per 5 ppb increase).

26 Although the subjects in the ACS cohort came from all regions of the United States, the majority  
27 of the 151 cities were located in the eastern United States, where both SO<sub>2</sub> and sulfate tend to be  
28 higher. PM<sub>2.5</sub> levels are also higher in the east. To address the influence of these spatial patterns,  
29 which may confound associations between mortality and these pollutants, Krewski et al. (2000)

1 conducted extensive two-stage regression modeling. In these models, the association between  
2 SO<sub>2</sub> and mortality was diminished but persisted after adjusting for sulfate, PM<sub>2.5</sub>, and other  
3 variables. For example, in the spatial filtering model (which resulted in the largest reduction of  
4 the SO<sub>2</sub> effect estimate when sulfate was included), the SO<sub>2</sub> total mortality RR estimate was 1.07  
5 (95% CI: 1.03, 1.11) in the single-pollutant model and 1.04 (95% CI: 1.02, 1.06) with sulfate in  
6 the two-pollutant model. The effect estimates for PM<sub>2.5</sub> and sulfate also were diminished when  
7 SO<sub>2</sub> was included in the models. The result further showed that SO<sub>2</sub> effect estimates were  
8 generally insensitive to adjustment for spatial correlation. Thus, these results suggest that the  
9 association between SO<sub>2</sub> and mortality may be confounded with PM, but the association cannot  
10 be accounted for by PM<sub>2.5</sub> or sulfate alone. Krewski et al. (2000) noted that their reanalysis of the  
11 ACS and Harvard Six Cities studies suggested that mortality might be attributed to more than  
12 one component of the complex mixture of ambient air pollutants in urban areas in the United  
13 States.

14 The original Pope et al. (1995) study and the Krewski et al. (2000) reanalysis both used the  
15 air pollution exposure estimates that are based on the average over the Metropolitan Statistical  
16 Area (MSA), which consists of multiple counties. To investigate the effects of geographic scale  
17 over which the air pollution exposures are averaged, Willis et al. (2003) reanalyzed the ACS  
18 cohort data using the exposure estimates averaged over the county scale, and compared the  
19 results with those based on the MSA-scale average exposure. Less than half of the cohort used in  
20 the MSA-based study was used in the county-scale based analysis, because of the limited  
21 availability of sulfate monitors and the reduced sample size due to the loss of subjects when  
22 using the five-digit ZIP codes. The mean (9.3 ppb versus 10.7 ppb) and range (0.0 to 29.3 ppb  
23 versus 0.0 to 27.2 ppb) of the MSA- and county-level SO<sub>2</sub> data sets were similar. In the analysis  
24 comparing the two-pollutant model with sulfate and SO<sub>2</sub>, they found that the inclusion of SO<sub>2</sub>  
25 reduced sulfate effect estimates substantially (> 25%) in the MSA-scale model but not  
26 substantially (< 25%) in the county-scale model. In the MSA-level analysis (with 113 MSAs),  
27 the SO<sub>2</sub> RR estimate was 1.04 (95% CI: 1.02, 1.06) per 5 ppb increase, with sulfate in the model.  
28 In the county-level analysis (91 counties) with sulfate in the model, the corresponding estimate  
29 was smaller (1.02 [95% CI: 1.00, 1.05]). It should also be noted that the correlation between  
30 covariates were different between the MSA-level data and county-level data. The correlation  
31 between SO<sub>2</sub> and sulfate was 0.48 in the MSA-level data, but it was 0.56 in the county-level

1 data. The correlation between poverty rate and SO<sub>2</sub> was -0.16 in the MSA-level data, but it was  
2 0.15 in the county-level data. Thus, the extent of confounding between SO<sub>2</sub> and PM components  
3 as well as among other covariates in the model can be affected by the geographic scale of  
4 aggregation of exposure estimates. It is not clear, however, if the smaller geographic scale  
5 increases or decreases exposure characterization error for SO<sub>2</sub>, because a certain extent of  
6 smoothing (averaging) over distance may reduce very local concentration peaks that are not  
7 relevant to the city-wide population.

8 Pope et al. (2002) extended analysis of the ACS cohort with double the follow-up time (to  
9 1998) and triple the number of deaths compared to the original Pope et al. (1995) study. In  
10 addition to PM<sub>2.5</sub>, all the gaseous pollutant data were retrieved for the extended period and  
11 analyzed for their associations with death outcomes. As in the 1995 analysis, the air pollution  
12 exposure estimates were based on the MSA-level averages. PM<sub>2.5</sub> was associated with total,  
13 cardiopulmonary, and lung cancer mortality but not with deaths for all other causes. SO<sub>2</sub> was  
14 associated with all the mortality outcomes, including all other causes of deaths. The SO<sub>2</sub> RR  
15 estimate for total mortality was 1.03 (95% CI: 1.02, 1.05) per 5 ppb increase (1982 to 1998  
16 average). The association of SO<sub>2</sub> with mortality for all other causes (sulfate also showed this  
17 pattern) makes it difficult to interpret the effect estimates. This lack of specificity for SO<sub>2</sub> (in  
18 contrast to PM) is not consistent with causal inference.

### **3.5.2.1.3. The EPRI-Washington University Veterans' Cohort Mortality Studies**

19 Lipfert et al. (2000b) conducted an analysis of a national cohort of ~70,000 male U.S.  
20 military veterans who were diagnosed as hypertensive in the mid 1970s and were followed up for  
21 about 21 years (up to 1996). This cohort was 35% black and 57% were current smokers (81% of  
22 the cohort had been smokers at one time). PM<sub>2.5</sub>, PM<sub>10</sub>, PM<sub>10-2.5</sub>, TSP, sulfate, CO, O<sub>3</sub>, NO<sub>2</sub>, SO<sub>2</sub>,  
23 and lead were examined in this analysis. No mean or median level of SO<sub>2</sub> was reported. The  
24 county of residence at the time of entry to the study was used to estimate exposures. Four  
25 exposure periods (from 1960 to 1996) were defined, and deaths during each of the three most  
26 recent exposure periods were considered. The results for SO<sub>2</sub> were presented only qualitatively  
27 as part of their preliminary screening regression results. Lipfert et al. (2000b) noted that lead and  
28 SO<sub>2</sub> were not found to be associated with mortality, thus were not considered further. They also  
29 noted that the pollution effect estimates were sensitive to the regression model specification,

1 exposure periods, and the inclusion of ecological and individual variables. The authors reported  
2 that indications of concurrent mortality risks were found for NO<sub>2</sub> and peak O<sub>3</sub>.

3 Lipfert et al. (2006b) examined associations between traffic density and mortality in the  
4 same cohort, whose follow-up period was extended to 2001. As in their 2000 study, four  
5 exposure periods were considered but included more recent years. The 95th percentiles of daily  
6 average in each of the exposure periods were considered for SO<sub>2</sub>. For the 1997–2001 data period,  
7 the estimated mortality RR for SO<sub>2</sub> was 0.99 (95% CI: 0.97, 1.01) per 5 ppb increase in a single-  
8 pollutant model. They reported that traffic density was a better predictor of mortality than  
9 ambient air pollution variables with the possible exception of O<sub>3</sub>. The log-transformed traffic  
10 density variable was only weakly correlated with SO<sub>2</sub> (r = 0.32) and PM<sub>2.5</sub> (r = 0.50) in this data  
11 set.

12 Lipfert et al. (2006a) further extended analysis of the veterans' cohort data to include the  
13 EPA's Speciation Trends Network (STN) data, which collected chemical components of PM<sub>2.5</sub>.  
14 They analyzed the STN data for year 2002, again using county-level averages. PM<sub>2.5</sub> and gaseous  
15 pollutants data for 1999 through 2001 were also analyzed. As in the previous Lipfert et al. (2006)  
16 study, traffic density was the most important predictor of mortality, but associations were also  
17 seen for elemental carbon, vanadium, nickel, and nitrate. O<sub>3</sub>, NO<sub>2</sub>, and PM<sub>10</sub> also showed  
18 positive but weaker associations. Once again, no associations were observed between long-term  
19 exposure to SO<sub>2</sub> and mortality.

#### **3.5.2.1.4. Seventh-day Adventist Study**

20 Abbey et al. (1999) investigated associations between long-term ambient concentrations of  
21 PM<sub>10</sub>, sulfate, SO<sub>2</sub>, O<sub>3</sub>, and NO<sub>2</sub> (1973 through 1992) and mortality (1977 through 1992) in a  
22 cohort of 6,338 nonsmoking California Seventh-day Adventists. Monthly indices of ambient air  
23 pollutant concentrations at 348 monitoring stations throughout California were interpolated to  
24 ZIP codes according to home or work location of study participants, cumulated, and then  
25 averaged over time. They reported associations between PM<sub>10</sub> and total mortality for males and  
26 nonmalignant respiratory mortality for both sexes. SO<sub>2</sub> was not associated with total mortality  
27 (RR 1.07 [95% CI: 0.92, 1.24] for males and 1.00 [95% CI: 0.88, 1.14] for females per 5 ppb  
28 increase in multiyear average SO<sub>2</sub>), cardiopulmonary deaths, or respiratory mortality for either  
29 gender.

### 3.5.2.2. European Cohort Studies

1 A study by Beelen et al. (2008) examined associations between traffic-related air pollution  
2 and mortality. They analyzed data from the Netherlands Cohort Study on Diet and Cancer with  
3 120,852 subjects who were followed from 1987 to 1996. BS, NO<sub>2</sub>, SO<sub>2</sub>, PM<sub>2.5</sub>, and four types of  
4 traffic-exposure estimates were analyzed. While the local traffic component was estimated for  
5 BS, NO<sub>2</sub>, and PM<sub>2.5</sub>, no such attempt was made for SO<sub>2</sub>, because there was “virtually no traffic  
6 contributions to this pollutant.” Thus, only “background” SO<sub>2</sub> levels were reflected in the  
7 exposure estimates. Traffic intensity on the nearest road was associated with all-cause mortality  
8 and a larger RR was observed for respiratory mortality. Results were similar for BS, NO<sub>2</sub> and  
9 PM<sub>2.5</sub>, but no associations were found for SO<sub>2</sub> (RR = 0.98 [95% CI: 0.93, 1.03] per 5 ppb  
10 increase in multiyear average SO<sub>2</sub>).

11 Nafstad et al. (2004) investigated the association between mortality and long-term  
12 exposure to air pollution exposure in a cohort of Norwegian men followed from 1972–1973  
13 through 1998. Data from 16,209 males (aged 0 to 49 years) living in Oslo, Norway, in 1972–  
14 1973 were linked with data from the Norwegian Death Register and with estimates of the  
15 average annual air pollution levels at the participants’ home addresses. PM was not considered in  
16 this study because measurement methods changed during the study period. Exposure estimates  
17 for nitrogen oxides (NO<sub>x</sub>) and SO<sub>2</sub> were constructed using models based on subject addresses,  
18 emission data for industry, heating, and traffic, and measured concentrations. While NO<sub>x</sub> was  
19 associated with total, respiratory, lung cancer, and ischemic heart disease deaths, SO<sub>2</sub> did not  
20 show any associations with mortality. The authors noted that the SO<sub>2</sub> levels were reduced by a  
21 factor of 7 during the study period (from 5.6 ppb in 1974 to 0.8 ppb in 1995), whereas NO<sub>x</sub> did  
22 not show any clear downward trend.

23 Filleul et al. (2005) investigated long-term effects of air pollution on mortality in 14,284  
24 adults who resided in 24 areas from seven French cities when enrolled in the Air Pollution and  
25 Chronic Respiratory Diseases (PAARC) survey in 1974. Daily measurements of SO<sub>2</sub>, TSP, BS,  
26 NO<sub>2</sub>, and NO were made in the 24 areas for 3 years (1974 through 1976). Models were run  
27 before and after exclusion of six area monitors influenced by local traffic as determined by a  
28 NO:NO<sub>2</sub> ratio of > 3. Before exclusion of the six areas, none of the air pollutants was associated  
29 with mortality outcomes. After exclusion of these areas, analyses showed associations between  
30 total mortality and TSP, BS, NO<sub>2</sub>, and NO but not SO<sub>2</sub> (RR = 1.01 [95% CI: 0.97, 1.06] per

1 5 ppb multiyear average) or acidimetric measurements. It should be noted that SO<sub>2</sub> levels in  
2 these French cities declined markedly between the 1974 through 1976 period and the 1990  
3 through 1997 period by a factor of 2 to 3, depending on the city. The changes in air pollution  
4 levels over the study period complicate interpretation of reported effect estimates.

### 3.5.2.3. Cross-Sectional Analysis Using Small Geographic Scale

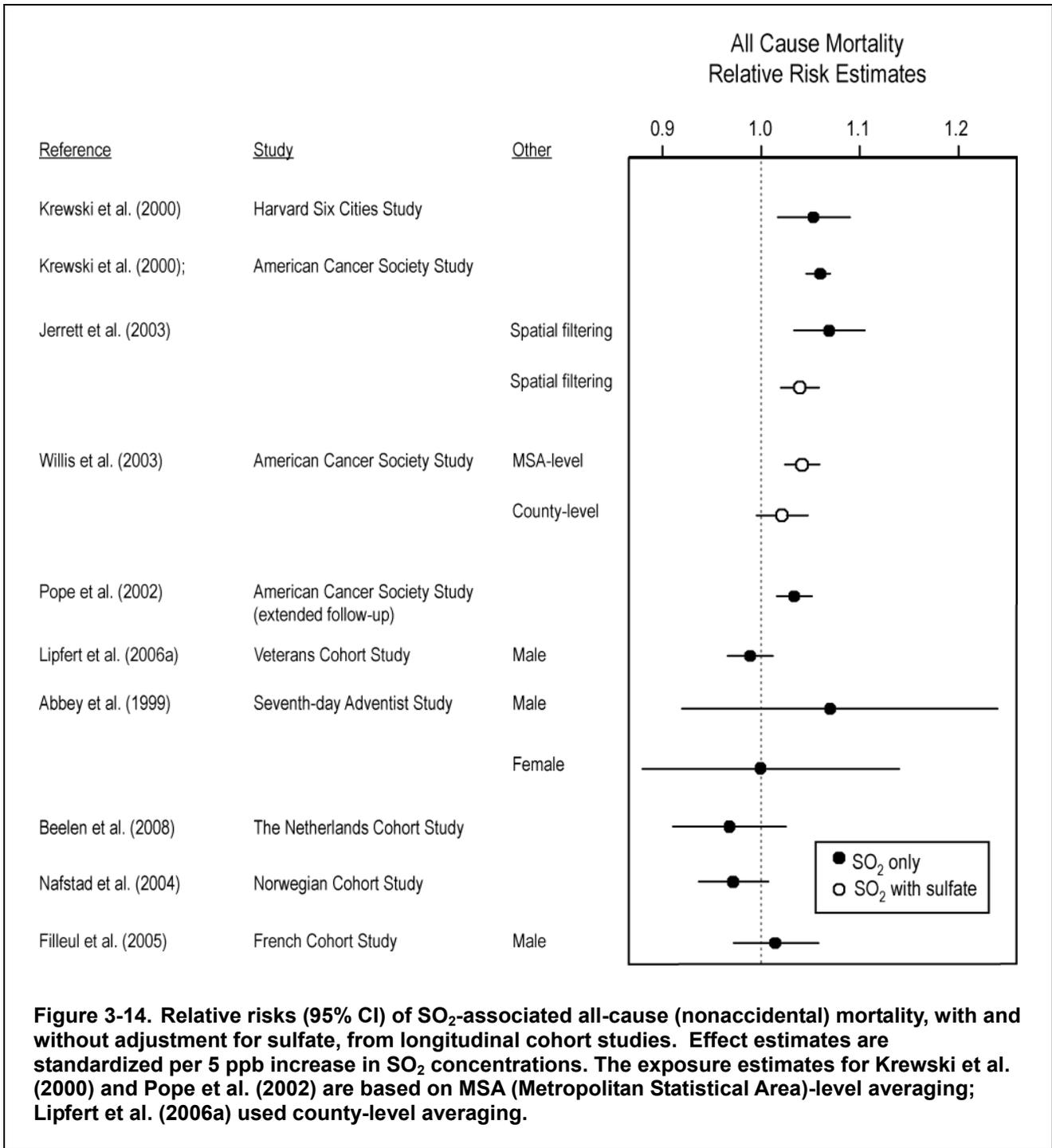
5 Elliott et al. (2007) examined associations of BS and SO<sub>2</sub> with mortality in Great Britain  
6 using a cross-sectional analysis. However, unlike the earlier ecological cross-sectional mortality  
7 analyses in the United States in which mortality rates and air pollution levels were compared  
8 using large geographic boundaries (i.e., MSAs or counties), in the Elliot et al. analysis, the  
9 mortality rates and air pollution were compared using a much smaller geographic unit, the  
10 electoral ward, with a mean area of 7.4 km<sup>2</sup> and a mean population of 5,301 per electoral ward.  
11 Death rates were computed for four successive 4-year periods from 1982 to 1994 and associated  
12 with 4-year exposure periods from 1966 to 1994. The number of deaths from all causes in the  
13 10,520 wards was 420,776. Of note, SO<sub>2</sub> levels declined from 41.4 ppb in the 1966 to 1970  
14 period to 12.2 ppb in 1990 to 1994. This type of analysis does not allow adjustments for  
15 individual risk factors, but the study did adjust for socioeconomic status data available for each  
16 ward from the 1991 census. Social deprivation and air pollution were more highly correlated in  
17 the earlier exposure windows. They observed associations for both BS and SO<sub>2</sub> and mortality  
18 outcomes. The estimated effects were stronger for respiratory illness than other causes of  
19 mortality for the most recent exposure period and most recent mortality period (when pollution  
20 levels were lower). The adjustment for social deprivation reduced the effect estimates for both  
21 pollutants. The adjusted mortality RRs for SO<sub>2</sub> for the pooled mortality periods using the most  
22 recent exposure windows were 1.021 (95% CI: 1.018, 1.024) for all causes, 1.015 (95% CI:  
23 1.011, 1.019) for cardiovascular, and 1.064 (95% CI: 1.056, 1.072) for respiratory causes per  
24 5 ppb increase in SO<sub>2</sub>. The effect estimates for the most recent mortality period using the most  
25 recent exposure windows were larger. Simultaneous inclusion of BS and SO<sub>2</sub> reduced effect  
26 estimates for BS but not SO<sub>2</sub>. Elliott et al. (2007) noted that the results were consistent with  
27 those reported in the Krewski et al. (2000) reanalysis of the ACS study. This analysis was  
28 ecological, but the exposure estimates in the smaller area compared to that in the U.S. cohort  
29 studies may have resulted in less exposure misclassification error, and the large underlying

1 population appears to be reflected in the narrow confidence bands of effect estimates. The results  
2 from this study suggest an association between long-term exposures (especially in recent years)  
3 to SO<sub>2</sub> and mortality.

### 3.5.3. Summary of Evidence on the Effect of Long-Term Exposure on Mortality

4 The available epidemiological evidence on the effect of long-term exposure to SO<sub>2</sub> on  
5 mortality is *inadequate to infer the presence or absence of a causal relationship* at this time. The  
6 ecological cross-sectional studies examined in the 1982 AQCD and 1986 Secondary Addendum  
7 found suggestive relationships between long-term exposure to SO<sub>2</sub> and mortality. However, there  
8 were concerns as to whether the observed association was due to SO<sub>2</sub> alone, because sulfate or  
9 other particulate SO<sub>x</sub> such as H<sub>2</sub>SO<sub>4</sub> could have been responsible. In the more recent longitudinal  
10 cohort studies, once again, positive associations have been observed between long-term exposure  
11 to SO<sub>2</sub> and mortality; however, several issues affect the interpretation of these results.

12 Figure 3-14 presents all-cause mortality RR estimates associated with long-term exposure  
13 to SO<sub>2</sub> from the U.S. and European cohort studies. The overall range of RRs spans 0.97 to 1.07  
14 per 5 ppb increase in the annual (or longer period) average SO<sub>2</sub>. The analyses of the Harvard Six  
15 Cities and the ACS cohort data, which likely provide effect estimates that are most useful for  
16 evaluating possible health effects in the United States, observed RRs of 1.02 to 1.07. Note that  
17 each of the U.S. cohort data has its own advantages and limitations. The Harvard Six Cities data  
18 have a small number of exposure estimates, but the location of the monitors were chosen  
19 carefully for epidemiological purposes. The ACS cohort had far more subjects, but the  
20 population was more highly educated than the representative U.S. population. Since educational  
21 status appeared to be an important effect modifier of air pollution effects in both studies, the  
22 overall effect estimate for the ACS cohort may underestimate that for the more general  
23 population. However, it should also be noted that several other U.S. and European studies did not  
24 observe an association between long-term exposure to SO<sub>2</sub> and mortality.



1           The geographic scale of analysis appears to influence SO<sub>2</sub> effect estimates and exposure  
2 error. In a reanalysis of the ACS data, the county-level analysis showed a smaller SO<sub>2</sub> effect  
3 estimate than MSA-level analysis. For sulfate, the opposite pattern was found. Thus, the impact  
4 of the geographic scale of analysis may also depend on the spatial distribution of air pollutants.  
5 The cross-sectional analysis in Great Britain using small-scale electoral wards observed an effect

1 estimate similar to the lower end of the range of effect estimates for all-cause mortality from  
2 U.S. cohort studies, though it is not clear if the effect estimates from this cross-sectional study  
3 are directly comparable to those from cohort studies.

4 Another important issue that these studies could not resolve was the possible confounding  
5 and/or interaction among PM indices and SO<sub>2</sub>. The possibility that the observed effects may not  
6 be due to SO<sub>2</sub>, but other constituents that come from the same source as SO<sub>2</sub>, or that PM may be  
7 more toxic in the presence of SO<sub>2</sub> or other components associated with SO<sub>2</sub>, cannot be ruled out.  
8 For example, the ACS cohort came from all regions of the United States, but a major fraction of  
9 the ACS cities were located in the eastern United States, where both SO<sub>2</sub> and sulfate levels tend  
10 to be higher. Therefore, even with sophisticated spatial modeling, separating possible  
11 confounding of SO<sub>2</sub> effects by PM is challenging. Future and on-going studies that take into  
12 consideration within- versus between-city variation of these pollutants may help elucidate this  
13 issue.

14 Overall, the results from two major U.S. epidemiological studies observe an association  
15 between long-term exposure to SO<sub>2</sub> or sulfur-containing particulate air pollution and mortality.  
16 However, several other U.S. and European cohort studies did not observe an association. The  
17 lack of consistency across studies, inability to distinguish potential confounding by copollutants,  
18 and uncertainties regarding the geographic scale of analysis limit the interpretation of a causal  
19 relationship.

# Chapter 4. Public Health Impact

1           This chapter addresses several issues relating to the broader public health impact from  
2 exposure to ambient SO<sub>2</sub>. First, the shape of the concentration-response relationship for SO<sub>2</sub> is  
3 discussed, with consideration of interindividual variability in responses and evaluation of the  
4 limited evidence available to assess a population threshold value for health effects. The next  
5 section identifies characteristics of subpopulations which may experience increased risks from  
6 SO<sub>2</sub> exposures, through either enhanced susceptibility (e.g., as a result of pre-existing disease,  
7 genetic factors, age) and/or differential vulnerability associated with increased exposure (e.g.,  
8 close proximity to sources, activities). The final section discusses the potential public health  
9 impact from adverse health effects associated with SO<sub>2</sub> by examining the prevalence of  
10 susceptible individuals in the U.S. population.

## 4.1. Assessment of Concentration-Response Function and Potential Thresholds

11           An important consideration in characterizing the public health impacts associated with SO<sub>2</sub>  
12 exposure is whether the concentration-response relationship is linear across the full concentration  
13 range, or if there are concentration ranges where there are departures from linearity (i.e.,  
14 nonlinearity). Of particular interest is the shape of the concentration-response curve at and below  
15 the level of the current SO<sub>2</sub> NAAQS level of a 24-h avg level of 0.14 ppm or the annual average  
16 of 0.03 ppm.

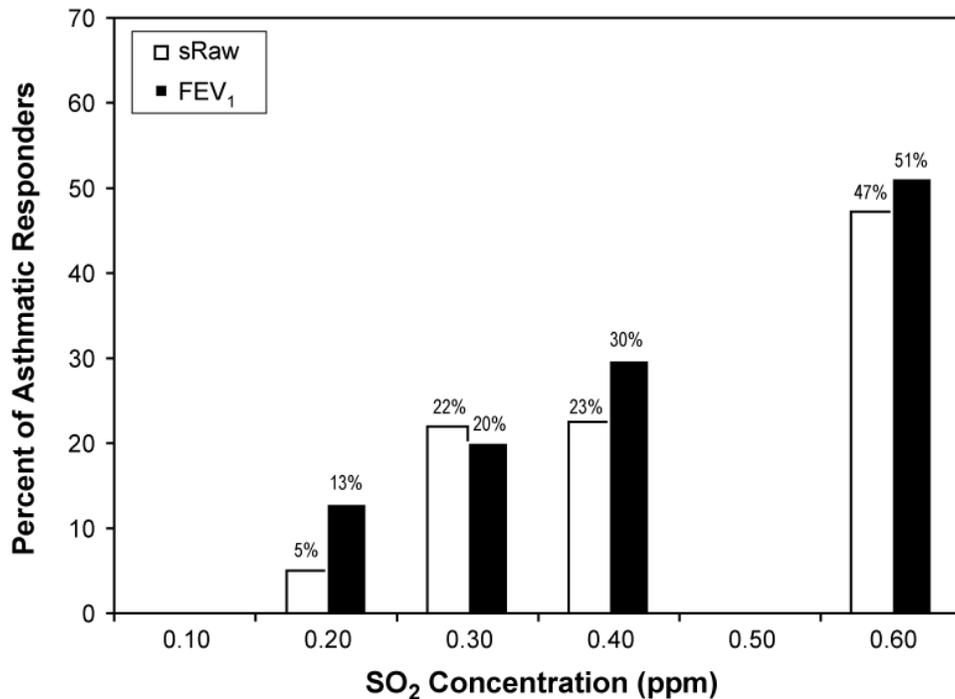
17           Some human clinical studies provide individual-level response data in relation to different  
18 levels of SO<sub>2</sub> exposure; this allows evaluation of both the percentage of individuals showing  
19 responses across the range of exposures as well as the concentration at which an individual  
20 begins to indicate a response. In epidemiological studies, rather than identifying interindividual  
21 differences in response, most studies evaluate whether there is a population-level threshold,  
22 which is the concentration of SO<sub>2</sub> that must be exceeded to elicit a health response in the study  
23 population. Low data density in the lower concentration range, measurement error in the  
24 response, and exposure measurement error are some of the factors that complicate the ability to  
25 determine the shape of the concentration-response curve, including the presence of any

1 threshold. Biological characteristics that tend to linearize concentration-response relationships  
2 include individual biological differences in susceptibility to air pollution health effects, additivity  
3 of SO<sub>2</sub>-induced effects to a naturally occurring background level, and additivity of effects from  
4 other pollutant exposures. Epidemiological and human clinical studies that examined the shape  
5 of the concentration-response function for different averaging times or exposure durations are  
6 presented below. The discussion focuses on respiratory morbidity effects associated with short-  
7 term exposure to SO<sub>2</sub>, for which the strongest causal evidence exists.

#### 4.1.1. Evidence from Human Clinical Studies

8 In human clinical studies of exercising asthmatics, moderate SO<sub>2</sub>-induced decrements in  
9 lung function have been observed at the lowest levels tested (i.e., 0.2 to 0.3 ppm, 5 to 10 min  
10 exposures) in the most sensitive individuals (approximately 5-20% of subjects). Statistically  
11 significant respiratory effects have been consistently observed at concentrations of 0.4-0.6 ppm,  
12 with 20-60% of asthmatics experiencing moderate to large decrements in lung function following  
13 5-10 min exposures (see Table 3-1). Smaller, yet statistically significant decrements in lung  
14 function have also been demonstrated at SO<sub>2</sub> concentrations < 0.2 ppm when preceded by  
15 exposure to O<sub>3</sub> (see Section 3.1.5.1).

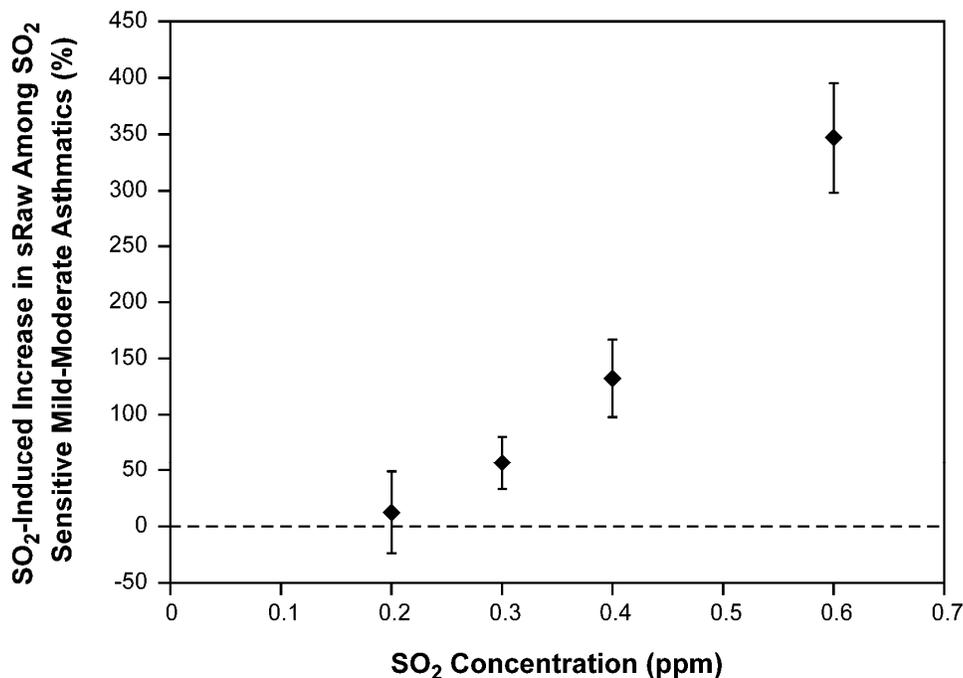
16 With increasing exposure concentration between 0.2 and 1.0 ppm, there is a clear increase  
17 both in magnitude of respiratory effect and percent of asthmatics affected (Table 3-1). A subset of  
18 the data presented in this table was taken from a series of studies conducted by Linn et al. (1987;  
19 1988; 1990) and is presented graphically in Figure 4-1 through Figure 4-3. In these studies, mild  
20 and moderate asthmatics were exposed for 10 min to SO<sub>2</sub> concentrations between 0 and 0.6 ppm  
21 during moderate to heavy exercise. These particular studies were selected for inclusion in this  
22 meta-analysis owing to similarities between exposure protocols, with all subjects being exposed  
23 to multiple concentrations of SO<sub>2</sub>. In the 1987 study, subjects were exposed to SO<sub>2</sub>  
24 concentrations of 0, 0.2, 0.4, and 0.6 ppm, while in the 1988 and 1990 studies, subjects were  
25 exposed to concentrations of 0, 0.3, and 0.6 ppm. The percent of asthmatics experiencing  
26 moderate or greater SO<sub>2</sub>-induced decrements in lung function (increase in sRaw  $\geq$  100% or  
27 decrease in FEV<sub>1</sub>  $\geq$  15%) is shown in Figure 4-1. At 0.2 ppm, between 5 and 13% of subjects are  
28 affected, and this fraction increases with increasing concentration, with approximately 50% of  
29 subjects experiencing respiratory effects at a concentration of 0.6 ppm.



**Figure 4-1. Percent of mild and moderate asthmatics ( $\dot{V}_E = 40\text{-}50$  L/min) experiencing an  $\text{SO}_2$ -induced increase in sRaw of  $\geq 100\%$  or a decrease in  $\text{FEV}_1$  of  $\geq 15\%$ , adjusted for effects of moderate to heavy exercise in clean air. The data represents lung function measurements from 40, 41, 40, and 81 subjects at concentrations of 0.2, 0.3, 0.4, and 0.6 ppm, respectively.**

Source: Data taken from Linn et al. (1987; 1988; 1990)

1            Figure 4-2 and Figure 4-3 present the concentration-response relationship between  $\text{SO}_2$  and  
 2 decrements in lung function in  $\text{SO}_2$ -sensitive asthmatics, i.e., those asthmatics experiencing  
 3 significant decrements in lung function at the highest exposure concentration (0.6 ppm) used in  
 4 the Linn et al. studies (1987; 1988; 1990). This analysis demonstrates a clear increase in the  
 5 magnitude of respiratory effects with increasing exposure concentration, with more marked  
 6 effects observed at  $\text{SO}_2$  concentrations greater than 0.3 ppm. The results of a study by Gong et al.  
 7 (1995) support this conclusion: the authors observed a linear relationship between  $\text{SO}_2$   
 8 concentration (0, 0.5, and 1.0 ppm) and both lung function (decrease in  $\text{FEV}_1$ , and increase in  
 9 sRaw) and respiratory symptoms.

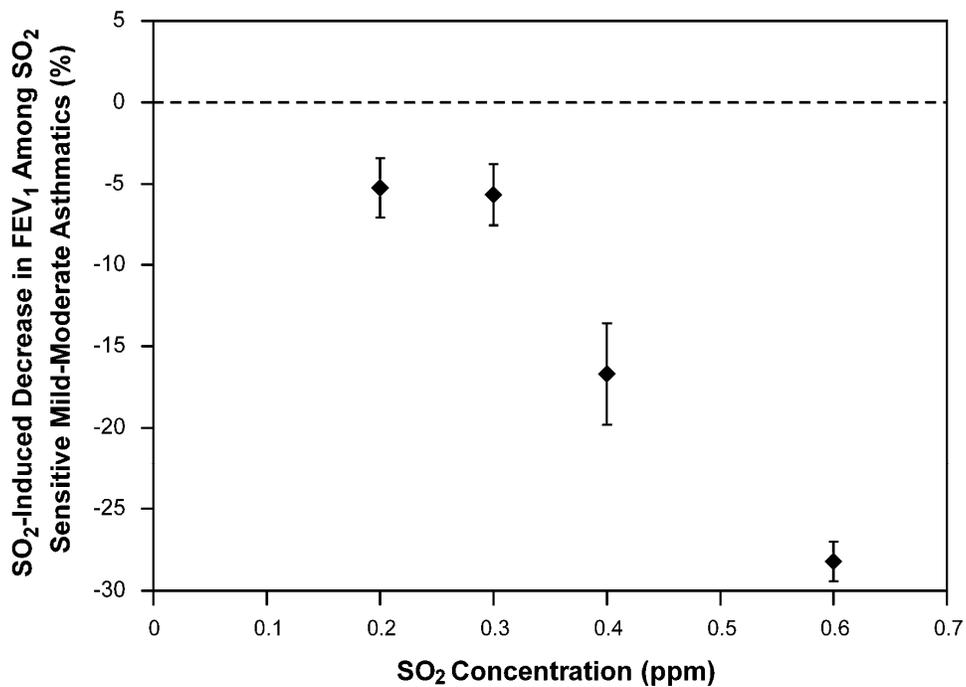


**Figure 4-2.** SO<sub>2</sub>-induced increase in sRaw among SO<sub>2</sub>-sensitive mild and moderate asthmatics (n=38) following 10-min exposures during moderate to heavy exercise ( $V_E = 40\text{-}50$  L/min). Only SO<sub>2</sub>-sensitive asthmatics, defined here as asthmatics experiencing  $\geq 100\%$  SO<sub>2</sub>-induced increase in sRaw at 0.6 ppm, were included in this analysis. The analysis includes data from 14 SO<sub>2</sub>-sensitive subjects from Linn et al. (1987) exposed to concentrations of 0.2, 0.4, and 0.6 ppm, as well as 24 SO<sub>2</sub>-sensitive subjects from Linn et al. 1988 and 1990 exposed to 0.3 and 0.6 ppm. Error bars =  $\pm 1$  SE.

#### 4.1.2. Evidence from Epidemiological Studies

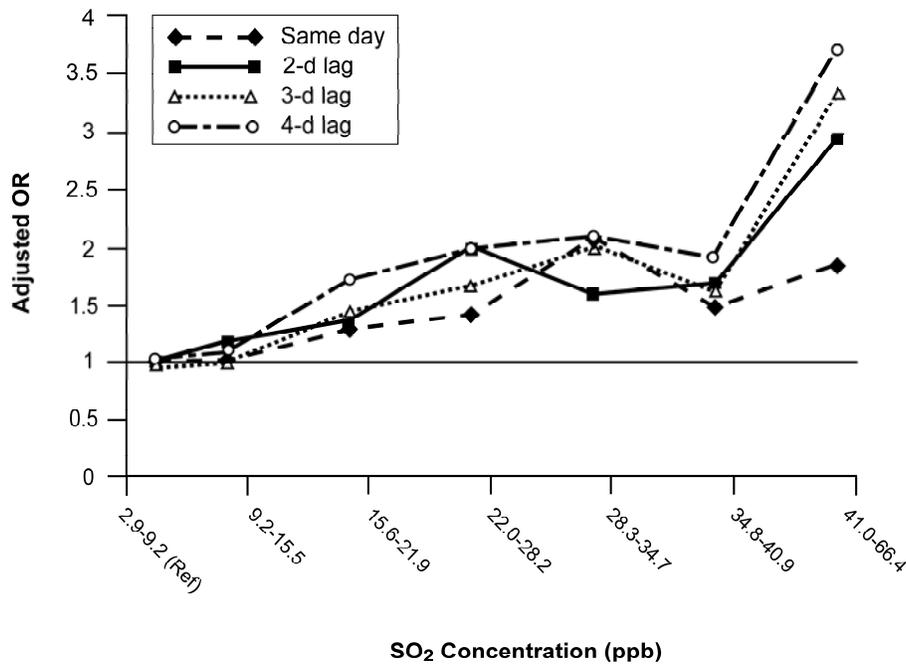
1 Although there are numerous epidemiological studies that examined the association  
 2 between SO<sub>2</sub> and various health effects, only a few of these studies attempted to evaluate the  
 3 concentration-response function. Most studies assumed a linear or log-linear relationship  
 4 between ambient SO<sub>2</sub> concentrations and the health outcome in their evaluations.

5 Epidemiological studies have examined the concentration-response relationship for SO<sub>2</sub>  
 6 using various statistical methods, including the comparison of effect estimates in increasing  
 7 quartiles or quintiles, plotting the risk observed against increasing SO<sub>2</sub> concentrations, and using  
 8 nonparametric smoothed curves to assess the nonlinearity of the SO<sub>2</sub>-effect relationship. Most of  
 9 the epidemiological studies that examined the concentration-response function between SO<sub>2</sub>  
 10 exposure and respiratory morbidity observed that the relationship was linear across the entire  
 11 concentration range.



**Figure 4-3.** SO<sub>2</sub>-induced decrease in FEV<sub>1</sub> among SO<sub>2</sub>-sensitive mild and moderate asthmatics (n=41) following 10 min exposures during moderate to heavy exercise ( $V_E = 40\text{-}50$  L/min). Only SO<sub>2</sub>-sensitive asthmatics, defined here as asthmatics experiencing  $\geq 15\%$  SO<sub>2</sub>-induced decrease in FEV<sub>1</sub> at 0.6 ppm, were included in this analysis. The analysis includes data from 21 SO<sub>2</sub>-sensitive subjects from Linn et al. (1987) exposed to concentrations of 0.2, 0.4, and 0.6 ppm, as well as 20 SO<sub>2</sub>-sensitive subjects from Linn et al. 1988 and 1990 exposed to 0.3 and 0.6 ppm. Error bars =  $\pm 1$  SE.

1 Only one epidemiological study investigated the concentration-response function of peak  
 2 SO<sub>2</sub> exposures. The association between asthma hospitalizations and ambient 1-h max SO<sub>2</sub>  
 3 concentrations was examined in a case-control study of children in Bronx County, NY (Lin et al.,  
 4 2004). The 1-h max concentration ranged from 2.9 to 66.4 ppb. The authors categorized 1-h max  
 5 SO<sub>2</sub> concentrations and estimated ORs for each category using the lowest exposure group as the  
 6 reference (2.9 to 9.2 ppb). They observed an increasing linear trend across the range of  
 7 concentrations, with more marked effects observed at 1-h max SO<sub>2</sub> concentrations greater than  
 8 40 ppb Figure 4-4. A 1-h max SO<sub>2</sub> concentration of 40 ppb falls between the 90th and 95th  
 9 percentiles of the ambient regulatory data for the years 2003-2005; during these years 24-h avg  
 10 SO<sub>2</sub> concentrations for the 90th and 95th percentiles were 10 and 13 ppb, respectively.

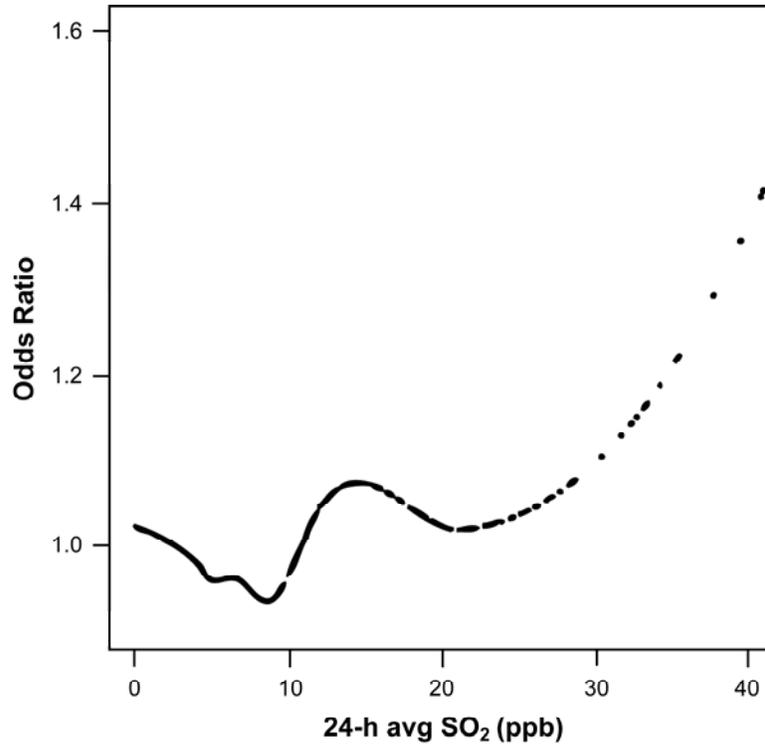


**Figure 4-4. Adjusted odds ratios of asthma hospitalizations by groupings of 1-h max SO<sub>2</sub> concentrations in Bronx County, New York. All groups were compared with the lowest exposure group (2.9-9.2 ppb). ORs for 1-h max SO<sub>2</sub> concentrations on the same day, as well as from a 2-day, 3-day, and 4-day moving average lag are presented.**

Source: Lin et al. (2004)

1 Most epidemiological studies investigating the concentration-response function examined  
 2 the effects of short-term 24-h avg exposures to SO<sub>2</sub>. The Harvard Six Cities study by Schwartz  
 3 et al. (1994) investigated the concentration-response function and observed a nonlinear  
 4 relationship between SO<sub>2</sub> concentrations and respiratory symptoms. A figure plotting the relative  
 5 odds of incidence of lower respiratory tract symptoms against SO<sub>2</sub> concentrations lagged 1 day  
 6 indicated that no statistically significant increase in the incidence of lower respiratory tract  
 7 symptoms was seen until concentrations exceeded a 24-h avg SO<sub>2</sub> of 22 ppb though an  
 8 increasing trend was observed at concentrations as low as 10 ppb (see Figure 4-5). In a study of  
 9 respiratory hospitalizations, Ponce de Leon et al. (1996) found that a weak relationship with SO<sub>2</sub>  
 10 was only observable at 24-h avg SO<sub>2</sub> concentrations above 23 ppb. In both this study and the  
 11 study by Schwartz et al. (1994), a statistically significant increased risk was observable only at  
 12 24-h avg SO<sub>2</sub> concentrations that were above the 90th percentile. The nonlinearity observed in

- 1 these concentration-response functions is dependent on only a few influential observations; thus,
- 2 the results should be viewed with caution.



**Figure 4-5. Relative odds ratio of incidence of lower respiratory tract symptoms smoothed against 24-h avg SO<sub>2</sub> concentrations on the previous day, controlling for temperature, city, and day of week.**

Source: Schwartz et al. (1994).

- 3 A study by Jaffe et al. (2003) examined the association between SO<sub>2</sub> and emergency
- 4 department (ED) visits for asthma in three cities in Ohio, and found significant associations only
- 5 in Cincinnati using Poisson regression analysis. To examine the concentration-response function,
- 6 they also conducted quintile analyses. In Cincinnati, an increasing linear trend in risk was
- 7 observed across the range of concentrations. Wong et al. (2002; using GAM with default
- 8 convergence criteria) constructed a plot of risk against 24-h avg SO<sub>2</sub> concentrations to examine
- 9 the concentration-response relationship in Hong Kong and London. In general, a linear
- 10 relationship between risk of respiratory hospitalizations and SO<sub>2</sub> was observed across the range

1 of SO<sub>2</sub> concentrations in Hong Kong, but not in London. Several other studies that examined the  
2 concentration-response relationship found that the association between respiratory  
3 hospitalizations and SO<sub>2</sub> did not deviate from linearity (Atkinson et al., 1999a; Burnett et al.,  
4 1997a; 1997b; 1999; Hajat et al., 2002).

### **4.1.3. Summary of Evidence on Concentration-Response Functions and Thresholds**

5 In the previous two sections, evidence from human clinical and epidemiological studies on  
6 the concentration-response function that may inform identification of any potential population  
7 threshold was presented. Evidence from human clinical studies indicates a clear increase in the  
8 magnitude of respiratory effects with increasing exposure concentration between 0.2 and 1.0  
9 ppm with 5-10 min SO<sub>2</sub> exposures. Epidemiological studies also have observed generally  
10 increasing trends across the entire range of SO<sub>2</sub> exposures; however, in a limited number of  
11 studies a marked increase in effect was observed only at the higher concentrations (above 90<sup>th</sup>  
12 percentile values).

13 Discerning a possible population-level threshold for air pollution-related effects in  
14 epidemiological studies is quite challenging. Using PM<sub>2.5</sub> as an example, Brauer et al. (2002)  
15 examined the relationship between ambient concentrations and mortality risk in a simulated  
16 population with specified common individual threshold levels. They found that no population  
17 threshold was detectable when a low threshold level was specified. Even at high-specified  
18 individual threshold levels, the apparent threshold at the population level was much lower than  
19 specified. Brauer et al. (2002) concluded that the use of surrogate measures of exposure (i.e.,  
20 those from centrally located ambient monitors) that were not highly correlated with personal  
21 exposures made it difficult to discern population-level thresholds in epidemiological studies even  
22 if a common threshold exists for individuals within the population.

23 The wide interindividual variability in sensitivity to SO<sub>2</sub> exposure further hinders the  
24 ability to discern a potential threshold level in population studies. Human clinical studies have  
25 shown that asthmatics experience greater increases in sRaw following peak SO<sub>2</sub> exposures  
26 compared to healthy individuals (Linn et al., 1987). Among asthmatics, interindividual  
27 differences in response also have been noted, with some asthmatics experiencing SO<sub>2</sub>-related  
28 effects at much lower levels than others (Horstman et al., 1986).

1 Another factor that complicates the identification of a possible threshold of effects is that  
2 currently deployed ambient monitors may be inadequate for accurate and precise measurements  
3 at lower 24-h avg SO<sub>2</sub> levels. Ambient concentrations of SO<sub>2</sub> have been declining since the  
4 1980s and are now at or very near the limit of detection of the ambient monitors in the regulatory  
5 network. The mean 24-h avg SO<sub>2</sub> concentration across the metropolitan statistical areas (MSAs)  
6 from 2003 through 2005 was 4 ppb (5th–95th percentile: 1, 13). Thus, there is greater uncertainty  
7 at the lower concentration range compared to the higher concentrations, which likely limits the  
8 ability to detect any clear-cut potential threshold.

9 In conclusion, evidence from human clinical studies indicates wide interindividual  
10 variability in response to SO<sub>2</sub> exposures, with peak (5 to 10 min) exposures at levels as low as  
11 0.2-0.3 ppm eliciting respiratory responses in some asthmatic individuals. Several  
12 epidemiological studies that examined the concentration-response function between short-term  
13 (24-h avg or 1-h max) exposure to SO<sub>2</sub> and respiratory morbidity observed that the relationship  
14 was linear across the entire concentration range, suggesting a lack of a threshold in effect.  
15 However, given the various limitations in observing a possible threshold in population studies,  
16 the lack of evidence does not necessarily indicate that there is indeed no threshold in SO<sub>2</sub> health  
17 effects. Some epidemiological studies did report that though there was generally an increasing  
18 trend at the lower SO<sub>2</sub> concentrations, a marked increase in SO<sub>2</sub>-related respiratory health effects  
19 was observed at higher concentrations. However, as these observations were based on a few  
20 potentially influential data points (24-h avg SO<sub>2</sub> concentrations above the 90th percentile), the  
21 results should be interpreted with caution. The overall limited evidence from epidemiological  
22 studies examining the concentration-response function of SO<sub>2</sub> health effects is inconclusive  
23 regarding the presence of an effect threshold at current ambient levels.

## 4.2. Susceptible and Vulnerable Populations

24 Interindividual variation in human responses to air pollutants indicates that not all  
25 individuals exposed to pollutants respond similarly. That is, some subpopulations are at increased  
26 risk to the detrimental effects of pollutant exposure. The NAAQS are intended to provide an  
27 adequate margin of safety for both general populations and sensitive subpopulations, or those  
28 subgroups potentially at increased risk for ambient air pollution health effects. For the purposes  
29 of this document, a susceptible population is defined as one that might exhibit an adverse health

1 effect to a pollutant at concentrations lower than those needed to elicit the same response in the  
2 general population, and a vulnerable population as one that might be differentially exposed to  
3 higher concentrations of a pollutant than the general population, regardless of health outcome.  
4 The previous review of the SO<sub>2</sub> NAAQS identified certain groups within the population that may  
5 be more susceptible to the effects of SO<sub>2</sub> exposure, including asthmatics, individuals not  
6 diagnosed as asthmatic but with atopic disorders (e.g., allergies), and individuals with COPD or  
7 cardiovascular disease. Other subgroups considered to be somewhat sensitive in this document  
8 include children and older adults; people with other respiratory disease; genetic factors;  
9 socioeconomic status (SES); and populations experiencing heightened exposure levels (e.g.,  
10 those living near roadways or other “hot spots” or engaged in outdoor work or exercise). Also of  
11 concern are individuals who generally may not be susceptible to SO<sub>2</sub>-related health effects but  
12 may experience transient airways reactivity to respiratory irritants such as SO<sub>2</sub> following a recent  
13 viral respiratory infection (Stempel and Boucher, 1981). These groups comprise a large fraction  
14 of the U.S. population. Given the likely heterogeneity of individual responses to air pollution, the  
15 severity of health effects experienced by a susceptible subgroup may be much greater than that  
16 experienced by the population at large (Zanobetti et al., 2000).

#### **4.2.1. Preexisting Disease as a Potential Risk Factor**

17 Several researchers have investigated the effect of air pollution among potentially  
18 susceptible groups with preexisting medical conditions. A recent report of the National Research  
19 Council emphasized the need to evaluate the effect of air pollution on susceptible groups,  
20 including those with respiratory illnesses and cardiovascular diseases (National Research  
21 Council., 2004). Generally, asthma, COPD, conduction disorders, congestive heart failure (CHF),  
22 diabetes, and myocardial infarction (MI) are conditions believed to put persons at greater risk of  
23 adverse events associated with air pollution. Asthmatics are known to be one of the most SO<sub>2</sub>-  
24 responsive subgroups in the population; the evidence related to respiratory illness, including  
25 asthma and other factors, is discussed in further detail below.

##### **4.2.1.1. Individuals with Respiratory Diseases**

26 The 1982 AQCD concluded that asthmatics are more susceptible to respiratory effects from  
27 SO<sub>2</sub> exposures than the general public. This conclusion was primarily drawn from the strong

1 human clinical evidence. Recent epidemiological studies have strengthened this conclusion,  
2 reporting associations between a range of health outcomes with both short-term and long-term  
3 SO<sub>2</sub> exposures in subjects with respiratory disease.

4 In human clinical studies, asthmatics have been shown to be more responsive to respiratory  
5 effects of SO<sub>2</sub> exposures than healthy non-asthmatics. While SO<sub>2</sub>-attributable decrements in lung  
6 function generally have not been demonstrated at concentrations < 1.0 ppm in non-asthmatics  
7 (Lawther et al., 1975; Linn et al., 1987; Schachter et al., 1984), statistically significant increases  
8 in respiratory symptoms and decreases in lung function have been observed in exercising  
9 asthmatics following peak (5 to 10 min) SO<sub>2</sub> exposures to concentrations as low as 0.4-0.6 ppm  
10 (Gong et al., 1995; Horstman et al., 1986; Linn et al., 1983). Respiratory effects have been  
11 observed in some sensitive asthmatics at concentrations as low as 0.2-0.3 ppm (Horstman et al.,  
12 1986; Linn et al., 1987). There is no evidence that individuals with COPD have increased  
13 susceptibility to SO<sub>2</sub>-induced respiratory effects.

14 A number of epidemiological studies reported increased respiratory morbidity associated  
15 with SO<sub>2</sub> exposures in asthmatics and atopic individuals. Notably, two U.S. multicity studies  
16 observed associations between ambient SO<sub>2</sub> concentrations and respiratory symptoms in  
17 asthmatic children (Mortimer et al., 2002; Schildcrout et al., 2006). Additional studies also have  
18 generally indicated positive associations for asthma among children and included a U.S. study  
19 (Delfino et al., 2003) and several European studies (Higgins et al., 1995; Neukirch et al., 1998;  
20 Peters et al., 1996; Roemer et al., 1993; Segala et al., 1998; Taggart et al., 1996; Timonen and  
21 Pekkanen, 1997; van der Zee et al., 1999). Studies of adults found no consistent association  
22 between respiratory symptoms among asthmatics and SO<sub>2</sub> concentrations (Desqueyroux et al.,  
23 2002a; 2002b; Romieu et al., 1996; van der Zee et al., 2000).

24 A suggestive association between ambient SO<sub>2</sub> concentrations and ED visits and  
25 hospitalizations provides further evidence that asthmatics are susceptible to the effects of SO<sub>2</sub>.  
26 The associations between ambient concentrations of 24-h avg SO<sub>2</sub> and ED visits and  
27 hospitalizations for asthma in the United States are generally positive (Jaffe et al., 2003; Lin et  
28 al., 2004; Michaud et al., 2004; Wilson et al., 2005), though a large time-series study conducted  
29 in Atlanta, GA did not find an association between ambient 1-h max SO<sub>2</sub> levels and ED visits  
30 (Peel et al., 2005). Studies conducted outside the United States (Atkinson et al., 1999a; Hajat et  
31 al., 1999; Sunyer et al., 1997; Thompson et al., 2001) also generally found positive results.

1 In summary, substantial evidence from epidemiological studies suggests that individuals  
2 with preexisting respiratory diseases, particularly asthma, are more susceptible to respiratory  
3 health effects, though not mortality, from SO<sub>2</sub> exposures than the general public. The  
4 observations from human clinical studies indicating increased sensitivity to SO<sub>2</sub> exposures in  
5 asthmatic subjects compared to healthy subjects provide coherence and biological plausibility for  
6 these observations in epidemiological studies.

#### **4.2.1.2. Individuals with Cardiovascular Diseases**

7 The evidence available to evaluate the susceptibility of individuals with cardiovascular  
8 disease for SO<sub>2</sub>-related health effects is very limited. One human clinical study observed no  
9 evidence to suggest that patients with stable angina were more susceptible to SO<sub>2</sub>-related health  
10 effects compared with healthy subjects (Routledge et al., 2006). The authors noted that this lack  
11 of response in the heart patients may be due to a drug treatment effect rather than decreased  
12 susceptibility, as a large portion of the angina patients were taking beta blockers, which are  
13 known to increase indices of cardiac vagal control.

14 Liao et al. (2004) investigated short-term associations between ambient pollutants and  
15 cardiac autonomic control and observed that consistently more pronounced associations were  
16 found between SO<sub>2</sub> and heart rate variability among persons with a history of coronary heart  
17 disease. In another epidemiological study, Henneberger et al. (2005) examined the association of  
18 repolarization parameters with air pollutants in East German men with preexisting coronary heart  
19 disease. Ambient SO<sub>2</sub> concentrations during the 24-h preceding the ECG were associated with  
20 the QT interval duration, but not with any other repolarization parameters.

21 Evidence is inconsistent in studies analyzing the associations between ambient levels of air  
22 pollutants and ED visits or hospitalizations for cardiovascular diseases. A recent epidemiological  
23 study investigated the association of SO<sub>2</sub> with cardiac-related hospital admissions among persons  
24 with preexisting cardiopulmonary conditions and observed no associations with ambient 1-h max  
25 SO<sub>2</sub> level for any cardiac disease investigated (i.e., ischemic heart disease [IHD], CHF, and  
26 dysrhythmia) across strata of comorbid disease status, including hypertension, diabetes, and  
27 COPD (Peel et al., 2007).

28 Goldberg et al. (2003) compared the risk estimates for death with the underlying cause of  
29 CHF and those deaths classified as having CHF 1 year before death and did not find associations

1 between air pollution and those with CHF as an underlying cause of death. The authors found  
2 associations between some of the air pollutants examined (coefficient of haze [CoH], SO<sub>2</sub>, and  
3 NO<sub>2</sub>) and the deaths that were classified as having CHF 1 year before death, but the association  
4 with the specific cause of death was not unique to SO<sub>2</sub>. This pattern of association, including but  
5 not specific to SO<sub>2</sub>, with specific causes of death also was observed in an additional cohort of  
6 patients with CHF (Kwon et al., 2001).

7 In conclusion, the very limited evidence examining the susceptibility of individuals with  
8 preexisting cardiovascular disease to adverse health effects from ambient SO<sub>2</sub> exposures is  
9 inconclusive.

#### **4.2.2. Genetic Factors for Oxidant and Inflammatory Damage from Air Pollutants**

10 A consensus now exists among scientists that genetic factors related to health outcomes  
11 and ambient pollutant exposures merit serious consideration (Gilliland et al., 1999; Kauffmann,  
12 2004). Several criteria must be satisfied in selecting and establishing useful links between  
13 polymorphisms in candidate genes and adverse respiratory effects. First, the product of the  
14 candidate gene must be significantly involved in the pathogenesis of the effect of interest, which  
15 is often a complex trait with many determinants. Second, polymorphisms in the gene must  
16 produce a functional change in either the protein product or in the level of expression of the  
17 protein. Third, in epidemiological studies, the issue of confounding by other genes or  
18 environmental exposures must be carefully considered.

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

26 Gilliland et al. (2002) examined effects of GSTM1, GSTT1, and GSTP1 genotypes and  
27 acute respiratory illness, specifically respiratory illness-related absences from school. The goal  
28 was to examine potential susceptibilities on this basis, but not specifically to air pollutants. They

1 concluded that fourth grade schoolchildren who inherited a GSTP1 Val-105 variant allele had a  
2 decreased risk of respiratory illness-related school absences, indicating that GSTP1 genotype  
3 influences the risk and/or severity of acute respiratory infections in school-aged children.

4 Lee et al. (2004) studied ninth grade schoolchildren with asthma in Taiwan for a gene-  
5 environmental interaction between GSTP1-105 genotypes and outdoor pollution. They examined  
6 general district air pollution levels of low (mean SO<sub>2</sub> level of 3.6 ppb from 1994 to 2001),  
7 moderate (mean SO<sub>2</sub> of 6.2 ppb), and high (mean SO<sub>2</sub> of 8.6 ppb) and found that compared with  
8 individuals with any Val-105 allele in the low air pollution district, Ile-105 homozygotes in the  
9 high air pollution district had a significantly increased risk of asthma.

10 Gauderman et al. (2007) describe a study method that uses principal components analysis  
11 computed on single nucleotide polymorphism (SNP) markers to test for an association between a  
12 disease and a candidate gene. For example, they evaluated the association between respiratory  
13 symptoms in children and four SNPs in the GSTP1 locus, using data from the Southern  
14 California Children's Health Study (CHS). The authors observed stronger evidence of an  
15 association using the principal components approach ( $p = 0.044$ ) than using either a genotype-  
16 based ( $p = 0.13$ ) or haplotype-based ( $p = 0.052$ ) approach. This method may be applied to  
17 relationships in this and other databases to evaluate aspects of air pollutants such as SO<sub>2</sub>.

18 Winterton et al. (2001) attempted to identify a genetic biomarker for susceptibility to SO<sub>2</sub>.  
19 They screened 62 asthmatic subjects for SO<sub>2</sub> responsiveness using an inhalation challenge and  
20 collected genetic material via buccal swabs to test for associations between SO<sub>2</sub> sensitivity and  
21 specific gene polymorphisms. Subjects inhaled 0.5 ppm SO<sub>2</sub> by mouthpiece for 10 min while  
22 wearing noseclips during moderate exercise on a treadmill. Subjects were defined as SO<sub>2</sub>-  
23 sensitive if FEV<sub>1</sub> was decreased 12%. Genetic polymorphisms as biomarkers of susceptibility  
24 were evaluated in five regions coding for the  $\beta$ 2-adrenergic receptor, the  $\alpha$  subunit of the  
25 interleukin-4 (IL-4) receptor, the Clara cell secretory protein (CC16), tumor necrosis factor- $\alpha$   
26 (TNF- $\alpha$ ), and lymphotoxin- $\alpha$  (also known as TNF- $\beta$ ). The authors found a significant association  
27 between response to SO<sub>2</sub> and the homozygous wild-type allele of TNF- $\alpha$ . All of the SO<sub>2</sub>-  
28 sensitive subjects had the homozygous wild-type allele for TNF- $\alpha$ , while 61% of the  
29 nonresponders had this genotype. Homozygosity for the TNF-1 allele was associated with a 5-  
30 fold increased risk of physician-diagnosed asthma relative to other genotypes. None of the other  
31 polymorphisms showed significant trends.

1 In summary, the differential effects of air pollution among genetically diverse  
2 subpopulations have been examined for a number of GST genes and other genotypes. The  
3 limited number of studies may provide some insight into susceptible groups and a potential  
4 genetic role in such. Only one of these studies specifically examined SO<sub>2</sub> as the exposure of  
5 interest, and it found a significant association with the homozygous wild-type allele for TNF- $\alpha$ .  
6 Khoury et al. (2005) states that while genomics is still in its infancy, opportunities exist for  
7 developing, testing, and applying its tools to public health research of outcomes with possible  
8 environmental causes. At this time, there are insufficient data on which to base a conclusion  
9 regarding the effect of SO<sub>2</sub> exposure on genetically distinct subpopulations.

### 4.2.3. Age-Related Susceptibility

10 The American Academy of Pediatrics (2004) notes that children and infants are among the  
11 most susceptible to many air pollutants, including SO<sub>2</sub>. Eighty percent of alveoli are formed  
12 postnatally and changes in the lung continue through adolescence; furthermore, the developing  
13 lung is highly susceptible to damage from exposure to environmental toxicants (Dietert et al.,  
14 2000). Children also have increased vulnerability as they spend more time outdoors, are highly  
15 active, and have high minute ventilation, which collectively increase the dose they receive  
16 (Plunkett et al., 1992; Wiley, 1991a; 1991b). In addition to children, the elderly are frequently  
17 classified as being particularly susceptible to air pollution. The basis of the increased sensitivity  
18 in the elderly is not known, but one possibility is that it may be related to changes in the  
19 respiratory tract lining fluid antioxidant defense network (Kelly and Mudway, 2003) or a general  
20 reduction in immune competence.

21 Adverse respiratory effects have been observed in adolescents following SO<sub>2</sub> exposure in a  
22 laboratory setting (Koenig et al., 1981; 1983; 1987; 1988; 1990). However, there is no evidence  
23 from human clinical studies to suggest that the respiratory effects in adolescents are more severe  
24 than those observed in adults. Similarly, a number of epidemiological studies have observed  
25 increased respiratory symptoms in children associated with increasing SO<sub>2</sub> exposures (Mortimer  
26 et al., 2002; Schildcrout et al., 2006; Schwartz et al., 1994), though there is no evidence from a  
27 limited number of studies suggesting this same effect in adults (Desqueyroux et al., 2002a;  
28 Romieu et al., 1996; van der Zee et al., 2000).

1 A number of studies, investigating the association between ambient SO<sub>2</sub> levels and ED  
2 visits or hospital admissions for all respiratory causes or asthma, stratified their analyses by age  
3 group. Figure 4-6 summarizes the evidence of age-specific associations between SO<sub>2</sub> and acute  
4 respiratory ED visits and hospitalizations. Several studies demonstrated that the excess risk of  
5 ED visits or hospitalizations for all respiratory causes or asthma was higher for children  
6 (Anderson et al., 2001; Atkinson et al., 1999a; Atkinson et al., 1999b; Petroeschevsky et al.,  
7 2001) and older adults (Anderson et al., 1998; Petroeschevsky et al., 2001; Ponce de Leon et al.,  
8 1996; Wilson et al., 2005) when compared to the risk for all ages together. Increased risks for  
9 children and older adults were more prevalent in the studies of all respiratory disease than those  
10 considering asthma as the outcome.

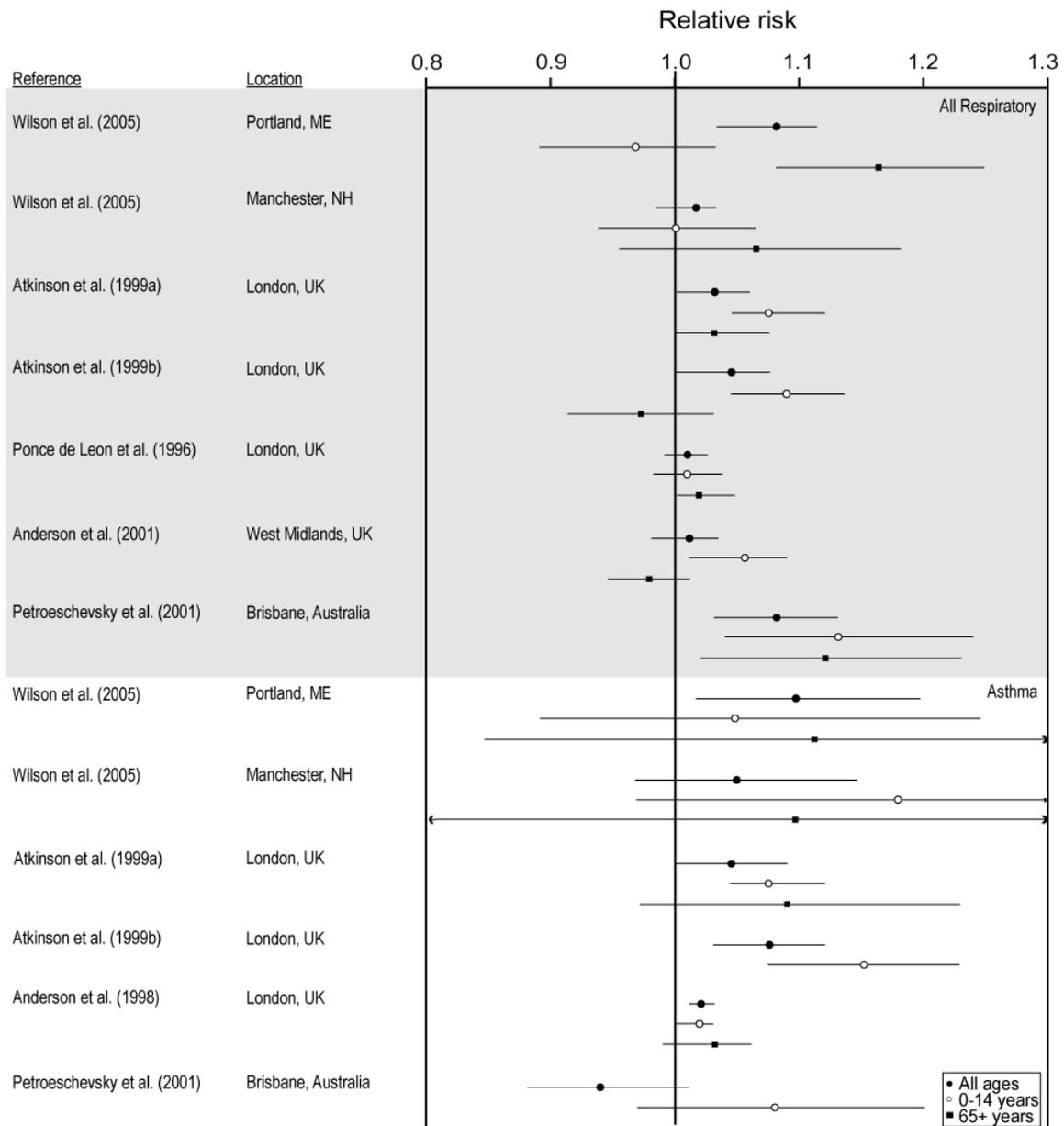
11 Cakmak et al. (2007) reported that among seven Chilean urban centers, the percent  
12 increase in nonaccidental mortality associated with a 10 ppb increase in 24-h avg SO<sub>2</sub> was 3.4%  
13 (95% CI: 0.7, 6.1) for those < 65 years of age and 5.6% (95% CI: 2.2, 9.1) for those > 85 years  
14 of age. The authors concluded that the elderly are particularly susceptible to dying from air  
15 pollution, and suggested that concentrations deemed acceptable for the general population may  
16 not adequately protect the very elderly.

17 There is limited epidemiologic evidence to suggest that children and older adults (65+  
18 years) are more susceptible to the adverse respiratory effects associated with ambient SO<sub>2</sub>  
19 concentrations when compared to the general population.

#### **4.2.4. Other Potentially Susceptible Populations**

20 There are a number of other potentially susceptible groups that, while not included here  
21 due to a lack of data specific to SO<sub>2</sub> exposures, deserve mention in this document. These include  
22 obese individuals, individuals in a chronic pro-inflammatory state (e.g., diabetics), and children  
23 born prematurely or with low birth weight.

24 Enhanced susceptibility for air pollution-related cardiovascular events has been shown for  
25 older individuals and persons with conditions associated with chronic inflammation, such as



**Figure 4-6. Relative risks (95% CI) of age-specific associations between short-term exposure to SO<sub>2</sub> and respiratory ED visits and hospitalizations. Risk estimates are standardized per 10 ppb increase in 24-h avg SO<sub>2</sub> concentrations or 40 ppb increase in 1-h max SO<sub>2</sub>.**

- 1 diabetes, coronary artery disease, and past myocardial infarctions (Bateson and Schwartz, 2004;
- 2 Goldberg et al., 2001; Zanobetti and Schwartz, 2002). Dubowsky et al. (2006) observed that
- 3 individuals with conditions associated with both chronic inflammation and increased cardiac risk
- 4 were more vulnerable to the short-term pro-inflammatory effects of air pollution. This included

1 individuals with diabetes; obesity; and concurrent diabetes, obesity and hypertension. Zanobetti  
2 and Schwartz (2001) reported more than twice the risk for hospital admissions for heart disease  
3 in persons with diabetes than in persons without diabetes associated with exposure to ambient air  
4 pollution, indicating that persons with diabetes are an important at-risk group. Data from the  
5 Third National Health and Nutrition Examination Survey indicate that 5.1% of the U.S.  
6 population older than 20 years of age have diagnosed diabetes and an additional 2.7% have  
7 undiagnosed diabetes (Harris et al., 1998). Moreover, another study found that subjects with  
8 impaired glucose tolerance without type II diabetes also had reduced heart rate variability  
9 (Schwartz, 2001). This suggests the at-risk population may be even larger.

10 Mortimer et al. (2000) reported that among asthmatic children, birth characteristics  
11 continue to be associated with increased susceptibility to air pollution later in life, demonstrating  
12 that air pollution-induced asthma symptoms are more severe in children born prematurely or of  
13 low birth weight. Specifically, the authors revealed asthmatic children born more than three  
14 weeks prematurely or weighing less than 2,500 grams (5.5 pounds) had a six-fold decrease in  
15 breathing capacity associated with air pollution compared to full-weight, full-term children. The  
16 low birth weight and premature children also reported a five-fold greater incidence of symptoms  
17 like wheezing, coughing and tightness in the chest.

#### **4.2.5. Factors that Potentially Increase Vulnerability to SO<sub>2</sub>**

18 A limited amount of information exists on exposures to SO<sub>2</sub> among vulnerable populations.  
19 Because indoor and personal SO<sub>2</sub> concentrations are generally much lower than outdoor or  
20 ambient measurements, individuals that spend most of their time indoors, such as older adults,  
21 are not anticipated to be vulnerable to high SO<sub>2</sub> exposures, though in some cases they may be  
22 more susceptible to the effects of these exposures than the general population due to preexisting  
23 health factors.

24 Other individuals with increased vulnerability include those who spend a lot of time  
25 outdoors at increased exertion levels, for example outdoor workers and individuals who exercise  
26 or play outdoor sports. Exercise may cause an increase in uptake of SO<sub>2</sub> resulting from an  
27 increase in ventilation rate and accompanying shift from nasal to oronasal breathing. Children,  
28 who generally spend more time playing outdoors, may qualify as both a susceptible population

1 due to their developing physiology and as a vulnerable population since ambient SO<sub>2</sub>  
2 concentrations are several-fold higher than indoor concentrations.

3 Residential location is not as strong of a predictor of exposure vulnerability for SO<sub>2</sub> as for  
4 traffic-related pollutants, because meteorological conditions have a greater impact on pollutant  
5 plume direction from primary point sources such as coal-fired power plants.

6 Social economic status (SES) is a known determinant of health and there is evidence that  
7 SES modifies the effects of air pollution (Makri and Stilianakis, 2007; O'Neill et al., 2003). Both  
8 higher exposures to air pollution and greater susceptibility to its effects may contribute to a  
9 complex pattern of risk among those with lower SES. Conceptual frameworks have been  
10 proposed to explain the relationship between SES, susceptibility and exposure to air pollution.  
11 Common to these frameworks is the consideration of the broader social context in which people  
12 live and its effect on health in general (Gee and Payne-Sturges, 2004; O'Neill et al., 2003), as  
13 well as on maternal and child health (Morello-Frosch and Shenassa, 2006), and asthma (Wright  
14 et al., 2007) specifically. Multilevel modeling approaches that allow parameterization of  
15 community level stressors such as increased life stress, as well as individual risk factors, are  
16 considered by these authors. In addition, statistical methods that allow for temporal and spatial  
17 variability in exposure and susceptibility, have been discussed in the recent literature (Jerrett and  
18 Finkelstein, 2005; Kunzli, 2005).

19 Most studies to date have examined modification by SES indicators on the association  
20 between mortality and PM (Finkelstein et al., 2003; Jerrett et al., 2004; Martins et al., 2004;  
21 O'Neill et al., 2003; Romieu et al., 2004) or other indices such as traffic density, distance to  
22 roadway or a general air pollution index (Finkelstein et al., 2005; Ponce et al., 2005; Woodruff et  
23 al., 2003). However, modification of SO<sub>2</sub> associations has been examined in a few studies. For  
24 example, in a study conducted in 10 large Canadian cities, living in communities in which  
25 individuals have lower household education and income levels increased the individual's  
26 vulnerability to air pollution (Cakmak et al., 2006). These effects were statistically significant for  
27 several gaseous criteria pollutants, but not for SO<sub>2</sub>. In addition, Finkelstein et al. (2003)  
28 evaluated neighborhood levels of income and air pollution in southern Ontario, Canada. They  
29 found that both income and SO<sub>2</sub> levels were associated with mortality differences. Specifically,  
30 among people with below-median income, the relative risk for those with above-median  
31 exposure to SO<sub>2</sub> was 1.18 (95% CI: 1.11, 1.26); the corresponding relative risk among subjects

1 with above-median income was 1.03 (95% CI: 0.83, 1.28). Overall, there is very limited  
2 evidence available from which conclusions on the human health effects from the interaction  
3 between SES and SO<sub>2</sub> can be drawn.

### 4.3. Potential Public Health Impacts

4 Exposure to ambient SO<sub>2</sub> is associated with a variety of outcomes including increases in  
5 respiratory symptoms, particularly among asthmatic children, and ED visits and hospital  
6 admissions for respiratory diseases among children and older adults (65+ years). In protecting  
7 public health, a distinction must be made between health effects that are considered “adverse”  
8 and those that are not. What constitutes an adverse health effect varies for different population  
9 groups. Some changes in healthy individuals are not viewed as adverse while those of similar  
10 type and magnitude in other susceptible individuals with preexisting disease are.

#### 4.3.1. Concepts Related to Defining Adverse Health Effects

11 The American Thoracic Society (ATS) published an official statement titled “What  
12 Constitutes an Adverse Health Effect of Air Pollution?” (ATS, 2000a). This statement updated  
13 the guidance for defining adverse respiratory health effects that had been published 15 years  
14 earlier (Society, 1985), taking into account new investigative approaches used to identify the  
15 effects of air pollution and reflecting concern for impacts of air pollution on specific susceptible  
16 groups. In the 2000 update, there was an increased focus on quality of life measures as indicators  
17 of adversity and a more specific consideration of population risk. Exposure to air pollution that  
18 increases the risk of an adverse effect to the entire population is viewed as adverse, even though  
19 it may not increase the risk of any identifiable individual to an unacceptable level. For example,  
20 a population of asthmatics could have a distribution of lung function such that no identifiable  
21 single individual has a level associated with significant impairment. Exposure to air pollution  
22 could shift the distribution to lower levels that still do not bring any identifiable individual to a  
23 level that is associated with clinically relevant effects. However, this shift to a lower level of lung  
24 function would be considered adverse because individuals within the population would have  
25 diminished reserve function and, therefore, would be at increased risk if affected by another  
26 agent.

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

7 The 2006 Ozone AQCD (EPA, 2006) provided information helpful in defining adverse  
 8 health effects associated with ambient O<sub>3</sub> exposure by describing the gradation of severity and  
 9 adversity of respiratory-related O<sub>3</sub> effects. The definitions that relate to responses in impaired  
 10 individuals are reproduced and presented here in Table 4-1. The severity of effects described in  
 11 the tables and the approaches taken to define their relative adversity are valid and reasonable in  
 12 the context of the new ATS (2000b) statement.

**Table 4-1. Gradation of individual responses to short-term SO<sub>2</sub> exposure in individuals with impaired respiratory systems.**

<b>FUNCTIONAL RESPONSE</b>	<b>NONE</b>	<b>SMALL</b>	<b>MODERATE</b>	<b>LARGE</b>
FEV <sub>1</sub> change	Decrements of < 3%	Decrements of 3 - 10%	Decrements of 10 - 20%	Decrements of > 20%
Nonspecific bronchial responsiveness <sup>a</sup>	Within normal range	Increases of < 100%	Increase of < 300%	Increases of > 300%
Airway resistance (sRaw)	Within normal range (±20%)	sRaw increased < 100%	sRaw increased up to 200% or up to 15 cm H <sub>2</sub> O · s	sRaw increased > 200% or more than 15 cm H <sub>2</sub> O · s
Duration of response	None	< 4 h	4 h - 24 h	> 24 h
<b>SYMPTOMATIC RESPONSE</b>	<b>NORMAL</b>	<b>MILD</b>	<b>MODERATE</b>	<b>SEVERE</b>
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 – 24 h	> 24 h
<b>IMPACT OF RESPONSES</b>	<b>NORMAL</b>	<b>MILD</b>	<b>MODERATE</b>	<b>SEVERE</b>
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

<sup>a</sup>An increase in nonspecific bronchial responsiveness of 100% is equivalent to a 50% decrease in PD20 or PD100. This table is adapted from the 2006 Ozone AQCD (Table 8-3, page 8-68) (EPA, 26).

1 As assessed in detail in earlier chapters of this document and briefly recapitulated in  
2 preceding sections of this chapter, exposures to a range of SO<sub>2</sub> concentrations have been reported  
3 to be associated with increasing severity of health effects, ranging from respiratory symptoms to  
4 ED visits and hospital admission for respiratory causes. Respiratory effects associated with  
5 short-term SO<sub>2</sub> exposures have been by far the most extensively studied and most clearly shown  
6 to be causally related to SO<sub>2</sub> exposure. Such effects are observed among children, older adults,  
7 and persons with respiratory impairments.

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

8 Although SO<sub>2</sub>-related health risk estimates may appear to be small, they may be significant  
9 from an overall public health perspective due to the large numbers of individuals in the potential  
10 risk groups. Several subpopulations have been identified as possibly having increased  
11 susceptibility or vulnerability to adverse health effects from SO<sub>2</sub>, including children, older adults,  
12 and individuals with preexisting pulmonary diseases. One consideration in the assessment of  
13 potential public health impacts is the size of various population groups that may be at increased  
14 risk for health effects associated with SO<sub>2</sub>-related air pollution exposure. Table 4-2 summarizes  
15 information on the prevalence of chronic respiratory conditions in the U.S. population in 2004  
16 and 2005 (NHIS, 2006a, 2006b).

17 Of most concern are those individuals with preexisting respiratory conditions, with  
18 approximately 10% of adults and 13% of children having been diagnosed with asthma and 6% of  
19 adults with COPD (chronic bronchitis and/or emphysema). As summarized in Section 3.1.3.5,  
20 human clinical studies indicate that a significant fraction (20-60%) of asthmatic individuals  
21 experience moderate or greater decrements in lung function as well as increased respiratory  
22 symptoms following peak (5-10 min) SO<sub>2</sub> exposures to concentrations of as low as 0.4-0.6 ppm  
23 (Table 3-1). Some sensitive asthmatics (5-20%) have been shown to experience moderate  
24 decrements in lung function at concentrations between 0.2 and 0.3 ppm. Among asthmatics, both  
25 the magnitude of SO<sub>2</sub>-induced decrements in lung function as well as the percent of individuals  
26 affected have been shown to increase with increasing exposure concentrations between 0.2 and  
27 1.0 ppm.

1 In addition, subpopulations based on age group also comprise substantial segments of the  
 2 population that may be potentially at risk for SO<sub>2</sub>-related health impacts. Based on U.S. Census  
 3 data from 2000, about 72.3 million (26%) of the U.S. population are under 18 years of age,  
 4 18.3 million (7.4%) are under 5 years of age, and 35 million (12%) are 65 years of age or older.  
 5 Hence, large proportions of the U.S. population are included in age groups that are considered  
 6 likely to have increased susceptibility and vulnerability for health effects from ambient SO<sub>2</sub>  
 7 exposure. For example, Figure 4-6 demonstrates that the SO<sub>2</sub>-related excess risk for asthma is,  
 8 on average, 50% higher among children when compared to risk estimates that include all ages  
 9 with a 10 ppb increase in 24-h avg SO<sub>2</sub> concentration.

**Table 4-2. Prevalence of selected respiratory disorders by age group in the United States (2004 [U.S. adults] and 2005 [U.S. children] National Health Interview Survey).**

CHRONIC CONDITION/DISEASE ADULTS (18+ YEARS)	AGE (YEARS)					
	ALL ADULTS		18-44	45-64	65-74	75+
	CASES (× 10 <sup>6</sup> )	%	%	%	%	%
Respiratory Conditions: Asthma	14.4	6.7	6.4	7.0	7.5	6.6
COPD: Chronic Bronchitis	8.6	4.2	3.2	4.9	6.1	6.3
COPD: Emphysema	3.5	1.7	0.3	2	4.9	6.0
CHRONIC CONDITION/DISEASE CHILDREN (<18 YEARS)	ALL CHILDREN		0-4	5-11	12-17	
	CASES (× 10 <sup>6</sup> )	%	%	%	%	
	Respiratory Conditions	6.5	8.9	6.8	9.9	9.6

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

10 Evidence indicates that several groups are potentially at increased risks from SO<sub>2</sub>  
 11 exposures compared to the average population. Susceptible subgroups include individuals with  
 12 preexisting disease, especially asthma, and children and older adults. Other individuals with  
 13 potentially increased vulnerability include those who spend a lot of time outdoors at increased  
 14 exertion levels (e.g., outdoor workers, children, individuals who exercise or play sports) and  
 15 those in proximity to large uncontrolled or poorly controlled sources. The considerable size of  
 16 the population groups at risk indicates that exposure to ambient SO<sub>2</sub> could have a potentially  
 17 significant impact on public health in the United States, with the greatest public health risks for  
 18 the smaller subset of susceptible individuals exposed to relatively high peak SO<sub>2</sub> concentrations.

# Chapter 5. Summary and Conclusions

1 Previous chapters present the most policy-relevant information related to the review of the  
2 NAAQS for SO<sub>x</sub>, which are 0.14 ppm averaged over a 24-hour period not to be exceeded more  
3 than once per year, and 0.030 ppm annual arithmetic mean, with SO<sub>2</sub> as the indicator. This  
4 chapter summarizes and integrates key findings from atmospheric sciences, ambient air data  
5 analyses, exposure assessment, dosimetry, and health evidence. The EPA framework for causal  
6 determinations described in Chapter 1 has been applied to the body of evidence in order to judge  
7 the scientific data about exposure to SO<sub>x</sub> and health effects in a two-step process. This  
8 framework draws from similar efforts across the Federal government and the wider scientific  
9 community, especially from the recent NAS Institute of Medicine document *Improving the*  
10 *Presumptive Disability Decision-Making Process for Veterans* (IOM, 2007). The first step is to  
11 determine the weight of evidence in support of causation at relevant pollutant exposures and  
12 characterize the strength of any resulting causal classification. The EPA framework applied here  
13 employs a five-level hierarchy for causal determination to be consistent with the *Guidelines for*  
14 *Carcinogen Risk Assessment* (EPA, 2005):

- 15       ▪ Sufficient to infer a causal relationship
- 16       ▪ Sufficient to infer a likely causal relationship (i.e., more likely than not)
- 17       ▪ Suggestive but not sufficient to infer a causal relationship
- 18       ▪ Inadequate to infer the presence or absence of a causal relationship
- 19       ▪ Suggestive of no causal relationship

20 The second step evaluates the quantitative evidence regarding the concentration-response  
21 relationships including levels and exposure durations at which effects are observed. These two  
22 steps characterize the health effects of SO<sub>x</sub> and levels at which effects may occur.

## 5.1. Emissions and Ambient Concentrations of SO<sub>2</sub>

23 Anthropogenic SO<sub>2</sub> is emitted mainly by fossil fuel combustion (chiefly coal and oil) and  
24 metal smelting. The largest source of emissions is from elevated point sources such as the stacks  
25 of power plants and industrial facilities. Since 1990, in response to controls applied under the  
26 Acid Rain Program (EPA, 2006), SO<sub>2</sub> emissions from these sources have declined substantially.

1 Emissions demonstrate a strong gradient increasing from west to east, owing to the high  
2 concentration of SO<sub>2</sub>-emitting electric generating utilities in the Ohio River Valley and regions to  
3 the south. PRB levels of SO<sub>2</sub> are estimated to be in the range of a few hundredths of a ppb (< 1%  
4 of typical ambient levels) across most of the United States, though much higher values are found  
5 in areas affected by volcanic or geothermal activity or in areas affected by episodic transport of  
6 high concentration plumes from Asia and Europe.

7 The levels of the current primary NAAQS for SO<sub>x</sub> are 0.14 ppm for 24-h avg SO<sub>2</sub>  
8 concentrations and 0.03 ppm for an annual avg SO<sub>2</sub> concentration. Exceedances in recent years  
9 have become rare, as the mean 24-h and annual avg SO<sub>2</sub> concentrations in the United States for  
10 the years 2003 to 2005 were ~4 ppb, with 99<sup>th</sup> percentile values of ~25 ppb for the 24-h avg, and  
11 ~15 ppb for both the 99<sup>th</sup> percentile and max values of the annual avg. Mean 1-h max  
12 concentrations in these years were ~13 ppb, with a 99<sup>th</sup> percentile value of ~120 ppb and  
13 maximum value of ~700 ppb. The large differences between 99<sup>th</sup> percentile and maximum values  
14 for the shorter term averages suggest that the maxima are strongly limited spatially and  
15 temporally and are not a major determinant of the mean values. The nonuniform spatiotemporal  
16 distribution of 5-min data, which are voluntarily supplied from a very few monitors without a  
17 specific regulatory mandate makes them very difficult to use quantitatively for determining  
18 concentrations and exposures at this very short time duration.

## 5.2. Health Effects of SO<sub>2</sub>

19 Evaluation of the health evidence, with consideration of issues related to atmospheric  
20 sciences, exposure assessment, and dosimetry, led to the conclusion that it is *sufficient to infer a*  
21 *causal relationship between respiratory morbidity and short-term exposure to SO<sub>2</sub>*. This  
22 conclusion is supported by the consistency, coherence, and plausibility of findings observed in  
23 human clinical studies with 5-10 min exposures, epidemiological studies mostly using 24-h avg  
24 exposures,<sup>7</sup> and animal toxicological studies using exposures of minutes to hours.

25 The respiratory health effects of SO<sub>2</sub> are consistent with the mode of action of SO<sub>2</sub> as it is  
26 currently understood. The immediate effect of SO<sub>2</sub> on the respiratory system is  
27 bronchoconstriction. This response is mediated by chemosensitive receptors in the  
28 tracheobronchial tree. These receptors trigger reflexes at the central nervous system level  
29 resulting in bronchoconstriction, mucus secretion, mucosal vasodilation, cough, and apnea

1 followed by rapid shallow breathing. In some cases, local nervous system reflexes also may be  
 2 involved. Asthmatics are more sensitive to the effects of SO<sub>2</sub> likely resulting from preexisting  
 3 inflammation associated with this disease. This inflammation may lead to enhanced release of  
 4 mediators, alterations in the autonomic nervous system and/or sensitization of the  
 5 chemosensitive receptors. These biological processes are likely to underlie the respiratory  
 6 symptoms; exacerbations of airways inflammation, reactivity, and responsiveness; and decreased  
 7 lung function observed in response to SO<sub>2</sub> exposure.

8 The strongest evidence for this causal relationship comes from human clinical studies  
 9 reporting respiratory symptoms and decreased lung functions following peak exposures of 5-  
 10 10 min duration to SO<sub>2</sub> at concentrations which have sometimes been measured in ambient air  
 11 for similarly short-time durations. These effects are particularly evident among exercising  
 12 asthmatics, with some sensitive asthmatics (5-20%) experiencing moderate or greater decrements  
 13 in lung function at SO<sub>2</sub> concentrations as low as 0.2-0.3 ppm (see Table 5-1). At concentrations

**Table 5-1. Key health effects of short-term exposure to SO<sub>2</sub> observed in human clinical studies.**

CONCENTRATION	EXPOSURE	EFFECTS	STUDIES
0.2-0.3 ppm	5-10 min	Moderate to large reductions in FEV <sub>1</sub> and increases in specific airway resistance (sRaw) observed among some asthmatic adults (5-20%) during moderate to heavy exercise. Bronchial responsiveness to SO <sub>2</sub> may be enhanced when preceded by exposure to O <sub>3</sub> . Limited evidence of SO <sub>2</sub> -induced increases in respiratory symptoms.	Bethel et al. (1985); Horstman et al. (1986); Koenig et al. (1990); Linn et al. (1983, 1987; 1988; 1990); Schachter et al. (1984); Sheppard et al. (1981); Trenga et al. (2001)
	1-6 h	Enhanced sensitivity to an inhaled allergen following exposure to SO <sub>2</sub> with NO <sub>2</sub> in resting asthmatics. No evidence of respiratory symptoms or decrements in lung function in resting asthmatics or healthy adults. Some weak and inconsistent evidence to suggest that SO <sub>2</sub> exposure may lead to changes in heart rate variability.	Devalia et al. (1994); Routledge et al. (2006); Rusznak et al. (1996); Tunnicliffe et al. (2001, 2003)
0.4-0.5 ppm	1-10 min	Decrements in lung function clearly demonstrated in asthmatics during exercise with significant interindividual variability in response (approximately 30% of asthmatics experienced moderate or greater decrements in lung function). Effects observed within 1-5 min of exposure generally not enhanced by increasing exposure duration. Respiratory symptoms (e.g., wheezing, chest tightness) observed at concentrations as low as 0.4 ppm and have been shown to increase with increasing exposure concentrations.	Balmes et al. (1987); Gong et al. (1995); Horstman et al. (1986); Koenig et al. (1983); Linn et al. (1983, 1987); Magnussen et al. (1990); Schachter et al. (1984); Sheppard et al. (1981); Trenga et al. (1999)
	~1-h	Decrements in lung function among asthmatics following 10 min of exercise at the end of a 60-75 min exposure are statistically significant, but less severe than effects observed following a 10 min period of exercise at the start of the exposure.	Linn et al. (1987); Roger et al. (1985)
0.6-1.0 ppm	1-10 min	Clear and consistent SO <sub>2</sub> -induced increases in respiratory symptoms observed among exercising asthmatics. Moderate to large decrements in lung function demonstrated in 35-60% of asthmatics. Respiratory effects attributed to SO <sub>2</sub> among asthmatics during exercise may be diminished after cessation of exercise, even with continued SO <sub>2</sub> exposure. No respiratory effects reported in healthy, non-asthmatics.	Balmes et al. (1987); Gong et al. (1995); Hackney et al. (1984); Horstman et al. (1986, 1988); Koenig et al. (1983); Linn et al. (1987; 1988; 1990); Roger et al. (1985); Schachter et al. (1984)
	1-6 h	Decrements in lung function among asthmatics following 5-10 min of exercise at the end of a 1-6 h exposure are statistically significant, but less severe than effects observed following a 5-10 min period of exercise at the start of the exposure.	Linn et al. (1984; 1987); Hackney et al. (1984); Roger et al. (1985)

1  $\geq 0.4$  ppm, a greater percentage (20-60%) of asthmatics experience SO<sub>2</sub>-induced decrements in  
2 lung function, which are frequently accompanied by respiratory symptoms. A clear  
3 concentration-response relationship has been demonstrated following exposures to SO<sub>2</sub> at  
4 concentrations between 0.2 and 1.0 ppm, both in terms of severity of effect and percentage of  
5 asthmatics adversely affected. Animal toxicological studies have also reported  
6 bronchoconstriction with short-term exposures of 0.5 to 1 ppm SO<sub>2</sub> (see Table 5-2).

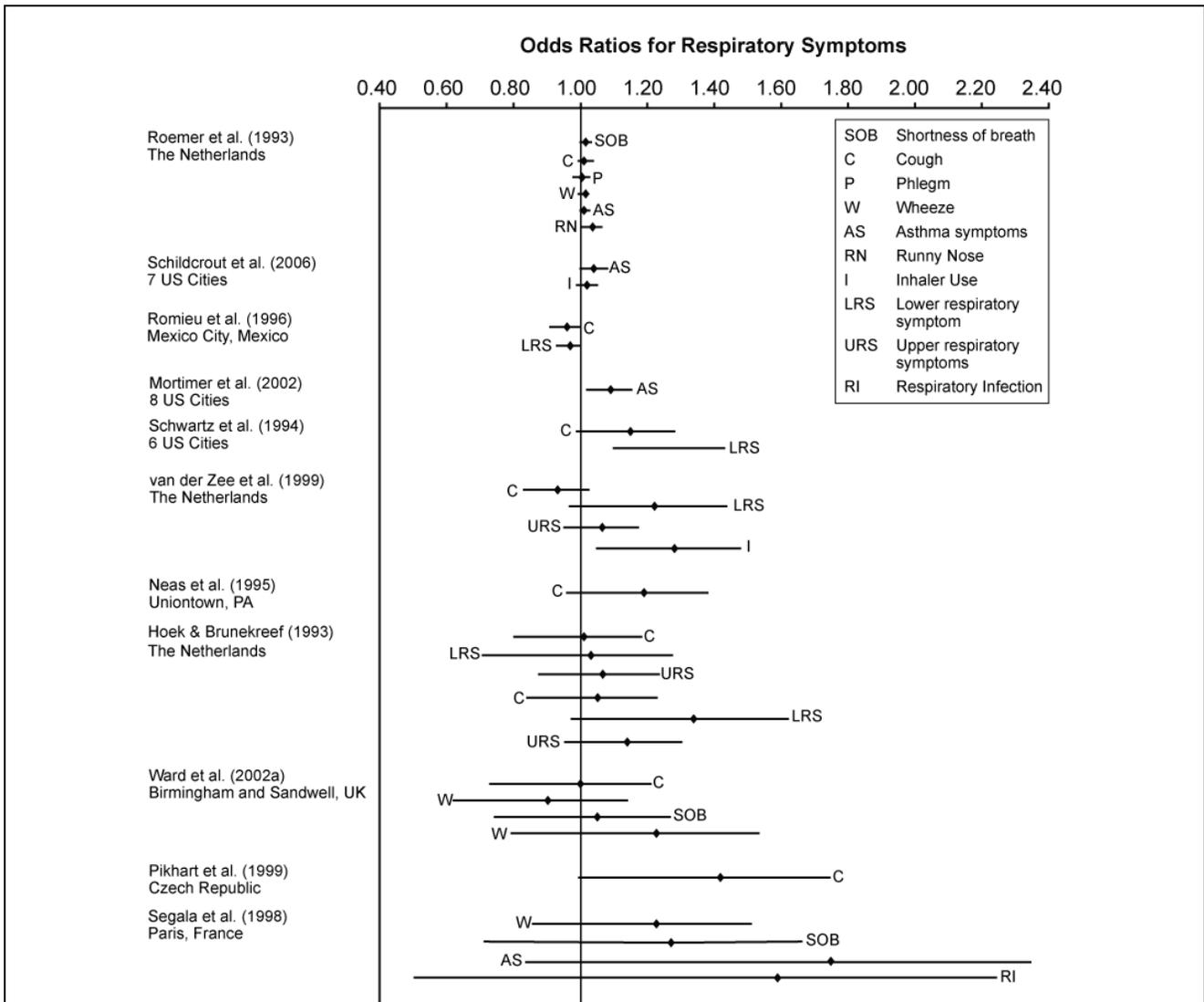
7 A larger body of evidence supporting this determination of causality comes from numerous  
8 epidemiological studies reporting associations with respiratory symptoms, ED visits, and hospital  
9 admissions with short-term SO<sub>2</sub> exposures, generally of 24-h avg. Almost all of these studies  
10 were conducted in areas where the maximum ambient 24-h avg SO<sub>2</sub> concentration was consis-  
11 tently below the current 24-h avg NAAQS level of 0.14 ppm. Important new multicity studies  
12 and several other studies have found an association between 24-h avg ambient SO<sub>2</sub>  
13 concentrations and respiratory symptoms in children, particularly those with asthma.  
14 Furthermore, limited epidemiological evidence indicates that atopic children and adults may be  
15 at increased risk for SO<sub>2</sub>-induced respiratory symptoms. Generally consistent associations also  
16 were observed between ambient SO<sub>2</sub> concentrations and ED visits and hospitalizations for all  
17 respiratory causes, particularly among children and older adults ( $\geq 65$  years), and for asthma.  
18 The SO<sub>2</sub>-related changes in ED visits or hospital admissions for respiratory causes ranged from -  
19 5% to 20% excess risk. Results of experiments in laboratory animals support these observations.  
20 Studies in animals sensitized with antigen demonstrated that repeated exposure to SO<sub>2</sub> levels as  
21 low as 0.1 ppm exacerbated allergic responses including mucin production, airway inflammation  
22 and airway hyperresponsiveness. These responses are consistent with exacerbation of asthma in  
23 humans.

24 The consistency and internal coherence of the epidemiological evidence for respiratory  
25 effects associated with short-term exposure to SO<sub>2</sub> are illustrated in Figures 5-1 and 5-2, which  
26 present effect estimates for respiratory symptoms, ED visits, and hospitalizations in children.  
27 Associations between short-term ambient SO<sub>2</sub> concentrations and respiratory symptoms, ED  
28 visits, and hospitalizations are largely positive, with several of the more precise effect estimates  
29 (suggestive of greater study power) indicating statistical significance. The epidemiological  
30 findings of asthma symptoms with 24-h avg SO<sub>2</sub> exposures are generally coherent with increases

**Table 5-2. Key respiratory health effects of exposure to SO<sub>2</sub> in animal toxicological studies.**

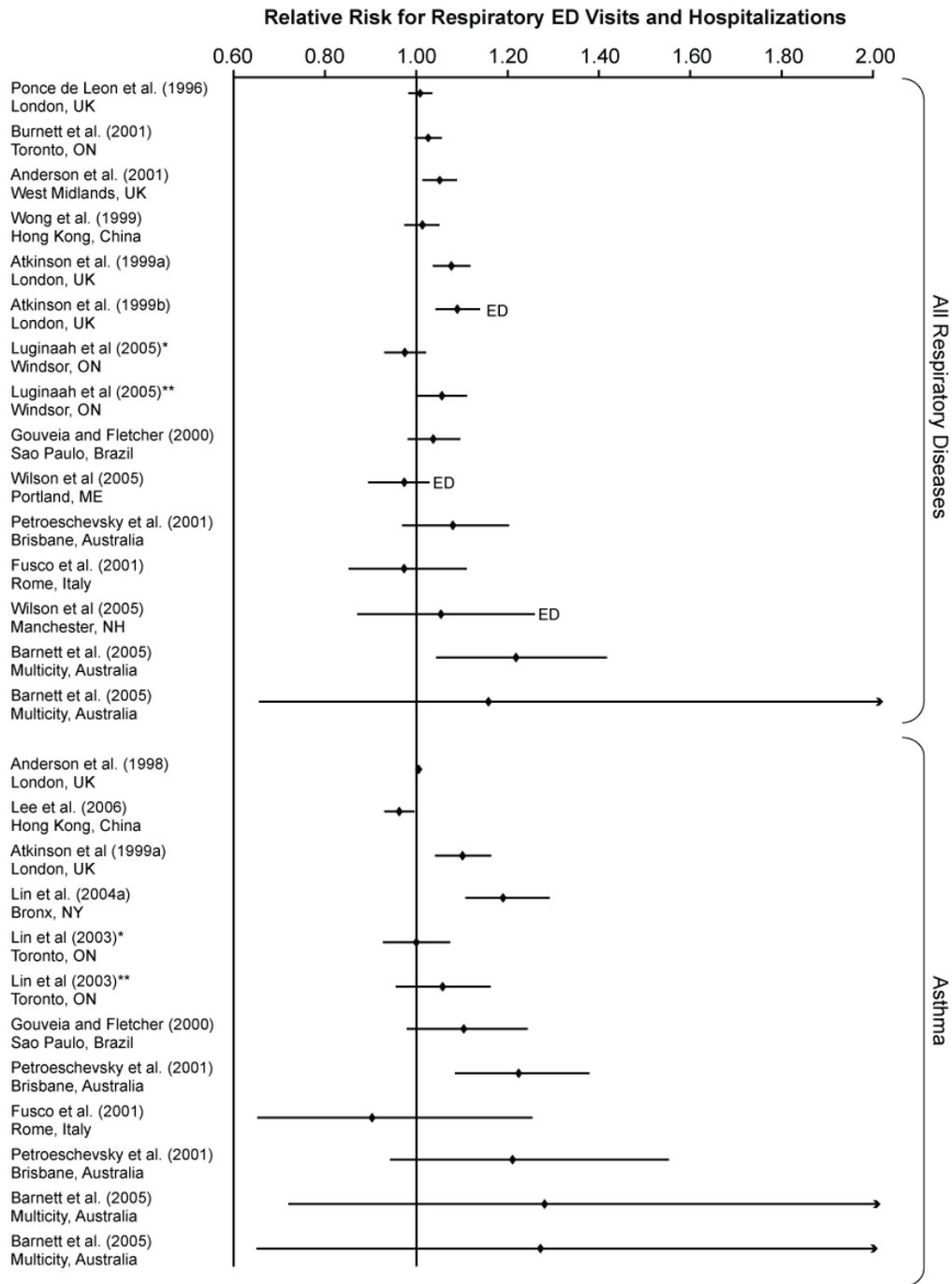
REFERENCE	EXPOSURE	SPECIES	EFFECTS
<b>LUNG FUNCTION</b>			
Amdur et al. (1983)	1 ppm SO <sub>2</sub> for 1-h	Male Hartley guinea pigs	An 11% increase in pulmonary resistance and 12% decrease in dynamic compliance were observed. Neither effect persisted into the 1-h period following exposure. No effects were observed for breathing frequency, tidal volume, or min volume.
Conner et al. (1985)	1 ppm (2.62 mg/m <sup>3</sup> ); nose only; 3-h/day for 6 days; animals evaluated for up to 48-h following exposure	Hartley guinea pig, male, age not reported, 250-320 g, n = ≤ 18 group/time point	No effect was observed on residual volume, functional reserve capacity, vital capacity, total lung capacity, respiratory frequency, tidal volume, pulmonary resistance, pulmonary compliance, diffusing capacity for carbon monoxide or alveolar volume at 1- or 48-h after last exposure.
Barthélemy et al. (1988)	0.5 or 5 ppm (1.3 or 13.1 mg/m <sup>3</sup> ); intratracheal; 45 min	Rabbit, sex not reported, adult, mean 2.0 kg, n = 5-9/group; rabbits were mechanically ventilated	Lung resistance increased by 16% and 50% in response to 0.5 and 5 ppm SO <sub>2</sub> , respectively. Bivagotomy had no effect on 5 ppm SO <sub>2</sub> -induced increases in lung resistance (54% increase before vagotomy and 56% increase after vagotomy). Reflex bronchoconstrictive response to phenyldiguanide (intravenously administered) was eliminated by exposure to SO <sub>2</sub> but SO <sub>2</sub> had no effect on lung resistance induced by intravenously-administered histamine. The study authors concluded that (1) vagal reflex is not responsible for SO <sub>2</sub> -induced increase in lung resistance at 45 min and (2) transient alteration in tracheobronchial wall following SO <sub>2</sub> exposure may have reduced accessibility of airway nervous receptors to phenyldiguanide.
<b>LUNG INJURY, INFLAMMATION AND MORPHOLOGY</b>			
Conner et al. (1989)	1 ppm (2.62 mg/m <sup>3</sup> ); nose only 3-h/day for 5 days; bronchoalveolar lavage performed daily	Hartley guinea pig, male, age not reported, 250-320 g, n = 4	No change in numbers of total cells and neutrophils, protein levels or enzyme activity in lavage fluid following SO <sub>2</sub> exposure.
Park et al. (2001)	0.1 ppm (0.26 mg/m <sup>3</sup> ); whole body; with and without exposure to ovalbumin, 5-h/day for 5 days	Dunkin-Hartley guinea pig, male, age not reported, 250-350 g, n = 7-12/group	After bronchial challenge, the ovalbumin/SO <sub>2</sub> -exposed group had significantly increased eosinophil counts in BAL fluids compared with all other groups, including the SO <sub>2</sub> -only group. The bronchial and lung tissue of the ovalbumin/SO <sub>2</sub> -exposed group showed infiltration of inflammatory cells, bronchiolar epithelial damage, and mucus and cell plug in the lumen.
Li et al. (2007b)	2 ppm (5.24 mg/m <sup>3</sup> ), with and without exposure to ovalbumin, 1-h/day for 7 days	Wistar rats, male, age not reported	Increased number of inflammatory cells in BALfluid, increased levels of MUC5AC and ICAM-1 and an enhanced histopathological response compared with those treated with ovalbumin or SO <sub>2</sub> alone
Conner et al. (1985)	1 ppm, 3-h/day/6 day. Evaluated up to 72-h postexposure	Male Hartely guinea pigs	No alveolar lesions.
Smith et al. (1989)	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.
<b>AIRWAY HYPERRESPONSIVENESS AND ALLERGY</b>			
Riedel et al. (1988)	0.1, 4.3, or 16.6 ppm (0, 0.26, 11.3, or 43.5 mg/m <sup>3</sup> ); whole body; 8-h/day for 5 days; animals were sensitized to ovalbumin on the last 3 days of exposure	Perlbright-White Guinea pig, female, age not reported, 300-350 g, n = 5 or 6/group (14 controls)	Bronchial provocation with ovalbumin was conducted every other day for 2 wks, starting at 1 wk after the last exposure. Numbers of animals displaying symptoms of bronchial obstruction after ovalbumin provocation was increased in all SO <sub>2</sub> groups compared to air-exposed groups. Anti-ovalbumin antibodies (IgG total and IgG1) were increased in BAL fluid and serum of SO <sub>2</sub> -exposed compared to air-exposed controls, with statistical significance obtained for IgG total in BAL fluid at ≥4.3 ppm SO <sub>2</sub> and in serum at all SO <sub>2</sub> concentrations. Results indicate that in this model, subacute exposure to even low concentrations of SO <sub>2</sub> can potentiate allergic sensitization of the airway.
Park et al. (2001)	0.1 ppm (0.26 mg/m <sup>3</sup> ); whole body; with and without exposure to ovalbumin; 5-h/day for 5 days	Dunkin-Hartley guinea pig, male, age not reported, 250-350 g, n = 7-12/group	After bronchial challenge, the ovalbumin/SO <sub>2</sub> -exposed group had significantly increased enhanced pause (indicator of airway obstruction) compared with all other groups, including the SO <sub>2</sub> group. Study authors concluded that low level SO <sub>2</sub> may enhance the development of ovalbumin-induced asthmatic reactions in guinea pigs.

1 in symptoms reported in asthmatics in human clinical studies with 5-10 min exposures; it is  
 2 possible that these epidemiological associations are determined in large part by peak exposures  
 3 within a 24-h period. The effects of SO<sub>2</sub> on respiratory symptoms, lung function, and airway  
 4 inflammation observed in the human clinical studies using peak exposures further provides a  
 5 basis for a progression of respiratory morbidity resulting in increased ED visits and hospital  
 6 admissions. Collectively, these findings provide biological plausibility for the observed  
 7 associations between ambient SO<sub>2</sub> levels and ED visits and hospitalizations for all respiratory  
 8 diseases and asthma, notably in children and older adults (≥ 65 years).



**Figure 5-1. Odds ratios (95% CI) for the association between short-term exposures to ambient SO<sub>2</sub> and respiratory symptoms in children. Odds ratios are standardized per 10-ppb increase in**

24-h avg SO<sub>2</sub> level. Studies are generally presented in the order of increasing width of the 95% CI.



**Figure 5-2. Relative risks (95% CI) for the association between short-term exposures to ambient SO<sub>2</sub> and emergency department (ED) visits/hospitalizations for all respiratory diseases and asthma in children. Relative risks are standardized per 10-ppb increase in 24-h avg SO<sub>2</sub> level. The**

**studies are generally presented in the order of increasing width of the 95% CI. For Luginaah et al. (2005) and Lin et al. (2003), risk estimates for males (\*) and females (\*\*) are shown separately.**

1 Overall, the epidemiological evidence for respiratory morbidity is consistent, with  
2 associations reported in studies conducted in numerous locations using a variety of  
3 methodological approaches. In the epidemiological studies that assessed potential confounding  
4 by copollutants using multipollutant models, SO<sub>2</sub> effect estimates were generally robust to the  
5 inclusion of copollutants, including PM, O<sub>3</sub>, CO, and NO<sub>2</sub>, suggesting that the observed effects  
6 of SO<sub>2</sub> on respiratory endpoints occur independent of the effects of other ambient air pollutants.

7 Intervention studies provide additional evidence that supports a causal relationship  
8 between SO<sub>2</sub> exposure and respiratory health effects. The proposition that intervention studies  
9 can provide strong support for causal inferences was emphasized by Hill (1965). Two notable  
10 studies conducted in several cities in Germany and in Hong Kong reported that decreases in SO<sub>2</sub>  
11 concentrations were associated with improvements in respiratory symptoms. In eastern Germany,  
12 a decrease in the prevalence of respiratory symptoms was correlated with a steep decline in  
13 ambient SO<sub>2</sub> concentrations of more than 90% from 1992-1993 to 1998-999. During this study  
14 period, decreases in other ambient air pollutants, including ~60% lower TSP concentrations, also  
15 occurred in these cities. In Hong Kong, respiratory health improved with similarly large  
16 reductions in SO<sub>2</sub> of up to 80% in the polluted district but with much smaller reductions in TSP  
17 (less than 20%) compared with those in the cities in eastern Germany. The possibility remains  
18 that these health improvements may be partially attributable to declining concentrations of air  
19 pollutants other than SO<sub>2</sub>, most notably PM or constituents of PM. Animal toxicological studies  
20 have reported that interactions of SO<sub>2</sub> and PM may lead to transformation of SO<sub>2</sub> to other sulfur-  
21 containing compounds which may have more potent biological effects; thus the improvements in  
22 respiratory health may be jointly attributable to declines in both SO<sub>2</sub> and PM.

23 The draft ISA also evaluates the evidence of other health outcomes and exposure durations.  
24 For short-term exposure to SO<sub>2</sub> and mortality, the evidence was found to be suggestive but not  
25 sufficient to infer a casual relationship. Recent epidemiological studies have consistently  
26 reported positive associations between mortality and SO<sub>2</sub>, with slightly larger effect estimates  
27 observed for respiratory mortality compared to cardiovascular mortality. However, the SO<sub>2</sub> effect  
28 estimates were generally reduced after adjusting for copollutants in the regression models,  
29 indicating some extent of confounding among these pollutants. The evidence between short-term

1 SO<sub>2</sub> exposure and cardiovascular effects, and morbidity and mortality with long-term SO<sub>2</sub>  
2 exposures is inadequate to infer a causal relationship. The key conclusions on the health effects  
3 of SO<sub>2</sub> exposure are briefly summarized in Section 5.5.

### 5.3. Interpretation of the Epidemiological Evidence

4 This section highlights some key considerations for the evaluation of epidemiological  
5 evidence in this draft ISA. As discussed above, clinical studies provide the strongest evidence  
6 that short-term SO<sub>2</sub> exposure is associated with respiratory morbidity. Numerous  
7 epidemiological studies report associations for a broader range of respiratory health outcomes, at  
8 lower concentrations than the clinical studies, at levels below the current standard. There is,  
9 however, uncertainty about the magnitude of the epidemiological effects estimates. Several  
10 sources of uncertainty and the implications for risk assessment are discussed below.

11 Although the numerous epidemiological studies provide supportive evidence in making a  
12 causal determination for the effect of SO<sub>2</sub> on respiratory health, much uncertainty remains in the  
13 magnitude of the effect estimates related to ambient SO<sub>2</sub> exposures. Exposure measurement error  
14 is a key source of this uncertainty as there are questions about the extent to which concentrations  
15 measured by the regulatory ambient monitoring network typically used in epidemiological  
16 studies can accurately represent an individual's exposure to SO<sub>2</sub> of ambient origin. Factors  
17 contributing to exposure measurement error include the spatial variation in ambient SO<sub>2</sub>,  
18 variation in time-activity patterns and the infiltration characteristics of microenvironments, as  
19 well as instrument error in the ambient and personal monitors.

20 SO<sub>2</sub> monitors currently deployed in the regulatory monitoring networks are adequate to  
21 determine compliance with current standards, since both the 24-h avg and annual standards are  
22 substantially above the operating limit of detection of these monitors. However, these monitors  
23 are inadequate for accurate and precise measurements at or near the current ambient mean 24-h  
24 avg SO<sub>2</sub> levels of ~4 ppb. Also, typical 24-h avg personal SO<sub>2</sub> exposures are often below the  
25 detection limit of commonly deployed passive SO<sub>2</sub> monitors. Therefore, the association between  
26 ambient concentrations and personal exposure may be inadequately characterized in recent  
27 studies at lower ambient concentrations.

28 For community time-series and short-term panel epidemiological studies using daily SO<sub>2</sub>  
29 concentrations from ambient monitors, these exposure and analytical measurement errors would

1 tend to bias the effect estimate towards the null, leading to uncertainty in accurately quantifying  
2 the magnitude of the effect. In long-term exposure studies, the variable ambient measurement  
3 and exposure error could also result in bias, but the extent and direction of this bias is unclear.

4 Another factor that contributes to uncertainty in estimating the SO<sub>2</sub>-related effect from  
5 epidemiological studies is that SO<sub>2</sub> is one component of a complex air pollution mixture  
6 including various other components, e.g., PM and NO<sub>2</sub>, known to affect respiratory health.

7 As a consequence of these uncertainties, the epidemiological observations of SO<sub>2</sub> health  
8 effects can be interpreted in several ways which are not mutually exclusive. First, the reported  
9 SO<sub>2</sub> effect estimates in epidemiological studies may reflect independent SO<sub>2</sub> effects on  
10 respiratory health. This is supported by evidence from human clinical studies which indicate that  
11 peak exposures (5-10 min) to SO<sub>2</sub> at levels as low as 0.2-0.3 ppm are capable of eliciting  
12 respiratory responses in some sensitive asthmatics. Because pure SO<sub>2</sub> does not appear alone in  
13 real-world ambient conditions but rather is part of a pollutant mixture, it is difficult to relate  
14 these peak exposures in the human clinical studies unequivocally to the 24-h avg SO<sub>2</sub>  
15 concentrations typically assessed in epidemiological studies. It is possible that higher, shorter-  
16 term concentrations of SO<sub>2</sub> may be driving the observed associations in epidemiological studies.  
17 Among the limited number of epidemiological studies evaluating the concentration-response  
18 function, several reported a linear relationship across the entire range of concentrations,  
19 suggesting the lack of a population effects threshold. However, other studies found that a marked  
20 increase in SO<sub>2</sub>-related respiratory health effects was only observed at higher concentrations  
21 (above 90<sup>th</sup> percentile values).

22 A second interpretation is that ambient SO<sub>2</sub> may be serving as an indicator of complex  
23 ambient air pollution mixtures sharing the same source as SO<sub>2</sub> (i.e., combustion of sulfur-  
24 containing fuels or metal smelting). Other components of mixed emissions from these sources  
25 include trace elements such as vanadium, nickel, selenium, and arsenic. Distinguishing effects of  
26 individual pollutants in multipollutant regression models is made difficult by the possibility that  
27 a given air pollutant may be acting as a surrogate for a less-well-measured or unmeasured  
28 pollutant, or that several pollutants may all be acting as surrogates for the same mixtures of  
29 pollutants. Therefore, reported SO<sub>2</sub>-related effects may represent those of the overall mixture or  
30 other chemical components within the mixture. However, analysis of ambient data compiled  
31 monthly for the years 2003 to 2005 showed that SO<sub>2</sub> concentrations were uncorrelated with SO<sub>4</sub><sup>2-</sup>

1 in 12 CMSAs having multiple monitors. Moreover, in multipollutant models adjusted for PM  
2 indices, SO<sub>2</sub> effect estimates were generally found to be robust.

3 A third interpretation is that in situations of complex pollution mixtures, copollutants may  
4 enhance the toxic capability of SO<sub>2</sub> or that SO<sub>2</sub> may influence the toxicity of copollutants.  
5 Findings from animal toxicological studies demonstrate that the effects of SO<sub>2</sub> may be  
6 exacerbated when aerosol particles act as carriers and deliver sulfur-containing compounds more  
7 effectively to the lower respiratory tract. The synergism observed with combined exposure to  
8 SO<sub>2</sub> and PM in the animal toxicological studies provides supportive evidence for the SO<sub>2</sub>-related  
9 respiratory effects observed under ambient conditions in the epidemiological studies.

## 5.4. Susceptible and Vulnerable Populations

10 Evidence from epidemiological and human clinical studies has indicated that certain  
11 subgroups within the population are more susceptible and/or vulnerable to the effects of SO<sub>2</sub>  
12 exposure. There is substantial evidence from epidemiological and human clinical studies  
13 indicating that asthmatics are more susceptible to respiratory health effects from SO<sub>2</sub> exposures  
14 than the general public. Limited epidemiological evidence further suggests that children and  
15 older adults ( $\geq 65$  years) are more susceptible to the adverse respiratory effects associated with  
16 ambient SO<sub>2</sub> concentrations when compared to the general population. A number of potentially  
17 susceptible groups, including obese individuals, individuals in a chronic pro-inflammatory state  
18 like diabetics, and children born prematurely or with low birth weight ( $< 2,500$  grams), may  
19 experience increased adverse effects associated with exposure to air pollution, but these  
20 relationships have not been examined specifically in relation to SO<sub>2</sub>. The differential effects of  
21 air pollution among genetically diverse subpopulations have been examined for a number of GST  
22 genes and other genotypes. While limited in number, these studies provide some insight into a  
23 potential genetic role in the determination of susceptibility to air pollution.

24 Human clinical studies have clearly shown that exercising asthmatics are at greatest risk of  
25 experiencing adverse respiratory effects related to SO<sub>2</sub> exposure. Oronasal breathing during  
26 exercise increases vulnerability as it allows a larger fraction of inhaled SO<sub>2</sub> to reach the lower  
27 airways. Therefore, individuals with increased vulnerability for SO<sub>2</sub>-related respiratory health  
28 effects include those who spend time outdoors at increased exertion levels, for example children,  
29 outdoor workers, and individuals who exercise or play sports.

## 5.5. Conclusions

1           The important findings of this draft ISA on the health effects of SO<sub>2</sub> exposure, including  
2 the levels at which effects are observed, are briefly summarized in Table 5-3. Also summarized  
3 are conclusions drawn in the previous review for comparison.

4           Collectively, the epidemiological, human clinical, and animal toxicological data support  
5 the finding of a causal relationship between short-term exposure to SO<sub>2</sub> and respiratory  
6 morbidity. Observed associations between SO<sub>2</sub> exposure and an array of respiratory outcomes,  
7 including respiratory symptoms, lung function, airway inflammation, airway  
8 hyperresponsiveness, and ED visits and hospitalizations from the human clinical, animal  
9 toxicological, and epidemiological studies, in combination, provide clear and convincing  
10 evidence of consistency, specificity, temporal and biologic gradients, biological plausibility, and  
11 coherence.

12           Human clinical studies provide strong evidence of respiratory morbidity among asthmatics  
13 following peak exposures (5-10 min) to SO<sub>2</sub> concentrations  $\geq 0.4$  ppm, with some evidence of  
14 respiratory effects at concentrations as low as 0.2 ppm in the most sensitive asthmatics. In the  
15 epidemiological studies, the SO<sub>2</sub>-related respiratory effects were consistently observed in areas  
16 where the maximum ambient 24-h avg SO<sub>2</sub> concentration was below the current 24-h avg  
17 NAAQS level of 0.14 ppm (Tables 5-4 and 5-5). Potentially susceptible and vulnerable  
18 subgroups include asthmatics, children, older adults, and individuals who spend a lot of time  
19 outdoors at increased exertion levels.

20           In addition to respiratory morbidity related to short-term exposure to SO<sub>2</sub>, studies of other  
21 health outcomes and exposure durations were also evaluated in this draft ISA. The evidence is  
22 suggestive but not sufficient to infer a causal relationship between short-term exposure to SO<sub>2</sub>  
23 and mortality. The evidence linking short-term SO<sub>2</sub> exposure and cardiovascular effects, and  
24 morbidity and mortality with long-term exposures to SO<sub>2</sub> is inadequate to infer a causal  
25 relationship.

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Table 5-3. Key findings on the health effects of SO<sub>2</sub> exposure

## Short-Term Exposure: RESPIRATORY MORBIDITY

### *Sufficient to infer a causal relationship*

#### RESPIRATORY SYMPTOMS

**Previous Conclusion:** Among exercising asthmatics, there is a clear, statistically significant increase in respiratory symptoms following peak exposures (5-10 min) to 0.6-1.0 ppm SO<sub>2</sub>. Significant, but less severe symptoms are associated with peak SO<sub>2</sub> exposures at concentrations of 0.4-0.5 ppm in human clinical studies.

In the epidemiological studies, an association with aggravation of bronchitis is consistently observed at 24-h avg SO<sub>2</sub> levels of 0.19 to 0.23 ppm and in some cases at levels below 0.19 ppm.

**Current Conclusion:** Recent human clinical studies provide additional evidence of respiratory symptoms in asthmatics following peak exposures (5-10 min) with exercise to 0.5 ppm SO<sub>2</sub>. Statistically significant increases in respiratory symptoms are observed at SO<sub>2</sub> concentrations of as low as 0.4 ppm, with the severity of symptoms shown to increase with increasing concentration between 0.4 and 0.6 ppm.

Epidemiological studies provide consistent evidence of an association between ambient SO<sub>2</sub> exposure and increased respiratory symptoms in children, particularly those with asthma or chronic respiratory symptoms. Multicity studies have observed these associations at a median range of 17 to 37 ppb (75th percentile: ~25 to 50) across cities for 3-h avg SO<sub>2</sub> and 2.2 to 7.4 ppb (90th percentile: 4.4 to 14.2) for 24-h avg SO<sub>2</sub>.

In contrast, the epidemiological evidence on the association between SO<sub>2</sub> and respiratory symptoms in adults are generally mixed, with some showing positive associations and others finding no relationship at current ambient levels.

#### LUNG FUNCTION

**Previous Conclusion:** Bronchoconstriction has been found to be the most sensitive indicator of lung function effects following acute exposure to SO<sub>2</sub>. Guinea pigs were found to be the most sensitive species, with bronchoconstriction observed using 0.16 ppm SO<sub>2</sub>. In human clinical studies, ≤ 10-20% of exercising asthmatic individuals experience large decrements in lung function (i.e., sRaw increases ≥ 200% or FEV<sub>1</sub> decreases ≥ 20%) following 5-10 min exposures to SO<sub>2</sub> concentrations of 0.2-0.5 ppm. At 0.6-1.0 ppm SO<sub>2</sub>, ≥ 20-25% of exercising asthmatics are similarly affected.

Small, reversible declines in lung function in children are observed in epidemiological studies at levels of 0.10 to 0.18 ppm but not at levels of 0.04 to 0.08 ppm.

**Current Conclusion:** Evaluation of the human clinical evidence focused on moderate or greater decrements in lung function in exercising asthmatics. SO<sub>2</sub>-induced increases in sRaw (≥ 100%) or decreases in FEV<sub>1</sub> (≥ 15%) following 5-10 min exposures are observed in 5-10% of individuals at 0.2 ppm, 10-20% of individuals at 0.3 ppm, and 20-60% of individuals at 0.4-1.0 ppm.

The results are inconsistent for the association between 24-h avg SO<sub>2</sub> and lung function in children and adults in the epidemiological studies.

#### AIRWAYS INFLAMMATION

**Previous Conclusion:** No overall conclusion.

**Current Conclusion:** A limited number of health studies have evaluated the effect of SO<sub>2</sub> on airway inflammation. One human clinical study observed an SO<sub>2</sub>-induced increase in sputum eosinophil counts in exercising asthmatics 2 h after a 10 min exposure to 0.75 ppm SO<sub>2</sub>. The results of this study provide some evidence that SO<sub>2</sub> may elicit an allergic inflammatory response in the airways of asthmatics which extends beyond the short time period typically associated with SO<sub>2</sub> effects.

Animal toxicological studies suggest that repeated exposures to SO<sub>2</sub>, at concentrations as low as 0.1 ppm in guinea pigs, may exacerbate inflammatory responses in allergic animals.

## **AIRWAYS RESPONSIVENESS**

**Previous Conclusion:** No conclusions in the previous review.

**Current Conclusion:** Animal toxicological evidence suggests that repeated exposures to SO<sub>2</sub>, at concentrations as low as 0.1 ppm in guinea pigs, can exacerbate airway responsiveness following allergic sensitization. In a human clinical study, concurrent exposure (6 h) to 0.2 ppm SO<sub>2</sub> and 0.4 ppm NO<sub>2</sub> has been observed to enhance airway responsiveness to an inhaled antigen among resting asthmatics. These findings are consistent with the very limited epidemiological evidence that suggests that exposure to SO<sub>2</sub> may lead to airway hyperresponsiveness in atopic individuals.

## **ED VISITS/HOSPITALIZATIONS**

**Previous Conclusion:** No conclusions in the previous review.

**Current Conclusion:** Epidemiological studies provide evidence of an association between ambient SO<sub>2</sub> concentrations and ED visits and hospitalizations for all respiratory causes, particularly among children and older adults (age 65+ years), and for asthma. The SO<sub>2</sub> effect estimates ranged from a 5% decreased risk to a 20% excess risk per 10-ppb increase in 24-h avg SO<sub>2</sub>, with the large majority of studies suggesting an increase in risk. These effects were observed in studies with mean 24-h avg concentrations as low as 4 ppb, but two studies evaluating the concentration-response function observed that a marked increase in SO<sub>2</sub>-related effects was only observed higher concentrations (above 90<sup>th</sup> percentile values).

## **Short-Term Exposure: CARDIOVASCULAR MORBIDITY**

***Inadequate to infer the presence or absence of a causal relationship***

### **CARDIOVASCULAR EFFECTS; ED VISITS/ HOSPITALIZATIONS**

**Previous Conclusion:** No conclusions in the previous review.

**Current Conclusion:** There was some suggestive evidence of an association between 24-h avg SO<sub>2</sub> exposure and heart rate variability in the epidemiological studies, but the evidence from two human clinical studies with were weak and inconsistent. Some epidemiological studies have observed positive associations between ambient SO<sub>2</sub> concentrations and ED visits or hospital admissions for cardiovascular diseases, but results are not consistent across studies and the SO<sub>2</sub> effect estimate was generally not robust to copollutant adjustment.

## **Short-Term Exposure: MORTALITY**

***Suggestive but not sufficient to infer a casual relationship***

### **NONACCIDENTAL AND CARDIOPULMONARY MORTALITY**

**Previous Conclusion:** Epidemiological studies based on historical air pollution episodes observed the clearest mortality associations when both black smoke (BS) and SO<sub>2</sub> concentrations were at high levels (24-h avg values exceeding 1,000 µg/m<sup>3</sup> [~400 ppb for SO<sub>2</sub>]). Later studies observed that an increased risk of mortality was associated with exposure to BS and SO<sub>2</sub> levels in the range 0.19 to 0.38 ppm. Because of the high colinearity between BS and SO<sub>2</sub> levels, it is difficult to readily separate the effects of these pollutants on mortality.

**Current Conclusion:** Recent epidemiological studies have consistently reported positive associations between mortality and SO<sub>2</sub>, often at mean 24-h avg levels < 10 ppb. The range of SO<sub>2</sub> excess risk estimates for nonaccidental mortality is 0.4 to 2% per 10 ppb increase in 24-h avg SO<sub>2</sub> in several multicity studies and meta-analyses. SO<sub>2</sub> effect estimates for respiratory mortality were generally larger than the cardiovascular mortality estimates, suggesting a stronger association of SO<sub>2</sub> with respiratory mortality compared to cardiovascular mortality. The SO<sub>2</sub> effect estimates were generally reduced when copollutants were added in the model, indicating some extent of confounding among these pollutants.

## Long-Term Exposure: RESPIRATORY MORBIDITY

*Inadequate to infer the presence or absence of a causal relationship*

### RESPIRATORY SYMPTOMS AND LUNG FUNCTION

**Previous Conclusion:** The limited available epidemiological data indicated associations between respiratory illnesses and symptoms and persistent exposures to SO<sub>2</sub> in areas with long-term averages exceeding 0.04 ppm.

**Current Conclusion:** Several epidemiological studies that examined the effects of long-term exposure to SO<sub>2</sub> on asthma, bronchitis, and respiratory symptoms observed positive associations in children. While the evidence is suggestive, the variety of outcomes examined and the inconsistencies in the observed results make it difficult to assess the direct impact of long-term exposure of SO<sub>2</sub> on respiratory symptoms. The epidemiological and animal toxicological evidence generally do not indicate that long-term exposure to SO<sub>2</sub> has a detrimental effect on lung function.

## Long-Term Exposure: OTHER MORBIDITY

*Inadequate to infer the presence or absence of a causal relationship*

### CARCINOGENIC EFFECTS

**Previous Conclusion:** Epidemiological evidence did not substantiate the hypothesized links between SO<sub>2</sub> or other SO<sub>x</sub> and cancer, though there was some animal toxicological evidence that led to the conclusion that SO<sub>2</sub> may be considered a suspect carcinogen/cocarcinogen.

**Current Conclusion:** Animal toxicological studies indicate that SO<sub>2</sub> at high concentrations may cause DNA damage but fails to induce carcinogenesis, cocarcinogenesis, or tumor promotion. Epidemiological studies did not provide evidence that long-term exposure to SO<sub>2</sub> is associated with an increased incidence of or mortality from lung cancer.

### PRENATAL AND NEONATAL OUTCOMES

**Previous Conclusion:** No conclusions in the previous review.

**Current Conclusion:** Epidemiological studies on birth outcomes have found suggestive positive associations between SO<sub>2</sub> exposure and low birth weight. However, the inconsistent results across trimesters of pregnancy and the lack of evidence to evaluate confounding by copollutants limit the interpretation of these studies.

## Long-Term Exposure: MORTALITY

*Inadequate to infer the presence or absence of a causal relationship*

### NONACCIDENTAL AND CARDIOPULMONARY MORTALITY

**Previous Conclusion:** The available studies on the effects of long-term exposure to SO<sub>2</sub> on mortality were all ecological cross-sectional studies which did not take into consideration potential confounders. In addition, it was concluded that effects from PM and SO<sub>2</sub> could not be distinguished in these studies.

**Current Conclusion:** Two major U.S. epidemiological studies observed associations between long-term exposure to SO<sub>2</sub> and mortality, but several other U.S. and European cohort studies did not observe an association. The relative risks ranged from 0.97 to 1.07 per 5-ppb increase in the long-term average SO<sub>2</sub>. Evaluation of these studies is further limited by the inability to distinguish potential confounding by copollutants and uncertainties regarding the geographic scale of analysis.

**Table 5-4. Effects of short-term exposure to SO<sub>2</sub> on respiratory symptoms among children.**

STUDY	POPULATION	MEAN CONCENTRATION	SO <sub>2</sub> (ppb) 98TH%	SO <sub>2</sub> (ppb) 99TH%	SO <sub>2</sub> (ppb) RANGE	SO <sub>2</sub> (ppb) UPPER %TILE	STANDARDIZED ODDS RATIO (95% CI) <sup>a</sup>
<b>United States</b>							
Schildcrout et al. (2006) Multicity, North America Seattle, WA; Baltimore, MD; St. Louis, MS (Nov 1993– Aug 1995); Denver, CO; San Diego, CA (Nov 1993– Jul 1995); Toronto, ON (Dec 1993–Jul 1995); Boston, MA (Jan 1994–Sep 1995) No SO <sub>2</sub> data available in Albuquerque, NM	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 <sub>2</sub> alone: 1.04 (1.00, 1.08), 3-day sum SO <sub>2</sub> & NO <sub>2</sub> : 1.04 (1.00, 1.09), 3-day sum SO <sub>2</sub> & PM <sub>10</sub> : 1.04 (0.99, 1.08), 3-day sum
Schwartz et al. (1994) Multicity, United States Watertown, MA (Apr-Aug 1985); Kingston-Harriman, TN; St. Louis, MO (Apr-Aug 1986); Steubenville, OH; Portage, WI (Apr-Aug 1987); Topeka, KS (Apr- Aug 1988)	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 <sub>2</sub> alone: 1.15 (1.02- 1.31), 4-day avg SO <sub>2</sub> , adjusting for PM <sub>10</sub> : 1.08 (0.93, 1.25), 4-day avg SO <sub>2</sub> , adjusting for NO <sub>2</sub> : 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: 0.2 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) Multicity, United States Bronx, NY; East Harlem, NY; Baltimore, MD; Washington, DC; Detroit, MI; Cleveland, OH; Chicago, IL; St. Louis, MO (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 <sub>2</sub> alone (8 cities): 1.19 (1.06, 1.35), lag 1-2 SO <sub>2</sub> , adjusting for O <sub>3</sub> & NO <sub>2</sub> (7 cities): 1.19 (1.04, 1.37), lag 1-2 SO <sub>2</sub> , adjusting for O <sub>3</sub> , NO <sub>2</sub> & PM <sub>10</sub> (3 cities): 1.23 (0.94, 1.62), lag 1-2
<b>Europe</b>							
Timonen and Pekkanen (1997) Kuopio (urban and suburban) Finland Winter 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, UK 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: Winter: 0.59 (0.25, 1.40), Summer: 0.90 (0.49, 1.66) Shortness of breath: Winter: 0.59 (0.32, 1.09), Summer: 0.81 (0.30, 2.17) Wheeze: Winter: 0.79 (0.38, 1.63), Summer: 0.77 (0.28, 2.08) (7-day avg lag for above)

STUDY	POPULATION	MEAN CONCENTRATION	SO <sub>2</sub> (ppb) 98TH%	SO <sub>2</sub> (ppb) 99TH%	SO <sub>2</sub> (ppb) RANGE	SO <sub>2</sub> (ppb) UPPER %TILE	STANDARDIZED ODDS RATIO (95% CI) <sup>a</sup>
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
Boezen et al. (1998) Amsterdam and Meppel (urban and rural), the Netherlands Winter 1993-1994	Children 7-11 yrs, with and w/o 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 6-12 yrs with chronic respiratory conditions  (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, the 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 resp 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

STUDY	POPULATION	MEAN CONCENTRATION	SO <sub>2</sub> (ppb) 98TH%	SO <sub>2</sub> (ppb) 99TH%	SO <sub>2</sub> (ppb) RANGE	SO <sub>2</sub> (ppb) UPPER %TILE	STANDARDIZED ODDS RATIO (95% CI) <sup>a</sup>
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 maxi- mums)	Lower respiratory symp- toms, urban, SO <sub>2</sub> 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  Lower respiratory symptoms, urban, SO <sub>2</sub> , adjusting for PM <sub>10</sub> : 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  Lower respiratory symptoms, 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  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  Cough, 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

<sup>a</sup>24-h avg SO<sub>2</sub> and 12-h avg SO<sub>2</sub> standardized to 10-ppb incremental change; 3-h avg SO<sub>2</sub> standardized to 20-ppb incremental change; and 1-h max SO<sub>2</sub> standardized to 40-ppb incremental change. NR = Not Reported BHR = Bronchial Hyperresponsiveness

**Table 5-5. Effects of short-term SO<sub>2</sub> exposure on emergency department visits and hospital admissions for respiratory outcomes.**

STUDY	POPULATION	MEAN CONCENTRATION	SO <sub>2</sub> (ppb) 98TH%	SO <sub>2</sub> (ppb) 99TH%	SO <sub>2</sub> (ppb) RANGE	SO <sub>2</sub> (ppb) UPPER %TILE	STANDARDIZED ODDS RATIO (95% CI) <sup>a</sup>
<b>EMERGENCY DEPARTMENT VISITS – ALL RESPIRATORY</b>							
<b>UNITED STATES</b>							
Wilson et al. (2005) Portland, ME Jan 1998-Dec 2000 Manchester, NH Jan 1996-Dec 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: 0% (-3, 5) 0-14: 0% (8, 8) 15-64: 0% (-3, 5) 65+: 8% (6, 23)
Tolbert et al. (2007) Atlanta, GA Jan 1993-Dec 2004	> 1,000,000 ED visits for all respiratory causes	1-h max: 14.9	NR	NR	1.0 - 149.0	75th: 20.0 90th: 35.0	0.75% (-0.75, 2.3)

STUDY	POPULATION	MEAN CONCENTRATION	SO <sub>2</sub> (ppb) 98TH%	SO <sub>2</sub> (ppb) 99TH%	SO <sub>2</sub> (ppb) RANGE	SO <sub>2</sub> (ppb) UPPER %TILE	STANDARDIZED ODDS RATIO (95% CI) <sup>a</sup>
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)
<b>EUROPE</b>							
Atkinson et al. (1999a) London, UK 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)
<b>EMERGENCY DEPARTMENT VISITS – ASTHMA</b>							
<b>UNITED STATES</b>							
Ito et al. (2007) New York, NY Jan 1999-Dec 2002	Asthma ED visits, all ages from 11 hospitals	24-h avg: 7.8 (4.6)	NR	NR	NR	75th: 10 95th: 17	35% (23%, 51%)
NY Department of Health (2006) Bronx & Manhattan, NY Jan 1999-Dec 2000	Asthma ED visits among children from 22 hospitals	24-h avg : 11 (7.2)	NR	NR	NR	NR	5-day moving average: Manhattan: -1% (-12, 12) Bronx: 11% (6, 17)
Jaffe et al. (2003) Cincinnati, OH Cleveland, OH 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 Jan 1998-Dec 2000 Manchester, NH Jan 1996-Dec 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)

STUDY	POPULATION	MEAN CONCENTRATION	SO <sub>2</sub> (ppb) 98TH%	SO <sub>2</sub> (ppb) 99TH%	SO <sub>2</sub> (ppb) RANGE	SO <sub>2</sub> (ppb) UPPER %TILE	STANDARDIZED ODDS RATIO (95% CI) <sup>a</sup>
<b>EUROPE</b>							
Atkinson et al. (1999a) London, UK 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, UK Jan 1992-Dec 1994	General practitioner visits for asthma	24-h avg: All yr: 8.0 (2.9) Warm: 7.7 (2.4) Cool: 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 yrs: 0.6% (-1.4, 2.7)
Galan et al. (2003) Madrid, Spain Jan 1995-Dec 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)
Tenias et al. (1998) Valencia, Spain Jan 1993-Dec 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, Spain; Helsinki, Finland; Paris, France; London, UK Jan 1986-Dec 1992	All ED visits for asthma	24-h avg: 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 yrs: 3.2% (-0.2, 6.8) 15-64: 0.2% (-2.2, 2.6)
Castellsague et al. (1995) Barcelona, Spain Jan 1986-Dec 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	15-64 yrs, summer: 5.5% (-2.1, 13.8) 15-64 yrs, winter: 2.1% (-4.2, 9.0)
<b>HOSPITAL ADMISSIONS – ALL RESPIRATORY</b>							
<b>UNITED STATES</b>							

STUDY	POPULATION	MEAN CONCENTRATION	SO <sub>2</sub> (ppb) 98TH%	SO <sub>2</sub> (ppb) 99TH%	SO <sub>2</sub> (ppb) RANGE	SO <sub>2</sub> (ppb) UPPER %TILE	STANDARDIZED ODDS RATIO (95% CI) <sup>a</sup>
Schwartz (1995) New Haven, CT Tacoma, WA Jan 1988-Dec 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)
<b>CANADA</b>							
Fung et al. (2006b) 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)
Cakmak et al. (2006) Multicity, Canada Calgary, Edmonton, Halifax, London, Ottawa, Saint John, Toronto, Vancouver, Windsor, Winnipeg Jan 1993-Dec 2000	> 200,000 hospital admissions for all respiratory causes	24-h avg: 4.6	NR	NR	2.8, 10.2	NR	2.4% (1.1, 3.9)
Yang et al. (2003b) Vancouver, BC Jan 1986-Dec 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 Jan 1980-Dec 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)
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)

STUDY	POPULATION	MEAN CONCENTRATION	SO <sub>2</sub> (ppb) 98TH%	SO <sub>2</sub> (ppb) 99TH%	SO <sub>2</sub> (ppb) RANGE	SO <sub>2</sub> (ppb) UPPER %TILE	STANDARDIZED ODDS RATIO (95% CI) <sup>a</sup>
<b>AUSTRALIA</b>							
Barnett et al. (2005) Multicity, Australia/New Zealand Auckland, Brisbane, Canberra, Christchurch, Melbourne, Perth, Sydney Jan 1998-Dec 2001	All respiratory hospital admissions	24-h avg: Auckland: 4.3 Brisbane: 1.8 Christchurch: 2.8 Sydney: 0.9  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		1-4 yrs: 5.1% (0.0, 9.1) 5-14: 3.7% (-9.9, 19.5)
Petroeschevsky et al. (2001) Brisbane, Australia Jan 1987-Dec 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)
<b>EUROPE</b>							
Oftedal et al. (2003) Drammen, Norway Jan 1994-Dec 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 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 age: 1.6% (-4.9, 8.8) 0-14: -2.7% (-4.6, 10.8)
Llorca et al. (2005) Torrelavega, Spain Jan 1992-Dec 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, UK 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)
Atkinson et al. (1999a) London, UK Jan 1992-Dec 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 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)

STUDY	POPULATION	MEAN CONCENTRATION	SO <sub>2</sub> (ppb) 98TH%	SO <sub>2</sub> (ppb) 99TH%	SO <sub>2</sub> (ppb) RANGE	SO <sub>2</sub> (ppb) UPPER %TILE	STANDARDIZED ODDS RATIO (95% CI) <sup>a</sup>
Spix et al. (1998) Multicity, Europe London, UK; Amsterdam & Rotterdam, the Netherlands; Paris, France; Milan, Italy Jan 1977-Dec 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 yrs: 0.5% (-0.4, 1.3) 65+: 1.1% (0.3, 2.4)
Dab et al. (1996) Paris, France Jan 1987-Sep 1992	Hospital admissions from 27 hospitals	All yr: 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 yr: 24-h avg: 50.0 99th: 50.0 1-h max: 87.5  Warm season 99th: 18.5 1-h max: 50.3  Cold season 24-h avg: 56.0 99th: 56.0 1-h max: 100.9	All ages: 1.1% (0.1, 2.1)

<sup>a</sup>24-h avg SO<sub>2</sub> and 12-h avg SO<sub>2</sub> standardized to 10-ppb incremental change; 3-h avg SO<sub>2</sub> standardized to 20-ppb incremental change; and 1-h max SO<sub>2</sub> standardized to 40-ppb incremental change.

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