United States Environmental Protection Agency

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Integrated Science Assessment for Sulfur Oxides – Health Criteria

Annexes

(Second External Review Draft)

Disclaimer

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Abbreviations and Acronyms

8-OHdG	8-hydroxy-2□-deoxyguanosine
AHH	aryl hydrocarbon hydroxylase
ALT	alanine-amino-transferase
AM	alveolar macrophages
AMMN	N-nitroso-acetoxymethylmethylamine
AP	alkaline phosphatase
AST	aspartate-amino-transferase
B[a]P	benzo[a]pyrene
BAL	bronchoalveolar lavage
BC	black carbon
BHPN	N-bis(2-hydroxypropyl) nitrosamine
bw	body weight
C	carbon or carbon black particles
CA	chromosome aberrations
CAT	catalase
Chol	cholesterol
CMD	count median diameter
CYP	Cytochrome P450
Dae	aerodynamic diameterAM alveolar macrophage
DEcCBP	DEP extract coated carbon black particles
DEN	diethylnitrosamine
DEP	diesel exhaust particles
DEP+C	diesel exhaust particle extract adsorbed to C
dG	2□-deoxyguanosine
DMBA	7, 12-dimethylbenzanthracene
DMSO	dimethyl sulfoxide
EC	elemental carbon
FHLC	fetal hamster lung cells
GCS	γ-glutamylcysteine synthetase
GPx	glutathione peroxidase
GPx	Se-dependent glutathione peroxidase
GPx	glutathione peroxidase
GRed	glutathione reductase
GSD	geometric standard deviation
GSH	glutathione
GSSG	glutathione disulfide
$GSSO_3H$	glutathione S-sulfonate
GST	glutathione-S-transferase
GT	γ-glutamyl transpeptidase
HP	hydrolyzed protein
HVA-ICa	high-voltage activated calcium currents
IgG	immunoglobulin

LDH	lactate dehydrogenase
MAD	median aerodynamic diameter
MMAD	mass median aerodynamic density
MMD	mass median diameter
MN	micronuclei
MNPCE	micronucleated PCE
Mo	molybdenum
NDMA	N-nitroso-dimethylamine
NMBzA	N-nitrosomethylbenzylamine
NR	Not Reported
OC	organic carbon
PAH	polycyclic aromatic hydrocarbons
PCE	polychromatic erythrocytes
PEC	pulmonary endocrine cells
PKA	cyclic AMP-dependent protein kinase A
PKI	synthetic peptide inhibitor of PKA
PL	phospholipids
PNC	particle number concentration
RBC	red blood cell or erythrocyte
RH	relative humidity
SCE	sister chromatid exchanges
SEPs	somatosensory-evoked potentials
SOD	superoxide dismutase
SPF	specific pathogen free
SPM	suspended particulate matter extract
SQCA	squamous cell carcinoma
SSO	seabuckthorn seed oil
SV40	simian virus 40
TBARS	thiobarbituric acid-reactive substance
TOC	potassium channel transient outward currents
TTX	tetrodotoxin
TTX-R	tetrodotoxin-resistant
TTX-S	tetrodotoxin-sensitive
$\dot{V}_E$	ventilation rate
VEPs	visual-evoked potentials
W	tungsten

Annex A. Literature Selection

Annex A of this second draft ISA includes detailed information on the methods used to identify and select studies, and on frameworks for evaluating scientific evidence relative to causality determination. While the overarching framework is outlined in the introduction to Chapter 1, this Annex provides supporting information for that framework, including excerpts from decision frameworks or criteria developed by other organizations.

A.1. Literature Search and Retrieval

Literature searches are conducted continuously, to identify studies published since the last review. The current review includes studies published subsequent to the 1982 AQCD for Sulfur Oxides (U.S. 1986). Search strategies are iteratively modified in an effort to optimize the identification of pertinent publications. Additional publications are identified for inclusion in several ways: review of pre-publication tables of contents for journals in which relevant papers may be published; independent identification of relevant literature by expert authors; and identification by the public and CASAC during the external review process. Generally, only information that has undergone scientific peer review and has been published, or accepted for publication, in the open literature is considered. Studies identified are further evaluated by EPA staff and outside experts to determine if they merit inclusion. Criteria used for study selection are summarized below.

A.2. General Criteria for Study Selection

In assessing the scientific quality and relevance of epidemiological and animal or human toxicological studies, the following considerations have been taken into account.

- Were the study populations adequately selected and are they sufficiently well defined to allow for meaningful comparisons between study groups?

- Are the statistical analyses appropriate, properly performed, and properly interpreted?

- Are likely covariates (i.e., potential confounders or effect modifiers) adequately controlled or taken into account in the study design and statistical analysis?

- Are the reported findings internally consistent, biologically plausible, and coherent in terms of consistency with other known facts?

- To what extent are the aerometric data, exposure, or dose metrics of adequate quality and sufficiently representative to serve as indicators of exposure to ambient SO_2?

Consideration of these issues informs our judgments on the relative quality of individual studies and allows us to focus the assessment on the most pertinent studies.

A.2.1. Criteria for Selecting Epidemiological Studies

In selecting epidemiological studies for this assessment, EPA considered whether a given study contains information on (1) associations with measured sulfur oxides concentrations using short- or long-term exposures at or near ambient levels of sulfur oxides, (2) health effects of specific sulfur oxides species or indicators related to sulfur oxides sources (e.g., combustion-related particles), (3) health endpoints and populations not previously extensively researched, (4) multiple pollutant analyses and other approaches to address issues related to potential confounding and modification of effects, and/or (5) important methodological issues (e.g., lag of effects, model specifications, thresholds, mortality displacement) related to interpretation of the health evidence. Among the epidemiological studies, particular emphasis has been placed on those most relevant to reviews of the NAAQS. Specifically, studies conducted in the United States or Canada may be discussed in more detail than those from other geographic regions. Particular emphasis has been placed o**N:** (A) recent multicity studies that employ standardized methodological analyses for evaluating effects of sulfur oxides and that provide overall estimates for effects based on combined analyses of information pooled across multiple cities, (B) recent studies that provide quantitative effect estimates for populations of interest, and (C) studies that consider sulfur oxides as a component of a complex mixture of air pollutants.

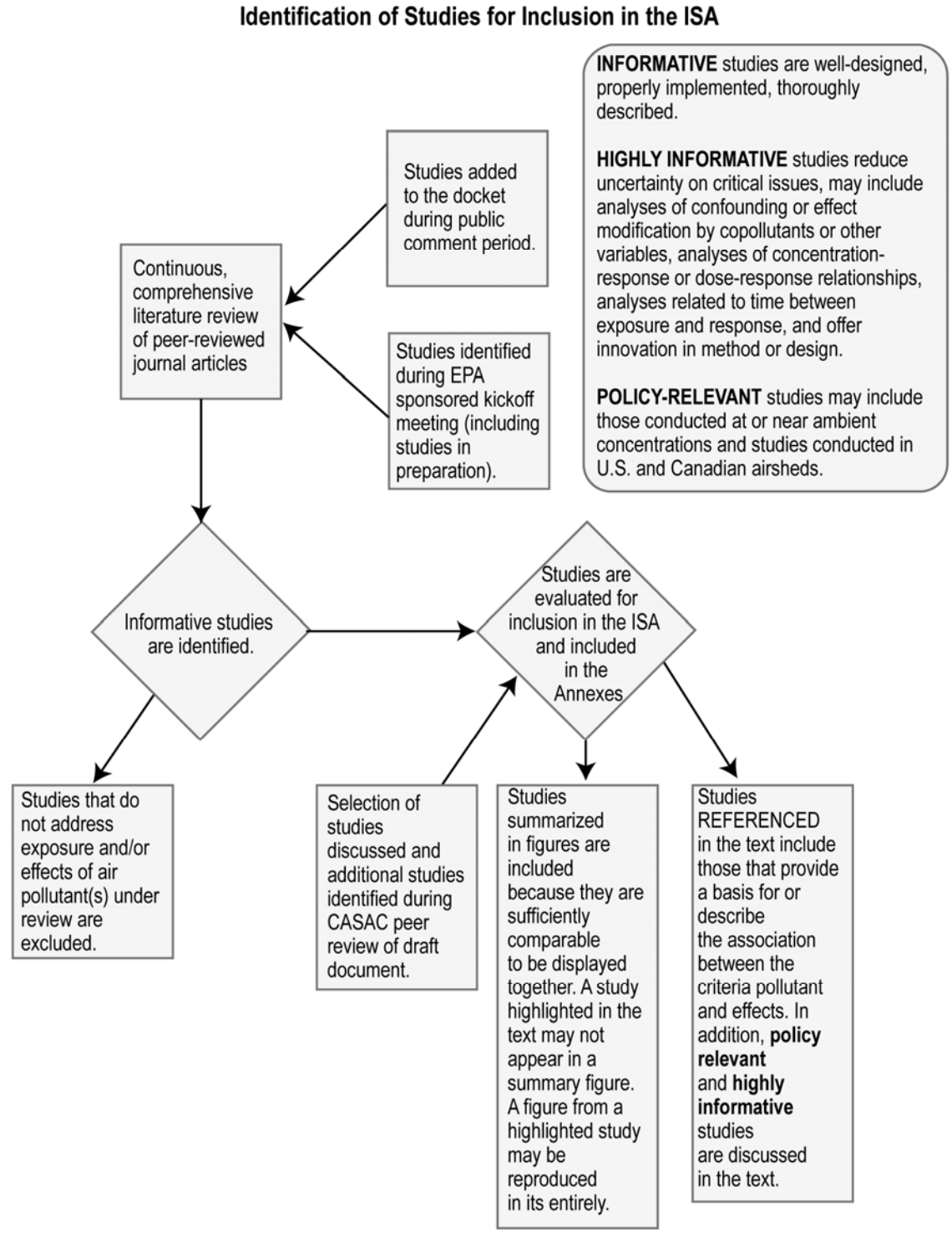

Figure A-1. Selection process for studies included in the ISA.

Not all studies were accorded equal weight in the overall interpretive assessment of evidence regarding SO_2-associated health effects. Among studies with adequate control for confounding, increasing scientific weight is accorded in proportion to the precision of their effect estimates. Small-scale studies without a wide range of exposures generally produce less precise estimates compared to larger studies with a broad exposure gradient. For time-series studies, the size of the study, as indicated by the duration of the study period and total number of events, and the variability of SO_2 exposures are important components that help to determine the precision of the health effect estimates. In evaluating the epidemiologic evidence in this chapter, more weight is accorded to estimates from studies with narrow confidence bands.

The goal was to perform a *balanced and objective* evaluation that summarizes, interprets, and synthesizes the most important studies and issues in the epidemiologic database pertaining to sulfur oxides exposure, illustrated by using newly created or previously published summary tables and figures. For each study presented, the quality of the exposure and outcome data, as well as the quality of the statistical analysis methodology, are discussed. The discussion incorporates the magnitude and statistical strengths of observed associations between SO_2 exposure and health outcomes.

A.2.2. Criteria for Selecting Animal and Human Toxicological Studies

Criteria for the selection of research evaluating animal toxicological or controlled human exposure studies included a focus on those studies conducted at levels within about an order of a magnitude of ambient SO_2 concentrations and those studies that approximated expected human exposure conditions in terms of concentration and duration. Studies that elucidate mechanisms of action and/or susceptibility, particularly if the studies were conducted under atmospherically relevant conditions, were emphasized whenever possible.

The selection of research evaluating controlled human exposures to sulfur oxides was mainly limited to studies in which subjects were exposed to < 5 ppm SO_2. For these controlled human exposures, emphasis was placed on studies that (1) investigated potentially susceptible populations such as asthmatics, particularly studies that compared responses in susceptible individuals with those in age-matched healthy controls; (2) addressed issues such as concentration-response or time-course of responses; (3) investigated exposure to SO_2 separately

and in combination with other pollutants such as O_3 and NO_2; (4) included control exposures to filtered air; and (5) had sufficient statistical power to assess findings.

A.3. Evaluation Guidelines

A.3.1. Background on Causality Decision Framework

The critical assessment of health evidence presented in that ISA was conceptually based upon consideration of salient aspects of the evidence so as to reach fundamental judgments about the likely causal significance of the observed associations. It is appropriate to draw from those aspects initially presented in Hill's classic monograph (Hill, 1965) and widely used by the scientific community in conducting such evidence-based reviews. A number of these aspects were judged to be particularly salient in evaluating the body of evidence available in this review, including the aspects described by Hill as strength, experiment, consistency, plausibility, and coherence. Other aspects identified by Hill, including temporality and biological gradient, were also relevant and considered here (e.g., in characterizing lag structures and concentration-response relationships), but were more directly addressed in the design and analyses of the individual epidemiologic studies included in this assessment. (As noted below, Hill's remaining aspects of specificity and analogy were not considered to be particularly salient in this assessment.) As discussed below, these salient aspects were interrelated and considered throughout the evaluation of the evidence presented in this chapter, and were more generally reflected in the ISA.

In the following sections, the general evaluation of the strength of the epidemiological evidence reflects consideration not only of the magnitude of reported sulfur oxides effects estimates and their statistical significance, but also of the precision of the effects estimates and the robustness of the effects associations. Consideration of the robustness of the associations took into account a number of factors, including in particular the impact of alternative models and model specifications and potential confounding by copollutants, as well issues related to the consequences of measurement error. Another aspect that is related to the strength of the evidence in this assessment was the availability of evidence from "found experiments," or so-called intervention studies, which have the potential to provide particularly strong support for making causal inferences.

Consideration of the consistency of the associations, as discussed in the following sections, involved looking across the results of multi- and single-city studies conducted by different investigators in different places and times. In this assessment, it is important to consider the aspect of consistency. Other relevant factors are also known to exhibit much variation across studies. These include, for example, the presence and levels of copollutants, the relationships between central measures of sulfur oxides and exposure-related factors, relevant demographic factors related to sensitive subpopulations, as well as climatic and meteorological conditions. Thus, in this case, consideration of consistency, and the issue of related heterogeneity of effects, was appropriately understood as an evaluation of the similarity or general concordance of results, rather than an expectation of finding quantitative results within a very narrow range. Particular weight was given in this assessment, consistent with Hill's views, to the presence of "similar results reached in quite different ways, e.g., prospectively and retrospectively" (Hill, 1965). On the other hand, in light of complexities of exposure and surrogate issues and its spatial and temporal variations, Hill's specificity of effects and analogy aspects were not viewed as being particularly salient here.

Looking beyond the epidemiological evidence, evaluation of the biological plausibility of the associations observed in epidemiologic studies reflected consideration of both exposure-related factors and dosimetric/toxicologic evidence relevant to identification of potential biological mechanisms. Similarly, consideration of the coherence of health effects associations reported in the epidemiologic literature reflected broad consideration of information pertaining to the nature of the various respiratory- and cardiac-related mortality and morbidity effects and biological markers evaluated in toxicologic and epidemiologic studies.

In identifying these aspects as being particularly salient in this assessment, it is also important to recognize that no one aspect was either necessary or sufficient for drawing inferences of causality. As Hill emphasized:

> "None of my nine viewpoints can bring indisputable evidence for or against the cause-and-effect hypothesis and none can be required as a *sine qua non*. What they can do, with greater or less strength, is to help us to make up our minds on the fundamental question – is there any other way of explaining the set of facts before us, is there any other answer equally, or more, likely than cause and effect?"

Thus, while these aspects frame considerations were weighed in assessing the epidemiologic evidence, they do not lend themselves to being considered in terms of simple formulas or hard-and-fast rules of evidence leading to answers about causality (Hill, 1965). One, for example, cannot simply count up the numbers of studies reporting statistically significant results for sulfur oxides and health endpoints evaluated in this assessment and reach credible conclusions about the relative strength of the evidence and the likelihood of causality. Rather, these important considerations were taken into account throughout this assessment with a goal of producing an objective appraisal of the evidence (informed by peer and public comment and advice), which included the weighing of alternative views on controversial issues.

A.3.2. Approaches to the Determination of Causality

The following sections include excerpts from several reports that have documented approaches for the determination of causality, or related decision-making processes. These sections provide supplementary documentation of approaches that are similar in nature to EPA's framework for evaluation of health evidence.

A.3.3. Surgeon General's Report: The Health Consequences of Smoking (CDC, 2004)

The Surgeon General's Report (U.S. Surgeon General, 2004) evaluated the health effects of smoking; it built upon the first Surgeon General's report published in 1964 (U.S. Surgeon General, 1964). It also updated the methodology for evaluating evidence that was first presented in the 1964 report. The 2004 report acknowledged the effectiveness of the previous methodology, but attempted to standardize the language surrounding causality of associations.

The Surgeon General's Reports on Smoking played a central role in the translation of scientific evidence into policy. As such, it is important that scientific evidence was presented in a manner that conveys most succinctly the link between smoking and a health effect. Specifically, the report stated:

> The statement that an exposure "causes" a disease in humans represents a serious claim, but one that carries with it the possibility of prevention. Causal determinations may also carry substantial economic implications for society and for those who might be held responsible for the exposure or for achieving its prevention.

To address the issue of identifying causality, the 2004 report provided the following summary of the earlier 1964 report:

> When a relationship or an association between smoking…and some condition in the host was noted, the significance of the association was assessed.
>
> The characterization of the assessment called for a specific term. …The word *cause* is the one in general usage in connection with matters considered in this study, and it is capable of conveying the notion of a significant, effectual relationship between an agent and an associated disorder or disease in the host.
>
> No member was so naive as to insist upon mono-etiology in pathological processes or in vital phenomena. All were thoroughly aware… that the end results are the net effect of many actions and counteractions.
>
> Granted that these complexities were recognized, it is to be noted clearly that the Committee's considered decision to use the words "a cause," or "a major cause," or "a significant cause," or "a causal association" in certain conclusions about smoking and health affirms their conviction (U.S. Surgeon General, 2004, p. 21).

This 2004 report created uniformly labeled conclusions that were used throughout the document. The following excerpts from the report also include a description of the methodology and the judgments used to reach a conclusion:

> **Terminology of Conclusions and Causal Claims**
>
> The first step in introducing this revised approach is to outline the language that will be used for summary conclusions regarding causality, which follows hierarchical language used by Institute of Medicine committees (IOM, 2007) to couch causal conclusions, and by IARC to classify carcinogenic substances (IARC, 2006). These entities use a four-level hierarchy for classifying the strength of causal inferences based on available evidence as follows:
>
> Evidence is **sufficient** to infer a causal relationship.
>
> Evidence is **suggestive but not sufficient** to infer a causal relationship.
>
> Evidence is **inadequate** to infer the presence or absence of a causal relationship (which encompasses evidence that is sparse, of poor quality, or conflicting).

Evidence is suggestive of no causal relationship.

For this report, the summary conclusions regarding causality are expressed in this four-level classification. Use of these classifications should not constrain the process of causal inference, but rather bring consistency across chapters and reports, and greater clarity as to what the final conclusions are actually saying. As shown in Table 1.1 [see original document], without a uniform classification the precise nature of the final judgment may not always be obvious, particularly when the judgment is that the evidence falls below the "sufficient" category. Experience has shown that the "suggestive" category is often an uncomfortable one for scientists, since scientific culture is such that any evidence that falls short of causal proof is typically deemed inadequate to make a causal determination. However, it is very useful to distinguish between evidence that is truly inadequate versus that which just falls short of sufficiency.

There is no category beyond "suggestive of no causal relationship" as it is extraordinarily difficult to prove the complete absence of a causal association. At best, "negative" evidence is suggestive, either strongly or weakly. In instances where this category is used, the strength of evidence for no relationship will be indicated in the body of the text. In this new framework, conclusions regarding causality will be followed by a section on implications. This section will separate the issue of causal inference from recommendations for research, policies, or other actions that might arise from the causal conclusions. This section will assume a public health perspective, focusing on the population consequences of using or not using tobacco and also a scientific perspective, proposing further research directions. The proportion of cases in the population as a result of exposure (the population attributable risk), along with the total prevalence and seriousness of a disease, are more relevant for deciding on actions than the relative risk estimates typically used for etiologic determinations. In past reports, the failure to sharply separate issues of inference from policy issues resulted in inferential statements that were sometimes qualified with terms for action. For example, based on the evidence available in 1964, the first Surgeon General's report on smoking and health contained the following statement about the relationship between cardiovascular diseases and smoking:

It is established that male cigarette smokers have a higher death rate from coronary artery disease than non-smoking males. Although the causative role of cigarette smoking in deaths from coronary disease is not proven, the Committee considers it more prudent from the public health viewpoint to assume that the established association has causative meaning, than to suspend judgment until no uncertainty remains (U.S. Surgeon General, 2004, p. 32).

> Using this framework, this conclusion would now be expressed differently, probably placing it in the "suggestive" category and making it clear that although it falls short of proving causation, this evidence still makes causation more likely than not. The original statement makes it clear that the 1964 committee judged that the evidence fell short of proving causality but was sufficient to justify public health action. In this report, the rationale and recommendations for action will be placed in the implications section, separate from the causal conclusions. This separation of inferential from action-related statements clarifies the degree to which policy recommendations are driven by the strength of the evidence and by the public health consequences acting to reduce exposure. In addition, this separation appropriately reflects the differences between the processes and goals of causal inference and decision making.

A.3.4. The EPA Guidelines for Carcinogen Risk Assessment

The EPA Guidelines for Carcinogen Risk Assessment, published in 2005 (U.S. EPA, 2005), was an update to the previous risk assessment document published in 1986. This document served to guide EPA staff and public about the Agency's risk assessment development and methodology. In the 1986 Guidelines, a step-wise approach was used to evaluate the scientific findings. However, this newer document was similar to the Surgeon General's Report on Smoking in that it used single integrative step after assessing all of the individual lines of evidence. Five standard descriptors were used to evaluate the weight of evidence:

1. Carcinogenic to Humans
2. Likely to Be Carcinogenic to Humans
3. Suggestive Evidence of Carcinogenic Potential
4. Inadequate Information to Assess Carcinogenic Potential
5. Not Likely to Be Carcinogenic to Humans.

The 2005 Guidelines recommend that a separate narrative be prepared on the weight of evidence and the descriptor. The Guidelines further recommend that the descriptors should only be used in the context of a weight-of-evidence discussion.

The following excerpt describes how a weight of evidence narrative should be developed and a how a descriptor should be selected (U.S. EPA, 2005):

The weight of the evidence should be presented as a narrative laying out the complexity of information that is essential to understanding the hazard and its dependence on the quality, quantity, and type(s) of data available, as well as the circumstances of exposure or the traits of an exposed population that may be required for expression of cancer. For example, the narrative can clearly state to what extent the determination was based on data from human exposure, from animal experiments, from some combination of the two, or from other data. Similarly, information on mode of action can specify to what extent the data are from *in vivo* or *in vitro* exposures or based on similarities to other chemicals. The extent to which an agent's mode of action occurs only on reaching a minimum dose or a minimum duration should also be presented. A hazard might also be expressed disproportionately in individuals possessing a specific gene; such characterizations may follow from a better understanding of the human genome. Furthermore, route of exposure should be used to qualify a hazard if, for example, an agent is not absorbed by some routes. Similarly, a hazard can be attributable to exposures during a susceptible lifestage on the basis of our understanding of human development.

The weight of evidence-of-evidence narrative should highlight:

- the quality and quantity of the data;
- all key decisions and the basis for these major decisions; and
- any data, analyses, or assumptions that are unusual for or new to EPA.

To capture this complexity, a weight of evidence narrative generally includes

- conclusions about human carcinogenic potential (choice of descriptor(s), described below)
- a summary of the key evidence supporting these conclusions (for each descriptor used), including information on the type(s) of data (human and/or animal, in vivo and/or in vitro) used to support the conclusion(s)
- available information on the epidemiologic or experimental conditions that characterize expression of carcinogenicity (e.g., if carcinogenicity is possible only by one exposure route or only above a certain human exposure level),
- a summary of potential modes of action and how they reinforce the conclusions,
- indications of any susceptible populations or lifestages, when available, and
- a summary of the key default options invoked when the available information is inconclusive.

To provide some measure of clarity and consistency in an otherwise free-form narrative, the weight of evidence descriptors are included in the first sentence of the narrative. Choosing a descriptor is a matter of judgment and cannot be reduced to a formula. Each descriptor may be applicable to a wide variety of potential data sets and weights of evidence. These descriptors and narratives are intended to permit sufficient flexibility to accommodate new scientific understanding and new testing methods as they are developed and accepted by the scientific community and the public. Descriptors represent points along a continuum of evidence; consequently, there are gradations and borderline cases that are clarified by the full narrative. Descriptors, as well as an introductory paragraph, are a short summary of the complete narrative that preserves the complexity that is an essential part of the hazard characterization. **Users of these cancer guidelines and of the risk assessments that result from the use of these cancer guidelines should consider the entire range of information included in the narrative rather than focusing simply on the descriptor**.

In borderline cases, the narrative explains the case for choosing one descriptor and discusses the arguments for considering but not choosing another. For example, between "suggestive" and "likely" or between "suggestive" and "inadequate," the explanation clearly communicates the information needed to consider appropriately the agent's carcinogenic potential in subsequent decisions.

Multiple descriptors can be used for a single agent, for example, when carcinogenesis is dose- or route-dependent. For example, if an agent causes point-of-contact tumors by one exposure route but adequate testing is negative by another route, then the agent could be described as likely to be carcinogenic by the first route but not likely to be carcinogenic by the second. Another example is when the mode of action is sufficiently understood to conclude that a key event in tumor development would not occur below a certain dose range. In this case, the agent could be described as likely to be carcinogenic above a certain dose range but not likely to be carcinogenic below that range.

Descriptors can be selected for an agent that has not been tested in a cancer bioassay if sufficient other information, e.g., toxicokinetic and mode of action information, is available to make a strong, convincing, and logical case through scientific inference. For example, if an agent is one of a well-defined class of agents that are understood to operate through a common mode of action and if that agent has the same mode of action, then in the narrative the untested agent would have the same descriptor as the class. Another example is when an untested agent's effects are understood to be caused by a human metabolite, in which case in the narrative the untested agent could have the same descriptor as the metabolite. As new testing methods are developed and used, assessments

may increasingly be based on inferences from toxicokinetic and mode of action information in the absence of tumor studies in animals or humans.

When a well-studied agent produces tumors only at a point of initial contact, the descriptor generally applies only to the exposure route producing tumors unless the mode of action is relevant to other routes. The rationale for this conclusion would be explained in the narrative.

When tumors occur at a site other than the point of initial contact, the descriptor generally applies to all exposure routes that have not been adequately tested at sufficient doses. An exception occurs when there is convincing information, e.g., toxicokinetic data that absorption does not occur by another route.

When the response differs qualitatively as well as quantitatively with dose, this information should be part of the characterization of the hazard. In some cases reaching a certain dose range can be a precondition for effects to occur, as when cancer is secondary to another toxic effect that appears only above a certain dose. In other cases exposure duration can be a precondition for hazard if effects occur only after exposure is sustained for a certain duration. These considerations differ from the issues of relative absorption or potency at different dose levels because they may represent a discontinuity in a dose-response function.

When multiple bioassays are inconclusive, mode of action data are likely to hold the key to resolution of the more appropriate descriptor. When bioassays are few, further bioassays to replicate a study's results or to investigate the potential for effects in another sex, strain, or species may be useful.

When there are few pertinent data, the descriptor makes a statement about the database, for example, "Inadequate Information to Assess Carcinogenic Potential," or a database that provides "Suggestive Evidence of Carcinogenic Potential." With more information, the descriptor expresses a conclusion about the agent's carcinogenic potential to humans. If the conclusion is positive, the agent could be described as "Likely to Be Carcinogenic to Humans" or, with strong evidence, "Carcinogenic to Humans." If the conclusion is negative, the agent could be described as "Not Likely to Be Carcinogenic to Humans."

Although the term "likely" can have a probabilistic connotation in other contexts, its use as a weight of evidence descriptor does not correspond to a quantifiable probability of whether the chemical is carcinogenic. This is because the data that support cancer assessments generally are not suitable for numerical calculations of the probability that an agent is a carcinogen. Other health agencies have expressed a comparable weight of evidence

using terms such as "Reasonably Anticipated to Be a Human Carcinogen" (NTP) or "Probably Carcinogenic to Humans" (IARC, 1989).

A.3.5. Improving the Presumptive Disability Decision-Making Process for Veterans

A recent publication by the Institute of Medicine also provided foundation for the causality framework adapted in this ISA (IOM, 2007). The Committee on Evaluation of the Presumptive Disability Decision-Making Process for Veterans was charged by the Veterans Association to describe how presumptive decisions are made for veterans with health conditions arising from military service currently, as well as recommendations for how such decisions could made in the future. The committee proposed a multiple-element approach that includes a quantification of the extent of disease attributable to an exposure. This process involved a review of all relevant data to decide the strength of evidence for causation, using one of four categories:

- Sufficient: the evidence is sufficient to conclude that a causal relationship exists.
- Equipoise and Above: the evidence is sufficient to conclude that a causal relationship is at least as likely as not, but not sufficient to conclude that a causal relationship exists.
- Below Equipoise: the evidence is not sufficient to conclude that a causal relationship is at least as likely as not, or is not sufficient to make a scientifically informed judgment.
- Against: the evidence suggests the lack of a causal relationship.

The following is an excerpt from this report and describes these four categories in detail:

> In light of the categorizations used by other health organizations and agencies as well as considering the particular challenges of the presumptive disability decision-making process, we propose a four-level categorization of the strength of the *overall evidence* for or against a *causal relationship* from exposure to disease.
>
> We use the term "equipoise" to refer to the point at which the evidence is in balance between favoring and not favoring causation. The term "equipoise" is widely used in the biomedical literature, is a concept familiar to those concerned with evidence-based decision-making and is used in VA processes for rating purposes as well as being a familiar term in the veterans' community.

Below we elaborate on the four-level categorization which the Committee recommends.

Sufficient

If the overall evidence for a causal relationship is categorized as Sufficient, then it should be scientifically compelling. It might include:

- replicated and consistent evidence of a causal association: that is, evidence of an association from several high-quality epidemiologic studies that cannot be explained by plausible noncausal alternatives (e.g., chance, bias, or confounding)
- evidence of causation from animal studies and mechanistic knowledge
- compelling evidence from animal studies and strong mechanistic evidence from studies in exposed humans, consistent with (i.e., not contradicted by) the epidemiologic evidence.

Using the Bayesian framework to illustrate the evidential support and the resulting state of communal scientific opinion needed for reaching the Sufficient category (and the lower categories that follow), consider again the causal diagram in Figure A-2. In this model, used to help clarify matters conceptually, the observed association between exposure and health is the result of: (1) measured confounding, parameterized by α; (2) the causal relation, parameterized by β; and (3) other, unmeasured sources such as bias or unmeasured confounding, parameterized by γ. The belief of interest, after all the evidence has been weighed, is in the size of the causal parameter β. Thus, for decision making, what matters is how strongly the evidence supports the proposition that β is above 0. As it is extremely unlikely that the types of exposures considered for presumptions reduce the risk of developing disease, we exclude values of β below 0. If we consider the evidence as supporting degrees of belief about the size of β, and we have a posterior distribution over the possible size of β, then a posterior like Figure A-2 illustrates a belief state that might result when the evidence for causation is considered Sufficient.

As the "mass" over a positive effect (the area under the curve to the right of the zero) vastly "outweighs" the small mass over no effect (zero), the evidence is considered sufficient to conclude that the association is causal. Put another way, even though the scientific community might be uncertain as to the size of β, after weighing all the evidence, it is highly confident that the probability that β is greater than zero is substantial; that is, that exposure causes disease.

Equipoise and Above

To be categorized as Equipoise and Above, the scientific community should categorize the overall evidence as making it more confident in the existence of a causal relationship than in the non-existence of a causal relationship, but not sufficient to conclude causation.

For example, if there are several high-quality epidemiologic studies, the preponderance of which show evidence of an association that cannot readily be explained by plausible noncausal alternatives (e.g., chance, bias, or confounding), and the causal relationship is consistent with the animal evidence and biological knowledge, then the overall evidence might be categorized as Equipoise and Above. Alternatively, if there is strong evidence from animal studies or mechanistic evidence, not contradicted by human or other evidence, then the overall evidence might be categorized as Equipoise and Above. Equipoise is a common term employed by VA and the courts in deciding disability claims (see Appendix D).

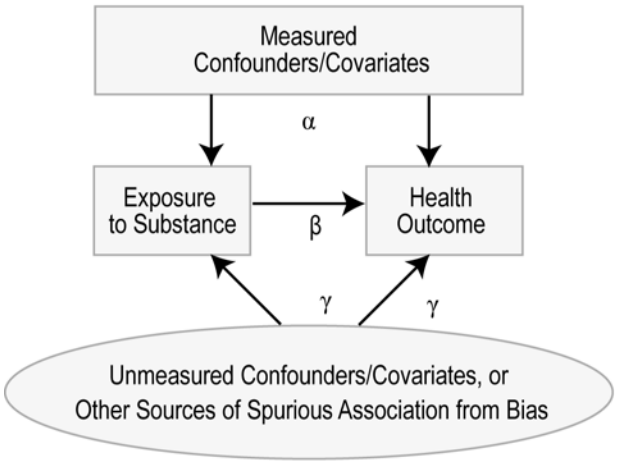

Figure A-2. Focusing on unmeasured confounders/covariates, or other sources of spurious association from bias.

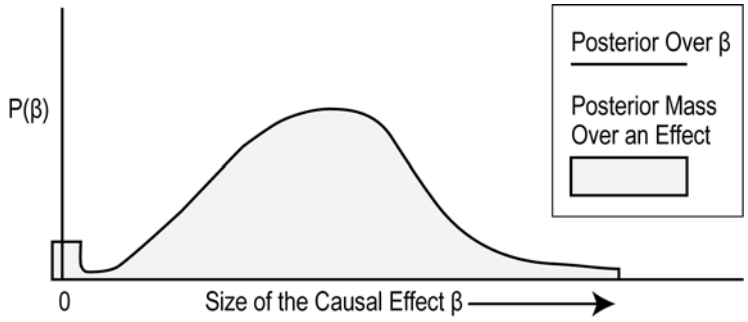

Figure A-3. Example posterior distribution for the determination of *Sufficient*.

Source: IOM (2007).

Again, using the Bayesian model to illustrate the idea of Equipoise and Above, Figure A-4 shows a posterior probability distribution that is an example of belief compatible with the category Equipoise and Above.

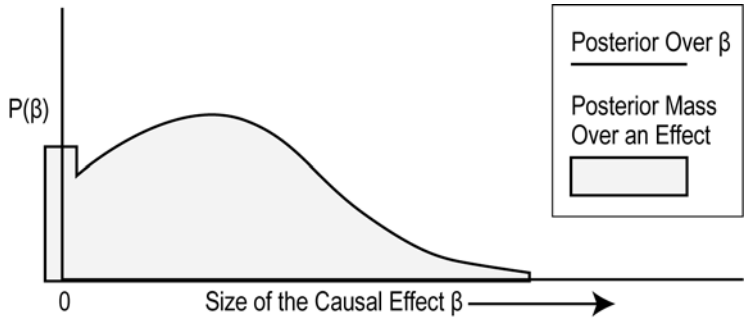

Figure A-4. Example posterior distribution for the determination of *Equipoise and Above*.

Source: IOM (2007).

In this figure, unlike the one for evidence classified as Sufficient, there is considerable mass over zero, which means that the scientific community has considerable uncertainty as to whether exposure causes disease at all; that is, whether β is greater than zero. At *least* half of the mass is to the right of the zero, however, so the community judges causation to be at least as likely as not, after they have seen and combined all the evidence available.

Below Equipoise

To be categorized as Below Equipoise, the overall evidence for a causal relationship should either be judged not to make causation at least as likely as not, or not sufficient to make a scientifically informed judgment.

This might occur:

- when the human evidence is consistent in showing an association, but the evidence is limited by the inability to rule out chance, bias, or confounding with confidence, and animal or mechanistic evidence is weak
- when animal evidence suggests a causal relationship, but human and mechanistic
- evidence is weak or inconsistent
- when mechanistic evidence is suggestive but animal and human evidence is weak or inconsistent
- when the evidence base is very thin.

Against

To be categorized as Against, the overall evidence should favor belief that there is no causal relationship from exposure to disease. For example, if there is human evidence from multiple studies covering the full range of exposures encountered by humans that are consistent in showing no causal association, or there are is animal or mechanistic evidence supporting the lack of a causal relationship, and combining all of the evidence results in a posterior resembling Figure A-5 then the scientific community should categorize the evidence as *Against* causation.

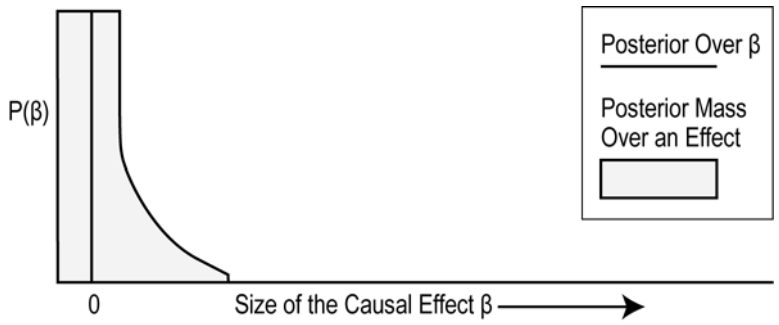

Figure A-5. Example posterior distribution for the determination of *Against*.

Source: IOM (2007).

A.3.6. Guidelines for Formulation of Scientific Findings to be Used for Policy Purposes

The following guidelines in the form of questions were developed and published in 1991 by the NAPAP Oversight Review Board for the National Acid Precipitation Assessment Program (Washington, 1991) to assist scientists in formulating presentations of research results to be used in policy decision processes.

> Is the statement sound? Have the central issues been clearly identified? Does each statement contain the distilled essence of present scientific and technical understanding of the phenomenon or process to which it applies? Is the statement consistent with all relevant evidence – evidence developed either through NAPAP research or through analysis of research conducted outside of NAPAP? Is the statement contradicted by any important evidence developed through research inside or outside of NAPAP? Have apparent contradictions or interpretations of available evidence been considered in formulating the statement of principal findings?
>
> Is the statement directional and, where appropriate, quantitative? Does the statement correctly quantify both the direction and magnitude of trends and relationships in the phenomenon or process to which the statement is relevant? When possible, is a range of uncertainty given for each quantitative result? Have various sources of uncertainty been identified and quantified, for example, does the statement include or acknowledge errors in actual measurements, standard errors of estimate, possible biases in the availability of data, extrapolation of results beyond the mathematical, geographical, or temporal relevancy of available information, etc. In short, are there numbers in the statement? Are the numbers correct? Are the numbers relevant to the general meaning of the statement?
>
> Is the degree of certainty or uncertainty of the statement indicated clearly? Have appropriate statistical tests been applied to the data used in drawing the conclusion set forth in the statement? If the statement is based on a mathematical or novel conceptual model, has the model or concept been validated? Does the statement describe the model or concept on which it is based and the degree of validity of that model or concept?
>
> Is the statement correct without qualification? Are there limitations of time, space, or other special circumstances in which the statement is true? If the statement is true only in some circumstances, are these limitations described adequately and briefly?
>
> Is the statement clear and unambiguous? Are the words and phrases used in the statement understandable by the decision makers of our society? Is

the statement free of specialized jargon? Will too many people misunderstand its meaning?

Is the statement as concise as it can be made without risk of misunderstanding? Are there any excess words, phrases, or ideas in the statement which are not necessary to communicate the meaning of the statement? Are there so many caveats in the statement that the statement itself is trivial, confusing, or ambiguous?

Is the statement free of scientific or other biases or implications of societal value judgments? Is the statement free of influence by specific schools of scientific thought? Is the statement also free of words, phrases, or concepts that have political, economic, ideological, religious, moral, or other personal-, agency-, or organization-specific values, overtones, or implications? Does the choice of how the statement is expressed rather than its specific words suggest underlying biases or value judgments? Is the tone impartial and free of special pleading? If societal value judgments have been discussed, have these judgments been identified as such and described both clearly and objectively?

Have societal implications been described objectively? Consideration of alternative courses of action and their consequences inherently involves judgments of their feasibility and the importance of effects. For this reason, it is important to ask if a reasonable range of alternative policies or courses of action have been evaluated? Have societal implications of alternative courses of action been stated in the following general form?

"If this [particular option] were adopted then that [particular outcome] would be expected."

Have the professional biases of authors and reviewers been described openly? Acknowledgment of potential sources of bias is important so that readers can judge for themselves the credibility of reports and assessments.

A.3.6.1. International Agency for Research on Cancer Guidelines for Scientific Review and Evaluation

The following is excerpted from the International Agency for Research on Cancer Monographs on the evaluation of carcinogenic risks to humans (IARC, 2006)

The available studies are summarized by the Working Group, with particular regard to the qualitative aspects discussed below. In general, numerical findings are indicated as they appear in the original report; units are converted when necessary for easier comparison. The Working Group may conduct additional analyses of the published data and use them in

their assessment of the evidence; the results of such supplementary analyses are given in square brackets. When an important aspect of a study that directly impinges on its interpretation should be brought to the attention of the reader, a Working Group comment is given in square brackets.

The scope of the *IARC Monographs* programme has expanded beyond chemicals to include complex mixtures, occupational exposures, physical and biological agents, lifestyle factors and other potentially carcinogenic exposures. Over time, the structure of a *Monograph* has evolved to include the following sections:

1. Exposure data

2. Studies of cancer in humans

3. Studies of cancer in experimental animals

4. Mechanistic and other relevant data

5. Summary

6. Evaluation and rationale

In addition, a section of General Remarks at the front of the volume discusses the reasons the agents were scheduled for evaluation and some key issues the Working Group encountered during the meeting.

This part of the Preamble discusses the types of evidence considered and summarized in each section of a *Monograph*, followed by the scientific criteria that guide the evaluations.

Evaluation and rationale

Evaluations of the strength of the evidence for carcinogenicity arising from human and experimental animal data are made, using standard terms. The strength of the mechanistic evidence is also characterized.

It is recognized that the criteria for these evaluations, described below, cannot encompass all of the factors that may be relevant to an evaluation of carcinogenicity. In considering all of the relevant scientific data, the Working Group may assign the agent to a higher or lower category than a strict interpretation of these criteria would indicate.

These categories refer only to the strength of the evidence that an exposure is carcinogenic and not to the extent of its carcinogenic activity (potency). A classification may change as new information becomes available.

An evaluation of the degree of evidence is limited to the materials tested, as defined physically, chemically or biologically. When the agents evaluated are considered by the Working Group to be sufficiently closely related, they may be grouped together for the purpose of a single evaluation of the degree of evidence.

(a) Carcinogenicity in humans

The evidence relevant to carcinogenicity from studies in humans is classified into one of the following categories:

Sufficient evidence of carcinogenicity: The Working Group considers that a causal relationship has been established between exposure to the agent and human cancer. That is, a positive relationship has been observed between the exposure and cancer in studies in which chance, bias and confounding could be ruled out with reasonable confidence. A statement that there is *sufficient evidence* is followed by a separate sentence that identifies the target organ(s) or tissue(s) where an increased risk of cancer was observed in humans. Identification of a specific target organ or tissue does not preclude the possibility that the agent may cause cancer at other sites.

Limited evidence of carcinogenicity: A positive association has been observed between exposure to the agent and cancer for which a causal interpretation is considered by the Working Group to be credible, but chance, bias or confounding could not be ruled out with reasonable confidence.

Inadequate evidence of carcinogenicity: The available studies are of insufficient quality, consistency or statistical power to permit a conclusion regarding the presence or absence of a causal association between exposure and cancer, or no data on cancer in humans are available.

Evidence suggesting lack of carcinogenicity: There are several adequate studies covering the full range of levels of exposure that humans are known to encounter, which are mutually consistent in not showing a positive association between exposure to the agent and any studied cancer at any observed level of exposure. The results from these studies alone or combined should have narrow confidence intervals with an upper limit close to the null value (e.g. a relative risk of 1.0). Bias and confounding should be ruled out with reasonable confidence, and the studies should have an adequate length of follow-up. A conclusion of *evidence suggesting lack of carcinogenicity* is inevitably limited to the cancer sites, conditions and levels of exposure, and length of observation covered by the available studies. In addition, the possibility of a very small risk at the levels of exposure studied can never be excluded.

In some instances, the above categories may be used to classify the degree of evidence related to carcinogenicity in specific organs or tissues.

When the available epidemiological studies pertain to a mixture, process, occupation or industry, the Working Group seeks to identify the specific agent considered most likely to be responsible for any excess risk. The evaluation is focused as narrowly as the available data on exposure and other aspects permit.

(b) Carcinogenicity in experimental animals

Carcinogenicity in experimental animals can be evaluated using conventional bioassays, bioassays that employ genetically modified animals, and other in-vivo bioassays that focus on one or more of the critical stages of carcinogenesis. In the absence of data from conventional long-term bioassays or from assays with neoplasia as the end-point, consistently positive results in several models that address several stages in the multistage process of carcinogenesis should be considered in evaluating the degree of evidence of carcinogenicity in experimental animals.

The evidence relevant to carcinogenicity in experimental animals is classified into one of the following categories:

Sufficient evidence of carcinogenicity: The Working Group considers that a causal relationship has been established between the agent and an increased incidence of malignant neoplasms or of an appropriate combination of benign and malignant neoplasms in (a) two or more species of animals or (b) two or more independent studies in one species carried out at different times or in different laboratories or under different protocols. An increased incidence of tumours in both sexes of a single species in a well-conducted study, ideally conducted under Good Laboratory Practices, can also provide *sufficient evidence*.

A single study in one species and sex might be considered to provide *sufficient evidence of carcinogenicity* when malignant neoplasms occur to an unusual degree with regard to incidence, site, type of tumour or age at onset, or when there are strong findings of tumours at multiple sites.

Limited evidence of carcinogenicity: The data suggest a carcinogenic effect but are limited for making a definitive evaluation because, e.g. (a) the evidence of carcinogenicity is restricted to a single experiment; (b) there are unresolved questions regarding the adequacy of the design, conduct or interpretation of the studies; (c) the agent increases the incidence only of benign neoplasms or lesions of uncertain neoplastic potential; or (d) the evidence of carcinogenicity is restricted to studies that

demonstrate only promoting activity in a narrow range of tissues or organs.

Inadequate evidence of carcinogenicity: The studies cannot be interpreted as showing either the presence or absence of a carcinogenic effect because of major qualitative or quantitative limitations, or no data on cancer in experimental animals are available.

Evidence suggesting lack of carcinogenicity: Adequate studies involving at least two species are available which show that, within the limits of the tests used, the agent is not carcinogenic. A conclusion of *evidence suggesting lack of carcinogenicity* is inevitably limited to the species, tumour sites, age at exposure, and conditions and levels of exposure studied.

(c) Mechanistic and other relevant data

Mechanistic and other evidence judged to be relevant to an evaluation of carcinogenicity and of sufficient importance to affect the overall evaluation is highlighted. This may include data on preneoplastic lesions, tumour pathology, genetic and related effects, structure–activity relationships, metabolism and toxicokinetics, physicochemical parameters and analogous biological agents.

The strength of the evidence that any carcinogenic effect observed is due to a particular mechanism is evaluated, using terms such as 'weak,' 'moderate' or 'strong.' The Working Group then assesses whether that particular mechanism is likely to be operative in humans. The strongest indications that a particular mechanism operates in humans derive from data on humans or biological specimens obtained from exposed humans. The data may be considered to be especially relevant if they show that the agent in question has caused changes in exposed humans that are on the causal pathway to carcinogenesis. Such data may, however, never become available, because it is at least conceivable that certain compounds may be kept from human use solely on the basis of evidence of their toxicity and/or carcinogenicity in experimental systems.

The conclusion that a mechanism operates in experimental animals is strengthened by findings of consistent results in different experimental systems, by the demonstration of biological plausibility and by coherence of the overall database. Strong support can be obtained from studies that challenge the hypothesized mechanism experimentally, by demonstrating that the suppression of key mechanistic processes leads to the suppression of tumour development. The Working Group considers whether multiple mechanisms might contribute to tumour development, whether different mechanisms might operate in different dose ranges, whether separate mechanisms might operate in humans and experimental animals and

whether a unique mechanism might operate in a susceptible group. The possible contribution of alternative mechanisms must be considered before concluding that tumours observed in experimental animals are not relevant to humans. An uneven level of experimental support for different mechanisms may reflect that disproportionate resources have been focused on investigating a favoured mechanism.

For complex exposures, including occupational and industrial exposures, the chemical composition and the potential contribution of carcinogens known to be present are considered by the Working Group in its overall evaluation of human carcinogenicity. The Working Group also determines the extent to which the materials tested in experimental systems are related to those to which humans are exposed.

(d) Overall evaluation

Finally, the body of evidence is considered as a whole, in order to reach an overall evaluation of the carcinogenicity of the agent to humans.

An evaluation may be made for a group of agents that have been evaluated by the Working Group. In addition, when supporting data indicate that other related agents, for which there is no direct evidence of their capacity to induce cancer in humans or in animals, may also be carcinogenic, a statement describing the rationale for this conclusion is added to the evaluation narrative; an additional evaluation may be made for this broader group of agents if the strength of the evidence warrants it.

The agent is described according to the wording of one of the following categories, and the designated group is given. The categorization of an agent is a matter of scientific judgement that reflects the strength of the evidence derived from studies in humans and in experimental animals and from mechanistic and other relevant data.

Group 1: The agent is *carcinogenic to humans*.

> This category is used when there is sufficient evidence of carcinogenicity in humans. Exceptionally, an agent may be placed in this category when evidence of carcinogenicity in humans is less than sufficient but there is sufficient evidence of carcinogenicity in experimental animals and strong evidence in exposed humans that the agent acts through a relevant mechanism of carcinogenicity.

Group 2.

> This category includes agents for which, at one extreme, the degree of evidence of carcinogenicity in humans is almost *sufficient*, as well as those for which, at the other extreme, there are no human data but for which there is evidence of carcinogenicity in

experimental animals. Agents are assigned to either Group 2A (*probably carcinogenic to humans*) or Group 2B (*possibly carcinogenic to humans*) on the basis of epidemiological and experimental evidence of carcinogenicity and mechanistic and other relevant data. The terms *probably carcinogenic* and *possibly carcinogenic* have no quantitative significance and are used simply as descriptors of different levels of evidence of human carcinogenicity, with probably carcinogenic signifying a higher level of evidence than possibly carcinogenic.

Group 2A: The agent is probably carcinogenic to humans.

This category is used when there is *limited evidence of carcinogenicity* in humans and *sufficient evidence of carcinogenicity* in experimental animals. In some cases, an agent may be classified in this category when there is *inadequate evidence of carcinogenicity* in humans and *sufficient evidence of carcinogenicity* in experimental animals and strong evidence that the carcinogenesis is mediated by a mechanism that also operates in humans. Exceptionally, an agent may be classified in this category solely on the basis of *limited evidence of carcinogenicity* in humans. An agent may be assigned to this category if it clearly belongs, based on mechanistic considerations, to a class of agents for which one or more members have been classified in Group 1 or Group 2A.

Group 2B: The agent is possibly carcinogenic to humans.

This category is used for agents for which there is *limited evidence of carcinogenicity* in humans and less than *sufficient evidence of carcinogenicity* in experimental animals. It may also be used when there is *inadequate evidence of carcinogenicity* in humans but there is *sufficient evidence of carcinogenicity* in experimental animals. In some instances, an agent for which there is *inadequate evidence of carcinogenicity* in humans and less than *sufficient evidence of carcinogenicity* in experimental animals together with supporting evidence from mechanistic and other relevant data may be placed in this group. An agent may be classified in this category solely on the basis of strong evidence from mechanistic and other relevant data.

Group 3: The agent is not classifiable as to its carcinogenicity to humans.

This category is used most commonly for agents for which the evidence of carcinogenicity is *inadequate* in humans and *inadequate* or *limited* in experimental animals.

Exceptionally, agents for which the evidence of carcinogenicity is *inadequate* in humans but *sufficient* in experimental animals may be placed in this category when there is strong evidence that the mechanism of carcinogenicity in experimental animals does not operate in humans.

Agents that do not fall into any other group are also placed in this category.

An evaluation in Group 3 is not a determination of non-carcinogenicity or overall safety. It often means that further research is needed, especially when exposures are widespread or the cancer data are consistent with differing interpretations.

Group 4: The agent is probably not carcinogenic to humans.

This category is used for agents for which there is *evidence suggesting lack of carcinogenicity* in humans and in experimental animals. In some instances, agents for which there is *inadequate evidence of carcinogenicity* in humans but *evidence suggesting lack of carcinogenicity* in experimental animals, consistently and strongly supported by a broad range of mechanistic and other relevant data, may be classified in this group.

(e) Rationale

The reasoning that the Working Group used to reach its evaluation is presented and discussed. This section integrates the major findings from studies of cancer in humans, studies of cancer in experimental animals, and mechanistic and other relevant data. It includes concise statements of the principal line(s) of argument that emerged, the conclusions of the Working Group on the strength of the evidence for each group of studies, citations to indicate which studies were pivotal to these conclusions, and an explanation of the reasoning of the Working Group in weighing data and making evaluations. When there are significant differences of scientific interpretation among Working Group Members, a brief summary of the alternative interpretations is provided, together with their scientific rationale and an indication of the relative degree of support for each alternative.

A.3.6.2. National Toxicology Program Criteria

The criteria for listing an agent, substance, mixture, or exposure circumstance in the National Toxicology Program's Report on Carcinogens (NTP, 2005) were as follows:

Known to Be Human Carcinogen:

There is sufficient evidence of carcinogenicity from studies in humans*, which indicates a causal relationship between exposure to the agent, substance, or mixture, and human cancer.

Reasonably Anticipated to Be Human Carcinogen:

There is limited evidence of carcinogenicity from studies in humans*, which indicates that causal interpretation is credible, but that alternative explanations, such as chance, bias, or confounding factors, could not adequately be excluded,

or

there is sufficient evidence of carcinogenicity from studies in experimental animals, which indicates there is an increased incidence of malignant and/or a combination of malignant and benign tumors (1) in multiple species or at multiple tissue sites, or (2) by multiple routes of exposure, or (3) to an unusual degree with regard to incidence, site, or type of tumor, or age at onset,

or

there is less than sufficient evidence of carcinogenicity in humans or laboratory animals; however, the agent, substance, or mixture belongs to a well-defined, structurally related class of substances whose members are listed in a previous Report on Carcinogens as either known to be a human carcinogen or reasonably anticipated to be a human carcinogen, or there is convincing relevant information that the agent acts through mechanisms indicating it would likely cause cancer in humans.

Conclusions regarding carcinogenicity in humans or experimental animals are based on scientific judgment, with consideration given to all relevant information. Relevant information includes, but is not limited to, dose response, route of exposure, chemical structure, metabolism, pharmacokinetics, sensitive sub-populations, genetic effects, or other data relating to mechanism of action or factors that may be unique to a given substance. For example, there may be substances for which there is evidence of carcinogenicity in laboratory animals, but there are compelling data indicating that the agent acts through mechanisms which do not operate in humans and would therefore not reasonably be anticipated to cause cancer in humans.

*This evidence can include traditional cancer epidemiology studies, data from clinical studies, and/or data derived from the study of tissues or cells from humans exposed to the substance in question that can be useful for evaluating whether a relevant cancer mechanism is operating in people.

Annex B. Additional Information on the Atmospheric Chemistry of Sulfur Oxides

B.1. Introduction

SO_2 is chiefly but not exclusively primary in origin; it is also produced by the photochemical oxidation of reduced sulfur compounds such as dimethyl sulfide (CH_3-S-CH_3), hydrogen sulfide (H_2S), carbon disulfide (CS_2), carbonyl sulfide (OCS), methyl mercaptan (CH_3-S-H), and dimethyl disulfide (CH_3-S-S-CH_3) which are all mainly biogenic in origin. Their sources are discussed in Section B.3. Table B-1 lists the atmospheric lifetimes of reduced sulfur species with respect to reaction with various oxidants. Except for OCS, which is lost mainly by photolysis (τ~6 months), these species are lost mainly by reaction with OH and NO_3 radicals. Because OCS is relatively long-lived in the troposphere, it can be transported upwards into the stratosphere.

Table B-1 Atmospheric lifetimes of SO_2 and reduced sulfur species with respect to reaction with OH, NO_3, and Cl radicals.

COMPOUND	OH		NO_3		CL	
	K X 10^{12}	T	K X 10^{12}	T	K X 10^{12}	T
SO_2	1.6	7.2d	NA		NA	
CH_3-S-CH_3	5.0	2.3 d	1.0	1.1-h	400	29 d
H_2S	4.7	2.2 d	NA		74	157 d
CS_2	1.2	9.6 d	< 0.0004	> 116 d	< 0.004	NR
OCS	0.0019	17 y	< 0.0001	> 1.3 y	< 0.0001	NR
CH_3-S-H	33	8.4 h	0.89	1.2 h	200	58 d
CH_3-S-S-CH_3	230	1.2 h	0.53	2.1-h	NA	

NA = Reaction rate coefficient not available.
NR = Rate coefficient too low to be relevant as an atmospheric loss mechanism. Rate coefficients were calculated at 298 K and 1 atmosphere.
y = year h = hour OH = 1 × 10^6/cm^3 NO_3 = 2.5 × 10^8/cm^3 Cl = 1 × 10^3/cm^3. [1]Rate coefficients were taken from JPL Chemical Kinetics Evaluation No. 14 (JPL, 2003)
Source: Seinfeld and Pandis (1998b).

Crutzen (1976) proposed that its oxidation serves as the major source of sulfate in the stratospheric aerosol layer sometimes referred to the "Junge layer," (Junge et al., 1961) during periods when volcanic plumes do not reach the stratosphere. However, the flux of OCS into the stratosphere is probably not sufficient to maintain this stratospheric aerosol layer. Myhre et al. (2004) proposed instead that SO_2 transported upwards from the troposphere is the most likely

source, as the upward flux of OCS is too small to sustain observed sulfate loadings in the Junge layer. In addition, in situ measurements of the isotopic composition of sulfur do not match those of OCS (Leung, 2002). Reaction with NO_3 radicals at night most likely represents the major loss process for dimethyl sulfide and methyl mercaptan. The mechanisms for the oxidation of DMS are still not completely understood. Initial attack by NO_3 and OH radicals involves H atom abstraction, with a smaller branch leading to OH addition to the S atom. The OH addition branch increases in importance as temperatures decrease, becoming the major pathway below temperatures of 285 K (Ravishankara, 1997). The adduct may either decompose to form methane sulfonic acid (MSA), or undergo further reactions in the main pathway, to yield dimethyl sulfoxide (Barnes et al., 1991). Following H atom abstraction from DMS, the main reaction products include MSA and SO_2. The ratio of MSA to SO_2 is strongly temperature dependent, varying from about 0.1 in tropical waters to about 0.4 in Antarctic waters (Seinfeld and Pandis, 1998b). Excess sulfate (over that expected from the sulfate in seawater) in marine aerosol is related mainly to the production of SO_2 from the oxidation of DMS. Transformations among atmospheric sulfur compounds are summarized in Figure B-1.

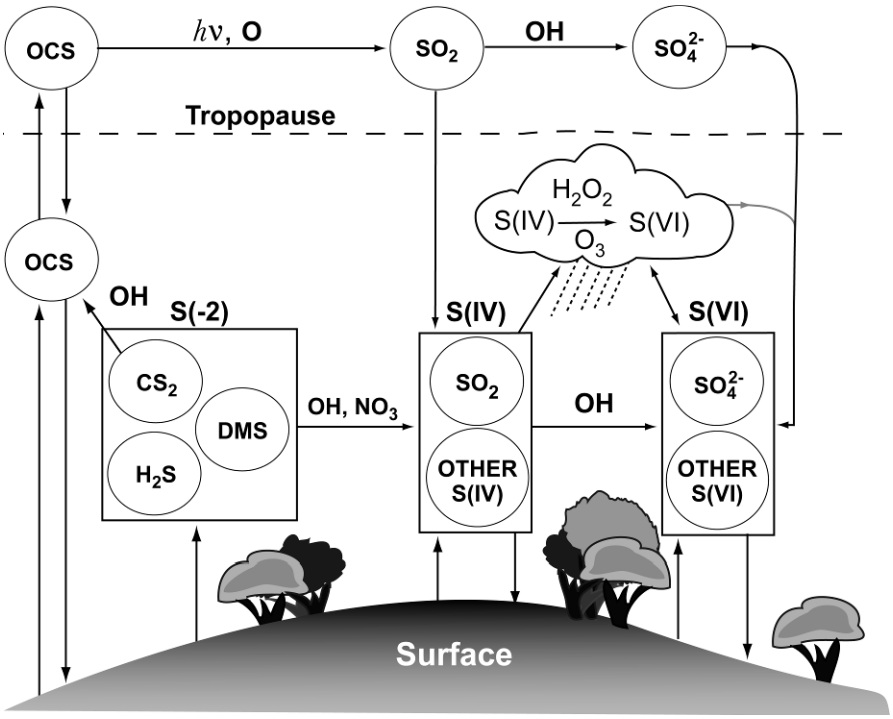

Figure B-1 Transformations of sulfur compounds in the atmosphere.

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

B.1.1. Multiphase Chemical Processes Involving Sulfur Oxides and Halogens

Chemical transformations involving inorganic halogenated compounds effect changes in the multiphase cycling of sulfur oxides in ways analogous to their effects on NO_X. Oxidation of dimethylsulfide $(CH_3)_2S$ by BrO produces dimethylsulfoxide $(CH_3)_2SO$ (Barnes et al., 1991; Toumi, 1994), and oxidation by atomic chloride leads to formation of SO_2 (Keene et al., 1996). $(CH_3)_2SO$ and SO_2 are precursors for methanesulfonic acid (CH_3SO_3H) and H_2SO_4. In the MBL, virtually all H_2SO_4 and CH_3SO_3H vapor condenses onto existing aerosols or cloud droplet, which subsequently evaporate, thereby contributing to aerosol growth and acidification. Unlike CH_3SO_3H, H_2SO_4 also has the potential to produce new particles (Korhonen et al., 1999; Kulmala et al., 2000), which in marine regions is thought to occur primarily in the free troposphere. Saiz-Lopez et al. (2004) estimated that observed levels of BrO at Mace Head Atmospheric Research Station in Ireland, would oxidize $(CH_3)_2S$ about six times faster than OH and thereby substantially increase production rates of H_2SO_4 and other condensible S species in the MBL. Sulfur dioxide is also scavenged by deliquesced aerosols and oxidized to H_2SO_4 in the aqueous phase by several strongly pH-dependent pathways (Chameides and Stelson, 1992; Keene et al., 1998; Vogt et al., 1996). Model calculations indicate that oxidation of S(IV) by O_3 dominates in fresh, alkaline sea salt aerosols, whereas oxidation by hypohalous acids (primarily HOCl) dominates in moderately acidic solutions. Additional particulate non-sea salt (nss) SO_4^{2-} is generated by SO_2 oxidation in cloud droplets (Clegg and Toumi, 1998). Ion-balance calculations indicate that most nss SO_4^{2-} in short-lived (two to 48 h) sea salt size fractions accumulates in acidic aerosol solutions and/or in acidic aerosols processed through clouds (e.g., Keene et al., 2004). The production, cycling, and associated radiative effects of S-containing aerosols in marine and coastal air are regulated in part by chemical transformations involving inorganic halogens (Von Glasow et al., 2002). These transformations include: dry-deposition fluxes of nss SO_4^{2-} in marine air dominated, naturally, by the sea salt size fractions (Huebert et al., 1996; Turekian et al., 2001); HCl phase partitioning that regulates sea salt pH and associated pH-dependent pathways for S(IV) oxidation (Keene et al., 2002; Pszenny et al., 2004); and potentially important oxidative reactions with reactive halogens for $(CH_3)2S$ and S(IV). However, both the absolute magnitudes and relative importance of these processes in MBL S cycling are poorly understood.

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

B.1.2. Mechanisms for the Aqueous Phase Formation of Sulfate

Warneck (1999) constructed a box model describing the chemistry of the oxidation of SO_2 and NO_2 including the interactions of N and S species and minor processes in sunlit cumulus clouds. The relative contributions of different reactions to the oxidation of S(IV) species to S(VI) and NO_2 to NO_3^- 10 min after cloud formation are given in Table B-2. The two columns show the

Table B-2 Relative contributions of various reactions to the total S(IV) oxidation rate within a sunlit cloud, 10 min after cloud formation.

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

[a]In the absence of transition metals. [b]In the presence of iron and copper ions.
Source: Adapted from Warneck (1999).

relative contributions with and without transition metal ions. As can be seen from Table B-2, SO_2 within a cloud (gas + cloud drops) is oxidized mainly by H_2O_2 in the aqueous phase, while and the gas-phase oxidation by OH radicals is small by comparison. A much smaller contribution in the aqueous phase is made by methyl hydroperoxide (CH_3OOH) because it is formed mainly in the gas phase and its Henry's Law constant is several orders of magnitude smaller that of H_2O_2. After H_2O_2, HNO_4 is the major contributor to S(IV) oxidation.

B.1.3. Multiphase Chemical Processes Involving Sulfur Oxides and Ammonia

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

$$NH_{3g} \overset{K_H}{\leftrightarrow} [NH_{3aq}] \overset{K_b}{\leftrightarrow} [NH_4^+] + K_W/[H^+]$$

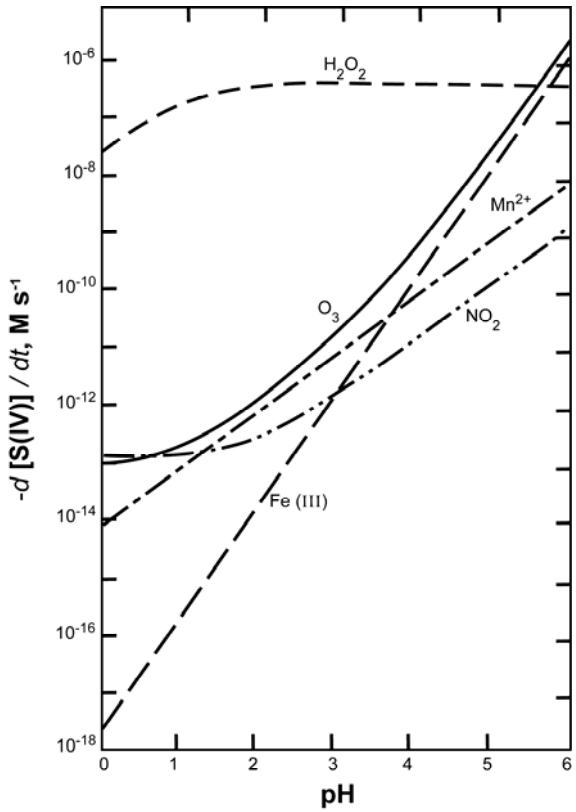

Figure B-2 Comparison of aqueous-phase oxidation paths. The rate of conversion of S(IV) to S(VI) is shown as a function of pH. Conditions assumed are: $[SO_{2(g)}]$ = 5 ppb; $[NO_{2(g)}]$ = 1 ppb; $[H_2O_{2(g)}]$ = 1 ppb; $[O_{3(g)}]$ = 50 ppb; $[Fe(III)_{(aq)}]$ = 0.3 µM; $[Mn(II)_{(aq)}]$ = 0.3 µM.

Source: Seinfeld and Pandis (1998a).

where K_H and K_b are the temperature-dependent Henry's Law and dissociation constants (62 M atm^{-1}) (1.8×10^{-5} M), respectively, for NH_3, and K_w is the ion product of water (1.0×10^{-14} M) (Chameides, 1984). It is evident that for a given amount of NH_X (NH_3 + particulate NH_4^+) in the system, increasing aqueous concentrations of particulate H^+ will shift the partitioning of NH_3 towards the condensed phase. Consequently, under the more polluted conditions characterized by higher concentrations of acidic sulfate aerosol, ratios of gaseous NH_3 to particulate NH_4^+ decrease (Smith et al., 2007). It also follows that in marine air, where aerosol acidity varies substantially as a function of particle size, NH_3 partitions preferentially to the more acidic sub-micron size fractions (e.g., Keene et al., 2004; Smith et al., 2007).

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

B.2. Transport of Sulfur Oxides in the Atmosphere

Crutzen and Gidel (1983), Gidel (1983), and Chatfield and Crutzen (1984) hypothesized that convective clouds played an important role in rapid atmospheric vertical transport of trace species and first tested simple parameterizations of convective transport in atmospheric chemical models. At nearly the same time, evidence was shown of venting the boundary layer by shallow, fair weather cumulus clouds (Greenhut et al., 1984; 1986). Field experiments were conducted in 1985 which resulted in verification of the hypothesis that deep convective clouds are instrumental in atmospheric transport of trace constituents (Dickerson et al., 1987). Once pollutants are lofted to the middle and upper troposphere, they typically have a much longer chemical lifetime and with the generally stronger winds at these altitudes, they can be transported large distances from their source regions.

B.3. Emissions of SO_2

As can be seen from Table B-3, emissions of SO_2 are due mainly to the combustion of fossil fuels by electrical utilities and industry. Transportation related sources make only a minor contribution. As a result, most SO_2 emissions originate from point sources. Since sulfur is a volatile component of fuels, it is almost quantitatively released during combustion and emissions can be calculated on the basis of the sulfur content of fuels to greater accuracy than for other pollutants such as NO_X or primary PM.

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

Volcanic sources of SO_2 are limited to the Pacific Northwest, Alaska, and Hawaii. Since 1980, the Mount St. Helens volcano in the Washington Cascade Range (46.20 N, 122.18 W,

summit 2549 m asl) has been a variable source of SO_2. Its major effects came in the explosive eruptions of 1980, which primarily affected the northern part of the mountainous western half of the United States. The Augustine volcano near the mouth of the Cook Inlet in southwestern Alaska (59.363 N, 153.43 W, summit 1252 m asl) has had variable SO_2 emission since its last major eruptions in 1986. Volcanoes in the Kamchatka peninsula of eastern region of Siberian Russia do not significantly effect surface SO_2 concentrations in northwestern North America. The most serious effects in the United States from volcanic SO_2 occurs on the island of Hawaii. Nearly continuous venting of SO_2 from Mauna Loa and Kilauea produces SO_2 in such large amounts that > 100 km downwind of the island SO_2 concentrations can exceed 30 ppbv (Thornton and Bandy, 1993). Depending on wind direction, the west coast of Hawaii (Kona region) has had significant deleterious effects from SO_2 and acidic sulfate aerosols for the past decade.

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

Emissions of reduced sulfur species are associated typically with marine organisms living either in pelagic or coastal zones and with anaerobic bacteria in marshes and estuaries. Mechanisms for their oxidation were discussed in Section B.1. Emissions of dimethyl sulfide (DMS) from marine plankton represent the largest single source of reduced sulfur species to the atmosphere (e.g., Berresheim et al., 1995). Other sources such as wetlands and terrestrial plants and soils probably account for less than 5% of the DMS global flux, with most of this coming from wetlands.

The coastal and wetland sources of DMS have a dormant period in the fall/winter from senescence of plant growth. Marshes die back in fall and winter, so dimethyl sulfide emissions from them are lower, reduced light levels in winter at mid to high latitudes reduce phytoplankton

growth which also tends to reduce DMS emissions. Western coasts at mid to high latitudes have reduced levels of the light that drive photochemical production and oxidation of DMS. Freezing at mid and high latitudes affects the release of biogenic sulfur gases, particularly in the nutrient-rich regions around Alaska. Transport of SO_2 from regions of biomass burning seems to be limited by heterogeneous losses that accompany convective processes that ventilate the surface layer and the lower boundary layer (Thornton et al., 1996, TRACE-P data archive).

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

Table B-3 Emissions of NO_x, ammonia, and SO_2 in the U.S. by source and category, 2002.

2002 EMISSIONS (TG/YR)	NO_x[1]	NH[2]	SO_2
Total All Sources	**23.19**	**4.08**	**16.87**
Fuel Combustion Total	**9.11**	**0.02**	**14.47**
Fuel Combustion Electrical Utilities	5.16	< 0.01	11.31
Coal	4.50	< 0.01	10.70
Bituminous	2.90		8.04
Subbituminous	1.42		2.14
Anthracite & Lignite	0.18		0.51
Other	< 0.01		
Oil	0.14	< 0.01	0.38
Residual	0.13		0.36
Distillate	0.01		0.01
Gas	0.30	< 0.01	0.01
Natural	0.29		
Process	0.01		
Other	0.05	< 0.01	0.21
Internal Combustion	0.17	< 0.01	0.01
Fuel Combustion Industrial	3.15	< 0.01	2.53
Coal	0.49	< 0.01	1.26
Bituminous	0.25		0.70

2002 EMISSIONS (TG/YR)	NO_X[1]	NH[2]	SO_2
Subbituminous	0.07		0.10
Anthracite & Lignite	0.04		0.13
Other	0.13		0.33
Oil	0.19	< 0.01	0.59
Residual	0.09		0.40
Distillate	0.09		0.16
Other	0.01		0.02
Gas	1.16	< 0.01	0.52
Natural	0.92		
Process	0.24		
Other	< 0.01		
Other	0.16	< 0.01	0.15
Wood/Bark Waste	0.11		
Liquid Waste	0.01		
Other	0.04		
Internal Combustion	1.15	< 0.01	0.01
Fuel Combustion Other	0.80	< 0.01	0.63
Commercial/Institutional Coal	0.04	< 0.01	0.16
Commercial/Institutional Oil	0.08	< 0.01	0.28
Commercial/Institutional Gas	0.25	< 0.01	0.02
Miscellaneous Fuel Combustion (Except Residential)	0.03	< 0.01	0.01
Residential Wood	0.03		< 0.01
Residential Other	0.36		0.16
Distillate Oil	0.06		0.15
Bituminous/Subbituminous	0.26		< 0.01
Other	0.04		< 0.01
INDUSTRIAL PROCESS TOTAL	**1.10**	**0.21**	**1.54**
Chemical & Allied Product Mfg	0.12	0.02	0.36
Organic Chemical Mfg	0.02	< 0.01	0.01
Inorganic Chemical Mfg	0.01	< 0.01	0.18
Sulfur Compounds			0.17
Other			0.02
Polymer & Resin Mfg	< 0.01	< 0.01	< 0.01
Agricultural Chemical Mfg	0.05	0.02	0.05
Ammonium Nitrate/Urea Mfg.		< 0.01	
Other		0.02	
Paint, Varnish, Lacquer, Enamel Mfg	0.00		0.00

2002 EMISSIONS (TG/YR)	NO_X[1]	NH[2]	SO_2
Pharmaceutical Mfg	0.00		0.00
Other Chemical Mfg	0.03	< 0.01	0.12
Metals Processing	0.09	< 0.01	0.30
Non-Ferrous Metals Processing	0.01	< 0.01	0.17
Copper			0.04
Lead			0.07
Zinc			0.01
Other			< 0.01
Ferrous Metals Processing	0.07	< 0.01	0.11
Metals Processing	0.01	< 0.01	0.02
Petroleum & Related Industries	0.16	< 0.01	.38
Oil & Gas Production	0.07	< 0.01	0.11
Natural Gas			0.11
Other			0.01
Petroleum Refineries & Related Industries	0.05	< 0.01	0.26
Fluid Catalytic Cracking Units		< 0.01	0.16
Other		< 0.01	0.07
Asphalt Manufacturing	0.04		0.01
Other Industrial Processes	0.54	0.05	0.46
Agriculture, Food, & Kindred Products	0.01	< 0.01	0.01
Textiles, Leather, & Apparel Products	< 0.01	< 0.01	< 0.01
Wood, Pulp & Paper, & Publishing Products	0.09	< 0.01	0.10
Rubber & Miscellaneous Plastic Products	< 0.01	< 0.01	< 0.01
Mineral Products	0.42	< 0.01	0.33
Cement Mfg	0.24		0.19
Glass Mfg	0.01		
Other	0.10		0.09
Machinery Products	< 0.01	< 0.01	< 0.01
Electronic Equipment	< 0.01	< 0.01	< 0.01
Transportation Equipment	< 0.01		< 0.01
Miscellaneous Industrial Processes	0.01	0.05	0.02
Solvent Utilization	0.01	< 0.01	< 0.01
Degreasing	< 0.01	< 0.01	< 0.01
Graphic Arts	< 0.01	< 0.01	< 0.01
Dry Cleaning	< 0.01	< 0.01	< 0.01
Surface Coating	< 0.01	< 0.01	< 0.01
Other Industrial	< 0.01	< 0.01	< 0.01

2002 EMISSIONS (TG/YR)	NO_X[1]	NH[2]	SO_2
Nonindustrial	< 0.01		
Solvent Utilization Nec	< 0.01		
Storage & Transport	< 0.01	< 0.01	0.01
Bulk Terminals & Plants	< 0.01	< 0.01	< 0.01
Petroleum & Petroleum Product Storage	< 0.01	< 0.01	< 0.01
Petroleum & Petroleum Product Transport	< 0.01	< 0.01	< 0.01
Service Stations: Stage II	< 0.01		< 0.01
Organic Chemical Storage	< 0.01	< 0.01	< 0.01
Organic Chemical Transport	0.01		< 0.01
Inorganic Chemical Storage	< 0.01	< 0.01	< 0.01
Inorganic Chemical Transport	< 0.01		< 0.01
Bulk Materials Storage	0.01	< 0.01	< 0.01
Waste Disposal & Recycling	0.17	0.14	0.03
Incineration	0.06	< 0.01	0.02
Industrial			
Other			< 0.01
Open Burning	0.10	< 0.01	< 0.01
Industrial			< 0.01
Land Clearing Debris			
Other			< 0.01
Public Operating Treatment Works	< 0.01	0.14	< 0.01
Industrial Waste Water	< 0.01	< 0.01	< 0.01
Treatment, Storage, And Disposal Facility	< 0.01	< 0.01	< 0.01
Landfills	< 0.01	< 0.01	< 0.01
Industrial			< 0.01
Other			< 0.01
Other	< 0.01	< 0.01	< 0.01
TRANSPORTATION TOTAL	**12.58**	**0.32**	**0.76**
Highway Vehicles	8.09	0.32	0.30
Light-Duty Gas Vehicles & Motorcycles	2.38	0.20	0.10
Light-Duty Gas Vehicles	2.36		0.10
Motorcycles	0.02		0.00
Light-Duty Gas Trucks	1.54	0.10	0.07
Light-Duty Gas Trucks 1	1.07		0.05
Light-Duty Gas Trucks 2	0.47		0.02
Heavy-Duty Gas Vehicles	0.44	< 0.01	0.01
Diesels	3.73	< 0.01	0.12

2002 EMISSIONS (TG/YR)	NO_X[1]	NH[2]	SO_2
Heavy-Duty Diesel Vehicles	3.71		
Light-Duty Diesel Trucks	0.01		
Light-Duty Diesel Vehicles	0.01		
Off-Highway	4.49	< 0.01	0.46
Non-Road Gasoline	0.23	< 0.01	0.01
Recreational	0.01		
Construction	0.01		
Industrial	0.01		
Lawn & Garden	0.10		
Farm	0.01		
Light Commercial	0.04		
Logging	< 0.01		
Airport Service	< 0.01		
Railway Maintenance	< 0.01		
Recreational Marine Vessels	0.05		
Non-Road Diesel	1.76	< 0.01	0.22
Recreational	0.00		
Construction	0.84		
Industrial	0.15		
Lawn & Garden	0.05		
Farm	0.57		
Light Commercial	0.08		
Logging	0.02		
Airport Service	0.01		
Railway Maintenance	< 0.01		
Recreational Marine Vessels	0.03		
Aircraft	0.09		0.01
Marine Vessels	1.11		0.18
Diesel	1.11		
Residual Oil			
Other			
Railroads	0.98		0.05
Other	0.32	< 0.01	0.00
Liquefied Petroleum Gas	0.29		
Compressed Natural Gas	0.04		
Miscellaneous	0.39	3.53	0.10
Agriculture & Forestry	< 0.01	3.45	< 0.01

2002 EMISSIONS (TG/YR)	NO_x[1]	NH[2]	SO_2
Agricultural Crops		< 0.01	
Agricultural Livestock		2.66	
Other Combustion		0.08	0.10
Health Services			
Cooling Towers			
Fugitive Dust			
Other			
Natural Sources	3.10	0.03	

[1] Emissions are expressed in terms of NO_2.
[2] Emissions based on Guenther et al. (2000)
Source: U.S. Environmental Protection Agency (2006a)

B.4. Methods Used to Calculate SO_x and Chemical Interactions in the Atmosphere

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

A brief overview of atmospheric chemistry-transport models is given in Section B.5. A discussion of emissions inventories of precursors used by these models is given in Section B.5. Uncertainties in emissions estimates have also been discussed in Air Quality Criteria for Particulate Matter (U.S. EPA, 1996). Chemistry-transport model evaluation and an evaluation of the reliability of emissions inventories are also presented in Section B.5.

B.5. Chemical-transport Models

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

Global scale CTMs are used to address issues associated with climate change, stratospheric O_3 depletion, and to provide boundary conditions for regional scale models. CTMs include mathematical (and often simplified) descriptions of atmospheric transport, the transfer of solar radiation through the atmosphere, chemical reactions, and removal to the surface by turbulent motions and precipitation for pollutants emitted into the model domain. Their upper boundaries extend anywhere from the top of the mixing layer to the mesopause (about 80 km in height), to obtain more realistic boundary conditions for problems involving stratospheric dynamics. There is a trade-off between the size of the modeling domain and the grid resolution used in the CTM that is imposed by computational resources.

There are two major formulations of CTMs in current use. In the first approach, grid-based, or Eulerian, air quality models, the region to be modeled (the modeling domain) is

subdivided into a three-dimensional array of grid cells. Spatial derivatives in the species continuity equations are cast in finite-difference there are also some finite-element models, but not many applications form over this grid, and a system of equations for the concentrations of all the chemical species in the model are solved numerically at each grid point. Time dependent continuity (mass conservation) equations are solved for each species including terms for transport, chemical production and destruction, and emissions and deposition (if relevant), in each cell. Chemical processes are simulated with ordinary differential equations, and transport processes are simulated with partial differential equations. Because of a number of factors such as the different time scales inherent in different processes, the coupled, nonlinear nature of the chemical process terms, and computer storage limitations, all of the terms in the equations are not solved simultaneously in three dimensions. Instead, operator splitting, in which terms in the continuity equation involving individual processes are solved sequentially, is used. In the second CTM formulation, trajectory or Lagrangian models, a large number of hypothetical air parcels are specified as following wind trajectories. In these models, the original system of partial differential equations is transformed into a system of ordinary differential equations.

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

B.5.1. Regional Scale Chemical-transport Models

Major modeling efforts within the U.S. Environmental Protection Agency center on the Community Multiscale Air Quality modeling system (CMAQ) (Byun and Ching, 1999; Byun and Schere, 2006). A number of other modeling platforms using Lagrangian and Eulerian frameworks have been reviewed in the 96 AQCD for O_3 (U.S. EPA, 2007), and in Russell and Dennis (2000). The capabilities of a number of CTMs designed to study local- and regional-scale air pollution problems are summarized by Russell and Dennis (2000). Evaluations of the

performance of CMAQ are given in Arnold et al. (2003), Eder and Yu (2006), Appel et al. (2005), and Fuentes and Raftery (2005). The domain of CMAQ can extend from several hundred km to the hemispherical scale. In addition, both of these classes of models allow the resolution of the calculations over specified areas to vary. CMAQ is most often driven by the MM5 mesoscale meteorological model (Seaman, 2000), though it may be driven by other meteorological models (e.g., RAMS). Simulations of O_3 episodes over regional domains have been performed with a horizontal resolution as low as 1 km, and smaller calculations over limited domains have been accomplished at even finer scales. However, simulations at such high resolutions require better parameterizations of meteorological processes such as boundary layer fluxes, deep convection and clouds (Seaman, 2000), and finer-scale emissions. Finer spatial resolution is necessary to resolve features such as urban heat island circulations; sea, bay, and land breezes; mountain and valley breezes, and the nocturnal low-level jet.

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

The vertical resolution of these CTMs is variable, and usually configured to have higher resolution near the surface and decreasing aloft. Because the height of the boundary layer is of critical importance in simulations of air quality, improved resolution of the boundary layer height

would likely improve air quality simulations. Additionally, current CTMs do not adequately resolve fine scale features such as the nocturnal low-level jet in part because little is known about the nighttime boundary layer.

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

Chemical kinetics mechanisms (a set of chemical reactions) representing the important reactions occurring in the atmosphere are used in CTMs to estimate the rates of chemical formation and destruction of each pollutant simulated as a function of time. Unfortunately, chemical mechanisms that explicitly treat the reactions of each individual reactive species are too computationally demanding to be incorporated into CTMs. For example, a master chemical mechanism includes approximately 10,500 reactions involving 3603 chemical species (Dentener et al., 2005). Instead, "lumped" mechanisms, that group compounds of similar chemistry together, are used. The chemical mechanisms used in existing photochemical O_3 models contain significant uncertainties that may limit the accuracy of their predictions; the accuracy of each of these mechanisms is also limited by missing chemistry. Because of different approaches to the lumping of organic compounds into surrogate groups, chemical mechanisms can produce somewhat different results under similar conditions. The CB-IV chemical mechanism (Gery et al., 1989), the RADM II mechanism (Stockwell et al., 1990), the SAPRC (e.g., Carter, 1990; Wang et al., 2000b; a) and the RACM mechanisms can be used in CMAQ. Jimenez et al. (2003) provide brief descriptions of the features of the main mechanisms in use and they compared concentrations of several key species predicted by seven chemical mechanisms in a box model simulation over 24 h. The average deviation from the average of all mechanism predictions for

O_3 and NO over the daylight period was less than 20%, and was 10% for NO_2 for all mechanisms. However, much larger deviations were found for HNO_3, PAN, HO_2, H_2O_2, C_2H_4, and C_5H_8 (isoprene). An analysis for OH radicals was not presented. The large deviations shown for most species imply differences between the calculated lifetimes of atmospheric species and the assignment of model simulations to either NO_X-limited or radical quantity limited regimes between mechanisms. Gross and Stockwell (2003) found small differences between mechanisms for clean conditions, with differences becoming more significant for polluted conditions, especially for NO_2 and organic peroxy radicals. They caution modelers to consider carefully the mechanisms they are using. Faraji et al. (2005) found differences of 40% in peak 1-h O_3 in the Houston-Galveston-Brazoria area between simulations using SAPRAC and CB4. They attributed differences in predicted O_3 concentrations to differences in the mechanisms of oxidation of aromatic hydrocarbons.

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

Spatial and temporal characterizations of anthropogenic and biogenic precursor emissions must be specified as inputs to a CTM. Emissions inventories have been compiled on grids of varying resolution for many hydrocarbons, aldehydes, ketones, CO, NH_3, and NO_X. Emissions inventories for many species require the application of some algorithm for calculating the dependence of emissions on physical variables such as temperature and to convert the inventories into formatted emission files required by a CTM. For example, preprocessing of emissions data for CMAQ is done by the Spare-Matrix Operator Kernel Emissions (SMOKE) system. For many species, information concerning the temporal variability of emissions is lacking, so long-term (e.g., annual or O_3-season) averages are used in short-term, episodic simulations. Annual emissions estimates are often modified by the emissions model to produce emissions more characteristic of the time of day and season. Significant errors in emissions can

occur if an inappropriate time dependence or a default profile is used. Additional complexity arises in model calculations because different chemical mechanisms are based on different species, and inventories constructed for use with another mechanism must be adjusted to reflect these differences. This problem also complicates comparisons of the outputs of these models because one chemical mechanism may produce some species not present in another mechanism yet neither may agree with the measurements.

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

The initial conditions, i.e., the concentration fields of all species computed by a model, and the boundary conditions, i.e., the concentrations of species along the horizontal and upper

boundaries of the model domain throughout the simulation must be specified at the beginning of the simulation. It would be best to specify initial and boundary conditions according to observations. However, data for vertical profiles of most species of interest are sparse. The results of model simulations over larger, preferably global, domains can also be used. As may be expected, the influence of boundary conditions depends on the lifetime of the species under consideration and the time scales for transport from the boundaries to the interior of the model domain (Liu et al., 2001).

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

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

Uncertainty also arises in modeling the chemistry of O_3 formation because it is highly nonlinear with respect to NO_X concentrations. Thus, the volume of the grid cell into which emissions are injected is important because the nature of O_3 chemistry (i.e., O_3 production or titration) depends in a complicated way on the concentrations of the precursors and the OH radical as noted earlier. The use of ever-finer grid spacing allows regions of O_3 titration to be more clearly separated from regions of O_3 production. The use of grid spacing fine enough to resolve the chemistry in individual power-plant plumes is too demanding of computer resources for this to be attempted in most simulations. Instead, parameterizations of the effects of sub-grid-

scale processes such as these must be developed; otherwise serious errors can result if emissions are allowed to mix through an excessively large grid volume before the chemistry step in a model calculation is performed. In light of the significant differences between atmospheric chemistry taking place inside and outside of a power plant plume (e.g., Ryerson et al., 1998; Sillman, 2000), inclusion of a separate, meteorological module for treating large, tight plumes is necessary. Because the photochemistry of O_3 and many other atmospheric species is nonlinear, emissions correctly modeled in a tight plume may be incorrectly modeled in a more dilute plume. Fortunately, it appears that the chemical mechanism used to follow a plume's development need not be as detailed as that used to simulate the rest of the domain, as the inorganic reactions are the most important in the plume see (e.g., Kumar and Russell, 1996). The need to include explicitly plume-in-grid chemistry only down to the level of the smallest grid disappears if one uses the adaptive grid approach mentioned previously, though such grids are more computationally intensive. The differences in simulations are significant because they can lead to significant differences in the calculated sensitivity of O_3 to its precursors (e.g., Sillman, 1995).

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

B.5.2. Global-scale CTMs

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

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

During the recent IPCC-AR4 tropospheric chemistry study coordinated by the European Union project Atmospheric Composition Change: the European Network of excellence (ACCENT), 26 atmospheric CTMs were used to estimate the impacts of three emissions scenarios on global atmospheric composition, climate, and air quality in 2030 (Dentener et al., 2006b). All models were required to use anthropogenic emissions developed at IIASA (Dentener et al., 2005) and GFED version 1 biomass burning emissions (Van der Werf et al., 2003) as described in Stevenson et al. (2006). The base simulations from these models were evaluated against a suite of present-day observations. Most relevant to this assessment report are the evaluations with ozone and NO_2, and for nitrogen and sulfur deposition (Dentener et al., 2006b; Stevenson et al., 2006; van Noije et al., 2006); see Figure B-3.

B.5.3. Modeling the Effects of Convection

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

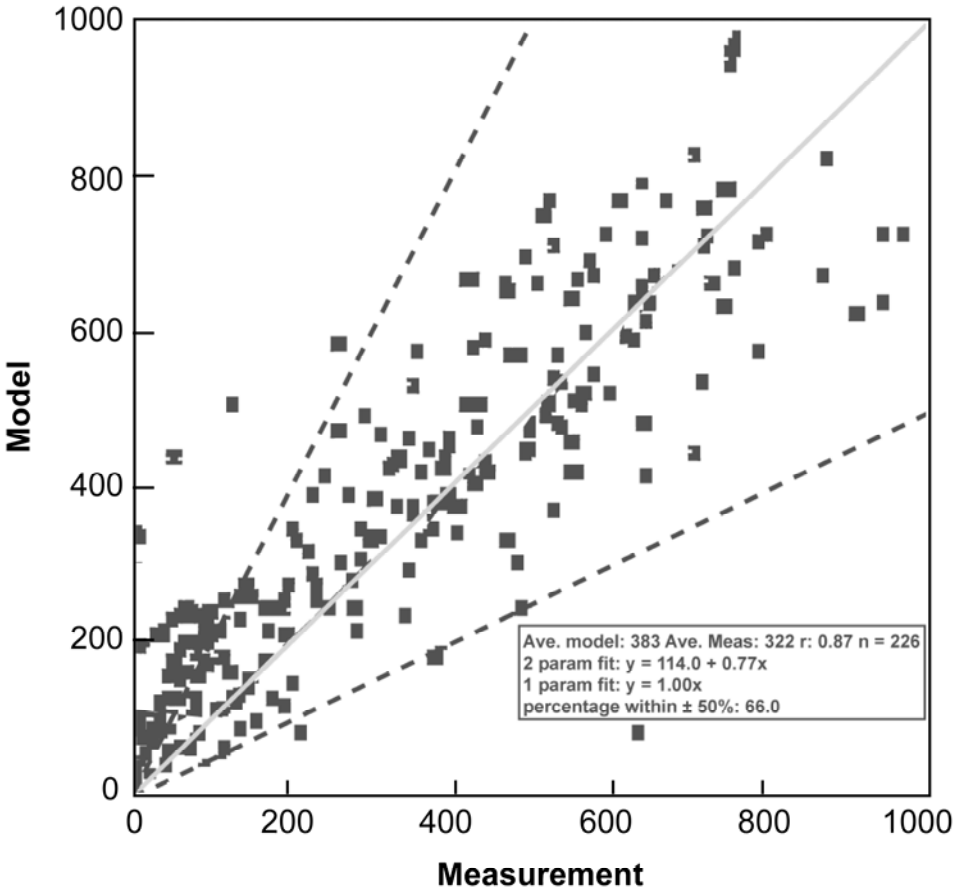

Figure B-3 Sulfate wet deposition (mg(S)$m^{-2}yr^{-1}$) of the mean model versus measurements for the North American Deposition Program (NADP) network. Dashed lines indicate factor of 2. The gray line is the result of a linear regression fitting through 0.

Source: Dentener et al. (2006).

B.5.4. CTM Evaluation

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

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

B.6. Sampling and Analysis of Sulfur Oxides

B.6.1. Sampling and Analysis for SO_2

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

$$SO_2 + h\nu_1 \rightarrow SO_2 *$$

$$SO_2 * \rightarrow SO_2 + h\nu_2$$

where SO_2* represents the excited state of SO_2, $h<_1$, and $h<_2$ represent the energy of the excitation and fluorescence photons, respectively, and $h<_2 < h<_1$. The intensity of the emitted light is proportional to the number of SO_2 molecules in the sample gas.

In commercial analyzers, light from a high intensity UV lamp passes through a bandwidth filter, allowing only photons with wavelengths around the SO_2 absorption peak (near 214 nm) to enter the optical chamber. The light passing through the source bandwidth filter is collimated

using a UV lens and passes through the optical chamber, where it is detected on the opposite side of the chamber by the reference detector. A photomultiplier tube (PMT) is offset from and placed perpendicular to the light path to detect the SO_2 fluorescence. Since the SO_2 fluorescence (330 nm) is at a wavelength that is different from the excitation wavelength, an optical bandwidth filter is placed in front of the PMT to filter out any stray light from the UV lamp. A lens is located between the filter and the PMT to focus the fluorescence onto the active area of the detector and optimize the fluorescence signal. The LOD for a non-trace level SO_2 analyzer is 10 parts per billion (ppb) (Code of Federal Regulations, Title 40, Part 53.23c). The SO_2 measurement method is subject to both positive and negative interference.

B.6.1.1. Other Techniques for Measuring SO_2

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

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

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

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

B.6.2. Sampling and Analysis for Sulfate, Nitrate, and Ammonium

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

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

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

The extent to which sampling artifacts for particulate NH_3^+ have been adequately addressed in the current networks is not clear. Recently, new denuder-filter sampling systems

have been developed to measure sulfate, nitrate, and ammonium with an adequate correction of ammonium sampling artifacts. The denuder-filter system, Chembcomb Model 3500 speciation sampling cartridge developed by Rupprecht & Patashnick Co, Inc. could be used to collect nitrate, sulfate, and ammonium simultaneously. The sampling system contains a single-nozzle size-selective inlet, two honeycomb denuders, the aerosol filter and two backup filters (Keck and Wittmaack, 2005). The first denuder in the system is coated with 0.5% sodium carbonate and 1% glycerol and collects acid gases such as HCL, SO_2, HONO, and HNO_3. The second denuder is coated with 0.5% phosphoric acid in methanol for collecting NH_3. Backup filters collect the gases behind denuded filters. The backup filters are coated with the same solutions as the denuders. A similar system based on the same principle was applied by Possanzini et al. (1999). The system contains two NaCl-coated annular denuders followed by other two denuders coated with $NaCO_3$/glycerol and citric acid, respectively. This configuration was adopted to remove HNO_3 quantitatively on the first NaCl denuder. The third and forth denuder remove SO_2 and NH_3, respectively. A polyethylene cyclone and a two-stage filter holder containing three filters is placed downstream of the denuders. Aerosol fine particles are collected on a Teflon membrane. A backup nylon filter and a subsequent citric acid impregnated filter paper collect dissociation products (HNO_3 and NH_3) of ammonium nitrate evaporated from the filtered particulate matter.

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

this volatilization are important if the PTFE filter is to be subjected to subsequent analyses of volatile species.

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

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

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

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

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

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

Annex C. Modeling Human Exposure

C.1. Introduction

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

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

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

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

First, it must be understood that there is significant variation in the definitions of many of the terms used in the exposure modeling literature; indeed, the science of exposure modeling is a

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

rapidly evolving field and the development of a standard and commonly accepted terminology is an ongoing process (see, e.g., WHO, 2004).

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

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

Finally, fourth, the concept of microenvironments, introduced in earlier sections of this document, should be clarified further, as it is critical in developing procedures for exposure modeling. In the past, microenvironments have typically been defined as individual or aggregate locations (and sometimes even as activities taking place within a location) where a homogeneous concentration of the pollutant is encountered. Thus a microenvironment has often been identified with an ideal (i.e. perfectly mixed) compartment of classical compartmental modeling. More recent and general definitions view the microenvironment as a control volume, either indoors or outdoors, that can be fully characterized by a set of either mechanistic or phenomenological governing equations, when appropriate parameters are available, given necessary initial and boundary conditions. The boundary conditions typically would reflect interactions with ambient air and with other microenvironments. The parameterizations of the governing equations generally include the information on attributes of sources and sinks within each

microenvironment. This type of general definition allows for the concentration within a microenvironment to be non-homogeneous (non-uniform), provided its spatial profile and mixing properties can be fully predicted or characterized. By adopting this definition, the number of microenvironments used in a study is kept manageable, but variability in concentrations in each of the microenvironments can still be taken into account. Microenvironments typically used to determine exposure include indoor residential microenvironments, other indoor locations (typically occupational microenvironments), outdoors near roadways, other outdoor locations, and in-vehicles. Outdoor locations near roadways are segregated from other outdoor locations (and can be further classified into street canyons, vicinities of intersections, etc.) because emissions from automobiles alter local concentrations significantly compared to background outdoor levels. Indoor residential microenvironments (kitchen, bedroom, living room, etc. or aggregate home microenvironment) are typically separated from other indoor locations because of the time spent there and potential differences between the residential environment and the work/public environment.

Once the actual individual and relevant activities and locations (for Individual Based Modeling), or the sample population and associated spatial (geographical) domain (for Population Based Modeling) have been defined along with the temporal framework of the analysis (time period and resolution), the comprehensive modeling of individual/population exposure to SO_2 (and related pollutants) will in general require seven steps (or components, as some of them do not have to be performed in sequence) that are listed below. This list represents a composite based on approaches and frameworks described in the literature over the last twenty-five years (WHO 2005; U.S. EPA, 1992; 1997; Georgopoulos and Lioy, 1994; Georgopoulos et al., 2005; 2006; Ott, 1982; Price et al., 2003) as well on the structure of various inhalation exposure models (see Annex Section C.2 that have been used in the past or in current studies to specifically assess inhalation exposures. Figure C-1, adapted from (Georgopoulos et al., 2005), schematically depicts the sequence of steps summarized here.

1) Estimation of the background or ambient levels of both SO_2 and related pollutants. This is done through either (or a combination of):

    a) multivariate spatio-temporal analysis of fixed monitor data, or

b) emissions-based, photochemical, air quality modeling (typically with a regional, grid-based model such as Models-3/CMAQ or CAMx) applied in a coarse resolution mode.

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

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

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

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

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

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

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

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

f) study-specific information, if available

g) existing databases based on composites of questionnaire information from past studies

h) time-activity databases, typically in a format compatible with EPA's Consolidated Human Activity Database (McCurdy et al., 2000)

5) Estimation of levels and temporal profiles of both SO_2 and related pollutants in various outdoor and indoor microenvironments such as street canyons, roadway intersections, parks, residences, offices, restaurants, vehicles, etc. This is done through either:

i) linear regression of available observational data sets,

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

k) lumped (nonlinear) gas or gas/aerosol chemistry models, or

l) detailed combined chemistry and Computational Fluid Dynamics modeling.

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

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

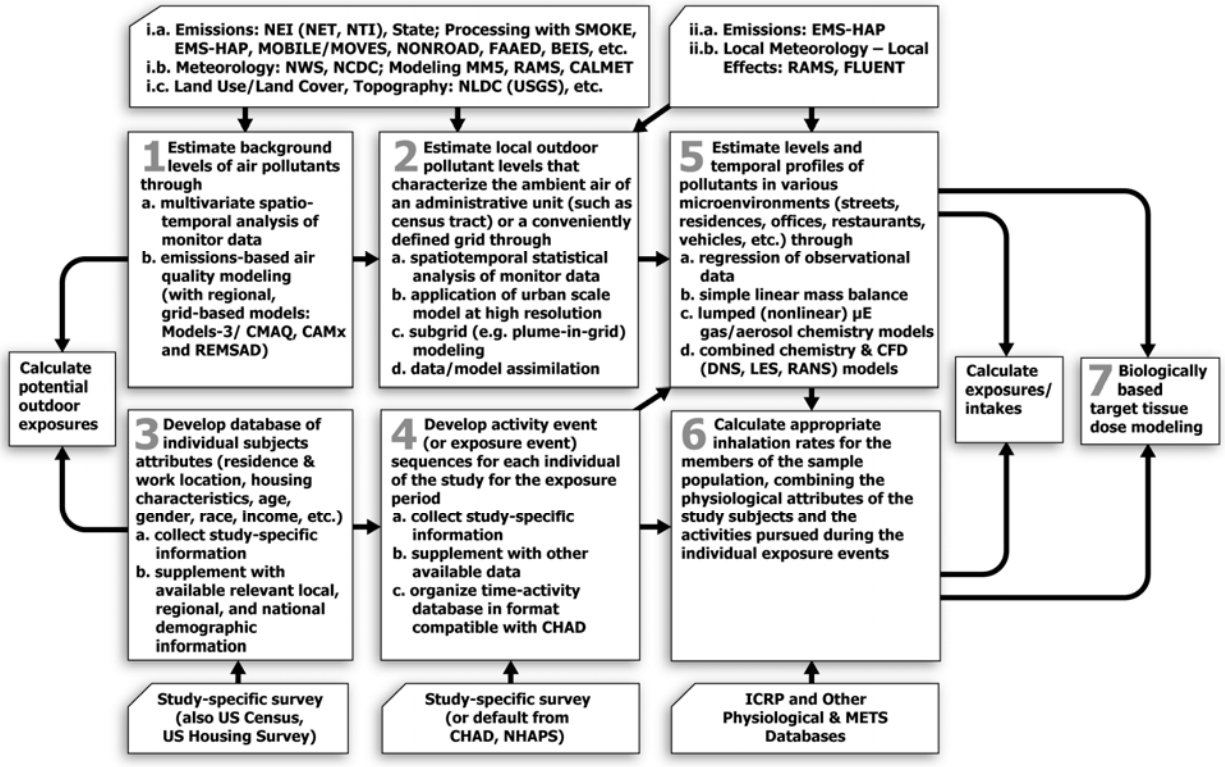

Figure C-1. Schematic description of a general framework identifying the processes (steps or components) involved in assessing inhalation exposures and doses for individuals and populations. In general terms, existing comprehensive exposure modeling systems such as SHEDS, APEX, and MENTOR-1A follow this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

Implementation of the above framework for comprehensive exposure modeling has benefited significantly from recent advances and expanded availability of computational

technologies such as Relational Database Management Systems (RDBMS) and Geographic Information Systems (GIS) (Georgopoulos et al., 2005; Purushothaman and Georgopoulos, 1997; 1999b; a).

In fact, only relatively recently comprehensive, predictive, inhalation exposure modeling studies for ozone, PM, and various air toxics, have attempted to address/incorporate all the components of the general framework described here. In practice, the majority of past exposure modeling studies have either incorporated only subsets of these components or treated some of them in a simplified manner, often focusing on the importance of specific factors affecting exposure. Of course, depending on the objective of a particular modeling study, implementation of only a limited number of steps may be necessary. For example, in a regulatory setting, when comparing the relative effectiveness of emission control strategies, the focus can be on expected changes in ambient levels (corresponding to those observed at NAAQS monitors) in relation to the density of nearby populations. The outdoor levels of pollutants, in conjunction with basic demographic information, can thus be used to calculate upper bounds of population exposures associated with ambient air (as opposed to total exposures that would include contributions from indoor sources) useful in comparing alternative control strategies. Though the metrics derived would not be quantitative indicators of actual human exposures, they can serve as surrogates of population exposures associated with outdoor air, and thus aid in regulatory decision making concerning pollutant standards and in studying the efficacy of emission control strategies. This approach has been used in studies performing comparative evaluations of regional and local emissions reduction strategies in the eastern United States (Foley et al., 2003; Georgopoulos et al., 1997; Purushothaman and Georgopoulos, 1997).

C.2. Population Exposure Models: Their Evolution and Current Status

Existing comprehensive inhalation exposure models consider the trajectories of individual human subjects (actual or virtual), or of appropriately defined cohorts, in space and time as sequences of exposure events. In these sequences, each event is defined by time, a geographic location, a microenvironment, and the activity of the subject. EPA offices (OAQPS and NERL) have supported the most comprehensive efforts in developing models implementing this general concept (see, e.g., Johnson, 2002). These families of models are the result: National Exposure

Model and Probabilistic National Exposure Model (NEM/pNEM, Whitfield et al., 1997); Hazardous Air Pollutant Exposure Model (HAPEM, Rosenbaum, 2005); Simulation of Human Exposure and Dose System (SHEDS, Burke et al., 2001); Air Pollutants Exposure Model (APEX, U.S. EPA, 2006a; 2006b); and Modeling Environment for Total Risk Studies (MENTOR, Georgopoulos et al., 2005; Georgopoulos and Lioy, 2006). European efforts have produced some formulations with similar general attributes as the above U.S. models but, generally, involving simplifications in some of their components. Examples of European models addressing exposures to photochemical oxidants (specifically, ozone) include the Air Pollution Exposure Model (AirPEx, Freijer et al., 1998), which basically replicates the pNEM approach and has been applied to the Netherlands, and the Air Quality Information System Model (AirQUIS, Clench-Aas et al., 1999).

The NEM/pNEM, SHEDS, APEX, and MENTOR for One-Atmosphere studies (MENTOR-1A) families of models provide exposure estimates defined by concentration and breathing rate for each individual exposure event, and then average these estimates over periods typically ranging from one hour to one year. These models allow simulation of certain aspects of the variability and uncertainty in the principal factors affecting exposure. An alternative approach is taken by the HAPEM family of models that typically provide annual average exposure estimates based on the quantity of time spent per year in each combination of geographic locations and microenvironments. The NEM, SHEDS, APEX, and MENTOR-type models are therefore expected to be more appropriate for pollutants with complex chemistry such as SO_2, and could provide useful information for enhancing related health assessments.

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

- pNEM divides the population of interest into representative cohorts based on the combinations of demographic characteristics (age, gender, and employment), home/work district, residential cooking fuel and replicate number, and then assigns an activity diary record from the CHAD to each cohort according to demographic characteristic, season, day-type (weekday/weekend) and temperature.

- HAPEM6 divides the population of interest into demographic groups based on age, gender and race, and then for each demographic group/day-type (weekday/weekend) combination, selects multiple activity patterns randomly (with replacement) from CHAD and combines them to find the averaged annual time allocations for group members in each census tract for different day types.

- SHEDS, APEX, and MENTOR-1A generate population demographic files, which contain a user-defined number of person records for each census tract of the population based on proportions of characteristic variables (age, gender, employment, and housing) obtained from the population of interest, and then assign a matching activity diary record from CHAD to each individual record of the population based on the characteristic variables. It should be mentioned that, in the formulations of these models, workers may commute from one census tract to another census tract for work. So, with the specification of commuting patterns, the variation of exposure concentrations due to commuting between different census tracts can be captured.

The conceptual approach originated by the SHEDS models was modified and expanded for use in the development of MENTOR-1A. Flexibility was incorporated into this modeling system, such as the option of including detailed indoor chemistry and other relevant microenvironmental processes, and providing interactive linking with CHAD for consistent definition of population characteristics and activity events (Georgopoulos et al., 2005).

Table C-1. The Essential Attributes of the pNEM, HAPEM, APEX, SHEDS, and MENTOR-1A

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

	PNEM	HAPEM	APEX	SHEDS	MENTOR-1A
Physiologically Based Dose	No	No	No	Yes	Yes
Variability/Uncertainty	Yes	No	Yes	Yes	Yes (Various "Tools")

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

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

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

profile. The EPA has applied APEX to the study of exposures to ozone and other criteria pollutants; APEX can be modified and used for the estimation of SO_2 exposures, if required.

Reconfiguration of APEX for use with SO_2 or other pollutants would require significant literature review, data analysis, and modeling efforts. Necessary steps include determining spatial scope and resolution of the model; generating input files for activity data, air quality and temperature data; and developing definitions for microenvironments and pollutant-microenvironment modeling parameters (penetration and proximity factors, indoor source emissions rates, decay rates, etc.) (ICF Consulting, 2005). To take full advantage of the probabilistic capabilities of APEX, distributions of model input parameters should be used wherever possible.

C.3. Characterization of Ambient Concentrations of SO_2 and Related Air Pollutants

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

Spatio-temporal distributions of pollutant concentrations such as ozone, PM, and various air toxics have alternatively been obtained using methods of the Spatio-Temporal Random Field (STRF) theory (Christakos and Vyas, 1998a; b). The STRF approach interpolates monitor data in both space and time simultaneously. This method can thus analyze information on temporal trends which cannot be incorporated directly in purely spatial interpolation methods such as standard kriging. Furthermore, the STRF method can optimize the use of data which are not uniformly sampled in either space or time. STRF was further extended within the Bayesian Maximum Entropy (BME) framework and applied to ozone interpolation studies (Christakos and Hristopulos, 1998; Christakos and Kolovos, 1999; Christakos, 2000). It should be noted that these studies formulate an over-arching scheme for linking air quality with population dose and health effects; however, they are limited by the fact that they do not include any microenvironmental effects. MENTOR has incorporated STRF/BME methods as one of the steps for performing a comprehensive analysis of exposure to ozone and PM (Georgopoulos et al., 2005).

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

C.4. Characterization of Microenvironmental Concentrations

Once the background and local ambient spatio-temporal concentration patterns have been derived, microenvironments that can represent either outdoor or indoor settings when individuals

come in contact with the contaminant of concern (e.g., SO_2) must be characterized. This process can involve modeling of various local sources and sinks, and interrelationships between ambient and microenvironmental concentration levels. Three general approaches have been used in the past to model microenvironmental concentrations:

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

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

- Transport processes: These can include advection/convection and dispersion that are affected by local processes and obstacles such as vehicle induced turbulence, street canyons, building structures, etc.
- Sources and sinks: These can include local outdoor emissions, indoor emissions, surface deposition, etc.
- Transformation processes: These can include local outdoor as well as indoor gas and aerosol phase chemistry, such as formation of secondary organic and inorganic aerosols.

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

C.4.1. Characterization of Activity Events

An important development in inhalation exposure modeling has been the consolidation of existing information on activity event sequences in the Consolidated Human Activity Database (CHAD) (McCurdy, 2000; McCurdy et al., 2000). Indeed, most recent exposure models are designed (or have been re-designed) to obtain such information from CHAD which incorporates 24-h time/activity data developed from numerous surveys. The surveys include probability-based recall studies conducted by Environmental Protection Agency and the California Air Resources Board, as well as real-time diary studies conducted in individual U.S. metropolitan areas using both probability-based and volunteer subject panels. All ages of both genders are represented in CHAD. The data for each subject consist of one or more days of sequential activities, in which each activity is defined by start time, duration, activity type (140 categories), and microenvironment classification (110 categories). Activities vary from one min to one h in duration, with longer activities being subdivided into clock-hour durations to facilitate exposure modeling. A distribution of values for the ratio of oxygen uptake rate to body mass (referred to as metabolic equivalents or METs) is provided for each activity type listed in CHAD. The forms and parameters of these distributions were determined through an extensive review of the exercise and nutrition literature. The primary source of distributional data was Ainsworth et al. (1996), a compendium developed specifically to facilitate the coding of physical activities and to promote comparability across studies.

C.4.2. Characterization of Inhalation Intake and Uptake

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

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

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

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

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

Annex D. Controlled Human Exposure

Table D-1 Effects of medications on SO_2-induced changes in lung function among human subjects.

STUDY	CONC.	DURATION	SUBJECTS	EXPOSURE STATUS	EFFECTS
Bigby and Boushey (1993)	0.25 – 8.0 ppm	4 min	10 asshmatics	Increasing concentrations of SO_2 during voluntary eucapnic hyperpnea (20 L/min) preceded by administration of nedocromil sodium (baseline, placebo, 2 mg, 4 mg, 8 mg).	Treatment with the inhaled anti-inflammatory agent, nedocromil sodium, significantly increased the concentration of SO_2 required to produce an 8 unit increase in sRaw. Increasing the dose of nedocromil sodium from 2 mg to 8 mg did not significantly affect the response.
Lazarus et al. (1997)	0.25 – 8.0 ppm	4 min	12 asthmatics	Subjects exposed using a mouthpiece to filtered air and increasing concentrations of SO_2 during eucapnic hyperventilation (20 L/min). Exposures occurred following pretreatment with zafirlukast (20 mg) or placebo.	Compared with placebo, zafirlukast significantly increased the SO_2 concentration required to produce an 8 unit increase in sRaw. This effect was observed with challenges occurring both at 2 and 10 h following treatment.
Field et al. (1996)	0.25 – 8.0 ppm	3 min	31 asthmatics	Increasing concentrations of SO_2 (including clean air exposure) in an exposure chamber during voluntary eucapnic hyperpnea (35 L/min) preceded by administration of placebo, ipratropium bromide (15 subjects), morphine (15 subjects), or indomethacin (16 subjects).	Both ipratropium bromide and morphine reduced the responsiveness to SO_2, significantly increasing the SO_2 concentration required to reduce specific airway conductance by 35%. Similarly, indomethacin was observed to attenuate airway responsiveness to SO_2, however, this effect was smaller than what was observed with either ipratropium bromide or morphine.
Gong et al. (1996)	0.75 ppm	10 min	10 asthmatics	Subjects exposed to SO_2 or clean air in a chamber while performing light exercise (29 L/min) at 1, 12, 18, and 24 h after pretreatment with salmeterol xinafoate or placebo (each subject exposed 4 times).	Observed a significant protective effect of salmeterol xinafoate at 1 and 12-h post-dosing. Following exercise/SO_2 exposure at 1, 12, 18, and 24 h, FEV_1 decreased (versus preexposure) by 7, 12, 25, and 26%, respectively. Exercise with SO_2 resulted in an approximate 26% decrease in FEV_1 at all time points with placebo.
Gong et al. (2001)	0.75 ppm	10 min	11 asthmatics	Exposure to SO_2 or clean air following three days of treatment with montelukast or placebo (each subject exposed 4 times). Exposures conducted in an exposure chamber during moderate levels of exercise (35 L/min).	Reported a statistically significant SO_2-induced increase in eosinophil count in induced sputum. Measures of lung function (FEV_1 and sRaw), as well as respiratory symptoms and eosinophil count all showed significant improvement after pretreatment with montelukast.

Table D-2 Summary of new studies of controlled human exposure to SO_2.

STUDY	CONC.	DURATION	SUBJECTS	EXPOSURE STATUS	EFFECTS
Trenga et al. (2001)	0.1, 0.25 ppm	10 min	17 asthmatics	SO_2-sensitive asthmatics exposed to SO_2 via mouthpiece while performing mild to moderate levels of exercise. Exposures preceded by 45 min exposures to filtered air or ozone (0.12 ppm), with or without pretreatment with dietary antioxidants.	Exposure to ozone slightly increased bronchial responsiveness to SO_2 as measured by FEV1 and peak expiratory flow. Pretreatment with dietary antioxidants was shown to have a protective effect on respiratory response, particularly among individuals with greater sensitivity to SO_2.
Devalia et al. (1994)	0.2 ppm	6 h	10 asthmatics	Exposures to filtered air, as well as 0.2 ppm SO_2 and 0.4 ppm NO_2, conducted separately and in combination in an exposure chamber (subjects at rest). All subjects sensitive to inhaled house dust mite antigen.	Neither SO_2 nor NO_2, alone or in combination, significantly affected FEV_1. The combination of SO_2 and NO_2 significantly reduced the amount of inhaled allergen (60.5% change, $p = 0.015$) required to produce a 20% decrease in FEV_1 ($PD20FEV_1$). Both SO_2 and NO_2 alone reduced $PD20FEV_1$, but this reduction was not statistically significant (32.2% ($p = 0.506$), and 41.2% ($p = 0.125$), respectively).

STUDY	CONC.	DURATION	SUBJECTS	EXPOSURE STATUS	EFFECTS
Rusznak et al. (1996)	0.2 ppm	6 h	10 asthmatics	Exposures to filtered air and a combination of 0.2 ppm SO_2 and 0.4 ppm NO_2 in an exposure chamber (subjects at rest). All subjects sensitive to inhaled house dust mite antigen.	Confirmed findings of Devalia et al. and further observed that the combination of SO_2 and NO_2 enhanced airway responsiveness to an inhaled allergen up to 48 h post-exposure (maximal response at 24 h).
Tunnicliffe et al. (2001)	0.2 ppm	1 h	12 healthy adults, 12 asthmatics	Exposures (head dome) at rest to filtered air and 0.2 ppm SO_2.	Among healthy subjects, an SO_2-induced increase in heart rate variability (total power) was observed, while a reduction in heart rate variability with SO_2 versus air was observed in asthmatics.
Tunnicliffe et al. (2003)	0.2 ppm	1 h	12 healthy adults, 12 asthmatics	Exposures (head dome) at rest to filtered air and 0.2 ppm SO_2.	Exposures to SO_2 at 0.2 ppm did not have a significant effect on lung function, respiratory symptoms, markers of inflammation, or antioxidant levels in healthy adults or mild asthmatics.
Routledge et al. (2006)	0.2 ppm	1 h	20 older adults with coronary artery disease (age 52-74), 10 healthy older adults (age 56-75)	Exposures (head dome) at rest to filtered air, as well as 0.2 ppm SO_2 and ultra-fine carbon particles (50 $\mu g/m^3$), separately and in combination.	In healthy subjects, exposure to SO_2 alone significantly decreased heart rate variability 4 h post-exposure compared to clean air. No effect was observed in subjects with coronary artery disease. The combination of SO_2 and carbon particles did not affect heart rate variability in either group. SO_2 was not observed to affect markers of inflammation or coagulation.
Nowak et al. (1997)	0.25 – 2.0 ppm	3 min	786 adults	Mouthpiece exposures to filtered air and increasing concentrations of SO_2 during eucapnic hyperventilation (40 L/min).	Among individuals who were not hyperresponsive to methacholine, less than 1% were found to be hyperresponsive to SO_2. However, more than 22% of the individuals who were hyperresponsive to methacholine were also hyperresponsive to SO_2. Individuals were considered hyperresponsive to SO_2 when exposure resulted in a 20% or greater decrease in FEV_1 versus baseline.
Trenga et al. (1999)	0.5 ppm	10 min	47 asthmatic	Subjects exposed to SO_2 via mouthpeice while performing light to moderate levels of exercise.	An SO_2-induced decrease in FEV_1 of at least 8% was observed in 53% of the subjects (range 8-44%). Increases in respiratory symptoms were significantly associated with decreases in FEV_1. Among SO_2-sensitive subjects, severity of asthma (as defined by medication use) was not a significant predictor of the level of response. It is not clear whether the response was adjusted for the effects of exercise in clean air.
Winterton et al. (2001)	0.5 ppm	10 min	62 asthmatics	Subjects exposed to SO_2 via mouthpiece while performing light to moderate levels of exercise.	Subjects who experienced at least at 12% decrease in FEV_1 following exposure were considered to be sensitive to SO_2. Out of 58 subjects who were genotyped for the polymorphism at position -308 in the promoter region of TNF-α, 21% (N: 12) were sensitive to SO_2. Sensitivity to SO_2 was found to be associated with the homozygous wild type allele (GG) (12 of 12 responders versus 28 of 46 subjects who were not responsive to SO_2).
Gong et al. (1995)	0.5, 1.0 ppm	10 min	14 asthmatics	Exposure to SO_2 and filtered air were conducted in an exposure chamber during low, moderate, and heavy levels of exercise (target ventilation ranges of 20-29, 30-39, and 40-49 L/min).	For the average individual, increasing SO_2 concentration resulted in a significant decrement in lung function (decrease in FEV1 and increase in sRaw) as well as a significant increase in respiratory symptoms. Increasing SO_2 concentration had a greater effect on lung function and respiratory symptoms than did increasing level of exercise.

Annex E. Toxicological Studies

Table E-1. Physiological effects of SO_2 exposure.

STUDY	CONC.	DURATION	SPECIES	EFFECTS
Acute and Subacute Exposures				
Lewis and Kirchner (1984)	10 or 30 ppm (26.2 or 78.6 mg/m^3); intratracheal	5 min	Mongrel dogs; male and female; age and weight NR; N: 5-15 /group	Initial transient bronchoconstriction approximately 10 min in duration followed by a gradual change in pulmonary mechanics (43% increase in airway resistance and 30% decrease in dynamic compliance) 4 hrs following 30 ppm but not 10 ppm SO_2.
Barthélemy et al. (1988)	0.5 or 5 ppm (1.3 or 13.1 mg/m^3); intratracheal	45 min	Rabbit; sex NR; 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_2, respectively. Bivagotomy had no effect on 5 ppm SO_2-induced increases in lung resistance. Reflex bronchoconstrictive response to phenyldiguanide (intravenously administered) was eliminated by exposure to SO_2 but SO_2 had no effect on lung resistance induced by intravenously-administered histamine. Authors concluded that (1) vagal reflex is not responsible for SO_2-induced increase in lung resistance at 45 min; (2) transient alteration in tracheobronchial wall following SO_2 exposure may have reduced accessibility of airway nervous recaptors to phenyldiguanide.
Amdur et al. (1983)	~1 ppm (2.62 mg/m^3); head only	1 h	Hartley guinea pig, male, age NR, 200-300 g, N: 8-23/group	An 11% increase in pulmonary resistance and 12% decrease in dynamic compliance were observed. Neither effect persisted into the 1 h period following exposure. No effects were observed for breathing frequency, tidal volume, or min volume.
Conner et al. (1985)	1 ppm (2.62 mg/m^3); nose only	3 h/day for 6 days; animals evaluated up to 48 h post-exposure	Hartley guinea pig, male, age NR, 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 CO or alveolar volume at 1 or 48 h after last exposure.
Douglas et al. (1994)	5 ppm (13.1 mg/m^3); whole body	2 h/day for 13 wks from birth	New Zealand White rabbit, male and female, 1 day old, weight NR, N: 3-4/ group, immunized against Alternaria tenuis	No effects on lung resistance, dynamic compliance, transpulmonary pressure, tidal volume, respiration rate, or min volume.
Subchronic and Chronic Exposure				
Scanlon et al. (1987)	15 or 50 ppm (39.3 or 131 mg/m^3); intratracheal exposure	2 h/day, 4 or 5 days/wk, for 5 mos (low dose group) or 10-11 mos (high dose group); authors stated that physiological changes were observed within 5 mos; 7-9 mo recovery period	Mongrel dogs, adult, sex NR, 10-20 kg; N: 3-4/group (3 hyperresponsive, 3 hyporesponsive, and 1 avg responsive)	At 15 ppm, there was no clinical evidence of bronchitis; pulmonary resistance increased by 35-38% in 2 of 3 dogs, and dynamic lung compliance decreased in 1 of 3 dogs, but the physiological changes were not significant for the group as a whole. At 50 ppm, cough and mucous hypersecretion were observed; the symptoms ceased during the recovery period. Pulmonary resistance increased by 56% during the treatment period and an additional 28% during the recovery period for a total increase of 99%; dynamic lung compliance decreased in 2 of 4 dogs and increased in 1 of 4 dogs during treatment but there were no significant changes in the group as a whole. Authors considered 15 ppm to be the lower limit of exposure that failed to produce physiological changes.
Smith et al. (1989)	1 ppm (2.62 mg/m^3); whole body	5 h/day, 5 days/wk for 4 mos	Sprague-Dawley rat, male, young adult, initial weight NR, N: 12-15/ data point	Physiological tests were conducted in anesthetized animals, many while rat breathed spontaneously and during paralysis. SO_2 exposure resulted in 11% decrease in residual volume during paralysis and reduced quasistatic compliance in paralyzed animals. Authors noted that because residual volume was only decreased in paralyzed rats and magnitude of effect was very small, it may have been due to chance. Quasistatic compliance values observed to be very high in controls; may have accounted for effect in treatment group.

Table E-2. Inflammatory responses following SO_2 exposure.

STUDY	CONC.	DURATION	SPECIES	EFFECTS
Acute/Subacute/Subchronic				
Clarke et al. (2000)	10 ppm (26.2 mg/m^3); nose only	4 h	Outbred Swiss mouse, female, age, weight NR, N: 10/ experimental value	No evidence was seen of inflammatory response in terms of total cell number, lymphocyte/polymorphonuclear leukocytes differentials, or total protein level taken from BAL fluid.
Meng et al. (2005a)	14, 28, or 56 mg/m^3; (5.35, 10.7, or 21.4 ppm); whole body	4 h/day for 7 days	Kunming albino mouse, male, age NR, 18-22 g, N: 10/group	In lung tissue, in vivo SO_2 exposure (low, mid concentrations) significantly elevated levels of the pro-inflammatory cytokines interleukin-6 and tumor necrosis factor-α, but did not affect levels of the anti-inflammatory cytokine transforming growth factor-β1. In serum, the only effect observed was a low-dose elevation of tumor necrosis factor-α.
Langley-Evans et al. (1996)	5, 50, or 100 ppm (13.1, 131, or 262 mg/m^3); whole body	5 h/day for 7-28 days	Wistar rat, male, 7 wks old, weight NR, N: 4-5/ treatment group, 8 controls	No lung injury was observed and evidence of inflammatory response was only observed in the 100 ppm group. A 4-fold increase in BAL fluid leukocyte numbers was observed in the 100 ppm group at day 14; the increase lessened at days 21 and 28 but remained higher than controls. The number of macrophages in BAL fluid was increased at day 28 in the 100 ppm group. Neutrophil numbers were 120 times higher than controls at day 14 in the 100 ppm group but returned to normal by day 21. Blood neutrophils were depleted in rats exposed to 50 ppm on days 7-21 but were increased in rats exposed to 5 ppm (significant) and 100 ppm (non-significant) at day 14. Lung epithelial permeability was not affected.
Conner et al. (1989)	1 ppm (2.62 mg/m^3); nose only	3 h/day for 5 days; bronchial-veolar lavage performed daily	Hartley guinea pig, male, age NR, 250-320 g, N: 4	No change in numbers of total cells and neutrophils, protein levels or enzyme activity in lavage fluid following SO_2 exposure.
Park et al. (2001a)	0.1 ppm (0.26 mg/m^3); whole body; with and without exposure to ovalbumin	5 h/day for 5 days	Dunkin-Hartley guinea pig, male, age NR, 250-350 g, N: 7-12/group	After bronchial challenge, the ovalbumin/SO_2-exposed group had significantly increased eosinophil counts in BAL fluids compared with all other groups, including the SO_2 group. The bronchial and lung tissue of this group showed infiltration of inflammatory cells, bronchiolar epithelial damage, and mucus and cell plug in the lumen.
Li et al. (2007)	2 ppm (5.24 mg/m^3) with and without exposure to ovalbumin	1 h/day for 7 days	Wistar rats, male, age NR	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_2 alone

Table E-3. Effects of SO_2 exposure on host lung defenses.

STUDY	CONC.	DURATION	SPECIES	EFFECTS
Clearance – Subchronic				
Wolff et al. (1989)	5 ppm (13.1 mg/m^3); nose only	2 h/day, 5 days/wk for 4 wks	F344/Crl rat, male and female, 10-11 wks old, weight NR, N: 6/sex/group	There was no effect on pulmonary clearance of radiolabeled alumi-nosilicate particles (MMAD 1.0 µM).
Immune Responses - Acute/Subacute				
Jakab et al. (1996)	10 ppm (26.2 mg/m^3); nose only	4 h	Specific patho-gen-free white Swiss mice, female, 5 wks old, 20-23 g, N: 5/ group	No effect was observed on in situ Fc-receptor-mediated phagocytosis of sheep red blood cells by AM, which was assessed 3 days after exposure to SO_2.

STUDY	CONC.	DURATION	SPECIES	EFFECTS
Clarke et al. (2000)	10 ppm (26.2 mg/m^3) SO_2; nose only	4 h	Outbred Swiss mouse, female, age and weight NR, N: 10/experimental value	No effect on in situ AM phagocytosis (data not shown) or on intrapulmonary bactericidal activity toward Staphylococcus aureus.
Azoulay-Dupuis et al. (1982)	10 ppm (26.2 mg/m^3); whole body	24 h, 1 wk, 2 wks, or 3 wks	OF_1 mice, female, age NR, mean 20.6 g, N: 768 (32/group)	Respiratory challenge with Klebsiella pneumoniae resulted in increased mortality and decreased survival time in the 1, 2, and 3 wk SO_2 exposure groups compared to controls. Differences did not correlate with exposure length.

Table E-4. Effects of SO_2 exposure on hypersensitivity/allergic reactions.

STUDY	CONC.	DURATION	SPECIES	EFFECTS
Antigen Sensitization/Allergic Reactions - Acute/Subacute				
Amdur et al. (1988)	1 ppm	1-h	Guinea pig, n=8	Airway responsiveness to acetylcholine was measured 2 h following SO_2 exposure. No changes were observed.
Abraham et al. (1981)	5 ppm (13.1 mg/m^3); head only	4 h	Sheep, sex and age NR, mean weight 38 ± 7 kg, N: 7/group	Acute exposure to 5 ppm SO_2 did not produce significant airway changes (pulmonary resistance, static compliance, dynamic compliance, tidal volume, breathing frequency) in either normal or allergic (sensitized to Ascaris suum antigen) sheep, nor increase airway reactivity (measured as pulmonary resistance increase after aerosolized carbachol provocation) in normal sheep. However, 5 ppm SO_2 did significantly increase airway reactivity in allergic sheep, which have antigen-induced airway responses similar to humans with allergic airway disease; may model airway responses to SO_2 in a sensitive human subpopulation.
Park et al. (2001a)	0.1 ppm (0.26 mg/m^3); whole body; with and without exposure to ovalbumin	5 h/day for 5 days.	Dunkin-Hartley guinea pig, male, age NR, 250-350 g, N: 7-12/group	After bronchial challenge, the ovalbumin/SO_2-exposed group had significantly increased enhanced pause (indicator of airway obstruction) compared with all other groups, including the SO_2 group. Authors concluded low level SO_2 may enhance the development of ovalbumin-induced asthmatic reactions in guinea pigs.
Riedel et al. (1988)	0.1, 4.3, or 16.6 ppm (0, 0.26, 11.3, or 43.5 mg/m^3); whole body; animals were sensitized to ovalbumin on the last 3 days of exposure.	8 h/day for 5 days	Perlbright-White Guinea pig, female, age NR, 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 last exposure. Numbers of animals displaying symptoms of bronchial obstruction after ovalbumin provocation increased in all SO_2 groups compared to air-exposed groups. Anti-ovalbumin antibodies (IgG total and IgG1) were increased in BAL fluid and serum of SO_2exposed compared to air-exposed controls; statistical significance obtained for IgG total in BAL fluid at ≥ 4.3 ppm SO_2 and in serum at all SO_2 concentrations. Results indicate subacute exposure to even low concentrations of SO_2 can potentiate allergic sensitization of the airway.
Antigen Sensitization/Allergic Reactions – Subchronic				
Kitabatake et al. (1992; 1995)	5 ppm (13.1 mg/m^3); whole body; sensitized with Candida albicans on day 1 and wk 4	4 h/day, 5 days/wk, 6 wks	Hartley guinea pig, male, age NR, ~200 g, N: 12/group	Respiratory challenge to Candida albicans 2 wks after last exposure. At 15 h after challenge increased number of SO_2-exposed animals displayed prolonged expiration, inspiration, or both. Authors concluded SO_2 exposure increased dyspneic symptoms.
General Bronchial Reactivity Studies – Acute				
Douglas et al. (1994)	5 ppm (13.1 mg/m^3); whole body	2 h	New Zealand White rabbit, sex NR, apparently 3 mos old, 2.2-3.1 kg, n=6/group	No effect on airway responsiveness to inhaled histamine, as measured by provocation concentrations of histamine required to increase pulmonary resistance by 50% and decrease dynamic compliance by 35%.

STUDY	CONC.	DURATION	SPECIES	EFFECTS
Lewis and Kirchner (1984)	10 or 30 ppm (26.2 or 78.6 mg/m^3); intratracheal	5 min; 2nd exposure 20 days later, after exposure to the antiallergic drug	Mongrel dogs, male and female, age and weight NR; **N:** 5-15/group	No effect observed at 10 ppm. At 30 ppm hyperresponsiveness and hypersensitivity to aerosolized methacholine and 5-hydroxytryptamine observed for up to 24 h following exposure. 20 days later, pretreatment with aerosolized 4% Wy-41,195 or disodium cromoglycate (antiallergic drugs) at high doses lessened the methacholine-induced hypersensitivity observed after exposure to 30 ppm SO_2. Calculations used to determine hyperresponsive and hyperreactivity were not clear.
General Bronchial Reactivity Studies – Chronic				
Scanlon et al. (1987)	15 or 50 ppm (39.3 or 131 mg/m^3); intratracheal	2 h/day, 4 or 5 days/wk for 5 mos (low dose group) or 10-11 mos (high dose group); physiological changes observed within 5 mos; 7-9 mo recovery period.	Mongrel dogs, adult, sex NR, 10-20 kg; N: 3-4/ group (3 hyperresponsive, 3 hyporesponsive, and 1 avg responsive)	Bronchial reactivity in response to inhaled histamine or methacholine was not affected in either treatment group, as determined by the concentration of histamine or methacholine required to double pulmonary resistance or the concentrations required to decrease dynamic compliance by 65% (ED65).

Table E-5. Effects of SO_2 exposure on cardiovascular endpoints.

STUDY	CONC.	DURATION	SPECIES	EFFECTS
In Vitro Exposure				
Nie and Meng (2005)	Bisulfite/sulfite, 1:3 molar/molar, 10 µM	NR	Ventricular myocytes isolated from Wistar rats, adult, 200-300 g, N: 8	Effects of the 10 µM bisulfite/sulfite mixture on sodium current included a shift of steady state inactivation curve to a more positive potential, a shift of the time- dependent recovery from inactivation curve to the left, accelerated recovery, and shortened inactivation and activation time constants. It was concluded the bisulfite/sulfite mixture stimulated cardiac sodium channels.
Nie and Meng (2006)	Bisulfite/sulfite, 1:3 molar/molar, 10 µM	NR	Ventricular myocytes isolated from 200-300 g, N: 8	Effects of the 10 µM bisulfite/sulfite mixture on voltage- dependent L-type calcium currents included a shift of steady-state activation and inactivation to more positive potentials, accelerated recovery from inactivation, and shortened fast and slow time inactivation constants. Authors stated that their results suggested the possibility cardiac injury following SO_2 inhalation.
Acute/Subacute Exposure				
Hälinen et al. (2000)	1.0, 2.5, or 5 ppm (2.62, 6.55, or 13.1 mg/m^3) in cold dry air; apparently intratracheal	In pre-exposure period 15-min exposure to warm humid air, 10-min to cold dry air, and 15-min to warm humid air. In exposure period, 10-min to each SO_2 concentration or cold dry air, preceded and followed by 15-min exposure to warm, humid air.	Duncan-Hartley guinea pigs, male, age and weight NR, N: 7-12/ group, mechanically ventilated; animals were hyperventilated during cold air and SO_2 exposure to simulate exercise	Arterial blood pressure increased transiently during exposure to 5 ppm SO_2 in cold dry air. No analyses were done to determine the effects on blood pressure were caused by exposure to cold air or SO_2.
Hälinen et al. (2000a)	1 ppm (2.62 mg/m^3) in cold dry air; apparently intratracheal	60 min	Duncan-Hartley guinea pigs, male, age and weight NR, N: 8-9/group, mechanically ventilated; animals were hyperventilated during cold air and SO_2 exposure to simulate exercise	Blood pressure and heart rate increased similarly with exposure to cold dry air or SO_2 in cold dry air. Blood pressure generally increased during the first 10-20 min of exposure and remained steady from that point forward. The increase in heart rate was gradual. No analyses were done to determine if the effects on blood pressure were caused by exposure to cold air or SO_2.

STUDY	CONC.	DURATION	SPECIES	EFFECTS
Nadziejko et al. (2004)	1 ppm (2.62 mg/m^3); nose only	4 h	F344 rat, male, 18 mos old, weight NR, N: 20 (crossover design)	SO_2 exposure had no effect on spontaneous arrythmia frequency in aged rats. Authors urged caution in the interpretation of effects because occurrence of arrhythmias in aged rats was sporadic and variable from day to day.
Meng et al. (2003a)	10, 20, or 40 ppm (26.2, 52.4 or 105 mg/m^3); whole body	6 h	Wistar rat, male, 7-8 wks old, 180-200 g; N: 10/group	A dose-related decrease in blood pressure was observed at ≥ 20 ppm.
Meng et al. (2003a)	10, 20, or 40 ppm (26.2, 52.4, or 104.8 mg/m^3); whole body	6 h/day for 7 days	Wistar rat, male, 7-8 wks old, 180-200 g; N: 10/group	Dose-related decreases in blood pressure were observed on exposure day 3 in the 10 ppm group, exposure days 2-6 in the 20 ppm group, and all exposure days in the 40 ppm group. The authors noted possible adaptive mechanism in the low but not the high dose group.
Langley-Evans et al. (1996)	5, 50, or 100 ppm (13.1, 131, or 262 mg/m^3); whole body	5 h/day for 7-28 days	Wistar rat, male, 7 wks old, weight NR, N: 4-5/treatment group, 8 controls	GSH was depleted in the heart at 5 and 100 ppm. At 50 ppm, GSH level decreased in heart at 7 days and returned to normal by 14 days. No effects observed for other GSHrelated enzymes. Injury not assessed in heart, but assessment in lung revealed no effect.
Meng et al. (2003a)	22, 56, or 112 mg/m^3 (8.4, 21, or 43 ppm); whole body	6 h/day for 7 days	Kunming albino mice, male and female, 5 wks old, 19 ± 2 g, N: 10/sex/group	Changes observed in heart (concentrations of effect) included: lower SOD activity in males and females (≥ 8.4 ppm), higher TBARS level in males and females (≥ 8.4 ppm), lower GPx activity in males (8.4 and 21 ppm; also 43 ppm according to text) and lower GSH level in males (43 ppm). Authors concluded that SO_2 induced oxidative damage in hearts of mice.
Wu and Meng (2003)	22, 64, or 148 mg/m^3 (8.4, 24.4, or 56.5 ppm); whole body	6 h/day for 7 days	Kunming-strain mice, male, age NR, 18-20 g, N: 10/group	GSH, GST, and glucose-6-phosphate dehydrogenase activities were decreased in the heart at 148 mg/m^3.

Table E-6. Neurophysiology and biochemistry effects of SO_2 and derivatives.

STUDY	CONC.	DURATION	SPECIES	EFFECTS
In Vitro/Ex Vivo				
Du and Meng (2004)	1, 10, 50, or 100 µM SO_2 derivatives (1:3, $NaHSO_3$ to Na_2SO_3)	Not specified	Wistar rat, sex NR, 6-12 days old, weight and number NR; typical observations made on 60 isolated hippocampal neurons per concentration	Exposure to SO_2 derivatives (sulfite, bisulfite) reversibly increased the amplitude of potassium channel TOCs in a dose-dependent and volt-age-dependent manner. Compared to controls, 10 µM SO_2 shifted inactivation of depolarization toward more positive potentials without significantly affecting the activation process. By increasing maximal TOC conductance and delaying TOC inactivation, micromolar concentrations of SO_2 derivatives may increase the excitability of hippocampal neurons and thus contribute to the enhanced neuronal activity associated with SO_2 intoxication.
Du and Meng (2004b)	1 or 10 µM SO_2 derivatives (1:3, $NaHSO_3$ to $Na2SO_3$)	2-4 min	Wistar rat, both sexes, 10-15 days old, weight and number NR; N: 6-13 isolated dorsal root ganglion neurons avgd per endpoint	Maximum sodium current amplitudes for both TTX-S and TTX-R channels were increased by exposure to SO_2 derivatives (10 or 1 µM, respectively), with amplitudes diminished at more negative evoking potentials and enhanced at less negative or positive potentials. SO_2 derivatives (a) slowed both current activation and inactivation for both types of sodium channels; (b) shifted activation currents to more positive potentials, increasing threshold voltages for action potential generation and contributing to reduced neuron excitability; and (c) caused even larger counteracting positive shifts in inactivation voltages tending to increase dorsal root ganglion neuron excitability. On balance, the data suggest micromolar concentrations of sulfite/bisulfite can increase the excitability of dorsal root ganglion neurons, providing a basis for SO_2-associated neurotoxicity.

STUDY	CONC.	DURATION	SPECIES	EFFECTS
Du and Meng (2006)	0.01, 0.1, 0.5, or 1 µM SO_2 derivatives (1:3, $NaHSO_3$ to $Na2SO_3$)	Not specified, but brief ("added to the external solution just before each experiment")	Wistar rat, both sexes, 10-15 days old, weight and number NR; N: 6-15 isolated dorsal root ganglion neurons avgd per endpoint	In isolated dorsal root ganglion neurons, SO_2 derivatives increased HVA-/Ca amplitudes in a concentration- and depolarizing volt-age-dependent manner (EC50 was ~0.4 µM) by altering Ca channel properties. This effect was partially reversible by SO_2 derivative washout, and was PKI-inhibitable, indicating involvement of PKA and secondary messengers. Additionally, exposure caused a positive shift in reversal potential. SO_2 derivatives also delayed activation and inactivation of Ca channels, but the latter was more pronounced, thus overall prolonging action potential duration and increasing HVA-/Ca. Exposure also slowed the fast component and accelerated the slow component of recovery from Ca channel inactivation. Thus, ≤ 1 µM sulfite/bisulfite caused prolonged opening and altered properties of Ca channels, elevated HVA-/Ca, and abnormal Ca signaling with neuronal cell injury. Authors speculate these effects may correlate to SO_2 inhalation toxicity, perhaps leading to abnormal regulation via peripheral neuron Ca channels of nociceptive impulse transmission.
Acute/Subacute/Subchronic Exposure				
Wu and Meng (2003)	22, 64, or 148 mg/m^3 (8.4, 24.4, or 56.5 ppm); whole body	6 h/day for 7 days	Kunming-strain mice, male, age NR, 18-20 g, N: 10/group	Decreased glutathione, glucose-6-phosphate dehydrogenase, and GST activities were observed in the brain at 64 and 148 mg/m^3.
Haider et al. (1981)	10 ppm (26.2 mg/m^3); whole body	1 h/day for 21 or 24 days	Guinea pig, sex NR, adult, 250-500 g, N: 12/group (6/subgroup)	The effects of SO_2 exposure on lipid profiles, lipid peroxidation and lipase activity in three regions of the brain (cerebral hemisphere, CH; cerebellum, CB; brain stem, BS) were examined. Significant ($p < 0.001$-0.05) findings include reductions in total lipids (CH, BS; also CB, but nonsignificant) and free fatty acids (CH, CB, BS). PL were elevated in CH, but reduced in CB; Chol was elevated in CH, but reduced in CB and BS; and esterified fatty acids were elevated in CB, but reduced in CH and BS. Levels of malonaldehyde and lipase activity were elevated in all regions. Results indicate that subacute brief exposures to SO_2 can lead to degradation of brain lipids, with the exact nature of the lipid alterations dependent upon brain region.
Haider et al. (1982)	10 ppm (26.2 mg/m^3); whole body	1 h/day for 30 days	Charles Foster rat, male, adult, 150-200 g, N: 12/group (6/subgroup)	The effects of SO_2 exposure on lipid profiles, lipid peroxidation and lipase activity in three regions of the brain (cerebral hemisphere, CH; cerebellum, CB; brain stem, BS) were examined. Significant ($p <$ 0.001-0.05) findings include reductions in total lipids (CH, BS, CB), while PL were elevated only in CB. Chol was elevated in CH and CB, but not BS; and gangliosides were elevated in CB and BS, but reduced in CH. Lipid peroxidation (malonaldehyde formation) was elevated in whole brain and all regions (although nonsignificantly in BS), as was lipase activity in CH, the only tissue examined. Despite regional differences in PL and Chol changes, Chol/PL ratios were elevated in all three brain regions (again nonsignificantly in BS). Results are somewhat different than those seen in guinea pig (Haider et al., 1981), but again suggest that subacute brief exposures to SO_2 can lead to degradation of brain lipids, with the exact nature of the lipid alterations dependent upon brain region.
Haider and Hasan (1984)	10 ppm (26.2 mg/m^3) SO_2 alternated with 20 ppm (14.7 mg/m^3) H_2S; whole body	1 h/day for 30 days (alter-nating SO_2 or H_2S)	Guinea pig, sex and age NR, 250-400 g, N: 18/group in 2 groups (6/group in some subgroups)	The effects of alternating SO_2 + H_2S exposure on lipid profiles, lipid peroxidation and lipase activity in four regions of the brain (cerebral hemisphere, CH; basal ganglia, BG; cerebellum, CB; brain stem, BS) and in the spinal cord (SC) were examined. Significant ($p < 0.001$-0.05) findings include reductions in total lipids and Chol, and elevated lipid peroxidation (malonaldehyde formation) and lipase activity, in all brain regions and SC. Chol/PL ratios were also reduced in all tissues (but nonsignificantly in BG and CB). For other parameters (PL, free fatty acids, esterified fatty acids, and gangliosides), changes were observed in most tissues but were region-specific. Results indicate that subacute brief, alternating exposures to SO_2 or H_2S lead to degradation of brain lipids, again with the exact nature of the lipid alterations dependent upon brain/spinal cord region. Additionally, some of the effects observed for this mixture vary from those seen with SO_2 alone (Haider et al., 1981; 1982).

STUDY	CONC.	DURATION	SPECIES	EFFECTS
Ağar et al. (2000)	10 ppm (26.2 mg/m^3) (± iv alloxan to induce experimental type 1 diabetes); whole body	1 h/day, 7 days/wk for 6 wks	Swiss albino rat, male, 3 mos old, weight NR, N: 10/group in 4 groups	In retina tissue, exposure elevated SOD activity and reduced GPx and catalase activities. TBARS were elevated only in non-diabetic rats exposed to SO_2. In brain tissue, exposure elevated SOD and reduced GPx activities in both non-diabetics and diabetics, while catalase activities were not affected; TBARS were elevated in both non-diabetics and diabetics. With respect to VEPs, exposure prolonged latencies in 4 of 5 VEP components in non-diabetics and 5 of 5 in diabetics, while reducing virtually all peak-to-peak amplitudes in non-diabetics and diabetics. For many endpoints, SO_2 effects were additive to those resulting from the induced diabetic condition. In summary, brain and retinal anti-oxidant and lipid peroxidation status, as well as neuro-visual performance were affected by subchronic exposure to brief periods of 10 ppm SO_2, and these effects were exacerbated by a diabetic condition.
Subchronic/Chronic Exposure				
Küçükatay et al. (2003)	10 ppm (26.2 mg/m^3) (± iv alloxan to induce experimental type 1 diabetes); whole body	1 h/day, 7 days/wk for 6 wks	Rat, male, 3 mos old, weight not reported, N: 10/group in 4 groups	In brain tissue, SO_2 exposure elevated SOD and reduced GPx activities in both non-diabetics and diabetics, while catalase activities were not affected; TBARS were elevated in both non-diabetics and diabetics. With respect to afferent peripheral nerve pathways (SEPs), exposure prolonged latencies in 4 of 4 SEP components in both non-diabetics and diabetics; also altered were some inter-peak latencies (non-diabetics and diabetics) and some peak-to-peak amplitudes (non-diabetics only). In some cases, SO_2 effects were additive to those resulting from the induced diabetic condition. In summary, brain anti-oxidant and lipid peroxidation status, as well as afferent peripheral nerve pathways, were affected by subchronic exposure to 10 ppm SO_2, and these effects were exacerbated by a diabetic condition. Authors suggest that SO_2 exposure could potentiate the incidence and/or severity of diabetes.
Yargiçoğlu et al. (1999)	10 ppm (26.2 mg/m^3); whole body	1 h/day, 7 days/wk for 6 wks	Swiss albino rat, male, 3, 12, or 24 mos old, weight not reported, N: 10/group in 6 groups	Effects of aging ± SO_2 exposure on levels of lipid peroxidation (TBARS), antioxidant enzyme status (catalase, GPx, SOD), and afferent peripheral nerve pathways (SEPs) were monitored in the brain of young (Y, 3 mo), middle-aged (M, 12 mo) and old (O, 24 mo) rats. In addition to age-related changes, SO_2 exposure significantly ($p < 0.0001$-0.02) elevated TBARS and SOD, while reducing GPx (Y, M, O); catalase levels were not affected. Of 4 monitored SEP component peaks, SO_2 significantly ($p < 0.01$-0.05) prolonged latencies in groups Y (4/4) and M (1/4), but not in O (0/4). Peak-to-peak amplitudes were decreased in Y, (2/3) and increased in M (1/3), but not affected in O (0/3). Taken together, these data indicate that subchronic exposure to brief periods of 10 ppm SO_2 can impact afferent peripheral nerve pathways and the lipid peroxidation and antioxidant enzyme status of the brain.
Kilic (2003)	10 ppm (26.2 mg/m^3); whole body	1 h/day, 7 days/wk for 6 wks	Swiss albino rat, male, 3, 12, or 24 mos old, weight not reported, N: 10/group in 6 groups	Effects of aging ± SO_2 exposure on levels of lipid peroxidation (TBARS), antioxidant enzyme status (catalase, GPx, SOD), and visual system function (VEPs) were monitored in the brain and eye (retina and lens) of young (Y, 3 mo), middle-aged (M, 12 mo) and old (O, 24 mo) rats. In addition to age-related changes, SO_2 exposure significantly ($p < 0.0001$-0.04) elevated TBARS in brain and lens (Y, M, O), and in retina (Y); reduced GPx in brain (Y) and lens (Y, M, O); reduced catalase in retina (Y, M, O); and elevated SOD in brain (Y, M), retina (Y, M, O) and lens (M, O). Of 5 monitored VEP component peaks, SO_2 prolonged latencies in groups Y (4/5), M (3/5) and O (1/5). Taken together, these data indicate that subchronic exposure to brief periods of 10 ppm SO_2 can impact the visual system and the lipid peroxidation and antioxidant enzyme status of the brain and eye.
Neurodevelopment/Neurobehavior				
Singh (1989)	32 or 65 ppm (83.8 or 170 mg/m^3); whole body	Gestation day 7-18	CD-1 mouse dams were exposed; numbers of dams exposed and offspring evaluated not indicated	Righting and negative geotaxis reflexes were delayed at both concentrations.

STUDY	CONC.	DURATION	SPECIES	EFFECTS
Petruzzi et al. (1996)	5, 12, or 30 ppm (13.1, 31.4, or 78.6 mg/m^3); whole body	Near continuous (80% of time) exposure from 9 days before mating through the 12-14th day of pregnancy	CD-1 mouse, adult male and female parental animals were exposed (N: 10/group/sex) and male and female offspring (N: 8 litters/group, fostered by unexposed dams at birth) were evaluated at 2-18 days of age; adult male offspring also evaluated (N: 8/group)	Off**Spring:** No effects observed for birth weight, postnatal body weight gain, somatic and neurobehavioral development (e.g., eyelid and ear opening, incisor eruption, and reflex development); no postnatal developmental data were shown by authors. No effects observed in passive avoidance testing of adult males. Adults: Observation of behavior outside the exposure chamber on exposure days 3, 6, and 9 revealed dose-related increases in digging and decreases in grooming by females in the 30 ppm group on exposure day 9; non-dose related increases were observed for crossing and wall rearing by females in the 30 ppm group on exposure day 9. Observance of behaviors in 2 breeding pairs/group in the 12 and 30 ppm groups revealed increased rearing and social interaction in the 30 ppm group shortly after the start of exposure, followed by return to baseline levels; effects were generally of greater magnitude in males.
Fiore et al. (1998)	5, 12, or 30 ppm (13.1, 31.4, or 78.6 mg/m^3); whole body	Near continuous (90% of time) exposure from 9 days before mating through the 14th day of pregnancy	CD-1 mouse, adult male and female parental animals were exposed and adult male offspring (fostered by unexposed dams at birth) were evaluated at ~120 days of age, N: 11-12 offspring/ group	In 20-min encounters with unexposed males, prenatally-exposed males compared to controls displayed (dose(s) of effect, time of testing effect observed) increased duration of self grooming (5 ppm, 15-20 min), decreased frequency and duration of tail rattling (≥ 5 ppm at 5-10 min and 12 ppm at 10-15 min), and decreased duration of defensive postures (≥ 12 ppm, 0-5 min). Authors also noted a non-significant decrease in freezing (apparently at all dose levels) and non-significant increases in social exploration (apparently at all doses) and rearing (apparently at ≥ 12 ppm).

Table E-7. Reproductive and developmental effects of SO_2.

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

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

Table E-8. Hematological effects of SO_2.

STUDY	CONC.	DURATION	SPECIES	EFFECTS
Acute/Subacute Exposure				
Baskurt (1988)	0.87 ppm (2.36 mg/m^3); whole body	24 h	Swiss Albino rat, male, age NR, 250-300 g, N: 51, 50	Effects of SO_2 exposure included increased hematocrit, sulfhemoglobin and osmotic fragility and decreased whole blood and packed cell viscosities. RBC number, hemoglobin, mean corpuscular volume, mean corpuscular hemoglobin concentration, and plasma viscosity were not significantly altered.
Gümüşlü et al. (1998)	10 ppm (26.2 mg/m^3); whole body	1 h/day, 7 days/wk for 8 wks	Swiss-Albino rat, male, 2.5-3.0 mos old, weight NR, N: 30 (14 controls, 16 treated)	Decreased Cu, Zn-SOD activity, increased GPx and GST activity, and increased TBARS formation were observed in RBC of treated rats. No significant effect on glucose-6-phosphate dehydrogenase or catalase levels was observed.
Yargiçoğlu et al. (2001)	10 ppm (26.2 mg/m^3); whole body	1 h/day, 7 days/wk for 6 wks	Albino rat, male, 3, 12, and 24 mos old, mean weight 213-448 g, N: 10/ group	Enzyme and GSH activity (GPx, catalase, GSH, and GST) were increased and copper-zinc SOD activity was decreased in RBCs of all experimental groups compared to controls. RBCs in older rats had lower levels of all antioxidants enzymes and increased TBARS activity compared to younger rats.
Subchronic Exposure				
Langley-Evans et al. (1997; 2007)	286 mg/m^3 (100 ppm); whole body. Units were initially reported as µg/m^3 but were corrected per correspondence w/author.	5 h/day for 28 days	Wistar rat, male, 7 wks old, weight NR, N: 4-16	Dams were fed diets containing casein at 180 [control], 120, 90, or 60 g/kg during pregnancy and their offspring were exposed to air or SO_2 as adults. In blood of offspring, SO_2 exposure significantly reduced the numbers of circulating total leukocytes and lymphocytes in the 180 and 120 g/kg dietary groups; neutrophils numbers were not affected in any group. GSH levels in the 180 and 60 g/kg (but not the two intermediate) dietary groups were reduced by SO_2 exposure.
Etlik et al. (1995)	10 ppm (26.2 mg/m^3); whole body	1 h/day for 30 days	Guinea pig, sex and age NR, 250-450 g, N: 12/group	SO_2 exposure resulted in RBC membrane lipoperoxidation (elevated levels of malonyldialdehyde) and other oxidative damage (elevated osmotic fragility ratios and levels of methemoglobin and sulfhemoglobin). All effects significantly ($p < 0.05$) mitigated by injections of Vitamin E+C three times per wk.
Ağar et al. (2000)	10 ppm (26.2 mg/m^3); whole body	1 h/day, 7 days/ wk for 6 wks	Swiss Albino rat, male, 3 mos old, weight NR, N: 10 per group in 4 groups	RBC parameters were monitored in non-diabetic rats, non-diabetic rats exposed to SO_2, alloxan-induced diabetic rats, and diabetic rats exposed to SO_2. In both non-diabetic and diabetic rats exposed to SO_2, levels of GPx, catalase, GSH, GST, and TBARS were elevated in RBC while those of SOD were reduced.

STUDY	CONC.	DURATION	SPECIES	EFFECTS
Etlik et al. (1997)	10 ppm (26.2 mg/m^3); whole body	1 h/day for 45 days	Rat, sex and age NR, 214-222 g, N: 6-8 per group	SO_2 exposure significantly elevated levels of methemoglobin, sulfhemoglobin and malonyldialdehyde, the latter of which was substantially reversed by Vitamin E+C treatment. RBC osmotic fragility was increased by SO_2, and again partially mitigated by Vitamin E+C. SO_2 elevated RBC, white blood cell, hemoglobin and hematocrit values, but not mean corpuscular volume, mean corpuscular hemoglobin or mean corpuscular hemoglobin concentration. Vitamin E+C exposure did not affect these parameters.

Table E-9. Endocrine system effects of SO_2.

STUDY	CONC.	DURATION	SPECIES	EFFECTS
Lovati et al. (1996)	5 or 10 ppm (13.1 or 26.2 mg/m^3); whole body	24 h/day for 15 days	Sprague-Dawley CD rat, male, age NR, 250-275 g, N: 9/subgroup in 9 subgroups	Subjects were rats fed standard diet (normal) or high cholesterol diet, and rats with streptozotocin-induced diabetes fed standard diet. In diabetic rats, there was no effect on glucose levels. Exposure to ≥ 5 ppm lowered plasma insulin level in normal and hypercholesterolemic diet groups, but elevated it (non-significantly) in diabetic rats. In each rat model, inhalation of SO_2 at levels without overt effects affected insulin levels. Specific effects varied according to diet or diabetes.
Ağar et al. (2000)	10 ppm (26.2 mg/m^3); whole body	1 h/day, 7 days/wk for 6 wks	Swiss Albino rat, male, 3 mos old, weight NR, N: 10/group	Effects were compared in non-diabetic rats and rats with alloxan induced diabetes. SO_2 increased blood glucose in diabetic and non-diabetic rats.
Küçükatay et al. (2003)	10 ppm (26.2 mg/m^3); whole body	1 h/day, 7 days/wk for 6 wks	Rat, male, 3 mos old, weight NR, N: 10/group in 4 groups	Effects were compared in normal rats and rats with alloxan induced diabetes. SO_2 elevated blood glucose levels in both non-diabetics and diabetics.

Table E-10. Effects of SO_2 exposure on respiratory system morphology.

STUDY	CONC.	DURATION	SPECIES	EFFECTS
Acute/Subacute Exposure				
Conner et al. (1985)	1 ppm (2.6 mg/m^3); nose only	3 h/day for 6 days; animals evaluated for up to 72 h following exposure	Hartley guinea pig, male, age NR, 250-320 g, N: 14/group/time point	In combined group of SO_2 exposed animals and furnace gas controls, no alveolar lesions were observed.
Subchronic/Chronic Exposure				
Wolff et al. (1989)	5 ppm (13 mg/m^3); nose only	2 h/day, 5 days/wk for 4 wks	F344/Crl rat, male and female, 10-11 wks old, weight NR, N: 3/sex/ group	No nasal or pulmonary lesions.
Smith et al. (1989)	1 ppm (2.62 mg/m^3); whole body	5 h/day, 5 days/wk for 4 or 8 mos; half the animals in the 8-mo group were allowed to recover for 3 mos.	Sprague-Dawley rat, male, young adult, initial weight NR, N: 12-15/data point	At 4 mos of SO_2 exposure, increases were observed for incidence of bronchial epithelial hyperplasia (80 vs. 40% in controls) and numbers of nonciliated epithelial cells (31.1 vs. 27.7% in controls); neither effect persisted past 4 mos of exposure.
Gunnison et al., (1987)	10 and 30 ppm	6 h/day and 5 day/wk for 21 wks	Sqrague-Dawley CD rat, 8 week of age	Mild epithelial hyperplasia in the trachea and larger bronchi, mucoid degeneration and desquamation of epithelium of the larger bronchi

Table E-11. Carcinogenic effects of SO_2.

STUDY	CONC.	DURATION	SPECIES	EFFECTS
Pulmonary Effects				
Gunnison et al. (1988)	0, 10, or 30 ppm (0, 26.2, or 78.6 mg/m^3) SO_2 (whole body) ± 1 mg B[a]P 0, 100 or 400 ppm W, or [400 ppm W + 40 ppm Mo] in a low-Mo diet, ± B[a]P (See Effects column) ± B[a]P	SO_2: 21 wk, 5 day/wk (minus holidays), 6 h/day High W, low Mo diet: 21 wk, 7 day/wk B[a]P: 15 wk, once per wk starting wk 4	Rat, Sprague- Dawley, male, 9 wk old, ~315- 340 g, N: 20-74/group	Purpose was to investigate arcinogenic/cocarcinogenic effects of SO_2 inhalation or dietary-induced high levels of systemic sulfite/bisulfite in conjunction with tracheal installation of B[a]P. High drinking water levels of W in conjunction with low-Mo feed induce sulfite oxidase deficiency in rats, and thus high systemic levels of sulfite and bisulfite (at 0, 100 or 400 ppm W, mean plasma sulfite was 0, 0 or 44 µM, while mean tracheal sulfite + bisulfite was 33, 69 or 550 nmol/g wet wt). Mortality in B[a]P groups (~50% after ~380-430 d) was due almost exclusively to SQCA of the respiratory tract; survival rate was excellent for other groups (~50% mortality after ~620-700 d). Results indicate no SQCA was induced in any of the SO_2 inhalation or systemic sulfite + bisulfite groups, nor were incidences in the B[a]P groups enhanced by such coexposures. This lack of cocarcinogenicity does not support the hypothesis that SO_2 exposure could elevate systemic sulfite/bisulfite, generating $GSSO_3H$, which would inhibit GST and reduce intracellular GSH, thus interfering with a major detoxication pathway for B[a]P and enhancing its carcinogenicity. Authors note that due to the high incidence of animals with tumors in the two B[a]P only groups (65/72 and 63/72), cocarcinogenicity of SO_2 or sulfite + bisulfite could only have been demonstrated by shortening of tumor induction time and/or increased rate of SQCA appearance—neither were observed.
Ohyama et al. (1999)	0, 0.2 mL C, or (0.2 mL DEP+C ± [4 ppm (10.48 mg/m^3) SO_2 or 6 ppm (11.28 mg/m^3) NO_2 or 4 ppm SO_2 + 6 ppm NO_2]; whole body [Note: 0.2 mL CBP = 1mg; 0.2 mL DEcCBP =1 mg CBP + 2.5 mg DEP)]	SO_2 and/or NO_2: 10 mo, 16 h/day CBP or DEcCBP: 4 wk, once/wk by intratracheal infusion	Rat, SPF F344/Jcl, male, 6 wk old, wt NR, N: 23-30 per group in 6 groups	Purpose was to study effects of DEP on rat lung tumorigenesis and possible tumor promoting effects of SO_2 or NO_2 singly or together. Alveolar hyperplasia and adenoma were significantly ($p < 0.01$-0.05) increased over controls in the CBP group, but not the DEcCBP group. This was ascribed to induction of alveolitis and AM infiltration (a tumor response specific to rat and of questionable relevance to humans) in the former group, but apparently prevented by DEP in the latter. Alveolar bronchiolization near small hyaline masses of deposited DEcCBP was observed in all DEcCBP groups, the masses presumably allowing long-term exposure to DEP extracts by contacted alveolar epithelium. DNA adducts were found only in the three gas-exposed groups. Discounting the CBA group, elevated alveolar hyperplasia was seen only in the DEcCBP + NO_2 group, and elevated incidences of alveolar adenoma in the DEcCBP + SO_2 and particularly the DEcCBP + NO_2 groups; neither effect was observed with coexposure to both gases—speculated by the authors to perhaps result from inhibition of the stronger NO_2 promotion by HSO_3^-. Thus, SO_2 appears to have weaker capacity than NO_2 for promoting tumor induction (and perhaps genotoxicity) by DEP extract, and may antagonize such effects by NO_2 during coexposure of the gases.
Ito et al. (1997)	0, C, or (25 mg SPM+C ± [4 ppm (10.48 mg/m^3) SO_2 or 6 ppm (11.28 mg/m^3) NO_2 or 4 ppm SO_2 + 6 ppm NO_2]); whole body	SO_2 and/or NO_2: 11 mo, 16 h/day C ± SPM: 4 wk, once/wk by intratracheal injection	Rat, SPF Fisher 344, male, 5 wk old, wt NR, N: 5 per group in 6 groups	Purpose was to study effects of Tokyo air SPM, with or without coexposure to SO_2 or NO_2 or their combination, on the development of proliferative lesions of PEC. PEC hyperplasia was significantly ($p < 05$) increased by exposure to SPM, but coexposure to either gas or their mixture was without additional effect. No PEC papillomas were observed in control groups, while a few were seen in the SPM groups, irrespective of gas coexposures. Thus, SO_2 demonstrated no tumor promotion or cocarcinogenic properties. [Study did not describe the nature of the carbon (C) used.]
Heinrich et al. (1989)	0 or [10 ppm (26.2 mg/m^3) SO_2 + 5 ppm (9.4 mg/m^3) NO_2] ± [3 or 6 mg/kg bw of DEN]; exposure to gases whole body	SO_2 + NO_2: 6, 10.5, 15, or 18 mo, 5 day/wk, 19 h/day DEN: once by s.c. injection, ~2 wk after the start of inhalation exposure	Hamster, Syrian golden, both sexes, 10 wk old, bw NR, N: 40/sex per each of 12 exposure groups	The principle focus of this large study was to examine whether two inhaled diesel-exhaust emission preparations (± particulates) could enhance the tumorigenesis of injected DEN. Ancillary aim was to see whether inhalation of the irritant SO_2 + NO_2 mixture could cause similar enhancement of DEN tumorigenicity. Gas mixture exposure did not affect bw gain, but slightly shortened survival times (although significantly only for females). Apart from effects attributed to DEN, serial sacrifices showed progressive increases in ciliated tracheal cell aberrations and in number of tracheal mucosal cells. the lung, gas mixture-related effects were limited to a progressing alveolar lesion involving lining with bronchiolar epithelium and the presence of some pigment- containing AM, and to a mild, diffuse thickening of the alveolar septa. SO_2 + NO_2 exposure did not by itself elevate tumor rate the upper respiratory tract, did it enhance increases induced by DEN. Thus the mixture appeared to have no tumor inducing or promoting effects.

STUDY	CONC.	DURATION	SPECIES	EFFECTS
Nonpulmonary Effects				
Klein et al. (1989)	0 or 6 ppm (0 or 15.72 mg/m^3) SO_2, ± 0.2 ppm (600 µg/m^3); whole body; NDMA	20 mo, 5 day/wk, 4 h/day	Rat, Sprague- Dawley, female, age and wt NR, N: 36 per group in 4 relevant groups	This is a preliminary report for observations after 20 mo (800 h inhalation in 200 exposures, with calculated inhaled cumulative doses of 77 mg SO_2 and 2-3 mg NDMA per rat). The effects of NDMA ± SO_2 inhalation were studied. Group mortality was as follows: control (3/36), SO_2 (5/36), NDMA (4/36), NDMA + SO_2 (7/36). The only tumors observed were nasal: control (0), SO_2 (0), NDMA (1), NDMA + SO_2 (3). No observable parameters, including body wt gain, were affected by the additional SO_2 exposure; assessment of tumor incidence effects could not yet be performed.

Table E-12. Respiratory system biochemistry effects of SO_2.

STUDY	CONC.	DURATION	SPECIES	EFFECTS
In Vitro Exposure				
Li et al. (2007)	0.1 µM-1mM $NaHSO_3$ and Na_2SO_3 1:3	4 h, followed by harvest at 0-24 h	BEP2D cell line of human bronchial epithelial cells	Increased mRNA and protein levels of MUC5AC and IL-13
Oxidation and Antioxidant Defenses – (Subacute/Subchronic Exposure)				
Meng et al. (2003b)	22, 56, or 112 mg/m^3 (8.4, 21, or 43 ppm); whole body	6 h per day for 7 days	Kunming albino mice, male and female, 5 wks old, 19 ± 2 g, N: 10/sex/group	Changes observed in lung tissue (concentrations of effect) included higher SOD activity in males (8.4 ppm) and females (8.4 and 21 ppm), lower SOD activity in males (21 and 43 ppm) and females (43 ppm), increased GPx activity in males and females (8.4 ppm), decreased GPx activity in males and females (≥ 21 ppm), decreased catalase activity in males (43 ppm), decreased reduced GSH level in males and females (≥ 8.4 ppm), increased TBARS level in males (≥ 8.4 ppm) and females ≥ 21 ppm). Authors concluded that sulfur dioxide induced oxidative damage in lungs of mice.
Wu and Meng (2003)	22, 64, or 148 mg/m^3 (8.4, 24.4, or 56.5 ppm); whole body	6 h/day for 7 days	Kunming-strain mice, male, age NR, 18-20 g, N: 10/ group	Glucose-6-phosphate dehydrogenase and GST activity were decreased in lung at 64 and 148 mg/m^3. Lung GSH levels were reduced in the 22 and 148 mg/m^3 exposure groups. Administration of buckthorn seed oil increased GST and decreased TBARS activity compared to mice exposed to 42 mg/m^3 SO_2 alone.
Langley-Evans et al. (1996)	5, 50, or 100 ppm (13.1, 131, or 262 mg/m^3); whole body	5 h/day for 7-28 days	Wistar rat, male, 7 wks old, weight NR, N: 4-5/treatment group, 8 controls	In the 5 and 100 ppm groups, GSH in BAL fluid decreased at 7 days and increased at 21 days; at 28 days GSH returned to normal in the 5 ppm group and further increased in the 100 ppm group. GSH was depleted in the lung, at 5 and 100 ppm but not at 50 ppm. With respect to GSH-related enzymes, exposure to 5 ppm lowered GCS, GPx, GST, and GRed activity in the lung. Effects in the 100 ppm group were similar to the 5 ppm group, except that lung GPx was not reduced. Exposure to 50 ppm did not affect lung GST, but reduced the number of inflammatory cells in circulation and decreased GCS, GPx, GRed, and GT in the lung. Authors concluded that sulfitolysis of glutathione disulphide occurs in vivo during SO_2 exposure and that SO_2 is a potent glutathione depleting agent, even in the absence of pulmonary injury.
Gümüşlü et al. (2001)	10 ppm (26.2 mg/m^3); whole body	1 h/day, 7 days/wk for 6 wks	Swiss albino rat, male, 3, 12, or 24 mos old, 210-450 g, N: 9-11/group in 6 groups	Effects of age on SO_2-induced oxidative effects in lung tissue were observed in young (3-mo-old), middle aged (12-mo-old), and old (24-mo old) rats. SO_2 exposure significantly elevated TBARS, SOD, GPx, and GST in all age groups; reduced catalase in young and middle-aged rats, but did not affect catalase in old rats. In rats not exposed to SO_2, SOD, GPx and GST increased with age and catalase decreased with age. General observations in SO_2-exposed animals were increases in SOD, GPx, and TBARS with age. The authors of the AQCD toxicology chapter noted that while lipid peroxidation increased with age, relative TBARS increases in response to SO_2 were inversely correlated with age (i.e., largest percent increase seen in young rats).

STUDY	CONC.	DURATION	SPECIES	EFFECTS
Langley-Evans et al. (1997; 2007)	286 mg/m^3 (~101 ppm by study author calculations); whole body Note: The study mistakenly listed units of µg/m^3 and it was verified with the authors that the units should have been listed as mg/m^3.	5 h/day for 28 days	Wistar rat, male, 7 wks old, weight NR, N: 4-16	This study explored the effects of maternal diet protein restriction during gestation on offspring lung enzyme responses after SO_2 exposure in adulthood. Adult offspring representing different maternal dietary concentrations of casein (180 [control], 120, 90 or 60 g/kg) were exposed either to air or SO_2. GSH levels in BAL fluid and the lung were not affected either by maternal diet or SO_2 exposure. In the lung GRed and GT were not affected by SO_2 in any maternal diet group; GPx was reduced only in the 120 g/kg maternal diet group; GCS was elevated in the 180 and 60 g/kg groups; and GST was reduced in the 180, 120 and 90 g/kg groups (to the level seen in both the air- and SO_2-exposed 60 g/kg maternal diet groups). This study does not provide information relevant to ambient exposures, but is being mentioned in this table to record that a low-concentration level study was not overlooked.
Differential Gene Expression - Subacute Exposure				
Qin and Meng (2005)	14, 28, or 56 mg/m^3 (5.35, 10.70, or 21.40 ppm); whole body	6 h/day for 7 days	Wistar Rat, male, age NR, 180-200 g, N: 6/group in 4 groups	Repeated acute exposure caused significant ($p < 0.001$-0.05) concentration-dependent reductions in enzyme activities and gene expression in the lung for both CYP1A1 and CP1A2. Effects were seen at the mid and high concentrations, but not the low. Authors speculate that underlying mechanisms may involve oxidative stress and/or cytokine release, and may represent an adaptive response to minimize cell damage.
Bai and Meng (2005a)	14, 28, or 56 mg/m^3 (5.35, 10.70, or 21.40 ppm); whole body	6 h/day for 7 days	Wistar rat, male, age NR, 180-200 g, N: 6/group in 4 groups	SO_2 exposure caused significant concentration-dependent changes in the mRNA (mid and high concentrations) and protein expression (all concentrations in lung, but statistical significance not indicated) of apoptosis-related genes: increases for *bax* and *p53* apoptosis-promoting genes, and decreases for the apoptosis-repressing gene *bcl-2*. Caspase-3 activity (occurring early in apoptosis process) was also increased at the mid and high concentration.

Table E-13. Respiratory system effects of SO_2 in disease models.

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

Table E-14. Effects of SO_2 layered on metallic or carbonaceous particles.

STUDY	SO_2	METAL	EFFECTS
Lam et al. (1982) 3 h exposure Hartley guinea pig, male, age not reported, 240-300 g, N: 7-16/group	~1 ppm (2.6 mg/m^3); whole body	Zinc oxide: 0.8, 2.7, or 6.0 mg/m^3 (0.05 µM projected area diameter, GSD 2.0) (sulfate, sulfite, and sulfur trioxide detected) 7.8 mg/m^3	Vital capacity: No effect with exposure to 7.8 mg/m^3 zinc oxide alone and 2.7 mg/m^3 zinc oxide in combination with SO_2, but decreased with exposure to 0.8 and 6.0 mg/m^3 zinc oxide in combination with SO_2. Total lung capacity: No effect with exposure to 7.8 mg/m^3 zinc oxide alone, but decreased with exposure to 6.0 mg/m^3 zinc oxide in combination with SO_2. Diffusion capacity for CO and ratio of diffusion capacity for CO to total lung capacity or alveolar volume: No effect with exposure to 7.8 mg/m^3 zinc oxide alone, but decreased with exposure to 2.7 and 6.0 mg/m^3 zinc oxide in combination with SO_2. Alveolar volume: No effect with exposure to 7.8 mg/m^3 zinc oxide alone, but decreased with exposure to 6.0 mg/m^3 zinc oxide in combination with SO_2.
Amdur et al. (1983) Hartley guinea pig, male, age not reported, 200-300 g, N: 8-23/group 1 h exposure	~1 ppm (2.6 mg/m^3); head only	Zinc oxide: ~1-2 (0.05 µM projected area diameter, GSD 2.0); mixed at 24 °C and 30% RH	Pulmonary functioN: SO_2 exposure alone resulted in an 11% increase in resistance and 12% decrease in compliance. Zinc oxide exposure alone resulted in a 9% decrease in compliance that persisted 1 h after exposure.
		~1-2; mixed at 24 °C and 30% RH	Pulmonary functioN: A 12% decrease in compliance and decreased tidal volume that persisted 1 h after exposure, and decreased min volume. There was no evidence of new compound formation. Authors concluded that effects on tidal volume and min volume mostly likely represented an additive effect.
		~1-2; mixed at 480 °C and 30% RH	Pulmonary functioN: A 12% decrease in compliance and decreased tidal volume that persisted 1 h after exposure and a 12% increase in resistance and decreased min volume. There was no evidence of new compound formation.
		~1-2; mixed at 480 °C and 80% RH with addition of water vapor downstream	Pulmonary functioN: A 13% decrease in compliance that persisted 1 h after exposure and a 29% increase in resistance. Sulfite formation was observed.
		~1-2; mixed at 480 °C and 30% RH with addition of water vapor during mixing.	Pulmonary functioN: A 19% increase in resistance that persisted 1 h after exposure, decreased tidal volume immediately after exposure, and a 26% decrease in compliance 1 h after exposure. Sulfate, sulfite, and sulfur trioxide formation was observed.
Chen et al. (1991) Hartley guinea pig, male, age not reported, 275-375 g; N: 8/group 1 h exposure	1.10-1.25 ppm (2.9-3.3 mg/m^3); head only	Copper oxide 1.16-2.70 (< 0.1 µM)	Pulmonary resistance: Increased 32-47% during exposure and at 1 and 2 h postexposure when SO_2 and copper oxide were mixed at 37 °C, a condition that resulted in formation of 0.36 µmol/m^3 sulfite on the copper oxide particles. No effect was observed with the compounds were mixed at 1411 °C, a condition that led to the formation of sulfate on the copper oxide particles. Dynamic lung compliance: No effect when mixed under conditions that led to the formation of either sulfate or sulfite on particles.
Chen et al. (1992) Hartley guinea pig, male, age not reported, 290-410 g, N: 6-9/group 1 h exposure	1.02 ppm 2.7 mg/m^3); head only	Zinc oxide (0.05 µM median diameter, GSD 2.0)	Baseline pulmonary resistance at 2 h following exposure: No effect in any group.
	0	2.76	Airway hyperresponsiveness to acetylcholine: No effect with exposure to SO_2 or zinc oxide alone; compared to furnace controls (3% argon). Hyperresponsiveness increased in both groups exposed to SO_2-layered zinc oxide particles.
	1.10 ppm (2.9 mg/m^3)	0.87	
	1.08 ppm (2.8 mg/m^3)	2.34	

STUDY	SO_2	METAL	EFFECTS
Jakab et al. (1996) Swiss mice, female, 5 wks old, 20-23 g, N: 5/group	10 ppm (26.2 mg/m^3); nose only	0	AM Fc-receptor mediated phagocytosis of sheep red blood cells at 3 days after exposure: Dose-dependent reductions in AM phagocytosis were observed at each concentration of SO_2 mixed with carbon black aerosol at 85% relative humidity, the only conditions under which SO_2 significantly chemisorbed to carbon black aerosol and oxidized to sulfate. AM phagocytic activity was reduced somewhat immediately after exposure (Day 0), was minimal on Days 1 and 3, began increasing on Day 7, and was fully recovered by Day 14. No effects were observed with exposure to SO_2 or carbon black alone. The data indicate that environmentally relevant respirable carbon particles can act as effective vectors for delivering toxic amounts of acid SO_4^{2-} to distal parts of the lung.
	0	Carbon black: 10 mg/m^3 (0.3 µM, GSD 2.7)	
	5 ppm (13.1 mg/m^3)	10 mg/m^3 (formed 6 µg sulfate at 85% humidity)	
	10 ppm (26.2 mg/m^3)	10 mg/m^3 (formed 13.7 µg sulfate at 85% humidity)	
	20 ppm (52.4 mg/m^3)	10 mg/m^3 (formed 48.7 µg sulfate at 85% humidity)	
Clarke et al. (2000) Outbred Swiss mouse, female, age and weight not specified, N: 10 or 12 per experimental value. 4 h exposure once or for 4, 5, or 6 days	10 ppm (26.2 mg/m^3); nose only	0	Inflammatory response after a single 4-h exposure: There was no effect on total cell number, lymphocyte/PMN differentials, or total protein levels in BAL fluid in any group.
	0	Carbon black: 10 mg/m^3 (10% humidity)	AM Fc-mediated phagocytosis after a single 4-h exposure: Suppressed by acid sulfate coated particles (at ~140 µg/m^3) at 1, 3, and 7 days postexposure; values returned to normal by Day 14.
	0	Carbon black: 10 mg/m^3 in 85% humidity to generate 8 µg/m^3 acid sulfate	Intrapulmonary bactericidal activity toward Staphylococcus aureus: Decreased by a single 4-h exposure to sulfate coated particles (at ~140 µg/m^3) at 1 and 3 days postexposure, with recovery by Day 7. Suppression was also observed after 5 and 6 days of repeated exposure to ~20 µg/m^3 sulfate coated particles a condition more relevant to potential ambient human exposures.
	10 ppm (26.2 mg/m^3)	Carbon black: 10 mg/m^3 in 10% humidity to generate 41 µg/m^3 acid sulfate	
	10 ppm (26.2 mg/m^3)	Carbon black: 10 mg/m^3 in 85% humidity to generate 137 µg/m^3 acid sulfate	
	1 ppm (2.62 mg/m^3)	Carbon black: 1 mg/m^3 in 85% humidity to generate 20 µg/m^3 acid sulfate	
Conner et al. (1985) Hartley guinea pig, male, age not reported, 250-320 g, N: 5-18/group/ time point 3 h/day for 6 days; Animals evaluated for up to 72 h following exposure	1 ppm (2.6 mg/m^3); nose only	Zinc oxide: 6 (0.05 µM projected area diameter, GSD 2.0)	Right lung to body weight ratio: No effect by SO_2. Increased for 48 h in group exposed to SO_2-layered zinc oxide. Right lung wet to dry weight ratio: No effect by SO_2. Increased at 1 h after exposure in SO_2-layered zinc oxide group. Lung morphology: No lesions observed in SO_2 group. In group exposed to SO_2-layered zinc oxide,as increased incidence of alveolar duct inflammation consisting of interstitial cellular infiltrate, increased numbers of macrophages, and replacement of squamous alveolar epithelium with cuboidal cells. Frequency and severity of lesions were greatest immediately following exposure and 72 h following exposure; lesions mild and infrequent. Tracheal secretory cell concentratioN: No effects with either exposure. Epithelial permeability: No effects with either exposure scenario. DNA synthesis (3H-tymidien uptake) terminal bronchial cells: Unaffected by SO_2. Increased at 24 and 72 h after exposure to zinc oxide/SO_2. Lung volumes: Unaffected by SO_2 exposure. Functional reserve capacity, vital capacity, and total lung capacity were decreased from 1 to 72 h following exposure to zinc oxide/SO_2. Diffusion capacity for carbon monoxide: Unaffected by SO_2 exposure. Decreased by ~40-50% from 1 to 24 h following zinc oxide/SO_2 exposure. Alveolar volume: Unaffected by SO_2 exposure. Decreased by ~10% from 1 to 24 h following exposure to zinc oxide/SO_2. Pulmonary mechanics: Respiratory frequency, tidal volume, pulmonary resistance, pulmonary compliance unaffected by either exposure. Author conclusioN: Changes were identical to those reported in a previous study in which guinea pigs were exposed to zinc oxide alone. Sulfur compounds deposited on surface are less important than zinc oxide particle.

STUDY	SO_2	METAL	EFFECTS
Amdur et al. (1988) Guinea pig, sex, age, weight not reported, N: 8-9 /group 3 h/day for 5 days	1 ppm (2.6 mg/m^3); head only	Zinc oxide: 1 or 2.5 (0.05 µM CMD, GSD 2.0) Sulfate was generated at 7 and 11 µg/m^3 at each respective dose; sulfuric acid level was reported at 21 and 33 µg/m^3 at each respective dose.	Pulmonary diffusing capacity: No effect with exposure to 1 ppm SO_2 or 2.5 mg/m^3 zinc oxide alone (data not shown by authors). Significant and dose related decreases on exposure days 4 and 5 at 7 µg/m^3 sulfate (20% less than control) and days 2-5 at 11 µg/m^3 sulfate (up to 40% less than control).
1 h exposure			Bronchial sensitivity to acetylcholine: No effect of 1 ppm SO_2 or 2.8 mg/m^3 zinc oxide alone. Increased with SO_2 administered in combination with either zinc oxide dose. The authors noted that responses were similar to those produced by 200 µg/m^3 sulfuric acid of similar particle size, thus indicating the importance of surface layer.
Shami et al. (1985) Fischer-344, male and female, 18-19 wks old, weight not reported, N: 2/sex/group at each evaluation time period 2 h/day for 4 days, followed by 2 days without exposure, followed by 5 more days of exposure; animals were evaluated for up to 28 days following exposure	5 ppm (13 mg/m^3); nose only	22 mg/m^3 gallium oxide (0.2 µM volume median diameter, GSD not reported), with and without addition of 7 mg/m^3 benzo(a)pyrene	Tracheal and large airways morphology: No effects observed with coexposure to gallium oxide and SO_2. Pulmonary morphology: Increase numbers of non-ciliated cells in terminal bronchial epithelium was observed in the SO_2/gallium oxide/benzo(a)pyrene group. Mild peribronchial and perivascular mononuclear inflammatory cell infiltrate and small hyperplastic epithelial cells in alveoli, and alveolar septal hypertrophy was observed in the SO_2/gallium oxide group, with and without benzo(a)pyrene exposure; effects were more prominent with benzo(a)pyrene exposure. Cell proliferation (^{3}H-thymidine intake) in trachea and large airways: In SO_2/ gallium oxide group: increased on days 1 and 14; basal cells primarily labeled. the SO_2/gallium oxide/benzo(a)pyrene group: increased on day 8. Cell proliferation (^{3}H-thymidine intake) in terminal bronchioles: In SO_2/gallium oxide group: increased on day 14; Clara cells primarily labeled. In the SO_2/gallium oxide/benzo(a)pyrene group: increased on day 11. Types of ^{3}H-thymidine-labeled cells in the alveolar regioN: In the SO_2/gallium oxide group: type II cells were primarily labeled in the alveolar region through 14 days of exposure. In the SO_2/gallium oxide/benzo(a)pyrene group: labeling was increased in Type II, Type I, and endothelial cells on day 8.
Wolff et al. (1989) F344/Crl rat, male and female, 10-11 wks old, weight not reported, n=6/sex/group 2 h/d, 5 d/wk, 4 wks	5 ppm (13 mg/m^3); nose only	Gallium oxide: 27 mg/m^3 (~0.20 µM MMD, GSD ~1.5-2), with and without 7.5 mg/m^3 of 1-nitropyrene and benzo[a]pyrene	Pulmonary particle clearance: No effect was observed with exposure to SO_2 alone; clearance was slowed only by gallium oxide, with or without coexposure to SO_2 or the other compounds; SO_2 in combination with the polyaromatic hydrocarbons had no effect on clearance rate. Authors concluded that toxicity was dominated by gallium oxide.

Table E-15. Effects of sulfite and mixtures of sulfite and sulfate.

STUDY	SULFITE	SULFATE	DURATION	SPECIES	EFFECTS
Acute					
Chen et al. (1983)	Sodium Sulfite 0.27-1.95 as SO_3^{2-}, submicron in size, oral breathing		1-h	Mixed breed rabbits, 6 mo, 2.5-2.7 kg, N: 8.	Clearance of tracer aerosol from bronchial tree: Accelerated clearance at > 1.2 mg/m^3 as SO_3^{2-}
Chen et al. (1987)	Sodium Sulfite 0.474-0.972 as SO_3^{2-}, submicron in size		1-h	Male Hartley guinea pigs, 200-400 g, N: 7-10	Pulmonary functioN: A 50% increase in airway resistance and a 19% decrease in compliance were observed at 0.972 mg/m^3. All concentrations resulted in decreased total lung capacity, vital capacity, functional residual capacity, residual volume, diffusion capacity for carbon monoxide and increased wet lung weights. The authors noted that the sulfur of both SO_2 and sulfite has a valence of IV and concluded that aerosols of S(IV) are 6x more potent than gaseous (IV) in terms of bronchoconstriction.

STUDY	SULFITE	SULFATE	DURATION	SPECIES	EFFECTS
Chronic					
Heyder et al. (1992) Maier et al. (1992) Kreyling et al. (1992) Schulz et al. (1992) Takenaka et al. (1992)	Neutral sulfite aerosol, 1.02 mg/m^3 with 0.31 mg/m^3 as S(IV) corresponding to 0.25 ppm SO_2; some contamination with particle-associated sulfur (VI) and gaseous sulfur (IV) i.e. SO_2; submicron in size		22.5 h/day for 290 days	Beagle dogs, male, N: 8	Lung mechanics: Decreased specific lung compliance Alveolar-capillary barrier: Increased permeability Macrophage-associated defenses: Decreased oxidative defense and phagocytic capacity. Increased lysosomal activity and intracellular particle dissolution Intrapulmonary particle transport: Increased transport to larynx Cell numbers in BAL fluid: Increased eosinophils and lymphocytes Oxidant status of extracellular proteins in BAL fluid: Decreased oxidant status Structural responses: Proliferative and inflammatory changes in nasal cavity; loss of cilia in larynx and trachea. Authors conclude that sulfite aerosols initial a mild histopathological response
Heyder et al. (1999) Maier et al. (1999) Kreyling et al. (1999) Schulz et al. (1999) Takenaka et al. (1999) Griese and Winzinger (1999)	Neutral sulfite aerosol, 1.53 mg/m^3 with 0.32 mg/m^3 as particle-associated S(IV), corresponding to 0.25 ppm SO_2; some minor contamination with particle-associated sulfur (VI) and gaseous sulfur (IV) i.e. SO_2; MMAD about a micron	Acidic sulfate aerosol, 5.66 mg/m^3, 15.2 $\mu mol/m^3$ hydrogen ion; MMAD about one micron	Sulfite: 16.5 h/day for 13 mo Sulfate: 6 h/day for 13 mo Exposures were sequential each day Authors state that this is equivalent to a dose received by a person living for 70 y in an urban environment	Beagle dogs, male, N: 8	Lung mechanics and airway reactivity to carbachol: No significant effects Alveolar-capillary barrier: No significant effects Macrophage-associated defenses: Decreased intracellular particle dissolution Intrapulmonary particle transport: Decreased transport to larynx; increased transport to tracheobronchial lymph nodes Cell numbers in BAL fluid/cell injury: No significant effects Antiproteolytic status: Increased elastase inhibitory capacity of BAL fluid Oxidant status of extracellular proteins: No significant effects Structural responses: Increase in volume density of bronchial glands. Proliferation of Type 2 cells in proximal alveolar region and thickening of the basal membrane beneath these cells. Increased volume density of alveolar ducts and alveolar sacs in acinus. Pulmonary surfactant system: No significant effects. Authors conclude that these responses were less pronounced than those in the previous study using sulfite alone.

Table E-16. Effects of mixtures containing SO_2 and ozone.

STUDY	SO_2	OZONE	DURATION	SPECIES	EFFECTS
Acute/Subacute Exposure					
Abraham et al. (1986)	3 ppm (7.9 mg/m^3); head only	0.3 ppm	5 h/day for 3 days	Sheep, sex NR, adult, 23-50 kg, N: 6	Tracheal mucus velocity: Decreased by 40% immediately after exposure and 25% at 24 h postexposure to the mixture of the 2 compounds. The effects of either compound alone were NR. Ciliary beat frequency: No effect
Chronic/Subchronic Exposure					
Aranyi et al. (1983)	13.2 mg/m^3 (5.0 ppm) in addition to 1.04 mg/m^3 ammonium sulfate; whole body	0.2 mg/m^3 (0.10 ppm)	5 h/day, 5 days/wk for up to 103 days	CD1 mice, female, 3-4 wks old, weight NR, N: 360/group total (14-154/group in each assay)	Mortality rate after Streptococcus aerosol challenge: Increased in groups exposed to ozone alone and mixture of ozone, SO_2, and ammonium sulfate. Alveolar macrophage bactericidal activity towards inhaled K. pneumoniae: Increased trend (non-significant) in ozone group but significantly increased in mixture group. Counts, viability, and ATP levels in cells obtained by pulmonary lavage: No effect of either treatment

STUDY	SO_2	OZONE	DURATION	SPECIES	EFFECTS
Raub et al. (1983)	1 ppm (2.62 mg/m^3); whole body	1 ppm in addition to 3 ppm trans-2-butene	23 h/day, 7 days/wk, for 4 wks	Golden hamster, male, age NR, ~105 g, **N:** 14 or 15/group; mild emphysema was induced in some animals by intratracheal administration of elastase	Lung volumes: End expiratory volume, residual volume, total lung capacity and vital capacity were unaffected in the mixture versus air exposure group in normal or emphysematous hamsters. Respiratory system compliance: Unaffected in the mixture versus air exposure group in normal or emphysematous hamsters. Distribution of ventilation (N2 washout slope): The N2 slope decreased in the mixture versus air exposure group in both normal and emphysematous hamsters. Diffusion capacity for carbon monoxide: Significantly increased in the mixture versus air-exposed normal animals. Although the text reported an increase in the mixture versus air-exposed emphysematous animals, Figure 3 of the study indicated that the effect was very small and did not obtain statistical significance. Significantly lower in emphysematous versus normal hamsters exposed to the mixture. The authors noted a significant interaction between exposure to the mixture and emphysema. Histopathology: Inflammatory lesions were found in the lungs of emphysematous hamsters exposed to air or the mixture. Hyperplasia incidence was higher in emphysema hamsters exposed to the mixture versus air. Inflammatory lesions were similar in emphysematous hamsters exposed to air or the mixture. Data were not shown for histopathology data. Overall author conclusio**N:** Animals with impaired lung function may have decreased capacity to compensate for the pulmonary insult caused by exposure to a complex pollutant mixture.

Table E-17. Effects of SO_2 and sulfate mixtures.

STUDY	SO_2	SULFATE	EFFECTS
Acute			
Mannix et al. (1982) Sprague Dawley rat, male, age NR, ~200 g, N: 8/group 4 h exposure	5 ppm (13.1 mg/m^3); nose only	Sulfate aerosol 1.5 (0.5 µM MMAD, GSD 1.6)	Lung clearance of radiolabeled tracer particles: No significant effect was observed with the mixture of the two compounds at 80-85% humidity.
Chronic/Subchronic			
Smith et al. (1989) Sprague-Dawley rat, male, young adult, initial weight NR, N: 12-15/data point Exposure: 5 h/day, 5 days/wk for 4 or 8 mos; half the animals in the 8-mo group were allowed to recover for 3 mos.	1 ppm (2.62 mg/m^3); whole body	0	Morphological observations at 4 mos exposure in "normal" rats: Bronchiolar epithelial hyperplasia and increased numbers of non-ciliated epithelial cells were observed in rats exposed to either compound alone but coexposure to both compounds did not magnify the effects. An increase in alveolar chord length was observed in the $(NH_4)_2SO_4$ group and no further changes were observed with coexposure to SO_2.
	0	$(NH_4)2SO4$: 0.5 mg/m^3 (MMAD = 0.42-0.44 ± 0.04 µm, GSD 2.2-2.6)	Morphological observations at 4 mos exposure in rats treated with elastase to induce an emphysema-like condition Bronchiolar epithelial hyperplasia was decreased in groups exposed to either compound alone or the mixture of the two compounds. A decrease in alveolar chord length was observed in the $(NH_4)_2SO_4$ group and no further changes were observed with coexposure to SO_2.

STUDY	SO_2	SULFATE	EFFECTS
	1 ppm (2.62 mg/m^3)	0.5 mg/m^3	Morphological observations at 8 mos exposure in "normal" rats: An increase in non-ciliated epithelial cells and alveolar birefringence (an indication of alveolar interstitial fibrosis) was observed only in the group exposed to $(NH_4)_2SO_4$. Morphological observations at 8 mos exposure in rats treated with elastase: An increase in lung volume per body weight and emphysema incidence was observed in groups treated with either compound alone or in combination; alveolar chord length was increased only in the group exposed to the mixture of compounds. Morphological observations at 12 mos exposure in normal rats: Increased alveolar chord length was observed only in the $(NH_4)_2SO_4$ group. Morphological observations at 12 mos exposure in rats treated with elastase: In increase in absolute lung volume was observed only in the group treated with the mixture of both compounds. Lung function effects at 4 mos exposure in normal rats: A decrease in residual volume was observed in the SO_2 group and decreased quasistatic compliance was observed in the SO_2 group and in the $(NH_4)_2SO_4$ group, but the effects were not observed with the mixture. Lung function effects at 4 mos exposure in elastase-treated rats: Ratio of residual volume/total lung capacity and N2 washout was decreased in the SO_2 group and in the $(NH_4)_2SO_4$ group, but the effects were not observed with the mixture. Overall conclusions: In general, pollutant effects were minimal and transient, and appeared obscured or repressed in elastase-treated groups; $(NH_4)_2SO_4$ was more bioactive than SO_2, with little evidence of mixture additivity (in several instances, effects seen with one or both pollutants individually were not seen with the mixture).

Table E-18. Effects of actual or simulated air pollution mixtures.

STUDY	EXPOSED	CONTROL	EFFECT
Acute/Subactute			
Mautz et al. (1988) Sprague-Dawley rat, male, age NR, 240-280 g, N: 6-9/group Exposure: 4 h	Air pollutant mixture at full concentration (tested in 2 studies): 0.35 ppm ozone, 1.3 ppm nitrogen dioxide, 2.5 ppm (6.6 mg/m^3) SO_2, 10 µg/m^3 manganese sulfate, 500 µg/m^3 ferric sulfate, 500 µg/m^3 ammonium sulfate, 500 µg/m^3 carbon aerosol. Mixture also tested ½ and ¼ concentrations. For aerosols: MMAD = 0.3-0.48 µM with GSD: 2.6-4.6. Nose-only exposure. Compounds formed: sulfate, nitrate, hydrogen ion, nitric acid.	Clean air	Breathing patterN: Effect of full concentration mixture in 2 studies: increased breathing frequency, trend or significant decrease in tidal volume, decreased or unaffected oxygen consumption, increased or unaffected ventilation equivalent for oxygen. Effect of half concentration mixture: increased min ventilation. Quarter concentratioN: no significant effects. Histopathology: Full concentratioN: Area of type 1 parenchymal lung lesions increased in 1 of 2 experiments; area of type 2 parenchymal lung lesions were increased in both experiments. Effects were equivalent to those observed with ozone exposure alone. Half and quarter concentrations: No effects. Mucociliary clearance: No effect on early or late clearance of ^{85}Kr-labeled polystyrene particles. Nasal epithelial injury (measured by tritiated thymidine uptake): No effect at any concentration.
Phalen and Kleinman (1987) Sprague-Dawley rat, male, age NR, 200-225 g, N: 5-13/group/ time period Exposure: 4 h/day for 7 or 21 days	2.55 ppm (6.7 mg/m^3) SO_2, 0.3 ppm ozone, 1.2 ppm nitrogen oxide, 150 µg/m^3 ferric oxide, 130 µg/m^3 nitric acid, 2.0 µM/m^3 hydrogen ion, and 500 µg/m^3 total Fe^{3+}, Mn^{2+}, and NH_4^{2+} combined; nose only	Purified air	Bronchoalveolar epithelial permeability to ^{99m}Tc-diethylenetriamine-pentaacetate: No effect at either time period.Nasal mucosal permeability to ^{99m}Tc-diethylenetriaminepentaacetate: No effect at either time period. Macrophage rosette formatioN: Decreased (indicating damage to F_c receptors) up to 4 days after 7- or 21-day exposure; magnitude of effect greater following 21-day exposure. By day 4 after exposure, numbers began increasing and by day 7 were equivalent to control values. Macrophage phagocytic activity: Rats exposed for 7 days, decreased activity observed for 2 days post-exposure. No effects after 21-day exposure.

STUDY	EXPOSED	CONTROL	EFFECT
Subchronic/Chronic			
Saldiva et al. (1992) Wistar rat, male, 2 mos old, weight NR, N: 14-30/group Exposure: 6 mos	Urban air: São Paulo, mean levels of air pollutants measured 200 m from the police station where rats were kept: 29.05 µg/m^3 (0.011 ppm) SO_2; 1.25 ppm carbon monoxide, 11.08 ppb ozone, 35.18 µg/m^3 particulates.	Rural air: Atibaia, an agricultural town 50 km from São Paulo was considered the control; air pollutant levels were not measured.	Death: 37 of 69 São Paulo rats died before study end; autopsy of 10 animals identified pneumonia; 10/56 Atibaia animals died. Respiratory mechanics: Nasal resistance higher in Atibaia animals. No differences for pulmonary resistance or dynamic lung elastance. Mucus properties: São Paulo animals' tracheal mucus output was lower, relative speed of tracheal mucus was slower, ratio between viscosity and elasticity was higher for nasal mucus, and rigidity of tracheal mucus was increased. Bronchoalveolar lavage: In lavage fluid from São Paulo animals, increased numbers of cells, lymphocytes, polymorphonuclear. Histochemical evaluatioN: Hyperplasia was observed in respiratory epithelium of rats housed in São Paulo. Ultrastructural studies: Animals housed in São Paulo had a higher frequency of cilia abnormalities including composite cilia, microtubular defect, vesiculation, and decreased microvelocity of luminal membrane.
Lemos et al. (1994) Rats from the same cohort as Saldiva et al. (1992). N: 15/group Exposure: 6 mos	Urban air: São Paulo, mean levels of pollutants measured 200 m from police station where rats were kept: 29.05 µg/m^3 (0.011 ppm) SO_2; 1.25 ppm carbon monoxide, 1.08 pb ozone, 35.18 µg/m^3 particulates.	Rural air: Atibaia, agricultural town 50 km from São Paulo, considered control; air pollutant levels not measured.	Nasal passage pathology: Rats housed in São Paulo had increased nasal epithelium volume, larger amounts of mucosubstances stored in epithelium, and more acidic mucus secretions in lamina propria glands.
Pereira et al. (1995) 4 groups of rats housed: 3 mos in São Paulo, 3 mos in São Paulo followed by 3 mos in Atibaia, 3 mos in Atibaia, or 6 mos at Atibaia. Wistar rats, male, 1.0-1.5 mos old, weight NR, N: 30/group	Urban air: São Paulo, levels of air pollutants measured were: ~8-50 µg/m^3 (0.003-0.019 ppm) SO_2, ~0.1-0.45 ppm nitrogen dioxide, ~4.8-7 ppm carbon monoxide, and ~50-120 µg/m^3 particulate matter.	Rural air: Atibaia, an agricultural town 50 km from São Paulo was considered the control; air pollutant levels were not measured.	Lung responsiveness to methacholine: Increased respiratory system elastance resulting from increased sensitivity to methacholine in rats housed in São Paulo for 3 mos compared to all the other groups. No exposure-related effects were observed for respiratory system resistance.

Table E-19. Effects of meteorological conditions on SO_2 effects.

STUDY	SO_2	CONDITION	EFFECT
Barthélemy et al. (1988) Rabbit, sex NR, adult, mean 2.0 kg, N: 5-10/group; animals were mechanically ventilated. Exposure: 45 min	0.5 or 5 ppm (1.31 or 13.1 mg/m^3); intratracheal	Drop in air temperature from 38 °C to 15 °C	Lung resistance: Exposure to cool air for 20 min resulted in a ~54% mean increase in lung resistance. Exposure to SO_2 for 20 min increased lung resistance by 16% at 0.5 ppm and 50% at 5 ppm. The difference in lung resistance from warm to cold air was halved (27%) by exposure to 0.5 ppm and was not significant at 5 ppm. The authors concluded that transient alteration in tracheobronchial wall following SO_2 exposure may have reduced accessibility of airway nervous receptors to cold air.
Hälinen et al. (2000a) Duncan-Hartley guinea pigs, male, age and weight NR, N: 7-12/group, mechanically ventilated; animals were hyperventilated during cold air and SO_2 exposure to simulate exercise. In pre-exposure period: 15-min exposure to warm humid air, 10-min exposure to cold dry air, and 15-min exposure to warm humid air. In the SO_2 exposure period: 10-min exposures to each SO_2 concentration in cold dry air or with cold dry air alone were preceded and followed by 15-min exposures to warm humid air.	1.0, 2.5, or 5 ppm (2.62, 6.55, or 13.1 mg/m^3); apparently intratracheal	Drop in intratracheal temperatures from ~35.5 °C to ~27 °C	Peak expiratory flow: Percent decreases were significantly greater with exposures to SO_2 in dry air at concentrations of 1.0 ppm (~32.7%) and 2.5 ppm (~35.6%) than with exposure to cold dry air (~27%); decrease at 5 ppm SO_2 in cold dry air (~25.3%) was similar to that with cold dry air. The effects did not persist following exposures. Tidal volume: Percent decreases were significantly greater with exposure to SO_2 in cold dry air at concentrations of 1.0 ppm (~22.4%) and 2.5 ppm (~28.3%) than with exposure to cold dry air (~18.1%); decrease at 5 ppm SO_2 in cold dry air (~17.8%) was similar to that of cold dry air. The effects did not persist following exposures. Bronchoalveolar lavage: The clean dry air group had significantly more macrophages, lymphocytes, and increased protein concentration in lavage than the warm humid air control. The cold dry air + SO_2 group had fewer macrophages than the clean dry air group and higher protein concentration than controls. Histopathology: Increased incidence of eosinophilic infiltration within and below tracheal epithelium with exposure to cold dry air or SO_2 in cold dry air.
Hälinen et al. (2000b) Duncan-Hartley guinea pigs, male, age and weight NR, N: 8-9/group, mechanically ventilated; animals were hyperventilated during cold air and SO_2 exposure to simulate exercise. Exposure: 60 min	1 ppm (2.62 mg/m^3); apparently intratracheal	Drop in intratracheal temperatures from ~37 °C to ~26 °C	Peak expiratory flow: Non-significant decreases compared to baseline (4.5-10.8%) at 10 and 20 min of exposure to cold dry air. With exposure to SO_2 in cold dry air: decreased significantly (11.4%, i.e., bronchoconstriction) compared to baseline at 10 min of exposure but recovered from 20 to 60 min of exposure. The effect with SO_2 exposure was not statistically significant compared to that of cold dry air alone. Tidal volume: Decreased from baseline throughout most of the exposure period with cold dry air or SO_2 in cold dry air; response with SO_2 was more shallow than that of cold dry air alone, but statistical significance compared to cold dry air was obtained only at 60 min of exposure. Bronchoalveolar lavage: Decreased neutrophil numbers in the SO_2 group compared to the warm humid air group but no significant difference compared to the cold dry air group. Histopathology: No effect in lung or tracheobronchial airway. General conclusions: Functional effects on the lower respiratory tract were weaker than in the previous study with 10-min exposures (Hälinen et al., 2000a).

Table E-20. In vitro or ex vivo respiratory system effects of SO_2 and metabolites.

STUDY	CONCENTRATION	DURATION	SPECIES	EFFECTS
In Vitro—Primary/Nonprimary				
Blanquart et al. (1995)	0, 5,10, 20, 30, or 50 ppm (0, 13.1, 26.2, 52.4, or 131 mg/m^3) SO_2	1-h	Fauve de Bourgogne rabbits, 1 mo old, tracheal epithelium explants	Relative to control cultures, cell viability was not reduced at 5 and 10 ppm, but was at 30 ppm (~70%) and 50 ppm (~60%). Ciliary beat frequency was significantly reduced ($p < 0.05$) at 10-30 ppm, and was correlated with swollen mitochondria and depletion of cellular ATP, as well as with blebbing of ciliated or microvilli-covered cells and with aggregation and flattening of cilia.
Menzel et al. (1986)	0, 0.1, 2, 20, or 40 mM (0, 4, 80, 800, or 1600 µg/mL) SO_3^{2-}	~1 min - 96 h	Rat, Sprague-Dawley, 200-250g; sex, age, and n NR; lung cells and liver cells. Human lung-derived cell line, A549	This study focused on intracellular covalent reactions of sulfite with primarily proteinaceous sulfhydryl compounds in cells isolated from rat lung and rat liver (for some comparative purposes), as well as in the human lung-derived cell line, A549. Sulfitolysis of protein disulfide bonds results in formation of cysteine S-sulfonate, and sulfitolysis of GSSG in formation of $GSSO_3H$. The latter was formed in dose-dependent fashion upon the addition of sulfite to A549 cells. In addition to fibronectin and albumin, this study identified a third sulfite-binding protein in rat lung cytosol. $GSSO_3H$ was shown to be a potent competitive inhibitor of GST in rat lung, liver and A549 cells. Results suggest that SO_2 could affect the detoxication of PAHs and other xenobiotics via formation of $GSSO_3H$ and subsequent inhibition of GST and enzymatic conjugation of GSH with reactive electrophiles.
Ex Vivo				
Riechelmann et al. (1995)	7.5, 15, 22.5, 30, or 37.5 mg/m^3 (2.9, 5.7, 8.6, 11.5, or 14.3 ppm); ex vivo expsoure of trachea	30 min	Guinea pig, sex, age, and weight NR, N: 4-8/group	No remarkable morphologic abnormalities in the tracheal mucociliary system of the 2.9 ppm group, though slight vacuolization, rare membrane blebs, and slightly widened intercellular spaces were observed. Abnormalities in the 5.7 and 8.6 ppm groups were similar and included loosened contact to the basal membrane, extensive intracellular edema and vacuolization, swollen mitochondria, polypoid extrusions and huge blebs in the cell membrane and ciliary membrane, widened intercellular space, and disrupted tight junctions. Additional abnormalities in the 11.5 and 14.3 ppm groups included marked epithelial sloughing, occasionally disrupted cell membranes and microtubules, and frequently disrupted ciliary membranes. Tracheal mucociliary activity was significantly decreased in all exposure groups (from 8.7 ± 1.0 Hz [controls] to 4.0 ± 1.1, 3.4 ± 2.7, 1.8 ± 2.2, 1.5 ± 1.8, and 2.0 ± 1.2 Hz in the 7.5, 15, 22.5, 30, and 37.5 mg/m^3 groups, respectively).
Knorst et al. (1994)	2.5, 5.0, 7.5, 10.0, or 12.5 ppm (6.6, 13.1, 19.7, 26.2, or 32.8 mg/m^3); ex vivo exposure of trachea	30 min	Guinea pig, sex, age, and weight NR, N: 4-7/group	63% decrease in tracheal mucociliary activity at 2.5 ppm with dose-dependent decrease to 81% at 7.5 ppm; higher concentrations did not further decrease mucociliary activity. Ciliary beat frequency decreased by 45% at 5.0 ppm with dose-dependent decrease to 72% at 12.5 ppm. All reductions are relative to baseline values; no effect on controls for either parameter.

Table E-21. Genotoxic effects of SO_2 and metabolites.

STUDY	CONCENTRATION	DURATION	SPECIES/SYSTEM	EFFECTS
In Vitro "Point Mutation"[1]				
Pool-Zobel et al. (1990)	0 or 50 ppm (131 mg/m^3) SO_2 or the equivalent agar concentration of SO_3^{2-}, 15 µg/ml)	48 h	Rat, Sprague-Dawley, female, liver enzyme preparations	In vitro induction of reverse mutation in cultures of S. typhimurium strain TA98 was not affected by incubating the bacterial-B[a]P-liver S9 enzyme activation system in the presence of SO_2/sulfite. An ancillary finding from the 0 µg B[a]P control exposures is that SO_2/sulfite itself did not appear mutagenic.
In Vitro Cytogenetic and DNA Damage[2]				
Pool et al. (1988)	0, 20, 50 or 200 ppm (0, 52.4, 131 or 524 mg/m^3) SO_2; 0, 0.1, 0.2 or 0.4 mM SO_3^{2-} 0 or 2.5 µmol HSO_3^- per microtiter plate well 0, 0.1, 0.2 or 0.4 mM SO_4^{2-} 0 or 10 µmol $MgSO_4$ per tube	1-24 h	Hamster, Syrian golden, fetal lung cells (FHLC, gestational Day 15) Rat, Sprague-Dawley, male, age NR, ~200g, hepatocytes Chinese hamster ovary cell line transformed by SV40, CO60 cells Precinorm U (human serum standard)	Toxicity and genotoxicity of SO_2, sulfite/bisulfite and sulfate (also NO_2/NO_x) were variously assessed in several in vitro test systems. It was noted that medium pH remained stable at [SO_2] ≤ 200 ppm. Precinorm LDH activity was substantially inhibited by 50 ppm SO_2 after 1-3-h, and by 0.1 mM sulfite ion almost immediately, but not by 0.1 mM sulfate ion; AST was modestly inhibited after 5 h by 200 ppm SO_2; other monitored enzymes were not affected. While trypan blue exclusion was not affected, SO_2 cytotoxicity to FHLC was demonstrated at 20 ppm by reduced plating efficiency; at 50 ppm, enzyme activity leaked into culture medium was reduced only for AP and especially LDH (not other enzymes). 200 ppm SO_2 did not induce DNA damage (single-strand breaks) by itself in either FHLC or rat hepatocytes, but did somewhat reduce that induced by AMMN. In hepatocytes, incubation with $MgSO_4$ also caused a small reduction in AMMN-induced DNA damage. A 1-h exposure to 200 ppm SO_2 did not induce selective amplification of SV40 DNA in CO60 cells, nor affect that induced by DMBA or B[a]P. However, while also not affecting induction by DMBA or B[a]P, HSO_3^- added directly to the medium for 24 h did induce SV40 DNA amplification on its own – authors appear to suggest this might result from arrest of cells in mid-S phase, which leads to DNA amplification. Thus, principal findings include inhibition of LDH by SO_2 or sulfite that could impair the cellular energy system; such an impairment could be responsible (possibly along with SO_4^{2-} conjugation of reactive intermediates) for the observed inhibition of AMMN-induced DNA damage by SO_2. Further, SO_2 does not appear by itself to induce DNA damage.
Shi and Mao (1994)	3 mM SO_3^{2-}	40 min (test tube reactions)	dG or DNA	Test tube reaction mixtures that caused sulfite to oxidize to sulfur trioxide radical (SO_3^-) resulted in the hydroxylation of dG (8-OHdG) and the generation of DNA double strand breaks.
Shi (1994)	5 mM SO_3^{2-} (as Na_2SO_3)	1.5 h (test tube reaction)	dG	Test tube reaction of sulfite ion with H_2O_2 shown to generate OH radicals capable of hydroxylating dG to the DNA damage marker, 8-OHdG. Furthermore, incubation of sulfite with nitrite or various transition metal ions was shown to generate sulfur trioxide anion radical (SO_3^-).
Acute/Subacute Exposure Cytogenetic and DNA Damage[2]				
Ruan et al. (2003)	0 mg/m^3 (0 ppm) SO_2 (+ 0 or 8 mg/kg bw SSO) or 28 mg/m^3 (10.7 ppm) SO_2 (+ 0, 2, 4, 6 or 8 mg/kg bw SSO); whole body	± SSO ip on Days 1-3; then SO_2 for 5 day (Days 4-8), 6 h/day	Kunming mouse, male and female, ~6 wk old, 20-25 g, **N:** 6/sex/conc.	Subacute inhalation of 28 mg/m^3 SO_2 induced a significant ($p < 0.001$) 10-fold increase in mouse bone marrow MNPCE, which was partially mitigated in dose-dependent fashion by pretreatment with SSO, a complex natural anti-oxidant substance. SO_2 exposure also resulted in organ:bw ratios that increased for liver and kidney, decreased for lung and spleen, and remained unchanged for heart. Such ratio changes were largely mitigated by SSO pretreatment.

STUDY	CONCENTRATION	DURATION	SPECIES/SYSTEM	EFFECTS
Meng et al. (2002)	0, 14, 28, 56, or 84 mg/m^3 (0, 5.35, 10.7, 21.4, or 32.1 ppm) SO_2; whole body	7 day, 4 h/day	Kunming mouse, male and female, ~6 wk old, 20-25 g, N: 10/sex/conc.	In vivo exposure caused significantly ($p < 0.01$-0.001) increased frequencies of bone marrow MNPCE similarly in both sexes at all concentrations in a dose-dependent manner, and with only minimal cytotoxicity at the 3 highest concentrations. The level of MNPCE (%) even at the low SO_2 conc. was triple that of the control value. Thus, subacute inhalation of SO_2 at noncytotoxic concentrations (though still notably higher than most human exposures) was clastogenic in mice.
Meng et al. (2005b)	0, 14, 28, 56, or 84 mg/m^3 (0, 5.35, 10.7, 21.4, or 32.1 ppm) SO_2; whole body	7 day, 6 h/day	Kunming mouse, male and female, ~5 wk old, 18-20 g, N: 6/sex/conc.	Following in vivo exposure to SO_2, it was shown by the single cell gel electrophoresis (comet) assay that such exposure induced significant ($p < .001$-.05) dose-dependent DNA damage (presumed mostly to be single-strand breaks and alkali-labile sites) in cells isolated from brain, lung, liver, intestine, kidney, spleen, and testicle, as well as in lymphocytes, and beginning at the lowest concentration (except male intestine—lowest response at 28 mg/m^3). Results demonstrate that SO_2, can cause systemic DNA damage in many organs, not just the lung. Authors note that potential occupational exposures and the fact that the obligate nose-breathing mouse removes ~95% of inhaled SO_2 in its nasal passages make this experimental concentration range relevant to possible human exposures.
Pool et al. (1988)	0 or 50 ppm (131 mg/m^3) SO_2	2 wk, 7 day/wk, 24 h/day	Rat, Sprague-Dawley, female, 4 mo old, wt NR, N: 5 per group	Assessments were conducted on isolated primary lung and liver cells, or on blood serum. In vivo SO_2 exposure did not affect viability (trypan blue exclusion) of cells either immediately after isolation or after 1 h incubation with 1% DMSO (used for enzyme leakage assays). In contrast to controls, hepatocytes from SO_2-exposed rats released no LDH activity into DMSO-medium after 1-h, and AST activity was reduced. Other enzyme (AP, ALT, GT) activity releases were not affected in lung cells, and none were in hepatocytes. In blood serum, the only effect was a marked increase in LDH activity. The only significant ($p < 0.001$-0.01) exposure effects on lung or liver activities (in x 9000 g supernatants of cell homogenates) of xenobiotic metabolizing enzymes (AHH, NDMA-D, GST) were elevated NDMA-D in the liver and reduced GST in the lung. Single-strand DNA breakage induced by three nitroso compounds (AMMN, NDMA, NMBzA) was reduced in hepatocytes from SO_2-exposed rats. Authors discuss possible mechanisms for the observed effects, and note they are similar to in vitro effects reported elsewhere (Pool et al., 1988).
Ohyama et al. (1999)	0, 0.2 mL C, or (0.2 mL DEP+C ± [4 ppm (10.48 mg/m^3) SO_2 or 6 ppm (11.28 mg/m^3) NO_2 or 4 ppm SO_2 + 6 ppm NO_2]); whole body [Note: 0.2 mL C = 1 mg; 0.2 mL DEcCBP = 1 mg C + 2.5 mg DEP)]	SO_2 and/or NO_2: 10 mo, 16 h/day C or DEP+C: 4 wk, once/wk by intratracheal infusion	Rat, SPF F344/Jcl, male, 6 wk old, wt NR, N: 23-30 per group in 6 groups	Purpose was to study effects of DEP on rat lung tumorigenesis and possible tumor promoting effects of SO_2 or NO_2 singly or together. [See Table C-11 for tumor-related effects.] DEP extract-DNA adducts were found only in the three gas-exposed groups. Chromatograms revealed two different adducts, one of which appears somewhat more abundant with SO_2 coexposure, the other substantially more so with NO_2; combined coexposure of both gases with DEP+C produced an adduct chromatogram appearing to be a composite of those for the individual gases. Thus, SO_2 and NO_2 appear capable of promoting the genotoxicity of DEP extract, though perhaps not in identical fashion.

[1]Encompasses classical mutant selection assays based upon growth conditions under which mutants (or prototrophic revertants), but not the wild type (or auxotrophic) population treated with the test agent, can successfully grow (e.g., "Ames test," CHO/HGRPT or mouse lymphoma L5178Y/TK mammalian cell systems, various yeast and Drosophila systems, etc.); while most viable mutation events detected in these assays are typically "point" mutations (DNA base substitutions, small deletions or frameshifts, etc.), some may involve larger losses/rearrangements of genetic material.

[2]Encompasses CA, induction of MN or SCE, aneuploidy/polyploidy, DNA adduct and crosslink formation, DNA strand breakage, etc.

Table E-22. Liver and gastrointestinal effects of SO_2.

STUDY	CONCENTRATION	DURATION	SPECIES	EFFECTS
Subacute/Subchronic Exposure				
Meng et al. (2003b)	22, 56, or 112 mg/m^3 (7.86, 20, or 40 ppm per author conversion); whole body	6 h/day for 7 days	Kunming albino mouse, male and female, 5 wks old, 19 ± 2 g, N: 6/sex/subgroup	Effects observed in stomach (concentration of effect) included: increase in SOD activity (7.86 ppm, males only) and TBARS level (≥ 7.86 ppm) and decreases in SOD (≥ 20 ppm, males only) and GPx activities (≥ 20 ppm, males only) and GSH level (40 ppm). Effects observed in intestine were increases in catalase activity (≥ 20 ppm in males, 40 ppm in females) and TBARS level (≥ 20 ppm) and decreases in SOD (≥ 7.86 ppm) and GPx (≥ 20 ppm) activities and GSH level (≥ 7.86 ppm).
Wu and Meng (2003)	22, 64, or 148 mg/m^3 (8.4, 24.4, or 56.5 ppm); whole body	6 h/day for 7 days	Kunming-strain mice, male, age NR, 18-20 g, N: 10/group	No effects were observed in the liver at 22 or 64 mg/m^3. GST and glucose-6-phosphate dehydrogenase activities and GSH level were decreased at 148 mg/m^3.
Bai and Meng (2005b)	14, 28, or 56 mg/m^3 (5.35, 10.70, or 21.40 ppm); whole body	6 h/day for 7 days	Wistar rat, male, age NR, 180-200 g, N: 6/group in 4 groups	Significant and concentration-dependent changes in mRNA (mid and high concentrations) and protein expreyssion (all concentrations) included increases for bax and p53 apoptosis-promoting genes, and decrease for bcl-2 apoptosis-repressing gene. Authors speculated potential impact on human apoptosis-deficient diseases.
Qin and Meng (2005)	14, 28, or 56 mg/m^3 (5.35, 10.70, or 21.40 ppm); whole body	6 h/day for 7 days	Wistar rat, male, age NR, 180-200 g, N: 6/group in 4 groups	SO_2 caused significant concentration-dependent reductions in liver enzyme activities and gene expression for CYP1A1 and CYP1A2. Effects were seen at the mid and high concentrations (only high for CYP1A1 enzyme activity), but not the low. Authors speculate that underlying mechanisms may involve oxidative stress and/or cytokine release, and may represent an adaptive response to minimize cell damage.
Lovati et al. (1996)	5 or 10 ppm (13.1 or 26.2 mg/m^3); whole body	24 h/day for 15 days	Sprague-Dawley CD rat, male, age NR, 250-275 g, N: 9/subgroup	Subjects were rats fed standard diet (normal) or high cholesterol diet, and rats with streptozotocin-induced diabetes fed standard diet. SO_2 (≥ 5 ppm) elevated plasma triglycerides in normal and hypercholesterolemic groups, while 10 ppm lowered plasma high density lipoprotein cholesterol in hypercholesterolemic rats. In diabetic rats, 10 ppm SO_2 lowered triglycerides and free fatty acids without affecting high density lipoprotein cholesterol or total cholesterol. In the liver, SO_2 elevated triglycerides in normal and hypercholesterolemic groups (at 10 ppm), but lowered it in diabetic rats (at ≥ 5 ppm); esterified cholesterol was elevated in normal rats (at 10 ppm), but lowered in diabetic rats (at ≥ 5ppm), and free cholesterol was unchanged in all groups. In normal rats, triglycerides secretion rate was inhibited by 10 ppm SO_2. SO_2 caused several changes in plasma apolipoprotein composition in normal and hypercholesterolemic groups, but not in diabetic rats. Leukotriene parameters were not affected. Thus, in each rat model, inhalation of SO_2 at levels without overt effects affected plasma and tissue lipid content. Specific effects varied according to diet or diabetes.
Langley-Evans et al. (1996)	5, 50, or 100 ppm (13.1, 131, or 262 mg/m^3); whole body	5 h/day for 7-28 days	Wistar rat, male, 7 wks old, weight NR, N: 4-5/treatment group, 8 controls	GSH was depleted in the liver at 5 and 100 ppm but not at 50 ppm. With respect to GSH-related enzymes, exposure to 5 ppm decreased GRed and GST activity in the liver. Exposure to 50 ppm did not affect liver GST, but decreased liver GRed and GPx.
Langley-Evans et al. (1997); Langley-Evans (2007)	286 mg/m^3 (100 ppm); whole body Units were incorrectly reported as µg/m^3 in the study but were corrected according to information provided by study author	5 h/day for 28 days	Wistar rat, male, 7 wks old, weight NR, N: 4-16	Adult rats exposed to air or SO_2 were born to dams fed diets with varying casein contents (180 [control], 120, 90 or 60 g/kg) during gestation. In the liver, SO_2 exposure elevated GSH level in the 120 g/kg dietary group but lowered it in the 60 g/kg dietary group. SO_2 did not affect liver GST in any group. SO_2 increased GCS levels in the 180 and 90 g/kg groups, GPx in the 60 g/kg group, and GRed in the 120 and 90 g/kg groups. This study provides information for an extremely high concentration level but is being acknowledged here with the unit corrected to verify that a low-concentration level study was not missed.

STUDY	CONCENTRATION	DURATION	SPECIES	EFFECTS
Gunnison et al. (1987)	10 or 30 ppm (26.2 or 78.6 mg/m^3); whole body	6 h/day, ~5 days/wk for 21 wks (total of 99 days)	Sprague-Dawley CD rat, male, 8 wks old, weight NR, N: 70/group in 3 groups (inhalation series)	No effects on relative liver weight or histopathology were found.
Ağar et al. (2000)	10 ppm (26.2 mg/m^3); whole body	1 h/day, 7 days/wk for 6 wks	Swiss Albino rat, male, 3 mos old, weight NR, N: 10/group	Effects were compared in non-diabetic rats, non-diabetic rats exposed to SO_2, alloxan-induced diabetic rats, and diabetic rats exposed to SO_2. SO_2 increased blood glucose in all groups, but did not affect total cholesterol, high density lipoprotein cholesterol, low density lipoprotein cholesterol, very low density lipoprotein cholesterol, or triglyceride levels in either normal or diabetic rats.
Küçükatay et al. (2003)	10 ppm (26.2 mg/m^3); whole body	1 h/day, 7 days/wk for 6 wks	Rat, male, 3 mos old, weight NR, N: 10/group in 4 groups	Effects compared in normal rats and rats with alloxan induced diabetes. Among the significant effects observed, SO_2 exposure enhanced the body weight loss seen in the diabetic group, but did not affect body weight gain in the control group. SO_2 elevated blood glucose levels in both controls and diabetics, but lowered triglycerides only in diabetics. Cholesterol parameters were not affected.

Table E-23. Renal effects of SO_2.

STUDY	CONCENTRATION	DURATION	SPECIES	EFFECTS
Wu and Meng (2003)	22, 64, or 148 mg/m^3 (8.4, 24.4, or 56.5 ppm)	6 h/day for 7 days	Kunming-strain mice, male, age NR, 18-20 g, N: 10/group	GST was decreased in the kidney at 64 and 148 mg/m^3 and glucose-6-phosphate dehydrogenase activity was decreased at 148 mg/m^3. Kidney GSH levels were reduced at all exposure levels.
Langley-Evans et al. (1996)	5, 50, or 100 ppm (13.1, 131, or 262 mg/m^3)	5 h/day for 7-28 days	Wistar rat, male, 7 wks old, weight NR, N: 4-5/ treatment group, 8 controls	GSH was depleted in the kidney in the 5 and 100 ppm groups but not in the 50 ppm group. No effects were observed for other GSH-related enzymes.

Table E-24. Lymphatic system effects of SO_2 and SO_2 mixtures.

STUDY	CONCENTRATION	DURATION	SPECIES	EFFECTS
Subchronic/Chronic Exposure				
Smith et al. (1989)	1 ppm (2.62 mg/m3); whole body	5 h/day, 5 days/wk for 4 mos.	Sprague- Dawley rat, male, young adult, initial weight NR, N: 12-15/ data point	No significant effects were reported for spleen weight or mitogen-induced activation of peripheral blood lymphocytes or spleen cells (data not shown by authors).
Aranyi et al. (1983)	13.2 mg/m^3 (5.0 ppm) SO_2 + 1.04 mg/m^3 ammonium sulfate + 0.2 mg/m^3 (0.10 ppm) ozone; whole body	5 h/day, 5 days/wk for up to 103 days	CD1 mice, female, 3-4 wks old, weight NR, N: 360/group total (14-154/group in each assay)	Cytostasis of MBL-2 leukemia target cells by peritoneal macrophage was increased in groups exposed to ozone alone or a mixture of the three compounds but was significantly higher with the mixture than with ozone alone at a macrophage:target cell ratio of 10:1; no significant effects were observed with macrophage:target cell ratio of 20:1. Reduction in splenic lymphocyte blastogenesis in response to phytohemagglutinin and concanavalin A occurred after exposure to ozone alone, but increased response occurred after exposure to the mixture; no response to alloantigen occurred after exposure to ozone alone but increased response occurred after exposure to mixture; there were no effects on S. typhosa lipopolysaccharide with either exposure scenario.

Annex F. Epidemiological Studies

Table F-1. Associations of short-term exposure to SO_2 with respiratory morbidity in field/panel studies.

STUDY	METHOD	POLLUTANTS	FINDINGS
UNITED STATES			
Delfino et al. (2003) Los Angeles, CA Nov 1999-Jan 2000	Panel study of 22 Hispanic children with asthma aged 10 to 16 yrs. Participants performed twice-daily PEF measurements and filled out symptom diaries. Analyses of symptoms conducted using GEE with exchangeable correlation. Linear mixed model used for PEF analyses. GEE models controlled for respiratory infections (data available for 20 subjects) and temperature.	Mean Levels:1-h max SO_2: 7.0 ppb (SD 4.0) IQR: 4.0 8-h max SO_2: 4.6 ppb (SD 3.0) IQR: 2.5 Copollutants: O_3 (r = −0.19) NO_2 (r = 0.89) CO (r = 0.69) PM_{10} (r = 0.73) EC (r = 0.87) OC (r = 0.83) VOCs	None of the VOCs or gaseous pollutants associated with PEF. Current-day, but not previous-day, SO_2 concentrations associated with symptom score > 1 and >2. OR for symptom score > 1 per IQR increase in SO_2: 1-h max SO_2: Lag 0: 1.31 (1.10, 1.55) Lag 1: 1.11 (0.91, 1.36) 8-h max SO_2: Lag 0: 1.23 (1.06, 1.41) Lag1: 1.11 (0.97, 1.28) OR for symptom score >2 per IQR increase: 1-h max SO_2: Lag 0: 1.37 (0.87, 2.18) Lag 1: 0.76 (0.35, 1.64) 8-h max SO_2: Lag 0: 1.36 (1.08, 1.71) Lag 1: 0.91 (0.51, 1.60)
Mortimer et al. (2002) Eight urban areas: St. Louis, MO; Chicago, IL; Detroit, MI; Cleveland, OH; Washington, DC; Baltimore, MD; East Harlem, NY; Bronx, NY Jun-Aug 1993	Panel study of 846 asthmatic children 4-9 yrs from the National Cooperative Inner-City Asthma Study (NCICAS). Study children either had physician-diagnosed asthma and symptoms in the past 12 mos or respiratory symptoms consistent with asthma that lasted more than 6 wks during the previous yr. Respiratory symptoms recorded in daily diary and included cough, chest tightness, and wheeze. Mixed effects models and GEE models used to evaluate the effect of air pollutants on PEF and respiratory symptoms. Models adjusted for day of study, previous 12-h mean temperature, urban area, diary number, rain in the past 24 h.	Mean Levels: 3-h avg SO_2 (8 a.m.-11 a.m.) for all 8 areas (shown in figure): 22 ppb Avg intradiary Range: 53 ppb Copollutants: O_3 (r = 0.29) NO_2 PM_{10}	None of pollutants associated with evening PEF or evening symptoms. Using single-pollutant model, SO_2 had little effect on morning PEF (data not shown). Significant associations between moving avg of 1- to 2-day lag of SO_2 and incidence of morning asthma symptoms. OR for morning symptoms associated with 20 ppb increase in 3-h avg SO_2 concentration (Lag 1-2 day): 8 urban areas: Single-pollutant model: 1.19 (1.06, 1.35) SO_2 with O_3 model: 1.18 (1.05, 1.33) 7 urban areas: Single-pollutant model: 1.22 (1.07, 1.40) SO_2 with O_3 and NO_2 model:1.19 (1.04, 1.37) 3 urban areas: Single-pollutant model: 1.32 (1.03, 1.70) SO_2 with O_3, NO_2, and PM_{10} model:1.23 (0.94, 1.62)
Neas et al. (1995) Uniontown, PA Summer 1990	Panel study of 83 fourth-fifth graders in Uniontown, Pennsylvania. Participants reported twice-daily PEF and presence of cold, cough, or wheeze. During summer of 1990, there were 3,582 child-days. PEF analyzed with autoregressive linear regression model that included a separate intercept for evening measure-ments, trend, temperature and 12-h avg air pollutant concentration, weighted by the number of hours child spent outdoors during the previous 12 h.	12-h avg SO_2: 10.2 ppb Max: 44.9; IQR: 11.1 Daytime 12-h avg SO_2 (8 am-8 pm): 14.5 ppb Overnight 12-h avg SO_2 (8 pm-8 am): 5.9 ppb Copollutants: PM_{10},$PM_{2.5}$,O_3 total sulfate particles particle-strong acidity (r = 0.44)	Incidence of new evening cough episodes significantly associated with the preceding daytime 12-h avg SO_2. Mean deviation in PEF not associated with SO_2. Effects associated with 10 ppb increase in 12-h avg SO_2: Change in mean deviation in PEF: −0.63 L/min (−1.33, 0.07) OR for evening cough: 1.19 (1.00, 1.42) Concentration weighted by proportion of hours spent outdoors during prior 12-h: Change in mean deviation in PEF: −1.25 L/min (−2.75, 0.25) OR for evening cough: 1.53 (1.07, 2.20)

STUDY	METHOD	POLLUTANTS	FINDINGS
Newhouse et al. (2004) Tulsa, OK Sep-Oct 2000	Panel study of 24 patients 9-64 yrs with physician-diagnosed asthma. Subjects performed twice-daily PEF (morning and evening) measurements, and recorded medications, symptoms. Simple linear regression, forward stepwise multiple regression, correlation analysis performed. Multiple regression analyses used to develop predictive models for other environmental factors. Analyses produced complex models with different predictor variables for each symptom.	Mean Levels: 24-h avg SO_2: 0.01 ppm Range: 0.00, 0.02 Copollutants: $PM_{2.5}$ CO O_3 pollen fungal spores	Of the atmospheric pollutants, avg and max O_3 were most significant factors that influenced symptoms. Quantitative results not provided for SO_2. Avg or max SO_2 found to be negative predictors of asthma in subgroup analyses of women and nonsmokers and rhinitis in all patients. Avg SO_2 also negative predictor of evening PEF. Quantitatively useful effect estimates not provided.
Ross et al. (2002) East Moline, IL May-Oct 1994	Panel study of 59 asthmatics 5-49 yrs. Analysis based on 40 subjects, due to withdrawal or failure to provide requested health data. Study assessed the effect of single and combined exposures to air pollutants and airborne allergens on PEF, symptom scores and medication use frequency. Multivariate linear-regression models with 1st order autoregression used for analysis of daily means of mean –standardized PEF, symptom scores and asthma medication use; logistic regression used for dichotomized data for symptom score and medication use, log-linear models for log-transformed symptom scores and medication use frequency.	24-h avg SO_2: 3.4 ppb (SD 3.1) Median: 2.8 IQR: 2.4 Range: 0, 27.3 Copollutants: PM_{10} O_3 NO_2 pollen fungi	No associations observed with SO_2. No effect estimates provided.
Schildcrout et al. (2006) Albuquerque, NM; Baltimore MD; Boston MA; Denver, CO; San Diego, CA; Seattle, WA; St. Louis, MO; Toronto, Ontario, Canada Nov 1993-Sept 1995	Meta-analysis of 8 panel studies with 990 children of the Childhood Asthma Management Program (CAMP), during the 22-mo prerandomization phase to investigate effects of criteria pollutants on asthma exacerbations (daily symptoms and use of rescue inhalers). Poisson regression and logistic regression models used in analyses. Within city models controlled for day of wk, ethnicity, annual family income, flexible functions of age and log-transformed sensitivity to the methacholine challenge using natural splines with knots fixed at 25th, 50th, and 75th percentiles. Also controlled for confounding due to seasonal factors. All city-specific estimates included in calculations of study-wide effects except Albuquerque where SO2 data were not collected.	24-h avg SO_2: Median (10th, 25th, 75th, 90th percentile): Albuquerque: NA Baltimore: 6.7 ppb (3.2, 4.7, 9.8, 14.2) Boston: 5.8 ppb (2.7, 3.7, 9.1, 14.1) Denver: 4.4 ppb (1.2, 2.5, 6.7, 9.5) San Diego: 2.2 ppb (1.2, 1.7, 3.1, 4.4) Seattle: 6.0 ppb (3.7, 4.7, 7.5, 9.5) St. Louis: 7.4 ppb (3.9, 5.3, 10.7, 13.6) Toronto: 2.5 ppb (0.2, 1.0, 4.8, 8.8) Copollutants: O_3 ($-0.03 \le r \le 0.44$) NO_2 ($0.23 \le r \le 0.68$) PM_{10} ($0.31 \le r \le 0.65$) CO ($0.19 \le r \le 0.67$)	All SO_2 Lags positively related to increased risk of asthma symptoms, but only the 3-day moving avg was statistically significant. Stronger associations observed for CO and NO_2. Data analyzed using 2-pollutant models based on the sum of the 2 within-subject pollutant effects, which were intended to provide insight into the increased risk of asthma symptoms associated with simultaneous shift in 2-pollutants. In 2-pollutant models with CO, NO_2, and PM_{10}, the SO_2 effect estimates remained robust. SO_2 not associated with rescue inhaler use rates. OR for daily symptoms associated with 10 ppb increase in within-subject 24-h avg SO_2 concentration: Lag 0: 1.06 (0.99, 1.13); Lag 1: 1.05 (0.95, 1.16) Lag 2: 1.06 (0.99, 1.12); 3-day moving sum : 1.04 (1.00, 1.08) Rate ratio for number of rescue inhaler used associated with 10 ppb increase within-subject concentration of SO_2 Lag 0: 1.01 (0.97, 1.06) Lag 1: 1.01 (0.97, 1.06) Lag 2: 1.04 (0.99, 1.09) 3-day moving sum: 1.02 (0.99, 1.05) Results for 2-pollutant models shown in figure.

STUDY	METHOD	POLLUTANTS	FINDINGS
Schwartz et al. (1994) Watertown, MA (Apr-Aug 1985); Kingston-Harriman, TN (Apr-Aug 1986); St. Louis, MO; (Apr-Aug 1986); Steubenville, OH; (Apr-Aug 1987); Portage, WI; (Apr-Aug 1987); Topeka, KS (Apr-Aug 1988)	Longitudinal study of 1,844 children in grades 2-5 from the Six Cities Study to examine the effects of PM and SO_x on respiratory health. Daily diaries completed by parents, recording symptoms, such as cough, chest pain, phlegm, wheeze, sore throat, and fever. Logistic regression models adjusting for aurocorrelation were used for the analysis. To examine possible non-linearity in the relationship, smooth functions of the air pollution variables were fit using GAM and the significance of the deviation from linearity was tested.	24-h mean SO_2: Median: 4.1 ppb IQR: 1.4, 8.2 Max: 81.9 Copolllutants: O_3 (r = −0.09) NO_2 (r = 0.51) PM_{10} (r = 0.53) $PM_{2.5}$ (r = 0.55) $PM_{2.5}$ sulfur (r = 0.50) H^+ (r = 0.23)	SO_2 associated with incidence of cough and lower respiratory symptoms. Local smooth showed increased cough incidence for only above a 4-day avg of 20 ppb (less than 5% of data). Test for nonlinearity was significant (p = 0.002). No increase in incidence of lower respiratory symptoms was seen until 24-h avg SO_2 concentrations exceeded 22 ppb. ORs for cough and lower respiratory symptoms related to were substantially reduced after adjustment for PM_{10}, suggesting the SO_2 associations might be confounded by particles. OR for cough incidence associated with 10 ppb increase in 4-day avg SO_2 concentration: Single-pollutant model: 1.15 (1.02, 1.31) SO_2 with PM_{10} model: 1.08 (0.93, 1.25) SO_2 with O_3 model: 1.15 (1.01, 1.31) SO_2 with NO_2 model: 1.09 (0.94, 1.30) OR for lower respiratory symptoms associated with 10 ppb increase in 24-h avg SO_2 concentration: Single-pollutant model: 1.28 (1.13, 1.46) SO_2 with PM_{10} model: Not presented. Stated as not statistically significant.
EUROPE			
Boezen et al. (1998) Amsterdam and Meppel, the Netherlands winter of 1993-1994	Panel study of 189 adults (48-73 yrs) w/ and w/out chronic respiratory symptoms in urban and rural areas to investigate whether bronchial hyperresponsiveness and PEF variability can be used to identify subjects who are susceptible to air pollution. Spirometry and methacholine challenge were performed and subjects with a fall in FEV_1 of 20% or greater were considered BHR. Subjects performed twice-daily peak flow for 3 mos. A subject's basal PEF variability calculated over an 8-day period with low air pollution. PEF variability expressed as (highest PEF-lowest PEF/mean) or amplitude % mean PEF. After calculation of daily PEF variability, number of days where the amplitude % mean was greater than 5% was determined. This resulted in 2 groups of subjects; those with ampli%mean PEF of 5% or less every day in the 8-day period, and those with an Amplitude % mean PEF greater than 5% on at least 1 day. Effects of air pollutants on prevalence of symptoms assessed with logistic regression models that adjusted for autocorrelation of the residuals, daily min temp, time trend and weekends/holidays.	24-h avg SO_2 Urban Mean: 11.8 µg/m^3 Range: 2.7, 33.5 Rural Mean: 8.2 Range: 0.8, 41.5 Copollutants: PM_{10} BS NO_2	No association between SO2 and respiratory symptoms in subjects with no BHR, BHR at < 2.0 mg of methacholine or BHR at 2 cumulative dose < cum 1.0 mg methacholine. In subjects with ampli% mean PEF > 5% and those with ampli%mean PEF > 5% for > 33% of days, SO2 was associated with the prevalence of phlegm. Odds ratio (per 40 µg/m3 SO_2) Subjects with no BHR URS: 0.86 (0.73, 1.03) LRS: 1.15 (0.90, 1.46) Cough: 1.01 (0.84, 1.21) Phlegm: 1.01 (0.86, 1.20) BHR at cum 2.0 Methacholine: URS: 1.11 (0.78, 1.56). LRS: 1.03 (0.72, 1.47) Cough: 0.89 (0.66, 1.19). Phlegm: 1.03 (0.78, 1.37) BHR at 1.0 Methacholine URS: 1.02 (0.65, 1.61). LRS: 0.96 (0.63, 1.47) Cough: 0.96 (0.64, 1.44). Phlegm: 1.00 (0.68, 1.46) Ampl%mean PEF 5% URS: 0.82 (0.62, 1.08). LRS: 1.38 (0.93, 2.03) Cough: 0.72 (0.52, 0.98). Phlegm: 0.79 (0.59, 1.05) Ampl%mean PEF > 5% URS: 1.04 (0.88, 1.23). LRS: 1.14 (0.96, 1.36) Cough: 1.07 (0.90, 1.26). Phlegm: 1.23 (1.05, 1.43) Ampl%mean PEF > 5%, >33% of days URS: 1.10 (0.85, 1.41). LRS: 1.14 (0.91, 1.42) Cough: 1.14 (0.89, 1.47). Phlegm: 1.36 (1.14, 1.63)

STUDY	METHOD	POLLUTANTS	FINDINGS
Boezen et al. (1999) Bodegraven, Meppel, Nuspeet, Rotterdam, Amsterdam, The Netherlands 3 winters of 1992-95	Panel study of 632 children (7 to 11 yrs) living in rural and urban areas of the Netherlands, to investigate whether children with bronchial hyperresponsiveness (BHR) and relatively high serum concentrations of total IgE were susceptible to air pollution. Methacholine challenge performed to determine bronchial hyperresponsiveness. Serum total IgE higher than the median (60kU/L) were defined as relatively high. Peak flow was measured twice daily and lower and upper respiratory symptoms were recorded daily for 3 mos. Association between symptoms and air pollutants assessed using logistic regression that adjusted for daily min temp, linear, quadratic and cubic time trend and weekends and holidays, and incidence of influenza. Examined 0, 1, 2 Lags and 5 day mean of air pollutants.	1992-9: Urban areas- Mean: 22.5 $\mu g/m^3$, Range: (1.4, 61.3) Rural areas- Mean: 9.8 Range: (1.3, 34.2) 1993-4: Urban areas- Mean: 11.8, Range: (2.7, 33.5) Rural areas- Mean: 8.2, Range: (0.8, 41.5) 1994-5: Urban areas- Mean: 8.3, Range: (0.6, 24.4); Rural areas- Mean: 4.3, Range: (0.5,17.0) Copollutants: PM_{10} Black smoke NO_2	459 children had complete data. For children with BHR and relatively high serum total IgE, the prevalence of LRS was associated with increases in PM_{10}, BS, SO_2, and NO_2. In the group with no BHR and relatively low IgE, and the group with BHR and low IgE, there was no consistent association between air pollutants with symptoms or decreased PEF. In children with no BHR but relatively high serum total IgE, there was a 28% to 149% increase in the prevalence of LRS per 40 $\mu g/m^3$ SO_2. Odds ratio (per 40 $\mu g/m^3$ SO_2) Children with BHR and relatively high IgE (N: 121) LRS Lag 0: 1.45 (1.13, 1.85). Lag 1: 1.41 (1.09, 1.82) Lag 2: 1.40 (1.10, 1.79). 5-day Mean: 2.25 (1.42, 3.55) URS Lag 0: 1.17 (0.99, 1.38). Lag 1: 1.06 (0.90, 1.25) >10% morning PEF decrease Lag 0: 1.09 (0.89, 1.34). Lag 1: 1.00 (0.81, 1.23) >10% evening PEF decrease Lag 0: 1.06 0.86, 1.30). Lag 1: 0.83 (0.68, 1.02) NO BHR and low IgE (N: 167) LRS Lag 0: 1.12 (0.76, 1.66). Lag 1: 0.61 (0.39, 0.94) URS Lag 0: 1.01 (0.89, 1.13). Lag 1: 1.08 (0.96, 1.22) >10 morning PEF decrease Lag 0: 1.02 (0.89, 1.16). Lag 1: 1.00 (0.87, 1.15) >10% evening PEF decrease Lag 0: 1.10 (0.97, 1.25). Lag 1: 1.06 (0.93, 1.21) With BHR and low IgE (N: 67) LRS Lag 0: 0.72 (0.41, 1.28). Lag 1: 1.03 (0.56, 1.91) URS Lag 0: 0.82 (0.62, 1.09). Lag 1: 0.84 (0.64, 1.12) >10% morning PEF decrease Lag 0: 0.74 (0.51, 1.07). Lag 1: 0.96 (0.67, 1.37) >10% evening PEF decrease Lag 0: 1.23 (0.88, 1.73). Lag 1: 1.32 (0.96, 1.82) With BHR and low IgE (N: 67) LRS. Lag 0: 0.72 (0.41, 1.28). Lag 1: 1.03 (0.56, 1.91) URS Lag 0: 0.82 (0.62, 1.09). Lag 1: 0.84 (0.64, 1.12) >10% morning PEF decrease Lag 0: 0.74 (0.51, 1.07). Lag 1: 0.96 (0.67, 1.37) >10% evening PEF decrease Lag 0: 1.23 (0.88, 1.73). Lag 1: 1.32 (0.96, 1.82) No BHR and high IgE (N: 104) LRS Lag 0: 1.44 (1.17,1.77). Lag 1: 1.28 (1.00, 1.64) Lag 2: (1.38 (1.08, 1.77). 5-day Mean: 2.49 (1.54, 4.04) URS Lag 0: 0.98 (0.84, 1.14). Lag 1: 1.01 0.87, 1.18) >10% morning PEF decrease Lag 0: 0.92 (0.79, 1.08). Lag 1: 1.03 (0.89, 1.21) >10% evening PEF decrease Lag 0: 1.00 (0.85, 1.17) . Lag 1: 1.05 (0.90, 1.23)

STUDY	METHOD	POLLUTANTS	FINDINGS
Boezen et al. (2005) Meppel, Nunspeet, Amsterdam, The Netherlands two winters 1993-1995	Panel study of 327 elderly patients (50 to 70 yrs) to determine susceptibility to air pollution by airway hyperresponsiveness (AHR), high total immunoglobulin (IgE), and sex. Methacholine challenges were performed and subjects with greater than or equal to 20% fall in FEV_1 after inhalation of up to 2.0 mg methacholine were considered AHR+. Subjects with total serum IgE > 20 kU/L were defined as high total IgE (IgE+). Twice daily PEF measurements and daily symptoms recorded for 3 mos. Data analysis performed using logistic regression with modeling of first-order autocorrelation in the residuals that adjusted for daily min temperature, time trend, weekend/holidays and influenza incident for the rural and urban areas and the two winters separately. Subjects were classified as IgE+ AHR+, IgE+ AHR−, IgE− AHR+ or IgE− AHR+. Examined effects of pollutants on the same day, Lag 1, Lag 2 and the 5-day mean concentration of Lag 0 to Lag 4 preceding that day. Groups that had effect estimates for PM_{10}, BS, SO_2, and NO_2 that were outside the 95% CI of the effect estimates for the AHR−/IgE− (control group) were considered to have increased susceptibility to air pollution.	24-h mean SO_2 ($\mu g/m^3$) in winter Winter 1993/1994 Urban: Mean: 11.8 $\mu g/m^3$ MediaN: 10.2 Range: 2.7, 33.5 Rural: Mean: 8.2 MediaN: 4.4 Range: 0.8, 41.5 Winter 1994/1995 Urban: Mean: 8.3 MediaN: 7.4 Range: 0.6, 24.4 Rural: Mean: 4.3 MediaN: .7 Range: 0.5, 17.0 Copollutants: PM_{10} BS NO_2	No consistent associations between the prevalence of LRS or >10% fall in evening PEF and air pollution in any of the four groups. In the AHR+/IgE group, the prevalence of URS was associated with SO2 at 1 day Lag, and the prevalence of >10% fall in morning PEF with SO_2 at Lag 1, Lag 2 and 5-day mean (avg of Lag 0 to Lag 4). For females who were AHR+/IgE+, the prevalence of >10% fall in PEF was associated with SO2 Lag 1, Lag 2 and 5-day mean. In subjects with AHR/IgE+ the prevalence of URS was associated with SO2 the previous day and the mean of Lag 0 to Lag 4. The effect estimate was outside the 95% CI of the estimate for the control group AHR/IgE. No consistent positive associations found between prevalences of URS, cough or >10% fall in morning PEF and air pollutants in subjects with AHR+/IgE or AHR/IgE. Based on results of the study, authors conclude that subjects with AHR+/IgE+ were the most responsive to air pollution. Odds ratio (per 10 µg/m3 SO_2). AHR/IgE URS Lag 0: 0.99 (0.93, 1.05). Lag 1: 1.02 (0.97, 1.08)fh Cough: Lag 0: 1.03 (0.98, 1.08). Lag 1: 0.97 (0.93, 1.02) >10% fall in morning PEF. Lag 1: 1.00 (0.92, 1.08) AHR/IgE+ URS Lag 0: 0.98 (0.92, 1.03). Lag 1: 1.07 (1.01, 1.12) 5-day mean 1.15 (1.02, 1.29), OR outside 95% CI of control group Cough: Lag 0: 1.01 (0.95, 1.07). Lag 1: 1.02 (0.96, 1.08) >10 % fall in morning PEF. Lag 1: 1.00 (0.92, 1.08) AHR+/IgE Lag 0: 1.05 (0.94, 1.17). Lag 1: 1.07 (0.96, 1.19) Cough: Lag 0: 1.03 (0.95, 1.12). Lag 1: 1.01 (0.93, 1.09) >10 % fall in morning PEF. Lag 1: 0.99 (0.87, 1.12) 5-day Mean: 0.78 (0.61, 0.98), OR outside 95% CI of control group AHR+/IgE+ Lag 0: 1.06 (0.97, 1.15). Lag 1: 1.13 (1.05, 1.23) Cough: Lag 0: 1.02 (0.94, 1.11). Lag 1: 1.02 (0.94, 1.10) >10 % fall in morning PEF. Lag 1: 0.99 (0.87, 1.12) AHR+/IgE+ URS. Lag 0: 1.06 (0.97, 1.15). Lag 1: 1.13 (1.05, 1.23), OR outside 95% CI of control group Cough: Lag 0: 1.02 (0.94, 1.11). Lag 1: 1.02 (0.94, 1.10) >10 % fall in morning PEF. Lag 1: 1.15 (1.04, 1.27), OR outside 95% CI of control group Lag 2 : 1.18 (1.07, 1.30), OR outside 95% CI of control group 5-day mean : 1.26 (1.07, 1.49), OR outside 95% CI of control group
Cuijpers et al. (1994) Maastricht, the Netherlands Nov-Dec 1990 (baseline) Aug 8-16 (smog episode)	The effects of exposure to summer smog on respiratory health were studied in 535 children (age unspecified). During a smog episode, 212 children were randomly chosen to be reexamined for lung function and symptomsOnly 112 of the had adequately completed summer questionnaires and were used for the symptom analysis. Lung function measurements made with forced oscillation technique were available for 212 children and valid spirometry was available for 208 children. Corrected baseline lung function compared using paired t test and difference in the prevalence in symptoms during baseline and episode compared.	24-h avg SO_2 Baseline 55 $\mu g/m^3$ Summer episode 23 $\mu g/m^3$ NO_2 BS O_3 PM_{10} Acid aerosol H^+	Small decrements in FEV_1 and FEF_{25-75} found in the 212 children during the episode compared to baseline. However, there was also a significant decrease in resistance parameters. No increases observed in the prevalence of acute respiratory symptoms. Change in lung function and impedance between baseline and smog episode: FEV_1: −0.032 L (SD 0.226), p < = 0.05 FEF_{25-75}: −0.086 L/s (SD 0.415), p < = 0.01 Resistance at 8 Hz: −0.47 cm H_2O (L/s) (SD 1.17), p < = 0.05

STUDY	METHOD	POLLUTANTS	FINDINGS
Desqueyroux et al. (2002) Paris, France Nov 1995-Nov 1996	Panel study of 60 patients with moderate to severe physician-diagnosed asthma (mean age 55 yrs). Asthma were noted by physician at each consultation (regular or emergency). Attacks defined as need to increase twofold the dose of beta2 agonist.	24-h avg SO_2 Summer 7 (5) µg/m^3 Range: 2, 27 Winter 19 (12) µg/m^3 Range: 3, 81 PM_{10}, NO_2, O_3	No association between asthma attacks and SO_2 for any Lag or season. Mean 24-h SO_2 (per 10 µg/m^3) OR on incident of asthma attacks Lag 1: day 0.98 (0.76, 1.27); Lag 2: day 0.92 (0.72, 1.19) Lag 3: day 1.01 (0.82, 1.23); Lag 4: day 1.01 (0.86, 1.19) Lag 5: day 1.05 (0.85, 1.29)Cumulative exposure mean (−1 to −5 days) 0.99 (0.76, 1.30)
Forsberg et al. (1993) Pitea, Northern Sweden Mar to Apr	Panel study of 31 asthmatic patients (9 to 71 yrs) to assess relationship between daily occurrence of asthma symptoms and fluctuations in air pollution and meteorological conditions. Subjects recorded symptoms (shortness of breath, wheezing, cough, phlegm) for 14 consecutive days.	24-h avg SO_2 (µg/m^3) Mean: 5.7 Range: 1.3, 12.9 Correlations: NO_2 (r = 0.24) BS (r = 0.70)	No significant association observed with SO_2. Positive association between severe shortness of breath and black smoke. Regression coefficient and 90% CI Subjects with shortness of breath (N: 28): 0.0345 (−0.49, 0.118) Subjects with 5 or more incident episodes of severe shortness of breath (N: 10): −0.0266 (−0.140, 0.087)
Higgins et al. (1995) United Kingdom	Panel study of 75 patients with physician diagnosed asthma or chronic bronchitis (mean age 50, range 18 to 82 yrs) to determine if air pollution affects respiratory function and symptoms. Subjects asked to keep symptom records and perform PEF for 28 days. PEF values recorded every 2 h beginning at 02.00 h each day. Methacholine challenge performed on each subjects. Those with PM_{20} FEV_1 of < 12.25 µmol were considered as methacholine reactors. PEF variability was calculated as the amplitude % Mean: (highest-lowest PEF value/mean) ×100. 75 patients had PEF records, 65 completed symptom questionnaires.	Max 24-h SO_2 117 µg/m^3 Copollutants: O_3 NO_2	The amplitude % mean was significantly associated with increasing levels of SO_2, on the same day for all subjects and among reactors. Mean daily PEF and min PEF associated with SO_2 among reactors only. Significant associations also observed with wheeze and SO_2 on the same day, at 24-h Lag, and 48-h Lag for all subjects and meta-choline reactors; and with bronchodilator use for all subjects at 24-h Lag. Regression coefficient per 10 µg/m^3 SO_2 All subjects Mean PEF (L/min). Same day 0.021 (0.031) 24-h Lag 0.003 (0.033). 8-h Lag 0.021 (0.032) Minimum PEF(L/min). Same day 0.062 (0.039) 24-h Lag 0.048 (0.041). 48-h Lag 0.001 (0.040) Amplitude (% mean). Same day: 0.167 (0.072) 24-h Lag 0.191 (0.76). 48-h Lag 0.022 (0.075) Wheeze. Same day: 1.14 (1.03, 1.26) 24-h Lag 1.22 (1.09, 1.37). 48-h Lag 1.14 (1.02, 1.27) Dyspnoea. Same day: 1.03 (0.94, 1.14) 24-h Lag 1.07 (0.96, 1.18). 48-h Lag 0.94 (0.85, 1.05) Cough. Same day: 1.03 (0.95, 1.12) 24-h Lag 1.04 (0.95, 1.13). 48-h Lag 1.02 (0.94, 1.12) Throat symptoms. Same day: 1.01 (0.92, 1.11) 24-h Lag 1.00 (0.91, 1.10). 48-h Lag 0.96 (0.87, 1.06) Eye symptoms. Same day: 1.08 (0.97, 1.20) 24-h Lag 1.11 (0.99, 1.24). 48-h Lag 1.10 (0.99, 1.21) Bronchodilator use. Same day 1.11 (0.97, 1.26) 24-h Lag 1.16 (1.01, 1.34). 48-h Lag 1.12 (0.98, 1.27) Reactors Mean PEF (l/min). Same day 0.087 (0.054) 24-h Lag 0.44 (0.058). 48-h Lag 0.012 (0.057) Minimum PEF(L/min). Same day 0.168 (0.071) 24-h Lag 0.078 (0.076). 48-h Lag 0.026 (0.075) Amplitude (% mean). Same day: 0.157 (0.120) 24-h Lag 0.083 (0.127). 48-h Lag 0.005 (0.126) Wheeze. Same day: 1.26 (1.08, 1.47) 24-h Lag 1.57 (1.30, 1.89). 48-h Lag 1.24 (1.06, 1.45) Dyspnoea. Same day:1.04 (0.90, 1.20) 24-h Lag 1.17 (1.00, 1.37). 48-h Lag 1.03 (0.89, 1.20) Cough. Same day:1.09 (0.96, 1.24) 24-h Lag 1.05 (0.91, 1.20). 48-h Lag 1.00 (0.87, 1.15) Throat symptoms. Same day: 1.06 (0.92, 1.21) 24-h Lag 1.06 (0.91, 1.23). 48-h Lag 1.01 (0.87, 1.17) Eye symptoms. Same day: 1.19 (1.01, 1.40) 24-h Lag 1.21 (1.01, 1.45). 48-h Lag 1.08 (0.91, 1.28) Bronchodilator use. Same day 1.18 (0.99, 1.42) 24-h Lag 1.23 (1.02, 1.50). 48-h Lag 1.31 (1.09, 1.58)

STUDY	METHOD	POLLUTANTS	FINDINGS
Hiltermann et al. (1998) Bilthoven, The Netherlands Jul-Oct 1995	Panel study of 60 adult (18 to 55 yrs) nonsmoking patients with intermittent to severe persistent asthma to examine the association of summertime air pollution (ozone and PM_{10}) with respiratory symptoms, medication use and PEF. Subjects were followed over 96 days. Twice daily PEF, respiratory symptoms, and medication use and whether they were exposed to environmental tobacco smoke were recorded daily. Analysis controlled for time trends, aeroallergens, environmental tobacco smoke exposures, day of wk and temperature. Examined Lag effects of 0 to 2 days.	24-h avg SO_2 ($\mu g/m^3$) Mean: 6.2 **Range:** 0.1, 16.2 Correlation with BS r = 0.53 O_3, PM_{10}, NO_2, BS Correlation with copollutants: O_3 (r = 0.30)PM_{10} (r = 0.37) NO_2 (r = 0.49) BS (r = 0.53)	SO_2 not included in the analysis since levels were negligible during the study period (< 17 $\mu g/m^3$) Effect estimates not provided.
Hoek and Brunekreff (1993) Wageningen, The Netherlands	Panel study of 112 children (7 to 12 yrs, non-urban) to assess effects of winter air pollution pulmonary function and respiratory symptoms. Parents filled out symptom diary that was turned in every 2 wks. Pulmonary function test performed by technician every 3 wks. Additional pulmonary function tests performed when SO_2 was predicted to be higher than 125 $\mu g/m^3$ or NO_2 > 90 $\mu g/m^3$.	Daily concentrations presented in graph; Highest 24-h avg conc SO_2: 105 $\mu g/m^3$ (air pollution episode) PM_{10}, BS, NO_2	During the winter episode, pulmonary function of schoolchildren was significantly lower than baseline. Significant negative associations between SO_2 and FVC, FEV_1 and MMEF. No significant associations found with prevalence of respiratory symptoms. Authors noted that it is not clear which components of episode mix responsible for association and that the concentrations of acid aerosol and SO_2 were too low for direct effects to be likely. SO_2 moderately correlated with PM_{10} (r = 0.69) and black smoke (r = 0.63) but not NO_2 (r = 0.28). Mean of individual regression slopes and SE FVC Same day −0.55 (0.10), p < 0.05 Lag 1: −0.74 (0.15) p < 0.05. 1 wk −0.94 (0.20) p < 0.05 FEV_1 Same day −0.51 (0.09) p < 0.05 Lag 1: −0.21 (−0.63) p < 0.05. 1 wk −0.78 (0.18) p < 0.05 PEF Same day −0.64 (−0.44) Lag 1: −0.21 (0.63). 1 wk −0.34 (0.81) p < 0.05 MMEF. Same day −0.54 (0.20) Lag 1: −0.40 (0.29). 1 wk −0.61 (0.37) Prevalence of acute respiratory symptoms regression coefficient from time-series model and SE Cough. Same day 0.02 (0.18) Lag 1: −0.14 (0.19). 1 wk 0.13 (0.76) Upper respiratory symptoms. Same day 0.12 (0.16) Lag 1: −0.02 (0.17). 1 wk −0.24 (0.76) Lower respiratory symptoms. Same day 0.06 (0.26) Lag 1: −0.11 (0.29). 1 wk −0.54 (0.92) Any respiratory symptoms. Same day 0.01 (0.13) Lag 1: −0.03 (0.13). 1 wk −0.11 (0.60)
Hoek and Brunekreff (1995) Deurne and Enkhuizen, The Netherlands Mar-Jul 1989	Panel study of 300 children (7-11 yrs) to examine the effects of photochemical air pollution on acute respiratory symptoms. Occurrence of respiratory symptoms recorded by parents in daily diary. Symptoms included cough, shortness of breath, upper and lower respiratory symptoms, throat and eye irritation, headache and nausea. Association of symptom prevalence and incidence assessed using first order autoregressive, logistic regression model.	Daily concentration of SO_2 < 43 $\mu g/m^3$ O_3 PM_{10} SO_4^{2} NO_3^{-}	Same day concentrations of SO_2 and NO_2 not associated with symptom prevalence. No effect estimates for SO_2 provided
Just et al. (Just et al., 2002) Paris, France 1996	Panel study consisting of 82 medically diagnosed asthmatic children, 7-15 yrs old, followed for 3 mos (Jan-Mar). Examined the association between air pollution and asthma symptoms using regression analyses based on generalized estimating equations (GEE).	24-h avg ($\mu g/m^3$): 11.6 (5.7) PM BS NO_2 O_3	SO_2 was not analyzed because it was only present at low concentrations.

STUDY	METHOD	POLLUTANTS	FINDINGS
Kopp et al. (1999) Two towns in Black Forest, Germsany Villingen and Freudenstadt Mar-Oct 1994	Panel study of 170 children (median age 9.1 yrs) to investigate nasal inflammation and subsequent adaptation after ambient ozone exposures. Nasal lavage was sampled over 11 time points, and skin prick tests performed. Nasal lavage samples were analyzed for eosinophil cationic protein, albumen, and leukocytes as markers of nasal inflammation. To avoid confounding with allergens, the study population was restricted to only children with no positive reaction to any of the tested inhalant allergens. GEE used in analysis.	Mean SO_2 (mg/m^3) Villingen Mean: 3 5%: 0 95%: 9 Freudenstadt Mean: 3 5%: 0 95%: 9 Copollutants: O_3, NO_2, TSP, PM_{10}	Results for only O_3. Authors noted that since there were very low concentrations of NO_x and SO_2, the confounding effects of these components in ambient air were negligible. Eosinophil cationic protein and leukocyte levels peaked after the first increase in ambient ozone levels.
Lagorio et al. (2006) May 24 to June 24, 1999 and Nov 18 to Dec 22, 1999 Rome, Italy	Panel study of 29 patients with either COPD (N: 11, mean age 67 yrs), asthma (N: 11, mean age 33 yrs) or ischemic heart disease (N: 7, mean age 63 yrs) to evaluate whether daily levels of air pollutants have a measurable impact on lung function in adults with preexisting lung or heart disease.	24-h mean SO_2 ($\mu g/m^3$) Spring mean 4.7 SD 1.8 Winter mean 7.9 SD 2.2 Overall mean 6.4 SD: 2.6 Copollutants: $PM_{2.5}$, $PM_{10-2.5}$, PM_{10}, CD, Cr, FE, NI, PB, PT, V, Zn, NO_2, CO, O_3 Correlation with copollutants: $PM_{2.5}$ (r = 0.34) $PM_{10-2.5}$ (r = −0.16) PM_{10} (r = 0.21) NO_2 (r = 0.01) O_3 (r = −0.61) CO (r = 0.65)	Because avg 24-h concentrations of SO_2 were low and showed little variability, SO_2 was not considered in the analysis

STUDY	METHOD	POLLUTANTS	FINDINGS
Neukirch et al. (1998) Paris, France Nov 15, 1992 to May 9, 1993	Panel study of 40 nonsmoking, mild to moderate asthmatics (16 to 70 yrs, mean 46) to examine the short-term effects of winter air pollution in asthma symptoms and three daily peak flow measurements. Patients were followed for 23 wks. Used GEE models that controlled for autocorrelation of responses, weather, and time trends. Analysis conducted on entire study population and for subgroup of subjects who took inhaled B2 agonists as needed. Assessed air pollution effect on both incident and prevalence of symptoms, Z-transformed morning PEF and daily PEF variability.	24-h avg SO_2 Mean: 21.7 (13.5) µg/m^3 **Range:** 4.4, 83.8 Copollutants NO_2, PM_{13}, Black smoke Correlation with copollutants: NO_2 (r = 0.54) PM_{13} (r = 0.83) BS (r = 0.89)	Significant effects on incidence and prevalence of symptoms. Effects at Lag days 3-6 and weekly avg exposures. Based on group avg PEF of 407 l/min, a 50 µg/m^3 increase SO_2 caused a maximum decrease in morning PEF of 5.5%. 24-h avg SO_2 (per 50 µg/m^3). Odds ratio: all subjects - Incident episodes: Wheeze: Lag 5: 1.66 (1.01, 2.70) Nocturnal cough: Lag 3: 1.60 (0.98, 2.62) Lag 4: 1.71 (0.86, 3.40). Lag 6: 1.72 (1.16, 2.55) Respiratory infections: Lag 3: 3.14 (1.30, 7.59) Lag 4: 2.70 (1.36, 5.37). Lag 5: 2.79 (0.95, 8.21) Wk: 8.52 (1.20, 60.5) Odds ratio: all subjects - Prevalent episodes: Wheeze: Lag 5: 1.35 (1.01, 1.81) Lag 6: 1.39 (1.04, 1.87). Wk: 1.64 (0.91, 2.94) Nocturnal cough: Lag 6: 1.34 (1.00, 1.79) Shortness of breath: Wk: 1.56 (1.06, 2.32) Respiratory infections: Lag 4: 2.40 (1.33, 4.33) Lag 5: 2.72 (1.67, 4.44). Lag 6: 2.94 (1.80, 4.79) Wk: 6.30 (1.31, 30.2) Odds ratio: Subjects taking B2 agonists - Incident episodes: Asthma attacks: Lag 6: 2.19 (0.91, 5.29) Wheeze: Lag 5: 1.84 (1.13, 3.00) Nocturnal cough: Lag 3: 2.41 (1.47, 3.93 Lag 4: 2.35 (0.88, 6.26). Lag 6: 1.86 (1.14, 3.04) Odds ratio: Subjects taking B2 agonists - Prevalent episodes: Asthma attacks: Lag 5: 1.88 (0.95, 3.73) Lag 6: 2.82 (1.57, 5.07) Wheeze: Lag 5: 1.51 (1.02, 2.23) Lag 6: 1.57 (1.06, 2.32) Nocturnal cough: Lag 3: 1.73 (1.06, 2.82) Lag 4: 2.28 (1.27, 4.11). Lag 5: 1.91 (1.17, 3.12) Lag 6: 1.91 (1.17, 3.12) Shortness of breath: Lag 4: 1.81 (1.22, 2.67) Lag 5: 1.65 (1.11, 2.44). Lag 6: 1.61 (1.20, 2.16) Wk: 3.03 (1.26, 7.33) Regression coefficients of the effects and SE (per 1 µg/m^3) Z-transformed morning PEF Lag 5; 0.450 (0.138) p = 0.001. Lag 6; 0.337 (0.164) p = 0.03 PEF daily variability. Lag 2: 0.025 (0.013) p = 0.05
Peacock et al. (2003) Southern England Nov 1, 1996 to Feb 14, 1997	Panel study of 177 children (mean age 10.7 yrs, range 7 to 13) from three schools (two urban and 1 rural location) to investigate effects of winter air pollution on respiratory function. Children were followed for 13 wks. Used two sources of air pollution in the rural area, one that was "locally validated" and the other "nationally validated."	24-h avg SO_2 (ppb) Rural (nationally validated) Mean: 5.1 (4.7) **Range:** 0.0, 35.6 Rural (locally validated) Mean: 5.4 (5.1) **Range:** 0.0, 39.1 Urban 1 Mean: 6.0 (6.0) **Range:** 0.5, 32.5 O_3 NO_2 PM_{10} SO_4	No statistically significant association between winter SO_2 and PEFR, 0.70% decline in PEFR for a 10 ppb increase in the five-day mean concentration of SO_2 (community monitor) 24-h avg $_{SO2}$ - Change in PEF per 1 ppb SO_2 - community monitor - Regression Coefficient (95% CI) Lag 0: 0.05 (−0.05, 0.16). Lag 1: −0.04 (−0.13, 0.06) Lag 2: −0.08 (−0.19, 0.04). Mean (0-4) −0.23 (−0.65, 0.18) Change in PEF per 1 ppb SO_2 - local regression coefficient (95% CI) Lag 0: −0.01 (−0.10, 0.07). Lag 1: 0.02 (−0.05, 0.10) Lag 2: −0.09 (−0.18, 0.01). Mean (0-4) −0.09 (−0.25, 0.07) Odds of 20% decrement in PEF below the median-all children Lag 0 0.987 (0.958, 1.017). Lag 1 1.007 (0.986, 1.030) Lag 2 0.992 (0.963, 1.023). Mean (0-4) 0.972 (0.887, 1.066) Odds of 20% decrement in PEF below the median-wheezy children Lag 0 0.981 (0.925, 1.041). Lag 1 0.999 (0.957, 1.042) Lag 2 0.995 (0.939 1.054). Mean (0-4) 1.019 (0.890 to 1.167)

STUDY	METHOD	POLLUTANTS	FINDINGS
Peters et al. (1996) Erfurt and Weimar, former German Democratic Republic; Sokolov, Czech Republic Sep 1990 to June 1992	Panel study of 102 adult (32 to 80 yrs) and 155 children (7 to 15 yrs) with asthma from the former German Democratic Republic and Czech Republic to investigate the acute effects of winter type air pollution on symptoms, medication intake and PEF. Used regression analyses and distributed Lag models.	Winter 1990/1991 Erfurt: Mean: 125 µg/m^3 Max: 564 µg/m^3 IQR: 113 µg/m^3 Weimar Mean: 236 µg/m^3 Max: 1018 µg/m^3 IQR: 207 µg/m^3 Sokolov Mean: 90 µg/m^3 Max: 492 µg/m^3 IQR: 94 µg/m^3 Winter 1991/1992 Erfurt Mean: 96 µg/m^3 Max : 462 µg/m^3, IQR: 80 µg/m^3 Weimar Mean: 153 µg/m^3 Max: 794 µg/m^3 IQR: 130 µg/m^3 Sokolov Mean: 71 µg/m^3 Max: 383 µg/m^3 IQR: 66 µg/m^3 Copollutants: TSP, PM_{10}, SO_4, PSA (particle strong acidity)	5-day mean concentration of SO_2 associated with PEF and symptoms in children (combined analysis from former German Democratic Republic and Czech Republic). Correlation coefficient between SO_2 and TSP in Erfurt was r = 0.8, 0.9 during both winters and in Weimar during the first winter. Correlation with TSP in Sokolov and in Weimar during the second winter was r = 0.4, 0.5. Combined analysis for children % change in PEF Concurrent day 0.18 (−0.44, 0.09) per 133 µg/m^3 5-day mean −0.90 (−1.35, −0.46) per 128 µg/m^3 % change in symptom score Concurrent day −0.1 (−5.9, 5.7) per 133 µg/m^3 5-day mean 14.7 (0.8, 28.6) per 128 µg/m^3 Combined analysis for adults % change in PEF Concurrent day −0.20 (−0.53, 0.12) per 133 µg/m^3 5-day mean −0.28 (−0.72, 0.16) per 128 µg/m^3
Pikhart et al. (2001) Czech 1993-1994	SAVIAH study of 3045 children by questionnaire to determine association of SO_2 to wheezing. Used ecological and multilevel analysis	MediaN: 73.9 µg/m^3 25th percentile: 63.5 75th percentile: 95.5 Copollutant: NO_2	Positive association of SO_2 with wheezing Odds Ratio (95% CI) Logistic RegressioN: Individual outcome and area exposure: 1.08 (0.98, 1.20). Individual outcome and individual exposure: 1.08 (0.98, 1.19). Ecological analysis: 1.05 (0.96, 1.16)
Ponka A. (1990) Helsinki, Finland 1991	Survey study to compare weekly changes in ambient SO_2, NO_2, and temperature and the incidence of respiratory diseases, and absenteeism for children in day-care centers and schools and for adults in the work place during a 1-yr period (1987).	Mean weekly concentration of SO_2 (µg/m^3) Mean: 21.1 SD: 11.7 MediaN: 17.0 Range: 9, 61.5 Mean of daily max Mean: 53 SD: 20.8 MediaN: 48 Range: 25.9, 130.3 Copollutant: NO_2	Mean SO_2 concentration correlated with the incidences of URI and tonsillitis reported from health centers. SO_2 also correlated with absenteeism due to febrile illness among children in day care centers and adults. When comparing incidences during the low and high levels of SO_2, the number of cases of URI and tonsillitis reported from health centers increased as well as absenteeism. After standardization for temperature, the only difference that was statistically significant was the occurrence of URI diagnosed at health centers. Frequency of URI was 15% higher during high levels of SO_2 compared to low. Statistical significance of product moment correlation coefficients (correlation coefficient) between SO_2 and respiratory disease and absenteeism Respiratory tract infections diagnosed at health centers: URI SO_2 arithmetic mean p < 0.001 (0.553) SO_2 mean of daily maximums: p = 0.0012 (0.437) Tonsillitis: Arithmetic Mean: 0.0098 (0.355) Mean of daily maximums: NS Absenteeism due to febrile illness: Day care centers SO_2 arithmetic Mean: p = 0.012 (0.404) Mean of daily maximums: p = 0.048 (0.323) School children SO_2 arithmetic Mean: NS Mean of daily maximums: NS Adults: SO_2 arithmetic Mean: p < 0.0001 (0.644) Mean of daily maximums: p < 0.0001 (0.604) No significant correlation between SO_2 and URI, tonsillitis, otitis, or LRI in day care center children Statistical significance of weekly frequency of respiratory tract disease and absenteeism during low and high levels of SO_2: Respiratory infections diagnosed at health centers: URI SO_2 arithmetic Mean: p < 0.001. Mean of daily max: p = 0.0005 Tonsillitis SO_2 arithmetic Mean: 0.0351. SO mean of daily max: NS Absenteeism due to febrile illness Day care center childreN: p = 0.0256 School childreN: p = 0.0014. Adults: p = 0.0005

STUDY	METHOD	POLLUTANTS	FINDINGS
Pinter et al. (1996) Tata Area, Hungary winter mos between Dec 1993-Mar 1994	Longitudinal (children < 14 yrs) and cross-sectional study (9 to 11 yrs) to examine air pollution and respiratory morbidity in children. In the longitudinal prospective study, respiratory morbidity was evaluated daily and on a weekly basis. In cross-sectional study, anthropometric parameters, physical status, pulse and blood pressure, lung function parameters, eosinophils in the nasal smear, hematological characteristics and urinary excretion of some metabolites were examine and measured. Anova and linear regression used in analysis.	Mean SO_2 exceeded the limit of yearly avg 150 µg/m^3 Daily peaks reached as high as 450 µg/m^3 No specific values given Copollutant: NO_2	Significant correlation between SO_2 levels and acute daily respiratory morbidity, but no correlation with weekly incidence. Authors stated that in the cross-sectional study, almost all health parameters were impaired but no results were shown. Results only provided in graph. No CI provided
Roemer et al. (1993) Wageningen and Bennekom, Netherlands	Panel of 73 children (mean age 9.3 yrs, range 6 to 12 yrs) with chronic respiratory symptoms to investigate effects of winter air pollution on lung function, symptoms and medication use. Subjects performed twice-daily PEF measurements, largest of three PEF readings used in regression analysis. Both incidence and prevalence of symptoms analyzed, using logistic regression.	Daily concentrations of SO_2 shown in graph Highest 24-h avg concentration SO_2: 105 µg/m^3 Copollutants; NO_2 PM_{10} BS Correlation with copollutants: NO_2 (r = 0.26) PM_{10} (r = 0.65) BS (r = 0.63)	Positive association between incidence of phlegm and runny nose with SO_2 on the same day. Significant association also found between evening PEF and SO_2 on, the same day, previous day and 1 wk (avg of same day and 6 days before). The use of bronchodilators also associated with SO_2. Mean of individual regression coefficient Morning PEF. Same day: −0.021 (0.024) Lag 1: −0.024 (0.031). Wk: −0.50 (0.069) Evening PEF. Same day: −0.048 (0.018) p < 0.05 Lag 1: −0.039 (0.021) p < 0.10. Wk: −0.110 (0.055) p < 0.05 Prevalence of symptoms (per 50 µg/m^3 SO_2) Asthma attack. Same day: 0.008 (0.012) Lag 1: 0.016 (0.011). 1 wk: 0.058 (0.027) p < 0.05 Wheeze. Same day: 0.033 (0.17) p < 0.10 Lag 1: 0.042 (0.016) p < 0.05. Wk: 0.069 (0.032) p < 0.05 Waken with symptoms. Same: day 0.033 (0.019) p < 0.10 Lag 1: 0.032 (0.018) p < 0.10. Wk: 0.058 (0.045) Shortness of breath. Same: day 0.029 (0.016) p < 0.10 Lag 1: 0.016 (0.015). Wk: 0.044 (0.035) Cough. Same day 0.018 (0.025) Lag 1: 0.012 (0.023). Wk 0.072 (0.066) Runny nose. Same day 0.070 (0.026) p < 0.05 Lag 1: −0.11 (0.025). Wk 0.153 (0.074) p < 0.05 Phlegm. Same day 0.011 (0.022) Lag 1: 0.014 (0.020). Wk −0.005 (0.056)
Roemer et al. (1998) 14 European Centers: Umea, Sweden; Malmo, Sweden; Kuopi, Finland; Oslo, Norway; Amsterdam, The Netherlands; Berlin, Germany; Katowice, Poland; Cracow, Poland; Teplice, Czech Republic; Prague, Czech Republic; Budapest, Hungary; Pisa, Italy; Athens, Greece Winter 1993-1994	Multicenter panel study of the acute effects of air pollution on respiratory health of 2010 children (aged 6 to 12 yrs) with chronic respiratory symptoms. Results from individual centers were reported by Kotesovec et al. (1998), Kalandidi et al. (1998), Haluszka et al. (1998), Forsberg et al. (1998), Clench-Aas et al. (1998), and Beyer et al. (1998). Calculated effect estimates of air pollution on PEF or the daily prevalence of respiratory symptoms and bronchodilator use from the panel-specific effect estimates	Range: −2.7 µg/m^3 (Umea, urban), 113.9 µg/m^3 (Prague, urban) Copollutants: PM_{10}, BS NO_2	No clear associations between PM_{10}, BS, SO_2, or NO_2 and morning PEF, evening PEF, prevalence of respiratory symptoms, or bronchodilator use could be detected. Previous day PM_{10} was negatively associated with evening PEF, but only in locations where BS was high compared to PM_{10} concentrations. No consistent differences in effect estimates between subgroups based on urban versus suburban, geographical location or mean levels of PM_{10}, BS, SO_2, and NO_2. Combined effect estimates with 95% CI of air pollution on PEF Morning Lag 0: 0.2 (−0.2, 0.6); Lag 1: 0.2 (−0.2, 0.6) Lag 2: 0.6 (0.2, 1.0); 7-day mean 0.6 (−1.3, 2.5) Afternoon Lag 0: 0.1 (−0.3, 0.5); Lag 1: 0.0 (−0.4, 0.4) Lag 2: 0.1 (−0.4, 0.6); 7-day mean 0.2 (−0.5, 0.9)

STUDY	METHOD	POLLUTANTS	FINDINGS
Segala et al. (1998) Paris, France Nov 15, 1992 to May 9, 1993	Panel study of 84 children (7 to 15 yrs) with physician diagnosed asthma to examine the effects of winter air pollution on childhood asthma. For 25 wks, parents recorded the presence or absence of asthma attacks, upper or lower respiratory infections with fever, the use of supplementary inhaled B2 agonist, the severity of symptoms (wheeze, nocturnal cough and shortness of breath). Children also recorded PEF three times a day. GEE models adjusted for age, sex, weather and time trend. Investigated effects of SO_2 at 0 to 6 day Lags.	SO_2 mean (SD): 21.7 (13.5) µg/m^3 Range: (4.4, 83.8) µg/m^3 Copollutants: NO_2 PM_{13} BS Correlation with copollutants: NO_2 (r = 0.54) PM_{13} (r = 0.43) BS (r = 0.89)	SO_2 associated with both incident and prevalent episodes of asthma, use of supplementary beta 2 agonist, incident episodes of nocturnal cough, prevalent episodes of shortness of breath and respiratory infection. OR per 50 µg/m^3 SO_2 (Only effects at 0 and 1-days lag shown below unless statistically significant) Incident episodes: Mild asthmatics (N: 43) Asthma: Lag 0: OR 2.86 (1.31, 6.27); Lag 1: 2.45 (1.01, 5.92) Wheeze: Lag 0: 1.47 (0.90, 2.41) ; Lag1: 1.27 (0.48, 3.38) Nocturnal cough: Lag 3: 1.93 (1.18, 3.15) ; Lag 4: 2.12 (1.43, 3.13) Respiratory infections: Lag 1: 1.52 (0.38, 5.98) Prevalent episodes: Mild asthmatics (N: 43) Asthma: Lag 0: 1.71 (1.15, 2.53) ; Lag 1: 1.55 (0.86, 2.78) Wheeze: Lag 4: 1.48 (0.90, 2.41) Shortness of breath : Lag 1: 1.36 (0.92, 2.01); Lag 2: 1.45 (0.98, 2.14) Lag 3: 1.52 (1.03, 2.25); Lag 4: 1.51 (1.02, 2.24) Respiratory infections: Lag 0: 1.58 (0.72, 3.46); Lag 1: 1.91 (0.79, 4.62) Lag 2: 2.13 (0.97, 4.67; Lag 3: 2.09 (1.05, 4.15) Lag 4: 2.05 (1.14, 3.68) Beta2 agonist: Lag 4: 1.63 (1.00, 2.66) Beta2 agonist: Lag 4: 2.02 (1.02, 4.01) Lag 5: 1.96 (0.99, 3.88) Moderate asthmatics (N: 41) Statistically significant (only) prevalent episodes: Beta2 agonist: Lag 0: 3.67 (1.25, 10.8); Lag 1: 4.60 (2.10, 10.1) Lag 2: 7.01 (3.53, 13.9); Lag 3: 4.74 (1.96, 11.5)
Taggart et al. (1996) Runcorn and Widnes in NW England Jul-Sep 1993	Panel study of 38 nonsmoking asthma subjects (18 to 70 yrs) to investigate the relationship between asthmatic bronchial hyperresponsiveness and pulmonary function (PEF, FEV_1, FVC) and summertime ambient air pollution. Used univariate nested (hierarchical) analysis of variance to test hypothesis that BHR or spirometry measurements varied with air pollution levels. Analysis was limited to within-subject variation of (BHR, FEV_1, or FVC).	24-h avg SO_2 Max: 103.7 µg/m^3 Copollutants: NO_2, O_3, smoke Correlation with copollutants: O_3 (r = 0.13) NO_2 (r = 0.65) Smoke (r = 0.48)	No association between SO_2 and FEV_1 or FVC. Changes in BHR correlated significantly with changes in 24-h mean SO_2, NO_2, and smoke. Percentage change in BHR per 10 µg/m^3 SO_2 24-h mean SO_2 −6.3 % (−13.6, 0.6) 48-h mean −2.9 % (−12.8, 8.2). 24-h Lag 7.4 % (−4.5, 20.8)

STUDY	METHOD	POLLUTANTS	FINDINGS
Timonen and Pekkanen (1997) Kuopio, Finland 1994	Panel study of 169 children (7 to 12 yrs) with asthma or cough symptoms living in urban and suburban areas of Kuopio, Finland to determine association between air pollution and respiratory health. In the urban areas there were 39 asthmatics and 46 with cough only; in the suburban areas there were 35 asthmatics and 49 with cough who were included in the final analysis. Twice daily PEF and daily symptoms were recorded for 3 mos. First order autoregressive models used to assess associations between air pollutants and PEF and logistic regression models used for symptom prevalences and incidences. Analysis conducted on daily mean PEF deviations. Mean morning or evening PEF calculated for each child was subtracted from the daily value of morning or evening PEF. The daily deviations were then Avgd to obtain daily mean PEF deviation for morning or evening PEF.	Avg daily SO_2 ($\mu g/m^3$) Urban area: Mean: 6.0 25th percentile: 2.6 50th percentile: 3.6 75th percentile: 7.1 Max: 32 Copollutants: PM_{10} BS NO_2 Correlation coefficient with SO_2 PM_{10} (r = 0.21) BS (r = 0.20) NO_2 (r = 0.22)	Among children with cough only, morning and evening deviations in PEF in the urban panel was negatively associated with SO_2. SO_2 was also associated with an increase in the incidence of URS in children with cough only in the urban area. When excluding the three highest SO_2 days, these effects were no longer statistically significant. No associations found between SO_2 and morning or evening PEF or respiratory symptoms in children with cough only in the suburban panel. Asthmatic: Lag 0: 0.198 (0.804) Lag 1: 0.382 (0.789). Lag 2: 0.648 (0.715) 4-day Mean: 1.39 (1.14) Odds ratio (per 10 $\mu g/m^3$) URS Lag 1: 1.46 (1.07, 2.00). Lag 2: 1.46 (1.14, 1.87) 4-day Mean: 1.55 (1.08, 2.24) Odds ratio when excluded 3 highest SO_2 days (no 95% CI provided, but effects were not significant) Lag 1: 1.13. Lag 2: 1.46. 4-day Mean: 1.12 PM_{10} r = 0.21 BS r = 0.20 NO_2 r = 0.22 Regression coefficient (SE) (per 10 $\mu g/m^3$ SO_2) Morning PEF deviations Children with cough alone Lag 0: −0.229 (0.608). Lag 1: −1.38 (0.564) Lag 2: −0.683 (0.523). 4-day Mean: −1.28 (0.633) Evening PEF deviations Children with cough alone Lag 0: −1.84 (0.673). Lag 1: −0.144 (0.711) Lag 2: −0.291 (0.613). 4-day Mean: −0.878 (0.868) Asthmatics Lag 0: 1.28 (0.711). Lag 1: 0.575 (0.727) Lag 2: 0.819 (0.642). 4-day Mean: 1.34 (1.05)

STUDY	METHOD	POLLUTANTS	FINDINGS
van der Zee et al. (1999) Netherlands 3 winters from 1992 to 1995 Rotterdam and Bodegrven/Reeuwijk (1992-1993) Amsterdam and Meppel (1993-1994) Amsterdam and Nunspeet (1994-1995)	Panel study of 633 children (aged 7 to 11 yrs) with and without chronic respiratory symptoms, living in urban and nonurban areas in the Netherlands. Volunteers measured daily PEF and reported the occurrence of respiratory symptoms and bronchodilator use in a diary. Association between air pollution and decrements in PEF, symptoms and bronchodilator use evaluated with logistic regression models that adjusted for first order autocorrelation, min daily temperature, day of wk, time trend, incidence of influenza and influenza-like illness.	Median and max 24-h mean concentration ($\mu g/m^3$) 1992-1993 Urban 23 (152); Nonurban 8.9 (43) 1993-1994 Urban 11 (34); Nonurban 5.0 (42) 1994-1995 Urban 6.0 (24); Nonurban 3.6 (17) Copollutants: PM_{10} Black smoke Sulfate NO_2	The correlation between SO_2 and PM varied from 0.5 to 0.8 during first two winters. Correlation with NO_2 about 0.50. In the urban areas, SO_2 was associated with > 10% decrements in evening PEF, LRS and use of bronchodilator in children with symptoms. Most consistent associations found with PM_{10}, BS, and sulfate. No association found between SO_2 and prevalence of URS, cough, phlegm, and > 10% decrements in morning PEF. In the nonurban areas, no associations found with SO_2. In children without symptoms, no consistent associations with SO_2. Authors concluded that children with symptoms are more susceptible to particulate air pollution effects and that use of medication for asthma did not prevent the adverse effects of PM in children with symptoms. Odds ratio (per 40 $\mu g/m^3$ SO_2) Children with symptoms Urban areas Evening PEF Lag 0: 1.32 (0.96, 1.80). Lag 1: 0.83 (0.60, 1.14) Lag 2: 1.67 (1.28, 2.19) Symptoms of lower respiratory tract Lag 0: 1.35 (1.01, 1.79) . Lag 1: 1.23 (0.93, 1.64) Symptoms of upper respiratory tract Lag 0: 0.97 (0.82, 1.14). Lag 1: 1.10 (0.94, 1.28) Cough Lag 0: 0.90 (0.77, 1.05). Lag 1: 1.12 (0.96, 1.30) Use of bronchodilator Lag 0: 0.92 (0.72, 1.18). Lag 1: 1.45 (1.13, 1.86) Odds ratio (per 40 $\mu g/m^3$ SO_2) Children without symptoms Evening PEF Lag 0: 1.13 (0.88, 1.47). Lag 1: 1.16 (0.90, 1.50) URS Lag 0: 0.92 (0.76, 1.11) Lag 1: 1.10 (0.91, 1.34). Lag 2: 0.83 (0.70, 0.99) Cough Lag 0: 0.93 (0.78, 1.11). Lag 1: 1.02 (0.84, 1.23) Nonurban areas Evening PEF Lag 0: 1.20 (0.91, 1.58). Lag 1: 0.89 (0.68, 1.17) Symptoms of lower respiratory tract Lag 0: 0.91 (0.69, 1.19). Lag 1: 0.91 (0.69, 1.22) Symptoms of upper respiratory Lag 0: 0.94 (0.81, 1.09). Lag 1: 0.97 (0.83, 1.13) 5-day Mean: 0.67 (0.47, 0.94) Cough. Lag 0: 1.08 (0.94, 1.23). Lag 1: 0.98 (0.85, 1.12) Use of bronchodilator Lag 0: 0.86 (0.59, 1.25). Lag 1: 1.18 (0.80, 1.74) Evening PEF Lag 0: 1.10 (0.87, 1.39). Lag 1: 1.07 (0.85, 1.35) URS. Lag 0: 1.07 (0.92, 1.25). Lag 1: 0.85 (0.72, 1.00) Cough. Lag 0: 0.86 (0.76, 0.97). Lag 1: 0.95 (0.83, 1.08)

STUDY	METHOD	POLLUTANTS	FINDINGS
van der Zee (2000) Netherlands, 3 winters from 1992 to 1995 Rotterdam 1992-1993	Panel study of 489 adults (aged 50 to 70 yrs) with and without chronic respiratory symptoms, living in urban and nonurban areas in the Netherlands. Volunteers measured daily PEF and reported the occurrence of respiratory symptoms and bronchodilator use in a diary. Association between air pollution and decrements in PEF, symptoms and bronchodilator use evaluated with logistic regression models that adjusted for first order autocorrelation, min daily temperature, day of wk, time trend, incidence of influenza and influenza-like illness.	Median (max) conc 1992/1993: Urban 25 (61) µg/m^3 1993/1994 Urban 11 (34) µg/m^3 Nonurban 5.0 (42) µg/m^3 1994/1995 Urban 6.0 (24) Nonurban 3.6 (17) µg/m^3 Copollutants PM_{10} BS Sulfate NO_2	Among symptomatic adults living in urban areas, the prevalence of >20% decrement in morning PEF was associated with SO2. Moreover, there were no associations found with prevalence of bronchodilator use, LRS, >10% decrement in morning PEF and >10% and >20% decrement in evening PEF. In the nonurban areas, there was no consistent association between air pollution and respiratory health. In the nonsymptomatic adults, no consistent associations observed between health effects and air pollutants, but a significant and positive association was observed with URS in the nonurban area at 1 day Lag. Range of Spearman correlation coefficients between 24-h avg conc SO2 and copollutants: PM_{10}: 0.31, 0.78 BS: 0.21, 0.75 Sulfate: 0.29, 0.69 NO_2: 0.47, 0.51 Odds ratio (per 40 µg/m^3 SO_2) symptomatic adults In urban areas >10% decline in PEF Morning Lag 0: 0.86 (0.60, 1.23); Lag 1: 0.97 (0.68, 1.39) >20% decline in PEF Morning Lag 0: 1.33 (0.66, 2.71); Lag 1: 1.98 (1.03-3.79) LRS Lag 0: 1.01 (0.84, 1.20); Lag1: .97 (0.82, 1.16) 5-day mean: 0.71 (95% CI: 0.53 to 0.95) URS Lag 0: 1.15 (0.97, 1.37); Lag 1: 1.06 (0.90, 1.26) Bronchodilator use Lag 0: 1.09 (0.93, 1.28); Lag 1: 1.05 (0.89, 1.24) Lag 2: 0.85 (0.72, 0.99) In nonurban areas >10 % decline in PEF Morning Lag 0: 79 (0.48, 1.29); Lag 1: 1.08 (0.68, 1.72) >20% decline in PEF Morning Lag 0: 0.79 (0.22, 2.88); Lag 1: 71 (0.13, 4.02) LRS Lag 0: 1.11 (0.94, 1.30); Lag 1: 1.04 (0.88, 1.22) URS Lag 0: 0.97 (0.79, 1.20); Lag 1: 1.20 (0.98, 1.47) Bronchodilator use Lag 0: 1.04 (0.91, 1.18); Lag 1: 1.08 (0.95, 1.22)
Ward et al. (2002) Birmingham and Sandwell, England 1996	Children ages 9-yrs old in 5 different schools were given a questionnaire and administered PEF measurement in summer and/or winter. Study used bivariate correlation, linear and logistic regressions for analysis	Median, Range (ppb): Winter: 5.4 (2-18) Summer: 4.7 (2-10) Copollutants: NO_2 ; O_3; PM_{10} ; $PM_{2.5}$; H+; Cl^-; HCl; HNO_3; NH_3; NH_4+; NO_3−; SO_4^{2-}	No consistent association was found between the 24-h avg SO_2 and risk of wheezing bronchitis. However, after a 7-day lag, a 10 ppb increase in the 24-h avg SO_2 was associated with a 21% increase in risk of wheezing bronchitis. Wake at night with cough- Lag 0 day Winter 1.00 (0.91, 1.10) Summer 1.00 (0.87, 1.14)

STUDY	METHOD	POLLUTANTS	FINDINGS
Ward et al. (2002) Birmingham and Sandwell, England Jan-Mar 1997 May-July 1997	Panel study of 162 children (9 yrs at time of enrollment) from two inner city locations to investigate the association between ambient acid species with PEF and symptoms. Daily symptoms and twice-daily peak flow measurements were recorded over 8 wk periods in the summer and winter. 39 of the children reported wheezing in the past 12 mos. Linear regression used for PEF and logistic regression for symptoms.	24-h avg SO_2 Winter: Jan 13-Mar 10, 1997 MediaN: 5.4 ppb Range: 2, 18 ppb Summer: May 19-July 14, 1997 MediaN: 4.7 ppb Range: 2, 10 ppb Copollutants: NO_2 , O_3, PM_{10} , H^+ , Cl^- , HCl , HNO_3 , NH_3 , NH_4^+ , NO_3^- , SO_4^{2-} SO_2 concentrations were not related to changes in PEF or respiratory symptoms	In the summer, changes in morning PEF were associated with SO_2 at 3-days lag and the 7-day mean SO_2. Prevalence of cough associated with SO_2 on the same day. In the winter SO_2 was only associated with symptom of feeling ill on the same day. 24-h avg SO_2 (per 4.0 ppb in winter; per 2.2 ppb in summer) Data also available for 3-,4-, and 7-day Lag Change in PEF (L/min) Morning- Lag 0-day Winter -0.60 (-2.51, 1.32). Summer 0.91 (-0.95, 2.78) Afternoon- Lag 0-day Winter -0.32 (-2.71, 2.04). Summer -0.89 (-2.61, 0.83) Morning- Lag 1-day Winter 0.08 (-1.67,1.86). Summer 0.29 (-1.56, 2.14) Afternoon- Lag 1-day Winter -0.88 (-2.87, 1.10). Summer -0.02 (-1.68, 1.65) Odds ratio for symptoms Cough-Lag 0-day Winter 0.92 (0.81, 1.05). Summer 1.08 (1.02, 1.15) Ill-Lag 0-day Winter 1.09 (1.01, 1.18). Summer 1.05 (0.96, 1.14) Shortness of breath-Lag 0-day Winter 1.02 (0.93, 1.13). Summer 0.98 (0.87,1.10) Cough-Lag 1-day Winter 1.00 (0.87, 1.15). Summer 1.04 (0.97, 1.11) Ill-Lag 1-day Winter 1.03 (0.95, 1.11). Summer 1.02 (0.94, 1.12) Shortness of breath-Lag 1-day Winter 1.00 (0.90, 1.09). Summer 1.00 (0.89, 1.13) Wake at night with cough- Lag 0 day Winter 1.00 (0.91, 1.10). Summer 1.00 (0.87, 1.14) Wake at night with cough- Lag 1 day Winter 1.05 (0.96, 1.15). Summer 1.02 (0.89, 1.16) Wheeze- Lag 0 day Winter 0.96, (0.85, 1.07). Summer 1.05 (0.92, 1.19) Wheeze-Lag 1 day Winter 0.96 (0.86, 1.07). Summer 1.00 (0.88, 1.13 Summer change in PEF 2.7 (1.03, 4.38) per 2.2 ppb SO_2 Lag 3 days ($p < 0.05$) Summer change in PEF 6.83 (0.98, 12.69) per 2.2 ppb SO_2 Lag 0-6 days ($p < 0.05$)
LATIN AMERICA			
Pino et al. (2004) Santiago, Chile 1995-1997	Cohort study of 492 infants recruited at 4 mos of age and followed through the first yr of life to determine the association between air pollution on wheezing bronchitis.	Mean concentration of SO_2 (ppb) Mean: 11.6 SD: 8.1 MediaN: 10.0 $PM_{2.5}$ NO_2	During summer, SO_2 played a role in adverse health effects after taking into account distance between community and health providers. During winter, no relationship was found. Study did not provide effect estimates.
Romieu et al. (1996) Mexico City, Mexico Apr-Jul 1991 Nov 1991-Feb 1992	Panel study of 71 mildly asthmatic children (5 to 13 yrs) to assess the relationship between air pollution and childhood asthma exacerbation. Children measured PEF three times daily and recorded daily symptoms and medication use. Examined both incidence and prevalence of symptoms. Lower respiratory symptoms, cough, phlegm, wheeze, and/or difficulty breathing.	24-h avg SO_2 (ppm) Mean: 0.09 SD: 0.05 Range: 0.02, 0.20 O_3 PM_{10} $PM_{2.5}$ NO_2	Found a short, marked decrease in FVC and FEV1 in smokers after exposure to SO_2 that lasted for up to 30 h. Relative risk per IQR SO_2 (5.68 ppb) Total absences: 1.03 (1.02, 1.05) Non-illness related absences: 0.95 (0.92, 0.99) Illness related absences: 1.09 (1.07, 1.12) 2-pollutant model with O_3: 1.10 (1.08, 1.13)

STUDY	METHOD	POLLUTANTS	FINDINGS
ASIA			
Chen et al. (1999) Three towns in Taiwan: Sanchun, Taihsi, Linyuan May 1995-Jan 1996	Cross-sectional panel study of 895 children (8 to 13 yrs) to evaluate the short-term effect of ambient air pollution on pulmonary function. Single and multipollutant models adjusted for sex, height, BMI, community, temperature, and rainfall. Examined 1, 2, and 7-day lag effects.	Peak concentrations of SO_2 Range: 0, 72.4 ppb Day-time avg and 1-day lag CO NO_3 PM_{10} (r = 0.63) NO_2 (r = 0.71)	During the dust days, SO_2 levels were significantly lower compared to control days. SO_2 had no significant effect on PEF variability or night symptoms. Regression estimate and standard error per ln SO_2 ($\mu g/m^3$) Height-adjusted FEV_1 (mL): −35.6 (17.3) Height-adjusted FVC (mL): −131.4 (18.8)
Jadsri et al. (2006) Thailand 1993-1996	Spatial regression analysis of outpatient disease occurrence (respiratory system diseases; ICD chapter 10) in 25 communities in Rayong Province.	--- TSP, NO_X	An inverse linear association found between ln outdoor SO_2 and FEV_1 and FVC after adjusting for age, height and sex.
Min et al. (2008) Korea	Panel study consisting of 867 smokers, former smokers, and never smokers 20-86 yrs old. Used linear regression analysis, adjusting for age, height, gender, and a diagnosis of asthma to examine the combined effects of cigarette smoking and SO_2 on lung function. Lung function measurements used in this analysis included forced vital capacity (FVC), forced expiratory volume in 1 sec (FEV1), percent predicted value of FVC (FVC % pred), and percent predicted value of FEV1 (FEV1 % pred).	24-h avg (ppm): 0.006	Found a short, marked decrease in FVC and FEV, in smokers after exposure to SO_2 that lasted for up to 30 h. Study did not provide effect estimates.
Park et al. (2002) Seoul, Korea Mar 2, 1996 to Dec 22, 1999	Time-series analysis of school absenteeism due to illness and air pollution in one elementary school in Seoul. School located in area with heavy traffic. Avg enrollment in 1996 was 1,264.	24-h avg SO_2 Mean: 9.19 ppb SD: 4.61 Range: 2.68, 28.11 PM_{10} NO_2 CO (r = 0.67) O_3	SO_2, PM_{10}, and O_3 associated with illness related school absenteeism. SP2 and O_3 are protective for non-illness related absences. Relative risk per IQR SO_2 (5.68 ppb) Total absences: 1.03 (1.02, 1.05) Non-illness related absences: 0.95 (0.92, 0.99) Illness related absences: 1.09 (1.07, 1.12) 2-pollutant model with O_3: 1.10 (1.08, 1.13)
Park et al. (2005a) Korea Mar to June 2002	Panel study of 69 patients (16 to 75 yrs) diagnosed with asthma by bronchial challenge or by bron-chodilator response. Patients recorded twice-daily PE, symptoms at the end of each day (cough, wheeze, chest tightness, shortness of breath, sputum changes and the next morning, night awakenings). During the study period, 14 Asian dust days were identified. GEE and generalized additive Poisson regression model used in analysis.	Daily avg SO_2 Control Days: 0.0069 (0.0019) ppm Dust days: 0.0052 (0.0010) ppm Copollutants: PM_{10}, NO_2, CO, O_3	During the dust days, SO_2 levels were significantly lower compared to control days. SO_2 had no significant effect on PEF variability or night symptoms. Relative risk based on Poisson log-linear regression analysis PEF variability (>20%) 0.76 (0.37, 1.56) Night symptoms: 0.98 (0.59, 1.51)

STUDY	METHOD	POLLUTANTS	FINDINGS
Xu et al. (1991) Beijing, China Three areas: industrial, residential, and suburban (control) Aug 1986	Cross sectional survey of 1140 adults (40 to 69 yrs) who had never smoked living in three areas of Beijing, to determine respiratory health effects of indoor and outdoor air pollution. A trained interviewer obtained pulmonary function measurements and determined history of chest illnesses, respiratory symptoms, cigarette smoking, occupational exposure, residential history, education level, and type of fuel used for cooking and heating.	Annual mean concentration of SO_2 ($\mu g/m^3$) Residential: 128 Industrial: 57 SuburbaN: 18 TSPM	An inverse linear association found between Ln outdoor SO_2 and FEV_1 and FVC after adjusting for age, height and sex. Regression estimate and standard error per Ln SO_2 ($\mu g/m^3$) Height-adjusted FEV_1 (mL): −35.6 (17.3) Height-adjusted FVC (mL): −131.4 (18.8)

Table F-2. Associations of short-term exposure to SO_2 with emergency department visits and hospital admissions for respiratory diseases

STUDY	METHODS	POLLUTANTS	FINDINGS
UNITED STATES			
Gwynn* et al. (2000) Buffalo and Rochester, NY United States Period of Study: 1988-1990 Days: 1,090	Hospital Admissions Outcome(s) (ICD9): Respiratory admissions: Acute bronchitis/ bronchiolitis (466); Pneumonia (480-4860); COPD and Asthma (490-493, 496) Age groups analyzed: 6 Study design: Time-series N: 24, Statistical analyses: Poisson regression with GLM and GAM Covariates: season, day of wk, holiday, temperature, relative humidity Lag: 0-3 days	24-h avg SO_2 (ppb): MiN: 1.63 25th: 8.4 Mean: 12.2 75th: 15.4 Max: 37.7 H+; r = 0.06 SO_4^{2-} (r = 0.19) PM_{10} (r = 0.19) O_3 (r = 0.02) NO_2 (r = 0.36) CO (r = 0.11) COH (r = 0.19)	Significant associations observed between several pollutants and various health-effect outcomes make it difficult to discriminate the influence of a single-pollutant. This is likely the a result of the relatively high intercorrelations among the various pollutants, as well as the possible interactive role of several pollutants in the reported associations. Increment: 25.5, 7.0 ppb (Max-Mean; IQR) SO_2 alone: Max-Mean RR 1.096 (t = 3.05) lag 0 IQR RR 1.025 (t = 3.05) lag 0

STUDY	METHODS	POLLUTANTS	FINDINGS
Ito et al. (2007) New York, NY 1999-2002	ED Visits Outcome(s): Asthma Study design: Time-series Statistical Analysis: Poisson GLM Age groups analyzed: All ages Covariates: Adjustment for temperature (same day and avg lag 1-3), dew point (same day and avg lag 1-3) # Hospitals: 11 Lag(s): Avg 0 and 1 day	All yr 24-h avg (ppb): 7.8 (4.6) 5th: 3 25th: 5 50th: 7 75th: 10 95th: 17 Warm mos (Apr-Sep) 24-h avg (ppb): 5.4 (2.2) 5th: 3 25th: 4 50th: 5 75th: 7 95th: 10 Cold Mos (Oct-Mar) 24-h avg (ppb): 10.2 (5.1) 5th: 4 25th: 6 50th: 9 75th: 13 95th: 19 Copollutants: $PM_{2.5}$; NO_2; O_3; CO	In single-pollutant models, NO_2 was found to have the most significant association with asthma ED visits for all-yr and warm mos. SO_2 was significantly associated with asthma ED visits for all single-pollutant models for all-yr and both the warm and cold mos. In copollutant models for the warm mos, NO_2 eliminated the association between SO_2 and asthma ED visits. This result is consistent with the monitor-to-monitor correlations, which suggested that NO_2 had less exposure error compared to SO_2. Warm Mos (Apr-Sep) (Weather model including smoothing terms for same day temperature and avg lag 1-3 day temperature.) Relative Risk (95% CI) (per 6 ppb SO_2) 1.20 (1.13, 1.28)
Jaffe et al. (2003) 3 cities, Ohio, United States (Cleveland, Columbus, Cincinnati) Period of Study: 7/91-6/96	ED Visits Outcome(s) (ICD9): Asthma (493) Age groups analyzed: 5-34 Study design: Time-series; N: 4,416 Statistical analyses: Poisson regression using a standard GAM approach Covariates: City, day of wk, wk, yr, min temperature, overall trend, dispersion parameter Season: June to Aug only Dose-response investigated: Yes Lag: 0-3 days	24-h avg: Cincinnati: 35.9 (25.1) µg/m^3 Range: 1.7, 132 Cleveland: 39.2 (25.3) µg/m^3 Range: 2.6, 167 Columbus: 11.1(8.5) µg/m^3 Range: 0, 56.8 Cincinnati: PM_{10} (r = 0.31) NO_2 (r = 0.07) O_3 (r = 0.14) Cleveland: PM_{10} (r = 0.29) NO_2 (r = 0.28) O_3 (r = 0.26) Columbus: PM_{10} (r = 0.22) NO_2 (r = NR) O_3 (r = 0.42)	Wide confidence intervals for data from Cleveland and Columbus make these data not significant and unstable. Only data for Cincinnati was considered statistically significant and demonstrated a concentration response function that was positive. No multipollutant models were utilized. Increment: 50 µg/m^3 Cincinnati: 35% (9, 21) lag 2 Cleveland: 6% (−7, 21) lag 2 Columbus: 26% (−25, 213) lag 3 All cities: 12% (1, 23) Attributable risk from SO_2 increment: Cincinnati: 4.2% Cleveland: 0.66% Columbus: 2.94%
Lin et al. (2004c) New York (Bronx County), United States Period of Study: 6/1991-12/1993	Hospital Admissions Outcome(s) (ICD9): Asthma (493) Age groups analyzed: 0-14 Study design: Case-control N: 2,629 cases; 2,236 controls Statistical analyses: logistic regression Covariates: Race and ethnicity, age, gender, season Statistical package: Lag: 0,1,2,3, 0-3	Cases: 24-h avg: 16.78 ppb 50th: 13.72 Range: 2.88, 66.35 Controls: 24-h avg: 15.57 ppb 50th: 13.08 Range: 2.88, 66.35 Quartile Concentrations (ppb) : Q1: 2.88, 8.37 Q2: 9.37, 13.38 Q3: 13.5, 20.91 Q4: 20.21, 66.35	Odds ratios for risk of hospitalization for asthma increased with each quartile of SO_2 concentration. Lag 1, 2, or 3 all showed a concentration response that was positive for odds ratio as each quartile was compared to the total exposure group (trend p > 0.001). Quartile (24-h avg) Q2 OR 1.26 lag 3 Q3 OR 1.45 lag 3 Q4 OR 2.16 (1.77, 2.65) lag 3 Quartile (1-h max) Q4 OR 1.86 (1.52, 2.27) lag 3 For a 4 ppb increase in SO_2 (24-h avg) RR 1.07 (1.04, 1.11)

STUDY	METHODS	POLLUTANTS	FINDINGS
Michaud et al. (2004) Hilo, Hawaii 2/21/1997-5/31/2001	ED Visits Outcome(s) (ICD9): COPD (490-496); Asthma (493, 495); bronchitis (490, 491), other COPD (492, 494, 496) Age groups analyzed: All Study design: Time-series Statistical analyses: Exponential regression models Covariates: temporal variables, day of wk, meteorology Statistical package: Stata, SAS Lag: 0,1,2,3 days	1-h max: 1.92 (12.2) ppb Range: 0.0, 447 24-h avg: 1.97 (7.12) ppb Range: 0.0, 108.5 PM1	The lack of organic carbon shows the pure SO_2 effect uncontaminated by vehicle emissions. Asthma is associated with Vog, but Vog is not a major cause of asthma in Hawaii. The strongest association was with the mo of the yr. Admission for asthma and respiratory conditions was higher in the winter compared to the summer, based on admission per day (observational-not statistical analysis). Increment: 10 ppb COPD RR 1.04 (0.99, 1.09) lag 1 RR 1.04 (1.00, 1.09) lag 2 RR 1.07 (1.03, 1.11) lag 3 Asthma RR 1.01 (1.00, 1.10) lag 1 RR 1.02 (1.03, 1.12) lag 2 RR 1.02 (1.03, 1.12) lag 3 Bronchitis RR 1.01 (0.93, 1.13) lag 1 RR 0.99 (0.88, 1.05) lag 2 RR 1.01 (1.00, 1.14) lag 3 Other COPD RR 1.00 (0.78, 1.23) lag 1 RR 0.96 (0.62, 1.11) lag 2 RR 0.98 (0.75, 1.16) lag 3
Moolgavkar* et al. (1997) United States: Minneapolis-St. Paul; Birmingham Period of Study: 1986-1991	Hospital Admissions Outcome(s) (ICD9): COPD including asthma (490-496), Pneumonia (480-487) Age groups analyzed: 65+ Study design: Time-series Statistical analyses: Semi-parametric Poisson regression, GAM Covariates: day of wk, season, temporal trends, temperature Statistical package: S Plus Lag: 0-3 days	SO_2 24-h avg (ppb): <u>Minneapolis:</u> Mean: 4.82 10th: 1.9 25th: 2.66 50th: 4.02 75th: 6.0 90th: 8.5 <u>Birmingham:</u> Mean: 6.58 10th: 2.2 25th: 3.7 50th: 6.0 75th: 8.6 90th: 11.6 <u>Minneapolis:</u> PM_{10} (r = 0.08) NO_2 (r = 0.09) CO (r = 0.07) O_3 (r = −0.12) <u>Birmingham:</u> PM_{10} (r = 0.17) CO (r = 0.16) O_3 (r = 0.02)	SO_2 with NO_2 and PM_{10} were associated with hospital admissions. Evidence of mixture effects was found. No single-pollutant was more important than the other for respiratory admissions. Each pollutant was associated with admissions except CO. Consideration of four pollutants together showed the strongest association with ozone. No pollutant other than O_3 was stable in its association with hospital admissions. No effects were reported for Birmingham. Positive results were only observed in Minneapolis. Increment: 3.5 ppb Sum of Pneumonia and COPD 1.6% (−0.1, 3.3) lag 2 Pneumonia Only Minneapolis: 65+ 0.9% (−1.1, 2.9) lag 2 20 df 0.5% (−1.5, 2.5) lag 2 130 dfS

STUDY	METHODS	POLLUTANTS	FINDINGS
Moolgavkar (2000) Reanalysis (2003a) Multicity, United States: Chicago, Los Angeles, Maricopa County, (Phoenix) Period of Study: 1987-1995	Hospital Admissions Outcome(s) (ICD9): COPD including asthma (490-496) Age groups analyzed: 0-19, 20-64, 65+ (LA only) Study design: Time-series Statistical analyses: Poisson regression, GAM Covariates: Day of wk, temporal trends, temperature, relative humidity Lag: 0-5 days	Chicago: MediaN: 6 ppb 25th: 4. 75th: 8 Range: 0.5, 36 Los Angeles: MediaN: 2 ppb 25th: 1. 75th: 4 Range: 0, 16 Maricopa: MediaN: 2 ppb 25th: 0.5. 75th: 4 Range: 0, 14 Chicago: PM_{10} (r = 0.42) CO (r = 0.35) NO_2 (r = 0.44) O_3 (r = 0.01) Los Angeles: $PM_{2.5}$ (r = 0.42) PM_{10} (r = 0.41) CO (r = 0.78) NO_2 (r = 0.74) O_3 (r = −0.21) Maricopa: PM_{10} (r = 0.11) CO (r = 0.53) NO_2 (r = 0.02) O_3 (r = −0.37)	In Los Angeles there was a significant association with and hospital admissions for COPD. SO_2 may be acting as a surrogate for other pollutants since heterogeneous responses found in different cities are inconsistent with a cause-effect model. Increment: 10 ppb COPD, >65 yrs Chicago lag 0: 4.87 (t = 3.18) GAM-100 LA lag 0: 2.84 (t = 13.32) GAM-30 LA lag 0: 1.80 (t = 9.60) GAM-100 LA lag 0: 1.78 (t = 7.72) NS-100

STUDY	METHODS	POLLUTANTS	FINDINGS
NY Department of Health (2006) Bronx and Manhattan, NY 1999-2000	ED Visits Outcome(s) (ICD9): Asthma (493), for infants (466.1 and 786.09) Study design: Time-series Statistical Analysis: Poisson regression with GLM Statistical package: S-Plus Age groups analyzed: All ages Covariates: Season, day-of-wk, temperature # Hospitals: 22 Lag(s): Avg 0- to 4-day lags	24-h avg (ppm): 0.011 (0.0072) PM_{10} $PM_{2.5}$ OC EC Cr Fe Pb Mn Ni Zn H+ Sulfate $O3$ NO_2 SO_2	In single-pollutant models, $PM_{2.5}$, SO_2, O_3, and NO_2 were all found to be significantly associated with asthma ED visits in a community, Bronx, with a high prevalence of asthma. This association was maintained in both two- and three-pollutant models for O_3 and SO_2. Single-Pollutant Models Relative Risk (95% CI) (per 0.011 ppm SO_2) 5-day moving avg Manhattan: 0.99 (0.88, 1.12) Bronx: 1.11 (1.06, 1.17) Relative Risk (95% CI) (per 0.0072 ppm SO_2) Bronx: 1.07 (1.04, 1.11) Relative Risk based on Daily Max Hourly SO_2 (95% CI) (per 0.0227 ppm SO_2) Manhattan: 0.96 (0.86, 1.07) Bronx: 1.07 (1.03, 1.12) Relative Risk (95% CI) (per 0.0072 ppm SO_2)-model excludes temperature ManhattaN: 0.99 (0.88, 1.11) Bronx: 1.11 (1.06, 1.17) Relative Risk (95% CI) (per 0.0072 ppm SO_2)- By Gender Manhattan Male: 0.90 (0.75, 1.07); Female: 1.08 (0.91, 1.29) Bronx Male: 1.08 (1.00, 1.17); Female: 1.14 (1.06, 1.23) Relative Risk (95% CI) (per 0.0072 ppm SO_2)-By Age Manhattan 0-4: 0.82 (0.59, 1.15). 5-18: 1.03 (0.77, 1.37) 19-34: 1.01 (0.76, 1.35) 35-64: 1.04 (0.86, 1.25). 65+: 0.88 (0.57, 1.37) Bronx 0-4: 1.13 (1.01, 1.26). 5-18: 1.03 (0.92, 1.16) 19-34: 1.06 (0.93, 1.21). 35-64: 1.18 (1.07, 1.30) 65+: 1.12 (0.88, 1.42) Two-Pollutant Models Relative Risk (95% CI) (per 0.0072 ppm SO_2) 5-day moving avg Manhattan SO_2 + Max 8-h O_3: 0.99 (0.88, 1.12) SO_2 + FRM $PM_{2.5}$: 0.97 (0.85, 1.11) SO_2 + Max $PM_{2.5}$: 0.98 (0.85, 1.12) SO_2 + NO_2: 1.01 (0.87, 1.16) Bronx SO_2 + Max 8-h O_3: 1.11 (1.05, 1.17) SO_2 + FRM $PM_{2.5}$: 1.11 (1.04, 1.18) SO_2 + Max $PM_{2.5}$: 1.09 (1.03, 1.16) SO_2 + NO_2: 1.11 (1.04, 1.17)
Norris et al. (1999) Seattle, Washington 1995-1996	ED Visits Outcome(s) (ICD9): Asthma (493) Study design: Time-series Statistical Analysis: Semiparametric Poisson regression model Statistical package: S-Plus Age groups analyzed: < 18 Covariates: Adjustments for day-of-wk indicator variables, time trends, temperature, dew point temperature # Hospitals: 6 Lag(s): 0, 2	24-h avg (ppb): 6.0 (3.0) Range: 1.0, 21.0 1-h max (ppb): 16.0 (14.0) Range: 2.0, 84.0 Copollutants: PM_{10}, Dry light scattering, NO_2,CO, O_3	A significant association was found between asthma emergency department visits in children and $PM_{2.5}$ and CO. Estimates were not found to be different between high and low hospital utilization areas. SO_2 was negatively associated with asthma emergency department visits in high utilization areas, and positively associated in low utilization areas. Relative Rates (95% CI) (per 3 ppb 24-h avg SO_2; per 12 ppb 1-h max SO_2) High Utilization Areas 24-h avg: 0.92 (0.83, 1.03); 1-h max: 0.99 (0.89, 1.10) Low Utilization Areas 24-h avg: 1.09 (1.00, 1.19); 1-h max: 1.09 (1.00, 1.19) All Areas 24-h avg: 0.97 (0.91, 1.04) lag 0; 1-h max: 1.02 (0.95, 1.09) lag 2

STUDY	METHODS	POLLUTANTS	FINDINGS
Peel et al. (2005) Atlanta, GA, United States Period of Study: 1/93-8/2000	ED Visits Outcome(s) (ICD 9): All respiratory (460-6, 477, 480-6, 480-6, 490-3, 496); Asthma (493); COPD (491-2, 496); Pneumonia (480-486); Upper Respiratory Infection (460-6, 477) Age groups analyzed: All Study design: Time-series. N: 484,830. # of Hospitals: 31 Statistical analyses: Poisson Regression, GEE, GLM, and GAM (data not shown for GAM) Covariates: Day of wk, hospital entry/exit, holidays, time trend; season, temperature, dew point temperature Statistical package: SAS, S-Plus Lag: 0 to 7 days. 3 day moving avgs.	1-h max: 16.5 (17.1) ppb 10th%: 2.0 90th%: 39.0 O_3 NO_2 CO $PM_{2.5}$ Evaluated multipollutant models (data not shown)	Estimates from distributed lag models (0-13 days) tend to be higher than for 3-day moving avg. Positive associations for URI and COPD with SO_2 were noted for unconstrained lags (0-13 days) that covered the previous two weeks of exposure. Increment: 20 ppb All respiratory RR 1.008 (0.997, 1.019) lag 0-2, 3-day moving avg Upper Respiratory Infection (URI) RR 1.010 (0.998, 1.024) lag 0-2, 3-day moving avg Asthma All: 1.001 (0.984, 1.017) lag 0-2, 3-day moving avg Pneumonia RR 1.003 (0.984, 1.023) lag 0-2, 3-day moving avg COPD RR 1.016 (0.985, 1.049) lag 0-2, 3-day moving avg
Schwartz (1995) New Haven, CT Tacoma, WA United States Period of Study: 1988-1990	Hospital Admissions Outcome(s) (ICD 9): All respiratory admissions (460-519) Age groups analyzed: ≥65 Study design: Time-series N: 13,470 Statistical analyses: Poisson regression, log linear regression using GLM and GAM Covariates: dewpoint, temp, long-term trends, days of wk Statistical package: S- Plus Lag: 0-1	24-h avg New Haven Mean 78 μg/m^3 (29.8 ppb) 10th: 23 25th: 35 50th: 78 75th: 100 90th: 159 Tacoma Mean: 44 μg/m^3 (16.8 ppb) 10th: 15 25th: 26 50th: 40 75th: 56 90th: 74 Copollutants: $PM_{2.5}$ O_3	In New Haven, risk associated with SO_2 was not affected by inclusion of $PM_{2.5}$ in the model and the effect of $PM_{2.5}$ was not strongly affected by inclusion of SO_2. This suggests that in New Haven, SO_2 and $PM_{2.5}$ acted independently. In Tacoma, 2-pollutant model analysis showed risk associated with SO_2 was attenuated by $PM_{2.5}$. This suggested risks associated with SO_2 and $PM_{2.5}$ were not independent. Possibly, SO_2 acts as a surrogate for $PM_{2.5}$ in this city. Increment: 50 μg/m^3 or 18.8 ppb New Haven, CT RR = 1.03 (CI 1.02,1.05), lag 0-1. $p < 0.001$ 2-pollutant model with $PM_{2.5}$: RR = 1.04 (CI 1.02, 1.06) $p < 0.001$ Tacoma, WA RR = 1.06 (CI 1.01, 1.12), lag 0-1. $p > 0.02$ 2-pollutant model with $PM_{2.5}$: RR = 0.99 (CI 0.93, 1.06) $p > 0.5$
Schwartz et al. (1996) Cleveland, OH Period of Study: 1988-1990	Hospital Admissions Outcome(s) (ICD9): All respiratory disease Age groups analyzed: ≥ 65 Study design: Time-series Statistical analyses: Poisson regression Covariates: Season, temperature, day of wk Statistical package: Lag: 0-1	24-h avg: 35 ppb 10th: 13 25th: 20 50th: 31 75th: 45 90th: 61 $PM_{2.5}$ O_3	Significant associations were seen for $PM_{2.5}$ and O_3, with somewhat weaker evidence for SO_2. Increment: 100 μg/m^3 RR 1.03 (0.99, 1.06) lag 0-1

STUDY	METHODS	POLLUTANTS	FINDINGS
Sheppard et al. (1999) Reanalysis (2003) Seattle, WA, United States Period of Study: 1987-1994	Hospital Admissions Outcome(s) (ICD9): Asthma (493) Age groups analyzed: < 65 Study design: Time-series N: 7,837 # of Hospitals: 23 Statistical analyses: Poisson regression with adjustment for auto-correlation. Covariates: Statistical package: S-Plus Lag: 0,1,2,3	24-h avg: 8 ppb IQR: 5 ppb 10th: 3.0 25th: 5.0 50th: 8.0 75th: 10.0 90th: 13.0 $PM_{2.5}$ (r = 0.31) $PM_{2.5}$ (r = 0.22) O_3 (r = 0.07) CO (r = 0.24)	Sources of SO_2 adjacent or near to monitoring site. Low concentrations. No association with SO_2 for asthma but positive association for appendicitis. Increment: 5 ppb (IQR) GAM with stricter criteria: 1.0% (−2.0, 3.0) lag 0 GLM with natural spline smoothing: 0.0% (−3.0, 4.0) lag 0
Sinclair and Tolsma (2004) Atlanta, GA 1998-2000	ED Visits Outcome(s): asthma, upper, and lower respiratory infections. Study design: Time-series investigation Statistical Analysis: Single pollutant Poisson general linear modeling Statistical package: SAS v. 8.02 Age Groups Analyzed: All # Hospitals: 10 Lag(s): 0-8 days	1-hour Max Mean: 19.28 ppbv SD:16.28 $PM_{2.5}$ PM_{10} NO_2 CO O_3	No significant findings for child or adult asthma. Significant negative associations with upper respiratory infections for 6-8 day lag (RR = 0.98). Significant positive association with lower respiratory infections for 0-2 day lag (RR = 1.067). Not provided.
Tolbert et al. (2007) Atlanta, GA 1993-2004	ED Visits Outcome(s) (ICD9): Cardiovascular (410-414, 427, 428, 433-437, 440, 443-445, 451-453); Respiratory (493, 786.07, 786.09, 491, 492, 496, 460-465, 477, 480-486, 466.1, 466.11, 466.19) Study design: Time-series Statistical Analysis: Poisson Generalized Linear Model (GLM). Statistical package: SAS Age groups analyzed: All ages Covariates: Adjustment for day-of-wk, hospital entry, holidays, time, temperature, dew point temperature # Hospitals: 41. N: 238,360 (Cardiovascular); 1,072,429 (Respiratory) Lag(s): 3-day moving avg	1-h max (ppb): 14.9 Range: 1.0, 149.0 10th: 2.0. 25th: 4.0 75th: 20.0. 90th: 35.0 PM_{10} $PM_{2.5}$ O_3 NO_2 CO Sulfate Total Carbon Organic Carbon EC Water-Soluble Metals Oxygenated Hydrocarbons	In single pollutant models, O_3, PM_{10}, CO, and NO_2 significantly associated with ED visits for respiratory outcomes. Relative Risk (95% CI) (per 16.0 ppb SO_2) 1.003 (0.997, 1.009)

STUDY	METHODS	POLLUTANTS	FINDINGS
Wilson et al. (2005) Multicity, United States (Portland, ME and Manchester, NH) Period of Study: 1996-2000 (Manchester) 1998-2000 (Portland)	ED Visits Outcome(s) (ICD 9 codes): All respiratory (460-519); Asthma (493) Age groups analyzed: 0-14 yrs; 15-64 yrs; ≥65 yrs Study design: Time-series Statistical analyses: Multiple regression analysis standard GAM with more stringent criteria parameters Covariates: Time-trend, season, influenza, temperature, humidity, precipitation Statistical package: S-Plus Lag: 0-2	SO_2 1-h max: Mean, (SD) (ppb) Portland All yr: 11.1 (9.1) Winter: 17.1 (12.0) Spring: 10.0 (7.1) Summer: 9.1 (8.0) Fall: 9.7 (7.1) Manchester All yr: 16.5 (14.7) Winter: 25.7 (15.8) Spring: 14.8 (12.0) Summer: 10.6 (15.1) Fall: 14.6 (11.1) Copollutants: O_3 $PM_{2.5}$	Elevated levels of SO_2 were positively associated with elevated respiratory and asthmatic ER visits. The significance of these relationships is not sensitive to analytic or smoothing techniques. Increment: 6.3 ppb (IQR) for Portland; IQR for Manchester Portland: All respiratory All ages RR 1.05 (1.02, 1.07) lag 0 0-14 yrs RR 0.98 (0.93, 1.02) lag 0 15-64 yrs RR 1.06 (1.03, 1.09) lag 0 >65 yrs RR 1.10 (1.05, 1.15) lag 0 Asthma All ages RR 1.06 (1.01, 1.12) lag 2 0-14 yrs RR 1.03 (0.93, 1.15) lag 2 15-64 yrs 1.07 (1.01, 1.15) lag 2 >65 yrs RR 1.07 (0.90, 1.26) lag 2 Manchester: All respiratory All ages RR 1.01 (0.99, 1.02) lag 0 0-14 yrs RR 1.00 (0.96, 1.04) lag 0 15-64 yrs RR 1.00 (0.98, 1.03) lag 0 >65 yrs RR 1.04 (0.97, 1.11) lag 0 Asthma All ages RR 1.03 (0.98, 1.09) lag 2 0-14 yrs RR 1.11 (0.98, 1.25) lag 2 15-64 yrs 1.02 (0.96, 1.08) lag 2 >65 yrs RR 1.06 (0.83, 1.36) lag 2
CANADA			
Bates et al. (1990) Vancouver Region, BC, Canada Period of Study: 7/1/1984-10/31/1986	ED Visits Outcome(s) (ICD 9): Asthma (493); Pneumonia (480-486); Chronic bronchitis (491,492,496); Other respiratory (466) Age groups analyzed: All; 15-60 Study design: # of Hospitals: 9 Statistical analyses: Pearson correlation coefficients were calculated between asthma visits and environmental variables Season: Warm (May-Oct); Cool (Nov-Apr) Covariates: NR Lag: 0, 1, 2	May-Oct SO_2 1-h max: Range: 0.0137, 0.0151 ppm Nov-Apr Range: 0.012, 0.0164 ppm Number of stations: 11 May-Oct O_3 (r = 0.23) NO_2 (r = 0.67) CoH (r = 0.34) SO4 (r = 0.46) Nov-Apr O_3 (r = 0.47) NO_2 (r = 0.61) CoH (r = 0.64) SO4 (r = 0.54)	SO_2 effects depend on the season. In the summer a rise in ambient SO_2 levels was seen to coincide with a rise in respiratory related hospital admissions. Correlation Coefficients: Warm Season (May-Oct) Asthma (15-60 yrs) r = 0.118 lag 0 p < 0.01 r = 0.139 lag 1 Respiratory (15-60 yrs) r = 0.134 lag 0 p < 0.001 r = 0.164 lag 1 p < 0.001 Cool Season (Nov-Apr) Respiratory 1-14 yrs r = 0.205 lag 0 p < 0.001 r = 0.234 lag 1 p < 0.001 r = 0.234 lag 2 p < 0.001 15-60 yrs r = 0.180 lag 0 p < 0.001 r = 0.214 lag 1 p < 0.001 r = 0.215 lag 2 p < 0.001 ≥ 61 yrs r = 0.257 lag 0 p < 0.001 r = 0.308 lag 1 p < 0.001 r = 0.307 lag 2 p < 0.001 Asthma (≥ 61 yrs) r = 0.125 lag 0 p < 0.001 r = 0.149 lag 1 p < 0.001 r = 0.148 lag 2 p < 0.001 Total ER admissions (≥ 61 yrs) r = 0.13 lag 1 p < 0.01 r = 0.13 lag 2 p < 0.01

STUDY	METHODS	POLLUTANTS	FINDINGS
Burnett et al. (1997a) 16 cities Period of Study: 4/1981-12/1991 Days: 3,927	Hospital Admissions Outcome(s) (ICD9): All respiratory admissions (466, 480-6, 490-4, 496) Study design: Time-series. N: 720,519. # of Hospitals: 134. Statistical analyses: random effects relative risk regression model Covariates: Long-term trend, season, day of wk, hospital Lag: 0, 1, 2 day	1-h max SO_2 (ppb) Mean: 14.4. SD: 22.2 25th: 3 50th: 10 75th: 19 95th: 45 99th: 97 O_3 r = 0.04 Copollutants: CO, NO_2, COH	Control of SO_2 reduced but did not eliminate the ozone association with respiratory hospital admissions. Increment: 10 ppb Single-pollutant SO_2 and respiratory admissions, p = 0.134 Multipollutant model (adjusted for CO, O_3, NO_2, COH, dew point): RR 1.0055 (0.9982, 1.0128) lag 0
Burnett et al. (1997b) Toronto, Canada Period of Study: 1992-1994	Hospital Admissions Outcomes (ICD 9 codes): Respiratory tracheobronchitis (480-6), COPD (491-4, 496) Study design: Time-series Statistical analyses: Poisson regression, GEE, GAM Covariates: Temperature, dew point temperature, Long-term trend, season, influenza, day of wk Season: Summers only Lag: 0,1,2,3,4 days	Mean SO_2: 7.9 ppb. CV: 64 Range: 0, 26 5th: 1 25th: 4 50th: 7 75th: 11 95th: 18 Number of stations: 6-11 CO (r = 0.37) H+ (r = 0.45) SO_4 (r = 0.42) TP (r = 0.55) FP (r = 0.49) CP (r = 0.44) COH (r = 0.50) O_3 (r = 0.18) NO_2 (r = 0.46)	Risks of hospitalization for respiratory disease were summed for O_3, NO_2, and SO_2 at 11% increase in admissions. The proportion associated with the single-pollutant SO_2 was 3.6%. CoH was the strongest predictor of hospitalization indicating particle associated pollutants are responsible for effects and outcomes measured. Increment: 4.00 ppb (IQR) Respiratory-percent increase 4.0% (t = 4.14) lag 0 Copollutant and multipollutant models RR (t-statistic): SO_2, COH: 1.012 (1.10) SO_2, H+: 1.022 (1.96) SO_2, SO_4: 1.021 (1.93) SO_2, TP: 1.021 (1.72) SO_2, FP: 1.022 (1.92) SO_2, CP: 1.023 (2.03) SO_2, O_3, NO_2: 1.019 (1.64)
Burnett et al. (1999) Metro Toronto, Canada Period of Study: 1980-1994	Hospital Admissions Outcome(s) (ICD9): Asthma (493); obstructive lung disease (490-2, 496); Respiratory infection (464, 466, 480-7, 494) Study design: Time-series Statistical analyses: Poisson regression model with stepwise analysis Covariates: Long-term trends, season, day of wk, daily max temperature, daily min temperature, daily avg dew point temperature, daily avg relative humidity Statistical package: S-Plus, SAS Lag: 0,1,2 days, cumulative	24-h Mean: 5.35 ppb CV = 110; 5th: 0 25th: 1 50th: 4 75th: 8 95th: 17 100th: 57 Number of stations: 4 $PM_{2.5}$ (r = 0.46) $PM_{10-2.5}$ (r = 0.28) $PM_{2.5}$ (r = 0.44) CO (r = 0.37) NO_2 (r = 0.54) O_3 (r = 0.02)	The percent hospital admissions associated with SO_2 increased for: asthma, COPD, and respiratory infection. However, in multipollutant models significant increases were only seen in asthma and respiratory infection. SO_2 effects could be largely explained by other variables in the pollution mix as demonstrated by the Multipollutant model. The greatest contribution of SO_2 is to respiratory infection. However, overall SO_2 is a small factor in total hospitalization response. Increment: 5.35 ppb (Mean) Single-pollutant model percent increase (t statistic) Asthma: 1.01% (1.76) lag 0-2 OLD 0.03% (0.05) lag 0-1 Respiratory infectioN: 2.40% (5.04) lag 0-2 Multipollutant model percent increase (SE) Asthma: SO_2 + CO + O_3: 0.89% (SE < 2) SO_2 + CO + O_3 + $PM_{2.5}$: 0.69% (SE < 2) SO_2 + CO + O_3 + $PM_{10-2.5}$: 0.16% (SE < 2) SO_2 + CO + O_3 + $PM_{2.5}$: 0.76% (SE < 2) Respiratory infection: SO_2 + NO_2 + O_3: 1.85% SO_2 + NO_2 + O_3 + $PM_{2.5}$: 0.67 (SE < 2) SO_2 + NO_2 + O_3 + $PM_{10-2.5}$: 1.71 (SE ≥ 3) SO_2 + NO_2 + O_3 + $PM_{2.5}$: 1.00 (SE > 2)

STUDY	METHODS	POLLUTANTS	FINDINGS
Burnett* et al. (2001) Toronto, Canada Period of Study: 1980-1994	Hospital Admissions Outcome(s) (ICD9): Croup (464.4), pneumonia (480-486), asthma (493), acute bronchitis/bronchiolitis (466) Age groups analyzed: < 2 yrs Study design: Time-series Statistical analyses: Poisson regression with GAM Covariates: Temporal trend, day of wk, temperature, relative humidity Statistical package: S-Plus Lag: 0-5 days	1-h max SO_2 (ppb) Mean: 11.8 CV: 93 5th: 0 25th: 5 50th: 10 75th: 15 95th: 32 99th: 55 100th: 110 Number of stations: 4 O_3 (r = 0.39) SO_2 CO $PM_{2.5}$ $PM_{10-2.5}$	SO_2 had the smallest effect on respiratory admissions of all pollutants considered. Increment: NR All respiratory admissions: Single-pollutant: Percent increase: 3.1% (t = 1.900) lag 3 Multipollutant (adjusted for O_3): Percent increase: 1.21% (t = 0.67) lag 3
Cakmak et al. (2006) Canada (Calgary, Edmonton, Halifax, London, Ottawa, Saint John, Toronto, Vancouver, Windsor, Winnipeg) 1993-2000	Hospital Admissions Outcome(s) (ICD9): Respiratory (466, 480-486, 490-494, 496) Study design: Time-series Statistical Analysis: Poisson Statistical package: S-Plus Age groups analyzed: All ages Covariates: Day-of-wk, mean daily temperature, max daily temperature, min daily temperature, change in barometric pressure, mean relative humidity N: 215,544 Lag(s): 2.6 days	24-h avg: 4.6 ppb Range: 2.8 ppb to 10.2 ppb O_3 NO_2 CO	SO_2 associated with increased hospital admissions. % increase (per 4.6 ppb SO_2) Overall Single-pollutant model 1.1% (0.5, 1.8) Multi-pollutant model 0.5% (0.1, 0.9) By Gender Male: 0.4% (−0.2, 1.1); Female: 0.9% (−0.4, 2.1) By Education <Grade 9: 0.8% (0.1, 1.5) Grades 9-13: 0.9% (−0.1, 1.9) Some university/trade school: 0.8% (−0.1, 1.7) University diploma: 0.3 % (−0.9, 1.5) By Income < 21,309: 0.7% (−0.1, 1.5) 21,309-28,161: 0.5% (−0.4, 1.4) 28,161-35,905: 0.0% (−1.0, 1.0) >35,905: 0.7% (−0.4, 1.8)
Fung et al. (2006) Vancouver, BC, Canada Period of Study: 6/1/95-3/31/99	Hospital Admissions Outcome(s) (ICD9): All respiratory hospitalizations (460-519) Age groups analyzed: 65+ Study design: (1) Time-series (2) Case-crossover, (3) DM-models (Dewanji and Moolgavkar, 2000, 2002) N: 40,974 Statistical analyses: (1) Poisson, (2) conditional logistic regression, (3) DM method–analyze recurrent data in which the occurrence of events at the individual level over time is available Covariates: Day of wk Statistical package: S-Plus and R Lag: Current day, 3 and 5 day lag	SO_2 24-h avg: Mean: 3.46 ppb SD: 1.82 IQR: 2.50 ppb Range: 0.00, 12.50 CO (r = 0.61) COH (r = 0.65) NO_2 (r = 0.57) PM_{10} (r = 0.61) $PM_{2.5}$ (r = 0.42) $PM_{10-2.5}$ (r = 0.57) O_3 (r = −30.35)	No significant association was found between hospital admissions and current day SO_2 levels (lag 0). Significant associations were found with SO_2 using a 3, 5, and 7 day moving avg, with the strongest association observed with a 7 day lag. The DM method produced slightly higher relative risks compared to the Time-series and case crossover results. Increment: 2.5 ppb (IQR) SO_2 Time-series RR 1.013 (0.997, 1.028) lag 0 RR 1.030 (1.010, 1.051) lag 0-3 RR 1.032 (1.008, 1.056) lag 0-5 RR 1.031 (1.003, 1.060) lag 0-7 SO_2 Case-crossover RR 1.010 (0.992, 1.027) lag 0 RR 1.028 (1.005, 1.050) lag 0-3 RR 1.030 (1.004, 1.057) lag 0-5 RR 1.028 (0.998, 1.058) lag 0-7 SO_2 DM model RR 1.013 (0.998, 1.027) lag 0 RR 1.034 (1.015, 1.053) lag 0-3 RR 1.039 (1.016, 1.061) lag 0-5 RR 1.044 (1.018, 1.070) lag 0-7 DM method produced slightly higher RR estimates on O_3, SO_2 and $PM_{2.5}$ compared to time-series and case-crossover, and slightly lower RR estimates on COH, NO_2, and PM_{10}, though the results were not significantly different from one another.

STUDY	METHODS	POLLUTANTS	FINDINGS
Kesten et al. (1995) Toronto, ON, Canada Period of Study: 1991-1992	ED Visits Outcome(s) (ICD 9): Asthma (493) Age groups analyzed: Study design: Time-series N: 854 # of Hospitals: 1 Statistical analyses: Auto regression Statistical package: SAS Lag: 1 or 7	SO_2 24-h avg No data was provided for concentration or for correlation with other pollutants. NO_2 O_3 API (TRS, CO, TSP)	Fit of an auto-regression model with covariates linked to same day gave no evidence of association between asthma and SO_2. Despite multiple attempts to correlate individual or combinations of pollutants with air quality indices, no association was found between ER visits for asthma and ambient daily, weekly, or monthly levels of SO_2, NO_2, or O_3. No relative risks were provided.
Lin et al. (2003) Toronto, ON Period of Study: 1981-1993	Hospital Admissions Outcome(s) (ICD9): Asthma (493) Age groups analyzed: 6-12 Study design: Bi-directional case-crossover N: 7,319 Statistical analyses: Conditional logistic regression Covariates: Daily max and min temperatures and avg relative humidity Lag: Cumulative lag of 1-7 days.	SO_2 24-h avg: 0.36 ppb SD: 5.90 Range: 0, 57.00 25th: 1.00 50th: 4.00 75th: 8.00 Number of stations: 4 CO (r = 0.37) NO_2 (r = 0.54) PM_{10} (r = 0.44) O_3 (r = −0.01) $PM_{2.5}$ (r = 0.46) $PM_{10-2.5}$ (r = 0.28)	SO_2 is positively associated with asthma hospitalizations, although the relationship varies in boys and girls. Increment: 7 ppb (IQR) Boys 6-12 yrs; Girls 6-12 yrs Lag 0: OR 1.00 (0.95, 1.05); 1.04 (0.97, 1.11) Lag 0-1: OR 0.99 (0.93, 1.06); 1.04 (0.95, 1.13) Lag 0-2: OR 0.98 (0.90, 1.06); 1.05 (0.95, 1.16) Lag 0-3: OR 0.96 (0.87, 1.05); 1.09 (0.98, 1.22) Lag 0-4: OR 0.95 (0.86, 1.05); 1.13 (1.00, 1.28) Lag 0-5: OR 0.93 (0.83, 1.03); 1.17 (1.02, 1.34) Lag 0-6: OR 0.93 (0.83, 1.04); 1.20 (1.04, 1.39) Multipollutant model with $PM_{10-2.5}$ and $PM_{2.5}$ Boys 6-12 yrs; Girls 6-12 yrs Lag 0: OR 0.98 (0.93, 1.04); 1.06 (0.98, 1.14) Lag 0-1: OR 0.99 (0.91, 1.06); 1.03 (0.93, 1.14) Lag 0-2: OR 0.96 (0.88, 1.05); 1.04 (0.92, 1.17) Lag 0-3: OR 0.95 (0.85, 1.05); 1.08 (0.95, 1.23) Lag 0-4: OR 0.94 (0.84, 1.06); 1.12 (0.97, 1.29) Lag 0-5: OR 0.91 (0.80, 1.04); 1.18 (1.00, 1.38) Lag 0-6: OR 0.91 (0.80, 1.04); 1.28 (1.08, 1.51)
Lin* et al. (2004b) Vancouver, BC Period of Study: 1987-1998	Hospital Admissions Outcome(s) (ICD9): Asthma (493) Age groups analyzed: 6-12 Study design: Time-series N: 3,754 (2,331 male, 1,423 female) Statistical analyses: Semi-parametric Poisson regression with GAM (with default and more stringent criteria) Covariates: Trend, day of wk, Statistical package: S-Plus Lag: Cumulative 1-7 day	24-h avg SO_2 (ppb) Mean: 4.77 SD: 2.75 MiN: 0 25th: 2.75 50th: 4.25 75th: 6.00 Max: 24.00 Number of stations: 30 CO (r = 0.67) NO_2 (r = 0.67) O_3 (r = −0.10)	Results presented are default GAM, but authors state that use of natural cubic splines with a more stringent convergence rate produced similar results Increment: 3.3 ppb (IQR) Boys 6-12 yrs by SES status: Low; High Lag 0 RR 1.02(0.94, 1.10); 1.03 (0.95, 1.12) Lag 0-1 RR 1.03 (0.94, 1.13); 1.06 (0.96, 1.17) Lag 0-2 RR 1.03 (0.93, 1.15); 1.06 (0.95, 1.18) Lag 0-3 RR 1.01 (0.90, 1.13); 1.04 (0.92, 1.17) Lag 0-4 RR 0.98 (0.88, 1.10); 1.02 (0.90, 1.14) Lag 0-5 RR 0.97 (0.86, 1.10); 1.02 (0.89, 1.16) Lag 0-6 RR 0.98 (0.86, 1.12); 1.05 (0.91, 1.21) Girls 6-12 yrs by SES status: Low; High Lag 0 RR 1.05 (0.95, 1.16); 1.07 (0.96, 1.19) Lag 0-1 RR 1.11 (0.99, 1.25); 1.07 (0.94, 1.21) Lag 0-2 RR 1.11 (0.97, 1.26); 1.07 (0.93, 1.23) Lag 0-3 RR 1.18 (1.02, 1.36); 1.02 (0.87, 1.19) Lag 0-4 RR 1.18 (1.02, 1.35); 0.99 (0.85, 1.15) Lag 0-5 RR 1.19 (1.01, 1.40); 0.95 (0.80, 1.13) Lag 0-6 RR 1.15 (0.97, 1.36); 0.98 (0.81, 1.17) Multipollutant model (adjusted for NO_2) Girls, Low SES: 1.17 (1.00, 1.37) lag 0-3 1.19 (1.00, 1.42) lag 0-5

STUDY	METHODS	POLLUTANTS	FINDINGS
Lin et al. (2005) Toronto, ON Period of Study: 1998-2001	Hospital Admissions Outcome(s) (ICD9): Respiratory infections (464,466, 480-487) Age groups analyzed: 0-14 Study design: Case-crossover N: 6,782 Statistical analyses: Conditional logistic regression Covariates: Statistical package: SAS 8.2 Lag: 0-6 days	24-h avg: Mean: 4.73 ppb SD: 2.58 ppb Range: 1.00, 19.67 25th: 3.00 50th: 4.00 75th: 6.00 Number of monitors: 5 $PM_{2.5}$ (r = 0.47) $PM_{10-2.5}$ (r = 0.29) PM_{10} (r = 0.48) CO (r = 0.12) NO_2 (r = 0.61)	Asthma hospitalization for boys was associated with SO_2 before the adjustment for fine and coarse PM. Asthma hospitalization for girls was not associated with SO_2 for any lag. Increment: 3 ppb (IQR) Unadjusted Model: Boys only: OR 1.06 (0.97, 1.16) lag 0-3 OR 1.02 (0.92, 1.13) lag 0-5 Girls only: OR 1.05 (0.94, 1.16) lag 0-3 OR 1.07 (0.95, 1.21) lag 0-5 Boys and Girls: OR 1.06 (0.99, 1.13) lag 0-3 OR 1.04 (0.96, 1.13) lag 0-5 Adjusted Boys only: OR 1.11 (1.01, 1.21) lag 0-3 OR 1.08 (0.97, 1.21) lag 0-5 Girls only: OR 1.07 (0.96, 1.19) lag 0-3 OR 1.12 (0.98, 1.28) lag 0-5 Boys and Girls: OR 1.10 (1.02, 1.18) lag 0-3 OR 1.10 (1.01, 1.20) lag 0-5 Multipollutant model with $PM_{2.5}$ and $PM_{2.5}$ Boys only: OR 1.02 (0.90, 1.15) lag 0-3 OR 0.99 (0.85, 1.16) lag 0-5 Girls only: OR 1.09 (0.0.94, 1.26) lag 0-3 OR 1.07 (0.90, 1.28) lag 0-5 Boys and Girls: OR 1.05 (0.95, 1.15) lag 4 OR 1.03 (0.91, 1.16) lag 6
Luginaah et al. (2005) Windsor, ON, Canada Period of Study: 4/1/95-12/31/00	Hospital Admissions Outcome(s) (ICD9): Respiratory admissions (460-519) Age groups analyzed: 0-14, 15-64, 65+, all ages Study design: (1) Time-series and (2) case-crossover N: 4,214. # of Hospitals: 4 Statistical analyses: (1)Poisson regression, GAM with natural splines (stricter criteria), (2) conditional logistic regression with Cox proportional hazards model Covariates: Temperature, humidity, change in barometric pressure, day of wk Statistical package: S-Plus Lag: 1,2,3 days	SO_2 mean 1-h Max: 27.5 ppb, SD: 16.5; Range: 0, 129 IQR: Number of stations: 4 NO_2 (r = 0.22) CO (r = 0.16) PM_{10} (r = 0.22) COH (r = 0.14) O_3 (r = −0.02) TRS (r = 0.13)	The effect of SO_2 on respiratory hospitalization varies considerably, especially at low levels of exposurer. Increment: 19.25 ppb (IQR) Time-series, females; males All ages, 1.041 (0.987, 1.098) 0.953 (0.900, 1.009) lag 1 0-14 yrs, 1.111 (1.011, 1.221) 0.952 (0.874, 1.037) lag 1 15-65 yr, 1.031 (0.930, 1.144) 0.971 (0.845, 1.15) lag 1 65+ yr, 1.030 (0.951, 1.115) 0.9409 (0.860, 1.029) lag 1 Case-crossover, females; males All ages, 1.047 (0.978, 1.122) 0.939 (0.874, 1.009) lag 1 0-14 yrs, 1.119 (0.995, 1.259) 0.923 (0.831, 1.025) lag 1 15-65 yr, 1.002 (0.879, 1.141) 0.944 (0.798, 1.116) lag 1 65+ yr, 1.020 (0.924, 1.126) 0.968 (0.867, 1.082) lag 1

STUDY	METHODS	POLLUTANTS	FINDINGS
Stieb et al. (1996) St. John, New Brunswick, Canada Period of Study: 1984-1992 (May-Sep only)	ED Visits. Outcome(s): Asthma ICD9 codes: NR Age groups analyzed: 0-15, >15 Study design: Time-series N: 1,163. # of Hospitals: 2 Statistical analyses: SAS NLIN (Equivalent to Poisson GEE) Covariates: Day of wk, long-term trends Season: Summers only (May-Sep). Dose-response investigated?: Yes Statistical package: SAS Lag: 0-3 days	1-h max SO_2 (ppb) Mean: 38.1 Range: 0, 390 95th 110 O_3 (r = 0.04) NO_2 (r = −0.03) SO_4^{2-} (r = 0.23) TSP (r = 0.16)	SO_2 did not affect the rate of asthma ED visits when O_3 was included in the model. Increment: NR $SO_2 + O_3$: ∃ = −0.0030 (0.0027) lag 0
Stieb* et al. (2000) Saint John, New Brunswick, Canada Period of Study: Retrospective: 7/92-6/94 Prospective: 7/94-3/96	ED Visits Outcome(s): Asthma; COPD; Respiratory infection (bronchitis, bronchiolitis, croup, pneumonia); All respiratory ICD9 codes: NR Age groups analyzed: All Study design: Time-series N: 19,821 Statistical analyses: Poisson regression, GAM Covariates: Day of wk, selected weather variables in each model Season: All yr, summer only Dose-response investigated: Yes Statistical package: S-Plus Lag: all yr = 0; summer only = 0-3	24-h avg: Annual Mean: 6.7 (5.6) ppb 95th: 18.0. Max: 60.0 Warm season Mean: 7.6 (5.2) ppb 95th: 18.0 .Max: 29.0 1-h max: Annual Mean: 23.8 (21.0) ppb 95th: 62.0. Max: 161.0 Warm season Mean: 25.4 (17.8) ppb 95th: 62.0. Max: 137.0 CO (r = 0.31) O_3 (r = 0.10) NO_2 (r = 0.41) TRS (r = 0.08) PM_{10} (r = 0.36) $PM_{2.5}$ (r = 0.31) H+ (r = 0.24) SO_4^{2-} (r = 0.26) COH (r = 0.3) H2S (r = −0.01) Assessed multipollutant models	Non-linear effect of SO_2 on summertime respiratory visits observed and log transformation strengthened the association. Increment: 23.8 ppb (mean) 1-h max: Respiratory visits: 3.9% lag 5 May to Sept: 3.9% lag 0-3 Multipollutant model (SO_2, O_3, NO_2) All yr: 3.7% (1.5, 6.0) lag 5 Multipollutant model (ln (NO_2), O_3, SO_2 COH) May to Sept: 3.9% (1.1, 6.7) lag 0-3

STUDY	METHODS	POLLUTANTS	FINDINGS
Villeneuve et al., (2006) Toronto, ON, Canada Period of Study: 1995-2000 Days: 2,190	GP Visits Outcome(s) (ICD9): Allergic Rhinitis (177) Age groups analyzed: ≥65 Study design: Time-series N: 52,691 Statistical analyses: GLM, using natural splines (more stringent criteria than default) Covariates: Day of wk, holiday, temperature, relative humidity, aero-allergens Season: All Yr; Warm, May-Oct; Cool, Nov-Apr Statistical package: S-Plus Lag: 0-6	24-h avg: 4.7 ppb SD: 2.8 IQR: 3.2 ppb Range: 0, 24.8 Number of stations: 9 NO_2 O_3 CO PM_{10} $PM_{10-2.5}$ $PM_{2.5}$	There were positive associations between allergic rhinitis and SO_2 for exposures occurring on the same day as physician visits, but only during the winter time. Increment: 10.3 ppb (IQR) All results estimated from Stick Graph: All Yr: Mean increase: 1.7% (−0.4, 2.8) lag 0 Warm: Mean increase: 0.3% (−1.9, 2.5) lag 0 Cool: Mean increase: 1.9% (−0.2, 4.1) lag 0
Yang et al. (2003b) Vancouver, Canada Period of Study: 1986-1998 Days: 4748	Hospital Admissions Outcome(s) (ICD9): All respiratory admissions (460-519) Study design: Case-crossover Age groups analyzed: < 3, ≥ 65 Statistical analyses: conditional logistic regression Lag: 0-5 days	24-h avg SO_2 (ppb): Mean: 4.84 SD: 2.84 5th: 1.50 25th: 2.75 50th: 4.25 75th: 6.25 100th: 24.00 IQR: 3.50 Number of stations: 30 CO NO_2 O_3 (r = −0.37) COH	SO_2 showed the weakest effect among children and the second weakest effect among older adults when compared to all other pollutants considered in the study. Increment: 3.50 ppb (IQR) All respiratory admissions < 3 yrs: SO_2 alone: OR 1.01 (0.98, 1.05) lag 2 SO_2 + O_3: OR 1.01 (0.97, 1.04) lag 2 SO_2 + O_3 + CO + COH + NO_2: OR 0.98 (0.94, 1.03) lag 2 All respiratory admissions ≥ 65 yrs: SO_2 alone: OR 1.02 (1.00, 1.04) lag 0 SO_2 + O_3: OR 1.02 (1.00, 1.04) lag 0 SO_2 + O_3 + CO + COH + NO_2: OR 1.01 (0.98, 1.03) lag 0
Yang et al. (2005) Vancouver, BC, Canada Period of Study: 1994-1998 Days: 1826	Hospital Admissions Outcome(s) (ICD9): COPD excluding asthma (490-2, 494, 496) Age groups analyzed: 65+ Study design: Time-series N: 6,027 Statistical analyses: Poisson regression with GAM (with more stringent criteria) Covariates: Temperature, relative humidity, day of wk, temporal trends, season Statistical package: S-Plus Lag: 0-6 days, moving averages	24-h avg: 3.79 ppb SD: 2.12; IQR: 2.75 ppb; Range: 0.75, 22.67 Winter: 4.10 (2.87) Spring: 3.40 (1.58) Summer: 4.10 (1.79) Fall: 3.56 (1.92) Number of stations: 31 PM_{10} (r = 0.62) NO_2 (r = 0.61) CO (r = 0.67) O_3 (r = −0.34)	This study produced a marginally significant association between COPD hospitalization and 6-day SO_2 exposure. Most previous studies have not detected a significant effect of SO_2 on respiratory ED visits or hospitalizations. Increment: 2.75 ppb (IQR) COPD >65 yrs, yr round RR 1.00 (0.97, 1.04) lag 0 RR 1.02 (0.98, 1.06) lag 0-1 RR 1.04 (0.99, 1.08) lag 0-2 RR 1.04 (0.99, 1.09) lag 0-3 RR 1.05 (0.99, 1.11) lag 0-4 RR 1.06 (1.00, 1.13) lag 0-5 RR 1.06 (0.99, 1.13) lag 0-6 2-pollutant model NO_2: RR 0.99 (0.91, 1.08) lag 0 CO: RR 0.97 (0.87, 1.07) lag 0-6 O_3: RR 1.07 (1.00, 1.14) lag 0-6 PM_{10}: 0.97 (0.88, 1.06) lag 0-6 Multipollutant models SO_2, CO, NO_2, O_3, PM_{10}: RR 0.94 (0.85, 1.05) SO_2, CO, NO_2, O_3: RR 0.96 (0.86, 1.06)

STUDY	METHODS	POLLUTANTS	FINDINGS
AUSTRALIA/NEW ZEALAND			
Barnett et al. (2005) Multicity, Australia/New Zealand; (Auckland, Brisbane, Canberra, Christchurch, Melbourne, Perth, Sydney) Period of Study: 1998-2001	Hospital Admissions Outcomes (ICD 9/ICD 10): All respiratory (460-519/J00-J99 excluding J95.4-J95.9, RO9.1, RO9.8), asthma (493/J45, J46, J44.8), COPD (490-492, 494-496/J40-J44, J47, J67), pneumonia with bronchitis (466, 480-486/J12-17, J18.0 j18.1 J18.8 J18.9 J20 J21) Age groups analyzed: 0, 1-4, 5-14 Study design: Case-crossover Statistical analyses: Conditional logistic regression, random effects meta-analysis Covariates: Temperature, current-previous day temperature, relative humidity, pressure, extremes of hot and cold, day of wk, holiday, day after holiday Season: Cool, May-Oct; Warm, Nov-Apr Statistical package: SAS Lag: 0-1 days	24-h avg (ppb) (range): Auckland: 4.3 (0, 24.3) Brisbane: 1.8 (0, 8.2) Canberra: NA Christchurch: 2.8 (0, 11.9) Melbourne: NA Perth: NA Sydney: 0.9 (0, 3.9) Daily 1-h max (range): Auckland: NA Brisbane: 7.6 (0, 46.5) Canberra: NA Christchurch: 10.1 (0.1, 42.1) Melbourne: NA Perth: NA Sydney: 3.7 (0.1, 20.2)	Increased hospital admissions were significantly associated with SO_2 for acute bronchitis, pneumonia, and respiratory diseases. In multipollutant models the impacts of particulate matter and NO_2 were isolated. There were seasonal impacts on pneumonia and acute bronchitis admissions in the 1- to 4-yr-old age group for SO_2. Increment: 5.4 ppb (1-h max IQR) Pneumonia and acute bronchitis 0 yrs 3.5% (−0.3, 7.3) lag 0-1 1-4 yrs 6.9% (2.3, 11.7) lag 0-1 Respiratory 0 yrs 3.2% (0.3, 6.3) lag 0-1 1-4 yrs 2.7% (0.6, 4.8) lag 0-1 5-14 yrs 2.0% (−5.5, 10.1) lag 0-1 Asthma 0 yrs No analysis (poor diagnosis) 1-4 yrs 3.4% (−4.3, 11.6) lag 0-1 5-14 yrs 3.3% (−5.6, 13.0) lag 0-1
Lam (2007) Australia (New South Wales; Sydney) 2001-2002	ED Visits Outcome(s): Fever, gastroenteritis, asthma/other respiratory problems Study design: Time-series Statistical Analysis: Auto Regression Integrated Moving Average (ARIMA) statistical modeling Statistical package: SPSS Age groups analyzed: < 6 Covariates: NR. Lag(s): NR	24-h avg (ppm): 0.35 (0.19) Range: 0.10, 0.90 1-h max (ppm): 0.38 (0.20) Range: 0.10, 1.80 Copollutants: PM_{10} $PM_{2.5}$ NO_2 O_3	Bivariate correlations resulted in ARIMA models for fever and NO_2 max, gastroenteritis and O_3 avg and NO_2 max; and respiratory problems and O_3 max. Neither NO_2 nor O_3 was significantly associated with any of the childhood illnesses analyzed. SO_2 was not significantly correlated with fever, gastroenteritis, or respiratory problems; therefore, SO_2 was not included in the ARIMA models.

STUDY	METHODS	POLLUTANTS	FINDINGS
Petroeschevsky et al. (2001) Brisbane, Australia Period of Study: 1987-1994 Days: 2922	Hospital Admissions Outcome(s) (ICD 9): All respiratory (460-519); Asthma (493) Age groups analyzed: 0-4, 5-14, 15-64, 65+, all ages Study design: Time-series N: 33,710 (13,246 = asthma) Statistical analyses: APHEA protocol, Poisson regression, GEE Covariates: Temperature, humidity, season, infectious disease, day of wk, holiday Season: Summer, Autumn, Winter, Spring, All yr Dose-response investigated? Yes Statistical package: SAS Lag: Single: 1,2,3 day Cumulative: 0-2, 0-4	Mean: 24-h avg: Overall: 4.1 ppb Summer: 3.9 ppb AutumN: 4.2 ppb Winter: 4.8 ppb Spring: 3.7 ppb Mean: 1-h max Overall: 9.2 ppb Summer: 7.8 ppb AutumN: 9.3 ppb Winter: 11.3 ppb Spring: 8.4 ppb # of stations: 3 Copollutants: BSP O_3 NO_2	SO_2 was highly correlated with max daily ER admissions for respiratory conditions. The highest association was observed in the winter followed by autumn, spring, and summer. For asthma, the highest association was observed in the winter and autumn. No statistically significant contributions for respiratory admissions were reported for the age group 5-14 yr olds for any pollutant. Increment: 0 ppb Respiratory: 0-4 yrs 24-h avg 1.224 (1.087, 1.377) lag 0-4 5-14 yrs 1-h max 1.049 (0.986, 1.116) lag 0-4 15-64 yrs 24-h avg 1.033 (0.895, 1.118) lag 1 65+ yrs 24-h avg 1.121 (1.019, 1.234) lag 0 All ages 24-h avg 1.080 (1.030, 1.131) lag 1 Asthma: 0-14 yrs 24-h avg 1.080 (0.971, 1.201) lag 0 15-64 yrs 1-h max 0.941 (0.900, 0.984) lag 0 All ages 24-h avg 0.941 (0.876, 1.011) lag 2
EUROPE			
Anderson et al. (1997) Multicity, Europe (Amsterdam, Barcelona, London, Paris, Rotterdam) Period of Study: 1977-1989 for Amsterdam and Rotterdam 1986-1992 for Barcelona 1987-1991 for London 1980-1989 for Milan 1987-1992 for Paris	Hospital Admissions Outcome(s) (ICD 9): COPD–unspecified bronchitis (490), chronic bronchitis (491), emphysema (492), chronic airway obstruction (496) Study design: Time-series Statistical analyses: APHEA protocol, Poisson regression, meta-analysis Covariates: Trend, season, day of wk, holiday, influenza, temperature, humidity Season: Cool, Oct-Mar; Warm, Apr-Sep Lag: 0,1,2 days and 0-3 cumulative	24-h all yr avg ($\mu g/m^3$): Amsterdam: 21 Barcelona: 40 LondoN: 31 MilaN: 53 Paris: 23 Rotterdam: 32 1-h max Amsterdam: 50 Barcelona: 60 LondoN: NR MilaN: NR Paris: 47 Rotterdam: 82 Copollutants: NO_2 BS TSP O_3	The effect of SO_2 varied considerably across the cities; however, the summer estimate was significantly associated with COPD for the 1-h measure and borderline significant for the daily mean. Both 24-h and 1-h SO_2 concentrations were significantly associated with COPD ER admissions in the warm season. Only cumulative lags of SO_2 showed borderline significance. Increment: 50 $\mu g/m^3$ COPD-Warm season 24 h avg 1.05 (1.01, 1.10) 1-h 1.02 (1.00, 1.04) COPD-Cool season 24 h avg 1.02 (0.98, 1.05) 1-h 1.01 (0.99, 1.03) COPD-All yr 24-h avg 1.022 (0.981, 1.055) lag 1 24-h avg 1.021 (0.998, 1.054) lag 0-3, cumulative 1-h max 1.01 (0.994, 1.029) lag 1 1-h max 1.015 (1.003, 1.027) lag 0-3, cumulative

STUDY	METHODS	POLLUTANTS	FINDINGS
Anderson et al. (1998) London, England Period of Study: Apr 1987-Feb 1992 Days: 1,782	Hospital Admissions Outcome(s) (ICD 9): Asthma (493) Age groups analyzed: < 15, 15-64, 65+ Study design: Time-series Statistical analyses: APHEA protocol, Poisson regression Covariates: Time trends, seasonal cycles, day of wk, public holidays, influenza epidemics, temperature, humidity Season: Cool (Oct- Mar); Warm (Apr-Sep) Lag: 0, 1, 2 days	24-h avg SO_2 ($\mu g/m^3$) Mean: 32.0 SD: 11.7 Range: 9, 100 5th: 16 10th: 18 25th: 24 50th: 31 75th: 38 90th: 46 95th: 52 # of monitors: 2 Copollutants: O_3 NO_2 BS	The strongest association between SO_2 and asthma admissions was for those ≥65 yrs in the cool season. A weaker association was observed for children in the warm season and all yr. The adult population showed no association. In 2-pollutant models ozone was overall the strongest pollutant associated with hospital admission with weaker associations with NO_2 and BS. The most consistent yr-round association for All ages was found with BS. When looking at all ages combined, SO_2 association remained significant in all 2-pollutant models except with NO_2, both for all yr and the summer (warm) season. Increment: 10 ppb in 24-h SO_2 0-14 yrs Whole yr 1.64% (0.29, 3.01) lag 1 2.04% (0.29, 3.83) lag 0-3 + O_3 1.77% (0.22, 3.36) lag 1 + NO_2 1.23% (−0.22, 2.69) lag 1 + BS 1.66% (0.23, 3.12) lag 1 Warm season 3.33% (1.09, 5.63) lag 1 3.40% (0.41, 6.48) lag 0-3 + O_3 3.35% (0.89, 5.87) lag 1 + NO_2 2.92% (0.58, 5.32) lag 1 + BS 3.66% (1.35, 6.02) lag 1 Cool season 0.56% (−1.16, 2.32) lag 1 1.24% (−0.95, 3.49) lag 0-2 15-64 yrs Whole yr −0.69% (−2.28, 0.94) lag 2 −0.71% (−2.69, 1.30) lag 0-2 Warm season −1.39% (−3.97, 1.27) lag 0 −2.2% (−5.46, 11.8) lag 0-2 Cool season −0.24% (−2.28, 1.84) lag 0 0.20% (−2.28, 2.74) lag 0-2 Multipollutant model with $PM_{2.5}$ and $PM_{2.5}$ Boys only: OR 1.02 (0.90, 1.15) lag 0-3 OR 0.99 (0.85, 1.16) lag 0-5 Girls only: OR 1.09 (0.0.94, 1.26) lag 0-3 OR 1.07 (0.90, 1.28) lag 0-5 Boys and Girls: OR 1.05 (0.95, 1.15) lag 4 OR 1.03 (0.91, 1.16) lag 6 65+ yrs Whole yr 2.82% (−0.82, 5.96) lag 2 3.06% (−0.72, 6.98) lag 0-3 Warm season −2.62% (−7.31, 2.31) lag 2 −4.27% (−9.89, 1.71) lag 0-3 Cool season 5.85% (1.81, 10.05) lag 2 7.28% (2.19, 12.62) lag 0-3 + O_3 7.84% (2.48, 13.48) lag 1 + NO_2 4.19% (−0.53, 9.13) lag 1 + BS 5.29% (0.42, 10.40) lag 1 All Ages Whole yr 1.64% (0.54, 2.75) lag 1 2.75% (1.22, 4.30) lag 0-3 + O_3 1.48% (0.24, 2.73) lag 1 + SO_2 1.14% (−0.04, 2.33) lag 1 + BS 1.54%(0.36, 2.73) lag 1 Warm season 2.02% (0.22, 3.85) lag 1 2.60% (0.02, 5.25) lag 0-3 + O_3 1.91% (0.05, 3.81) lag 1 + NO_2 1.64% (−0.23, 3.56) lag 1 + BS 2.18% (0.32, 4.07) lag 1 Cool season 1.41% (0.0, 2.83) lag 1 2.83% (0.89, 4.81) lag 0-3 + O_3 −0.09% (−1.61, 1.82) lag 1 + NO_2 0.83% (−0.67, 2.34) lag 1 + BS 1.11% (−0.41, 2.66) lag 1

STUDY	METHODS	POLLUTANTS	FINDINGS
Anderson et al. (2001) West Midlands conurbation, United Kingdom Period of Study: 10/1994-12/1996	Hospital Admissions Outcome(s) (ICD9): All respiratory (460-519), Asthma (493), COPD (490-496, excluding 493) Age groups analyzed: 0-14, 15-64, 65+ Study design: Time-series Statistical analyses: followed APHEA 2 protocol, GAM Covariates: Season, temperature, humidity, epidemics, day of wk, holidays Statistical package: S-Plus 4.5 Pro Lag: 0,1,2,3, 0-1, 0-2, 0-3	24-h avg: 7.2 ppb, 4.7 (SD) MiN: 1.9 ppb Max: 59.8 ppb 10th: 3.3 ppb 90th: 12.3 ppb # of monitors: 5 PM_{10} (r = 0.55) $PM_{10-2.5}$ (r = 0.31) $PM_{2.5}$ (r = 0.52) BS (r = 0.50) SO_4 (r = 0.19) NO_2 (r = 0.52) O_3 (r = 0.22)	When admissions were analyzed by subgroups, respiratory and asthma admissions were positively correlated with SO_2. SO_2 significantly associated with asthma and respiratory admissions for the 0 to 14-yr-age group; however, little evidence of a seasonal interaction was observed. Increment: 9 ppb (90th-10th) All respiratory All ages 1.3% (−0.7, 3.4) lag 0-1 0-14 yrs 4.6% (1.40, 7.8) lag 0-1 15-64 yrs −0.9% (−4.8, 3.3) lag 0-1 ≥ 65 yrs −2.0% (−4.9, 1.1) lag 0-1 COPD with asthma 0-14 yrs 10.9% (4.50, 17.8) lag 0-1 15-64 yrs 2.4% (−5.5, 10.9) lag 0-1 ≥ 65 yrs −4.2% (−8.9, 0.8) lag 0-1
Atkinson et al. (1999b) London, England Period of Study: 1992-1994	Hospital Admissions Outcome(s) (ICD9): All respiratory (460-519); Asthma (493); Asthma and COPD (490-496); LRD (466,480-486) Age groups analyzed: all ages, 0-14 yr, 15-64 yr and ≥65 yr Study design: Time-series N: 165,032 Statistical analyses: Poisson regression following APHEA protocol Covariates: Long-term seasonal patterns, day of wk, temperature, humidity, influenza. Statistical package: SAS Investigated Dose/Response: Yes Lag: 0,1,2,3 days	SO_2− 24-h ($\mu g/m^3$) Mean: 21.2 (7.8) $\mu g/m^3$ MiN: 7.4 10th: 13 50th: 19.8 90th: 31 Max: 82.2 # of monitors: 5 O_3,CO, PM_{10}, BS, NO_2 Correlation coefficients ranged between r = 0.5 and 0.6	Asthma was closely linked with PM, CO, NO_2, and traffic pollution. When SO_2 and PM_{10} were included in the same model, the magnitude of the individual associations was reduced, as were their statistical significance. This reduction occurred in children, adults and the elderly. The other pollutants all had the effect of reducing the magnitude of the individual SO_2 and $PM_{2.5}$ associations, although their statistical significance was unaffected. This indicates that both SO_2 and $PM_{2.5}$ were indicators of the same pollutant mixture. Increment: 18 $\mu g/m^3$ All respiratory All ages 2.01% (0.29, 3.76) lag 1 0-14 yrs 5.14% (2.59, 7.76) lag 0 15-64 yrs 1.90% (−0.79, 4.660 lag 3 ≥ 65 yrs 2.25 (−0.09, 4.65) lag 3 Asthma All ages 3.38 (0.42, 6.43) lag 1 0-14 yrs 6.74% (2.92, 10.69) lag 1 15-64 yrs 4.58% (−0.18, 9.57) lag 3 ≥ 65 yrs 6.31% (−1.59, 14.83) lag 2 COPD and Asthma ≥ 65 yrs 1.53% (−1.83, 5.00) lag 3 Lower Respiratory ≥ 65 yrs 5.16% (1.19, 9.28) lag 3

STUDY	METHODS	POLLUTANTS	FINDINGS
Atkinson et al. (1999a) London, United Kingdom Period of Study: 1/92-1294	ED Visits Outcome(s) (ICD 9): Respiratory ailments (490-496), including asthma, wheezing, inhaler request, chest infection, COPD, difficulty in breathing, cough, croup, pleurisy, noisy breathing Age groups analyzed: 0-14; 15-64; ≥ 65; All ages Study design: Time-series N: 98,685 # of Hospitals: 12 Statistical analyses: Poisson regression, APHEA protocol Covariates: Long-term trend, season, day of wk, influenza, temperature, humidity Statistical package: SAS Lag: 0,1,0-2 and 0-3 days	24-h avg: 21.2 $\mu g/m^3$, SD: 7.8 10th: 13.0 50th: 19.8 90th: 31.0 Range: 7.4, 82.2 # of Stations: 5 SO_2 O_3 (8 h) CO (24 h avg), PM_{10} (24 h avg) BS	SO_2 was closely related to PM_{10}, but 2-pollutant models showed that the effect of SO_2 was decreased by NO_2 and PM_{10} inclusion. Inclusion of other pollutants did not significantly decrease the influence of SO_2 on ER admissions in 2-pollutant models. Increment: 18 $\mu g/m^3$ in 24-h Single-pollutant model Asthma only 0-14 yrs 9.92% (4.75, 15.34) lag 1 15-64 yrs 4.19% (−0.53, 9.13) lag 1 All ages 4.95% (1.53, 8.48) lag 1 All respiratory 0-14 yrs 6.01% (2.98, 9.12) lag 2 15-64 yrs 2.72% (−0.18, 5.70) lag 3 65+ yrs −1.82% (−5.72, 2.25) lag 3 All Ages 2.81% (0.72, 4.93) lag 1 Copollutant models for asthma among children: SO_2 + NO_2: 5.42% (0.18, 10.93) SO_2 + O_3: 8.39% (3.82, 13.17) SO_2 + CO: 8.05% (3.45, 12.86) SO_2 + PM_{10}: 5.63 (0.53, 10.98) SO_2 + BS: 8.03 (3.32, 12.96)
Atkinson et al. (2001) Multicity, Europe (Barcelona, Birmingham, London, Milan, Netherlands, Paris, Rome, Stockholm) Period of Study: 1998-1997	Hospital Admissions Outcome(s) (ICD 9): Asthma (493), COPD (490-496), All respiratory (460-519) Study design: Time-series Statistical analyses: APHEA protocol, Poisson regression, meta-analysis Covariates: Season, temperature, humidity, holiday, influenza Lag: NR	1-h max of SO_2 ($\mu g/m^3$) Barcelona: NR Birmingham: 24.3 LondoN: 23.6 MilaN: 29.1 Netherlands: 8.5 Paris: 17.7 Rome: 9.8 Stockholm: 3.8 NO_2, O_3, CO, BS, PM_{10} Barcelona: 0.32 B'gham: 0.77 LondoN: 0.72 MilaN: 0.64 Netherlands: 0.67 Paris: 0.63 Rome: 0.15 Stockholm: 0.36	The inclusion of SO_2 in the models only modified PM_{10} associations in the 0- to 14-yr age group. Increment: 10 $\mu g/m^3$ for PM_{10}; change in SO_2 not described. Asthma, 0 to 14 yrs: For PM_{10}: 1.2 (0.2, 2.3) For PM_{10} + SO_2: 0.8 (−3.7, 5.6) Asthma, 15 to 64 yrs: For PM_{10}: 1.1 (0.3, 1.8) For PM_{10} + SO_2: 1.6 (0.6, 2.6) COPD + Asthma, ≥ 65 yrs For PM_{10}: 1.0 (0.4, 1.5) For PM_{10} + SO_2: 1.3 (0.7, 1.8) All respiratory, ≥ 65 yrs of age For PM_{10}: 0.9 (0.6, 1.3) For PM_{10} + SO_2: 1.1 (0.7, 1.4)
Boutin-Forzano et al. (2004) Marseille, France Period of Study: 4/97-3/98	ED Visits Outcome(s): Asthma ICD 9 Code(s): NR Age groups analyzed: 3-49 Study design: Case-crossover N: 549 Statistical analyses: Logistic regression Covariates: Minimal daily temperature, max daily temperature, min daily relative humidity, max daily relative humidity, day of wk Lag: 0-4 days	Mean: SO_2: 22.5 $\mu g/m^3$ Range: 0.0, 94.0 NO_2 (r = 0.56) O_3 (r = −0.25)	No association was observed between ER visits for asthma and SO_2 levels. Only single-pollutant models were utilized. Increment: 10 $\mu g/m^3$ Increased ER visits OR 1.0023 (0.9946, 1.0101) lag 0 OR 0.9995 (0.9923, 1.0067) lag 1 OR 0.9996 (0.9923, 1.0069) lag 2 OR 0.9970 (0.9896, 1.0045) lag 3 OR 0.9964 (0.9889, 1.0040) lag 4

STUDY	METHODS	POLLUTANTS	FINDINGS
Buchdahl et al. (1996) London, United Kingdom Period of Study: 3/1/92-2/28/93	ED visits. Outcomes: Daily acute wheezy episodes. Age groups analyzed: ≤ 16 Study design: Case-control N: 1,025 cases, 4,285 controls. # of Hospitals: 1 Statistical analyses: Poisson regression Covariates: Season, temperature, wind speed Season: Spring (Apr-Jun), Summer (Jul-Sep) Autumn (Oct-Dec), Winter (Jan-Mar) Statistical package: Stata. Lag: 0-7 days	SO_2 24-h yr round Mean: 22 µg/m^3, SD: 14 IQR: µg/m^3 Spring: 20 (14) Summer: 18 (22) Fall: 24 (14) Winter: 25 (14) NO_2 (r = 0.62) O_3 (r = −0.28)	Variations in SO_2 could not explain the U-shaped relationship between ozone and incidence of asthma. Increment: 14 µg/m^3 (Std. Dev.) No adjustments to model RR 1.16 (1.10, 1.23) lag not specified Adjusted for temperature and season. RR 1.12 (1.06, 1.19) lag not specified Adjusted for temperature, season and wind speed. RR 1.08 (1.00, 1.16) lag not specified
Castellsague et al. (1995) Barcelona, Spain Period of Study: 1986-1989	ED visits. Outcome(s): Asthma Age groups analyzed: 15-64 Study design: Time-series. # of Hospitals: 4 Statistical analyses: Poisson regression Covariates: Long time trend, day of wk, temperature, relative humidity, dew point temperature Seasons : Winter : Jan-Mar; Summer : Jul-Sep Dose-response investigated: Yes Lag: 0, 1-5 days and cumulative. Summer: lag 2 daysWinter: lag 1 day	Mean SO_2 (µg/m^3) Summer: 40.8 25th: 25. 50th: 36 75th: 54. 95th: 82 Winter: 52.0 25th: 36. 50th: 49 75th: 67. 95th: 94 # of Stations: 15 manual, 3 automatic NO_2 O_3	Interaction between pollutants and asthma emergency room visits was influenced by soy-bean dust in the air. The daily mean of asthma visits and level of SO_2 were higher in the winter than in the summer. A positive but not statistically significant increase in relative risk was found for SO_2 in the summer. SO_2 levels were higher in the winter, but the RR was lower compared to the RR in the summer. SO_2 was not significantly associated with asthma related ER visits. Increment: 25 µg/m^3 Seasonal differences Summer: RR 1.052 (0.980, 1.129) lag 2 Winter: RR 1.020 (0.960, 1.084) lag 1
Dab et al. (1996) Paris, France Period of Study: 1/1/87-9/30/92	Hospital Admissions Outcome(s) (ICD 9): All respiratory (460-519), Asthma (493), COPD (490-496) Age groups analyzed: All ages Study design: Time-series Number of hospitals: 27 Statistical analyses: Poisson regression, followed APHEA protocol Covariates: Temperature, relative humidity, influenza, Long-term trend, season, holiday, medical worker strike Lag: 0,1,2 days, 0-3 cumulative	All Yr: 24-h avg: 29.7 µg/m^3 Median:23.0 5th: 7.0. 99th: 125.0 1-h max: 59.9 Median:46.7 5th: 14.0., 99th: 232.7 Warm season 24-h avg: 20.1 Median:18.3.5th: 6.0 99th: 49.3 1-h max:42.7 Median:37.0 5th: 13.0. 99th: 133.7 Cold season 24-h avg: 40.1 µg/m^3 Median:31.3 5th: 8.7. 99th: 149.0 1-h max:78.3 Median:60.7 5th: 17.0. 99th: 268.3 NO_2, O_3, PM_{13}, BS	1-h max SO_2 levels yielded lower relative risk when compared to 24-h avg levels. COPD effects were only significantly associated with SO_2 with no lag. The strongest association was observed with PM_{13}; 4.5% increase in respiratory admission per 100 µg/m^3 increment. SO_2 was a close second. Neither analysis by age or by season showed a significant sensitivity for hospital admissions. The strongest association for asthma admission for all pollutants was with SO_2 24-h avg of 7% (0.14, 14.10), but 1-hr max level was not significant. The strongest association for admission with COPD diagnosis was also for 24-h avg of SO_2 (9.9% [2.3, 18]). Increment: 100 µg/m^3 All respiratory (1987-1990) 24-h avg RR 1.042 (1.005, 1.080) lag 0-2 1-h max RR 1.018 (0.988, 1.048) lag 0-2 Asthma (1987-1992) 24-h avg RR 1.070 (1.004, 1.141) lag 2 1-h max RR 1.047 (0.998, 1.098) lag 2 COPD 24-h avg RR 1.099 (1.023, 1.180) lag 0 1-h max RR 1.051 (1.025, 1.077) lag 0

STUDY	METHODS	POLLUTANTS	FINDINGS
de Diego Damiá et al. (1999) Valencia, Spain Period of Study: 3/1994-3/1995	ED visits. Outcome(s) (ICD 9): Asthma (493) Age groups analyzed: > 12 N: 515. # of Hospitals: 1 Statistical analyses: Stepwise regression and ANOVA; Linear regression Covariates: Season and temperature Statistical package: SPS	24-h avg SO_2 ($\mu g/m^3$) Winter Mean: 56. Range: 30, 86 Spring Mean: 47. Range: 34, 75 Summer Mean: 40. Range: 12, 62 Autumn Mean: 50. Range: 42, 59 Number of monitors: 1 BS; r = 0.54	The SO_2 concentration was averaged for each season and quartiles of concentration determined. Asthma visits that occurred in each season were examined. There were no significant associations with asthma ER visits with any season or with any quartile of SO_2 exposure. Mean number of asthma-related ED visits based on quartile of SO_2 All yr: < 41 $\mu g/m^3$: 8.6 41-50 $\mu g/m^3$: 9.1. 51-56 $\mu g/m^3$: 11.6 >56 $\mu g/m^3$: 11.9
Fusco et al. (2001) Rome, Italy Period of Study: 1/1995-10/1997	Hospital Admissions Outcomes (ICD 9 codes): All Respiratory (460-519, excluding 470-478); Acute respiratory infections including pneumonia (460-466, 480-486), COPD (490-492, 494-496), asthma (493) Age groups analyzed: All ages, 0-14 Study design: Time-series Statistical analyses: Poisson regression with GAM Covariates: Influenza epidemics, day of study, temperature, humidity, day of wk, holidays Statistical package: S-Plus 4 Lag: 0, 1, 2, 3, 4	24-h avg: 9.1 (5.8) $\mu g/m^3$ 25th: 5.1 50th: 7.9 75th: 12.0 # of monitors: 5 O_3 (r = −0.35) CO (r = 0.56) NO_2 (r = 0.33) Particles; r = 0.25	SO_2 did not have an effect on respiratory hospitalizations. Increment: 6.9 $\mu g/m^3$ (IQR) Respiratory conditions: All ages: 0.4% (−1.3, 2.2) lag 0 0.8% (−0.9, 2.4) lag 1 0.3% (−1.3, 1.8) lag 2 0-14 yrs: −0.7% (−4.0, 2.7) lag 0 −2.0 (−5.2, 1.3) lag 1 −0.8 (−3.8, 2.3) lag 2 Acute respiratory infections: All ages: 0.4% (−2.1, 3.0) lag 0 1.4% (−1.0, 3.9) lag 1 1.2% (−1.0, 3.5) lag 2 0-14 yrs: −0.1% (−3.9, 3.8) lag 0 −2.7% (−6.3, 1.0) lag 1 −1.2% (−4.5, 2.2) lag 2 Asthma: All ages: −1.5% (−6.6, 3.9) lag 0 −1.5% (−6.5, 3.7) lag 1 2.5% (−2.2, 7.4) lag 2 0-14 yrs: −2.6 (−10.4, 6.0) lag 0 4.3% (−3.5, 12.7) lag 1 5.5% (−1.8, 13.2) lag 2 COPD: All ages: 1.0% (−1.9, 4.0) lag 0 −1.1% (−3.9, 1.8) lag 2 −0.5% (−3.1, 2.1) lag 2
Galan et al. (2003) Madrid, Spain Period of Study: 1995-1998	ED Visits Outcome(s) (ICD9): Asthma (493) Age groups analyzed: All Study design:Time-series N: 4,827 Statistical analyses: Poisson regression, (1) classic APHEA protocol and (2) GAM with stringent criteria Covariates: Trend, yr, season, day of wk, holidays, temperature, humidity, influenza, acute respiratory infections, pollen Lag: 0-4 days	24-h Mean: 23.6 $\mu g/m^3$ SD: 15.4 10th: 9.2 25th: 12.3 50th: 18.7 75th: 31.3 90th: 43.9 Range: 5, 121.2 # of Stations: 15 PM_{10} (r = 0.581) NO_2 (r = 0.717) O_3 (r = −0.188)	SO_2 registered a predominately winter based pattern, and was positively correlated with $PM_{2.5}$, NO_2. The lag that described the strongest association was 3 days. Multipollutant models were fitted for cold season pollutants. SO_2 was the most affected when $PM_{2.5}$ was included in the model. Parametric estimates using APHEA protocol produced similar results as GAM. The SO_2 association may be due to the concealing effects of other pollutants. $PM_{2.5}$ accounted for most of the observed effects. Increment : 10 $\mu g/m^3$ Asthma : RR lag 0 1.018 (0.984, 1.054) RR lag 1 1.005 (0.972, 1.039) RR lag 2 1.002 (0.970, 1.036) RR lag 3 1.029 (0.997, 1.062) RR lag 4 1.025 (0.994, 1.058) Multipollutant model: SO_2/PM_{10} 0.966 (0.925, 1.009)

STUDY	METHODS	POLLUTANTS	FINDINGS
Garty et al. (1998) Tel Aviv, Israel Period of Study: 1993	ED Visits Outcome(s): Asthma ICD 9 Code(s): NR Age groups analyzed: 1-18 Study design: Descriptive study with correlations N: 1,076 Statistical analyses: Pearson correlation and partial correlation coefficients Covariates: Max and min ambient temperatures, relative humidity and barometric pressure Statistical package: Statistix	24-h mean of SO_2 (estimated from histogram): 27 µg/m^3 Range: 11, 64 NOx SO_2 O_3	Asthma morbidity was higher in the autumn and winter than the rest of the yr. The number of ER visits is Sep was exceptionally high. The percent of total variance showed positive correlation between asthma ER visits in children and high levels of NOX, SO_2, and increased barometric pressure. NOX enhances the effects of SO_2, whereas O_3 had a reverse relation to SO_2. Air borne pollen was not a significant contributor to ER visits. Correlation between SO_2 and ER visits for asthma: All Yr: Daily data r = 0.24 Running mean for 7 days r = 0.53 Excluding Sep: Daily data r = 0.31 Running mean for 7 days r = 0.64
Hagen et al. (2000) Drammen, Norway Period of Study: 1994-1997	Hospital Admissions Outcome(s) (ICD 9): All respiratory admissions (460-519) Age groups analyzed: All ages Study design: Time-series Number of hospitals: 1 Statistical analyses: Poisson regression with GAM (adhered to HEI phase 1.B report) Covariates: Time trends, day of wk, holiday, influenza, temperature, humidity Lag: 0,1,2,3 days	SO_2 24-h avg (µg/m^3): 3.64, SD: 2.41 25th: 2.16 50th: 2.92 75th: 4.38 # of Stations: 2 PM_{10} (r = 0.42) NO_2 (r = 0.58) benzene (r = 0.29) NO (r = 0.47) O_3 (r = −0.24) Formaldehyde (r = 0.54) Toluene (r = 0.48)	SO_2 was significantly associated with respiratory hospital admissions. This relationship was robust to the inclusion of $PM_{2.5}$, but attenuated when both $PM_{2.5}$ and benzene were included in the model. Increment: SO_2: 2.22 µg/m^3 (IQR) Single-pollutant model Respiratory disease only 1.056 (1.013, 1.101) All disease 0.990 (0.974, 1.007) 2-pollutant model with PM_{10} 1.051 (1.005, 1.099) 3-pollutant model with PM_{10} + Benzene 1.040 (0.993, 1.089)

STUDY	METHODS	POLLUTANTS	FINDINGS
Hajat et al. (1999) London, United Kingdom Period of Study: 1992-1994	GP visits Outcome(s) (ICD9): Asthma (493); Lower respiratory disease (464, 466, 476, 480-3, 490-2, 485-7, 4994-6, 500, 503-5, 510-5) Age groups analyzed: 0-14; 15-64; 65+; all ages Study design: Time-series analysis Statistical Analysis: Poisson regression, APHEA protocol Covariates: Long-term trends, seasonality, day of wk, temperature, humidity Season: Warm, Apr-Sep; Cool, Oct-Mar; All-yr Dose-response investigated? Yes Statistical package: SAS Lag: 0-3 days, cumulative	All yr 24-h avg: 21.2 $\mu g/m^3$, SD: 7.8 10th: 13.0 90th: 31.0 Warm: 24-h avg: 20.5 $\mu g/m^3$, SD: 6.5 10th: 13.4 90th: 28.4 Cool: 24-h avg: 22.0 $\mu g/m^3$, SD: 9.0 10th: 12.8 90th: 33.3 NO_2 (r = 0.61) BS (r = 0.57) CO (r = 0.51) PM_{10} (r = 0.63) O_3 (r = −0.11)	This study showed weak, but consistent associations between SO_2 and consultations for asthma and other LRD, especially in children. Bubble plot suggests a concentration-response relationship. Increment: 18 $\mu g/m^3$ (90th-10th percentile) Asthma All ages 3.6% (0.3, 6.9) lag 2; 4.4% (0.9, 7.9) lag 0-2 0-14 yrs 4.9% (0.1, 9.8) lag 1; 4.4% (−0.7,9.7) lag 0-2 Warm: 9.0% (2.2, 16.2) lag 1 Cool: 2.0% (4.5, 8.9) lag 1 15-64 yrs 3.6% (−0.6, 8.0) lag 2; 3.5% (−1.0, 8.2) lag 0-3 Warm: 2.5% (−3.3, 8.7) lag 2 Cool : 4.5% (−1.4, 10.7) lag 2 65 + yrs 4.5% (−3.5, 13.1) lag 1; 4.8% (−2.9, 13.2) lag 0-1 Warm: 7.5% (−4.0, 20.3) lag 1 Cool: 2.0% (−8.6, 13.9) lag 1 Lower respiratory disease All ages 1.8% (0.2, 3.4) lag 2; 2.2% (0.4, 4.1) lag 0-2 0-14 yrs 4.5% (1.4, 7.8) lag 2; 5.7% (1.7, 9.7) lag 0-3 Warm: 2.4% (−2.6, 7.7) lag 2 Cool: 5.8% (1.6, 10.2) lag 2 15-64 yrs 1.5% (−0.7, 3.7) lag 1; 1.6% (−0.9, 4.1) lag 0-3 Warm: −0.5% (−3.8, 2.9) lag 1 Cool: 2.5% (−0.5, 5.5) lag 1 65 + −2.2% (−4.9, 0.6) lag 0; −1.4% (−4.4, 1.7) lag 0-1 Warm: −3.1% (−6.9, 0.9) lag 0 Cool: −1.6 % (−5.3, 2.3) lag 0 2-pollutant model – Asthma SO_2 alone 4.9% (0.1, 9.8) SO_2/O_3 5.9% (1.1, 10.9) SO_2/NO_2 2.7% (−2.7, 8.4) $SO_2/PM_{2.5}$ 3.4% (−3.0, 10.2) 2-pollutant model-Lower respiratory disease SO_2 alone 4.5% (1.4, 7.8) SO_2/O_3 4.8% (1.6, 8.1) SO_2/NO_2 3.1% (−0.6, 6.9) $SO_2/PM_{2.5}$ 3.8% (0.4, 7.2)

STUDY	METHODS	POLLUTANTS	FINDINGS
Hajat* et al. (2001) London, United Kingdom Period of Study: 1992-1994	GP visits Outcome(s) (ICD9): Allergic Rhinitis (477) Age groups analyzed: 0-14; 15-64; 65+; all ages Study design:Time-series analysis N: 4,214 Statistical Analysis: Poisson regression, GAM Covariates: Long-term trends, seasonality, day of wk, temperature, humidity, variation in practice population, counts for lagged allergic pollen measures, daily number of consultations for influenza Dose-response investigated? Yes Statistical package: S-Plus Lag: 0-6 days, cumulative	24-h avg: 21.2 µg/m^3, SD: 7.8 10th: 13.0 90th: 31.0 NO_2 (r = 0.61) BS (r = 0.57) CO (r = 0.51) PM_{10} (r = 0.63) O_3 (r = −0.11)	The number of allergic rhinitis admissions peaked in Apr and June. After 2-pollutant model analysis, SO_2 still remained highly significant in the presences of other pollutants. For both children and adults exposure-response associations showed that risk levels off at higher SO_2 levels. Increment: 18 µg/m^3 (90th-10th percentile) Single-pollutant model < 1 to 14 yrs 24.5% (14.6, 35.2) lag 4 24.9% (11.9, 39.4) lag 0-4 15 to 64 yrs 14.3% (6.2, 23.0) lag 3 15.5% (9.1, 22.3) lag 0-5 >64 yrs-too small for analysis 2-pollutant models < 1 to 14 yrs SO_2 & O_3: 22.1% (12.0, 33.1) SO_2 & NO_2: 28.5% (15.5, 42.9) SO_2 & PM_{10}: 27.2% (15.3, 40.2) 15 to 64 yrs SO_2 & O_3: 8.5% (3.4, 13.9) SO_2 & NO_2: 8.3% (1.7, 15.3) SO_2 & PM_{10}: 6.7% (0.7, 13.0)
Hajat* et al. (2002) London, United Kingdom Period of Study: 1992-1994	GP visits Outcome(s) (ICD9): Upper respiratory disease, excluding Rhinitis (460-3, 465, 470-5, 478) Age groups analyzed: 0-14; 15-64; 65+; all ages Study design: Time-series analysis Statistical Analysis: Poisson regression, GAM Covariates: Long-term trends, seasonality, day of wk, holidays, temperature, humidity, variation in practice population, counts for lagged allergic pollen measures, daily number of consultations for influenza Season: Warm, Apr-Sep; Cool, Oct-Mar Dose-response investigated? Yes Statistical package: S-Plus Lag: 0,1,2,3 days	All yr 24-h avg: 21.2 µg/m^3, SD: 7.8 10th: 13.0 90th: 31.0 Warm: 24-h avg: 20.5 µg/m^3, SD: 6.5 10th: 13.4 90th: 28.4 Cool: 24-h avg: 22.0 µg/m^3, SD: 9.0 10th: 12.8 90th: 33.3 # of Stations: 3 NO_2 (r = 0.61) BS (r = 0.57) CO (r = 0.51) PM_{10} (r = 0.63) O_3 (r = −0.11)	Increased consultations for URD were most strongly associated with SO_2 in children. For adults and the elderly the strongest associations were for PM_{10} and NO_2. The most consistent lag in adults and the elderly for development of URD was 2 days (one day after a pollution event). Increment: 18 µg/m^3 (90th-10th percentile) Single-pollutant model All yr 0-14 yr 3.5% (1.4, 5.8) lag 0 15-64 yrs 3.5% (0.5, 6.5) lag 1 >65 yrs 4.6% (0.4, 9.0) lag 2 Warm 0-14 yrs 3.2% (−0.5, 7.0) lag 0 15-64 yrs 4.6% (1.5, 7.7) lag 1 ≥ 65 yrs 1.6% (−4.8, 8.5) lag 2 Cool 0-14 yrs 5.5% (2.4, 8.7) lag 0 15-64 yrs 2.7 (0.0, 5.4) lag 1 >65 yrs 5.7% (0.4, 11.4) lag 2 2-pollutant models 0-14 yrs SO_2 & O_3: 1.0% (−2.2, 4.2) SO_2 & NO_2: 4.7% (2.2, 7.4) SO_2 & PM_{10}: 4.6% (2.1, 7.2) For 15-64 yrs SO_2 & O_3: 3.7% (0.6, 7.0) SO_2 & NO_2: 2.6% (−0.0, 5.2) SO_2 & PM_{10}: 2.4% (−0.1, 5.0) For >65 yrs SO_2 & O_3: 9.0% (1.7, 16.9) SO_2 & NO_2: 4.3% (−1.2, 10.2) SO_2 & PM_{10}: 3.2% (−1.9, 8.7)

STUDY	METHODS	POLLUTANTS	FINDINGS
Llorca et al. (2005) Torrelavega, Spain Period of Study: 1992-1995 Days: 1,461	Hospital Admissions Outcome(s) (ICD 9): All respiratory admissions (460-519) Age groups analyzed: All ages Study design:Time-series Number of hospitals: 1 Statistical analyses: Poisson regression Covariates: Short and Long-term trends Statistical package: Stata Lag: NR	24-h avg SO_2: 13.3 µg/m^3, SD: 16.7 # of Stations: 3 NO_2 (r = 0.588) NO (r = 0.544) TSP (r = −0.40) SH2 (r = 0.957)	Associations between SO_2 and admissions observed in the Single-pollutant model disappear in a 5-pollutant model. Only NO_2 was significantly associated with admissions. No relation was described for sulphur compounds including H2S or SO_2. The concentration of SO_2 changes with temperature changes, which may be responsible for cardiac stress. SO_2 was not significantly associated with cardiac respiratory or cardio-respiratory admissions Increment: 100 µg/m^3 Single-pollutant model All cardio-respiratory admissions: RR 0.98 (0.89, 1.07) Respiratory admissions: 1.04 (0.90, 1.19) 5-pollutant model All cardio-respiratory admissions: RR 0.98 (0.80, 1.21) Respiratory admissions: 0.89 (0.64, 1.24)
Oftedal et al. (2003) Drammen, Norway Period of Study: 1994-2000	Hospital Admissions Outcomes (ICD 10): All respiratory admissions (J00-J99) Age groups analyzed: All ages Study design: Time-series Statistical analyses: Semi-parametric Poisson regression, GAM with more stringent criteria Covariates: Temperature, humidity, influenza Lag: 2,3 days	Mean: 2.9 µg/m^3, SD: 2.1 IQR: 2.03 µg/m^3 PM_{10} NO_2 O_3 Benzene Formaldehyde Toluene	The study found positive associations between daily number of hospital admissions for acute respiratory diseases and concentrations of SO_2; associations did not change substantially from the first to the second 3-yr period. Increment: 2.03 µg/m^3 (IQR) All respiratory disease 1.042 (1.011, 1.073)
Ponce de Leon et al. (1996) London, England Period of Study: 04/1987-1988; 1991-02/1992	Hospital Admissions Outcome(s) (ICD 9): All respiratory (460-519) Age groups analyzed: 0-14, 15-64, 65+, all ages Study design: Time-series N: 19,901 Statistical analyses: APHEA protocol, Poisson regression GAM Covariates: Long-term trend, season, influenza, day of wk, holiday, temperature, humidity Season: Cool, Oct-Mar; Warm: Apr-Sep Dose-response Investigated?: Yes Statistical package: SAS Lag: 0, 1, 2 days, 0-3 cumulative avg.	SO_2 24-h avg: 32.2 µg/m^3, SD: 12.6 5th: 15 10th: 18 25th: 24 50th: 31 75th: 39 90th: 47 95th: 54 # of stations: 2 NO_2 (r = 0.44) BS (r = 0.44) O_3 (r = −0.067)	Though significant effects were observed with SO_2 in some age groups, they were not consistent or similar in magnitude to those of O_3. Increment: 90th-10th percentile (24-h avg: 29 µg/m^3). All yr All ages 1.0092 (0.9926, 1.0261) lag 1 0-14 yrs 1.0093 (0.9837, 1.0356) lag1 15-64 yr 1.0223 (0.9942, 1.0511) lag 1 ≥ 65 yr 1.0221 (0.9970, 1.0478) lag 2 Warm season All ages 1.0111 (0.9864, 1.0364) lag 1 0-14 yrs 1.0468 (1.0066, 1.0885) lag 1 15-64 yr 0.9996 (0.9596, 1.0411) lag 1 >65 yr 1.0124 (0.9772, 1.0489) lag 2 Cool season All ages 1.0079 (0.9857, 1.0306) lag 1 0-14 yrs 0.9848 (0.9515, 1.0192) lag 1 15-64 yr 1.0389 (1.0010, 1.0783) lag 1 >65 yr 1.0280 (0.9945, 1.0625) lag 2

STUDY	METHODS	POLLUTANTS	FINDINGS
Pönkä (1991) Helsinki, Finland Period of Study: 1987-1989	Hospital Admissions Outcome(s) (ICD9): Asthma (493) Age groups analyzed: 0-14; 15-64; ≥ 65 yrs Study design: Time-series N: 4,209 Statistical analyses: Correlations and partial correlations Covariates: Min temperature Statistical package: Lag: 0-1	24-h avg: 19.2 (12.6) μg/m^3 Range: 0.2, 94.6 Number of monitors: 4 NO_2 (r = 0.4516) NO (r = 0.4773) O_3 (r = 0.1778) TSP (r = 0.1919) CO	The frequency of all admissions for asthma was significantly correlated to SO_2. Child asthma admissions were not significantly correlated with SO_2, but were correlated to O_3 and NO. SO_2 was also significantly correlated with elderly admissions. Increased hospitalization correlated with SO_2 was also observed for adults. Hospital admissions were more strongly correlated with SO_2 than other pollutants. ER visits were more strongly correlated with a mixture of pollutants (TSP, SO_2, O_3, and temperature). Multipollutant model co-linear results of SO_2, CO, NO_2, and NO suggest a mixture of pollutants is responsible for asthma admissions. Correlations between hospital admissions (HA) for asthma and pollutants and temperature by ages. 0-14 yrs HA: −0.01391 Emergency HA: 0.0332 15-64 yrs HA: 0.1039 p = 0.0006 Emergency HA: 0.1199 p < 0.0001 ≥ 65 yrs HA: 0.0796 p = 0.0085 Emergency HA: 0.1169 p < 0.0001 Partial correlations between admissions for asthma and SO_2 were standardized for temperature. HA: 0.0770 p = 0.0172 Emergency HA: 0.1050 p = 0.0011
Pönkä and Virtanen (1994) Helsinki, Finland Period of Study: 1987-1989 Days: 1096	Hospital Admissions Outcome(s) (ICD 9): Chronic bronchitis and emphysema (493) Age groups analyzed: < 65, ≥ 65 Study design: Time-series Statistical analyses: Poisson regression Covariates: Season, day of wk, yr, influenza, humidity, temperature Season: Summer (Jun-Aug), Autumn (Sep-Nov), Winter (Dec-Feb), Spring (Mar-May) Lag: 0-7 days	24-h Mean: 19 μg/m^3, SD: 12.6; Range: 0.2, 95 # of stations: 2 NO_2 O_3 TSP	SO_2 was significantly associated with increased admissions for chronic bronchitis and emphysema for patients < 65 yrs of age with a lag of 0 and 3 days. In the steps leading to regression analysis no association was observed between SO_2 levels and the ≥65 population. Multipollutant models were only used to examine NO_2 and SO_2. SO_2 had no significant association with morbidity caused by chronic bronchitis and emphysema in the ≥ 65 yr old population. Increment: NR Chronic bronchitis and emphysema < 65 yrs RR 1.31 (1.01, 1.70) lag 0 RR 0.96 (0.73, 1.27) lag 1 RR 0.78 (0.59, 1.03) lag 2 RR 1.39 (1.05, 1.86) lag 3 RR 0.89 (0.68, 1.16) lag 4 RR 1.28 (0.97, 1.70) lag 5 RR 0.91 (0.69, 1.20) lag 6 RR 1.09 (0.84, 1.40) lag 7 65+ yrs: NR
Pönkä and Virtanen (1996) Helsinki, Finland Period of Study: 1987-1989	Hospital Admissions Outcome(s) (ICD9): Asthma (493) Age groups analyzed: 0-14, 15-64, 65+ Study design: Time-series Statistical analyses: Covariates: Long-term trend, season, epidemics, day of wk, holidays, temperature, relative humidity Statistical package: Lag: 0-2	24-h avg (μg/m^3): Winter: 26 Spring: 22 Summer: 13 Fall: 15 NO_2 O_3 TSP	Significant associations were observed between daily SO_2 concentrations and daily counts of hospitalizations among 15- to 64-yr-old patients and among those over 64 yrs old, but not among children. These effects were observed when mean daily SO_2 values were lower than the max value recommended by WHO (125 μg/m^3). Parameter estimates (PE) and standard erro (SE) for a 1-unit increase: Asthma 15-64 yrs : PE 0.2176 (0.1081) p = 0.44 lag 2 PE 0.3086 (0.1545) p = 0.046 lag 0-3 Asthma 65+ yrs : PE 0.2412 (0.0956) p = 0.012 lag 2

STUDY	METHODS	POLLUTANTS	FINDINGS
Prescott et al. (1998) Edinburgh, United Kingdom Period of Study: 10/92-6/95	Hospital Admissions Outcome(s) (ICD 9): Pneumonia (480-7), COPD + Asthma (490-496) Age groups analyzed: < 65, 65+ Study design: Time-series Statistical analyses: Poisson log linear regression Covariates: Trend, seasonal and weekly variation, temperature, wind speed, day of wk Lag: 0,1, or 3 day rolling avg	SO_2: 14.5 (9.0) ppb MiN: 0 ppb Max: 153 ppb # of Stations: 1 CO PM_{10} NO_2 O_3 BS	No effect of SO_2 on hospitalizations observed in either age category. Increment: 10 ppb Respiratory admissions >65 yrs −2.5 (−11.0, 6.9) lag 0-2 < 65 yrs 0.0 (−8.3, 9.1) lag 0-2
Rossi et al. (1993) Oulu, Finland Period of Study: 10/1/1985-9/30/1986	ED Visits Outcome(s) (ICD 9): Asthma (493) Age groups analyzed: 15-85 Study design: Time-series N: 232 Statistical analyses: Pearson's and partial correlation coefficients and multiple regression with stepwise discriminate analysis Covariates: Temperature, humidity Statistical package: BMDP software Lag: 0,1,2,3	24-h Mean: 10.0 µg/m^3 Range: 0, 56 1-h max: 31.0 µg/m^3 Range: 1, 24 # of monitoring stations: 4 NO_2; r = 0.48 TSP; r = 0.31 H2S	Same day ER visits were correlated to daily SO_2 levels, but the significance was lost with longer lag periods. When asthma visits were analyzed, SO_2 was positively and significantly correlated with asthma visits in the same wk and the wk after. After regression analyses, SO_2 became insignificant. Pearson correlation coefficients ED asthma visits and same day SO_2: r = 0.13 p < 0.01 lag 0 Weekly ED asthma visits and same wk SO_2: r = 0.28 p < 0.05 Weekly ED asthma visits and previous wk SO_2: 0.30 p < 0.05 Multipollutant (NO_2; TSP; H2S) Regression coefficient: All yr: ∃ = 0.037, p = 0.535 Winter: ∃ = −0.024, p = 0.710 Summer: ∃ = −0.003, p = 0.991

STUDY	METHODS	POLLUTANTS	FINDINGS
Schouten et al. (1996) Multicity, The Netherlands (Amsterdam, Rotterdam) Period of Study: 04/01/77-09/30/89	Hospital Admissions Outcome(s) (ICD 9): All respiratory (460-519), COPD (490-2, 494, 496), Asthma (493) Age groups analyzed: 15-64, 65+, all ages Study design: Time-series Statistical analyses: APHEA protocol, Poisson regression Covariates: Long-term trend, season, influenza, day of wk, holiday, temperature, humidity Season: Cool, Nov-Apr; Warm: May-Oct Lag: 0,1,2 days; and cumulative 0-1 and 0-3 day lags	24-h avg SO_2 Amsterdam Mean/Med: 28/21 µg/m^3 Rotterdam Mean: 40/32 µg/m^3 Daily 1-h max Amsterdam Mean/Med: 65/50 µg/m^3 Rotterdam Mean/Med: 99/82 µg/m^3 # of stations: 1 per city NO_2 BS O_3	The relationship between short-term air pollution and hospital admissions was not always consistent at low levels of exposure. One statistically significant association between hospital admissions and asthma (all ages) occurred in Amsterdam after a cumulative lag of 1-3 days in the summer. Higher SO_2 levels were reported for the winter; therefore, this association was not a concentration response. In Rotterdam neither 1 day nor cumulative lags in the summer or winter increased asthma admissions to statistical significance. Rotterdam had much higher mean SO_2 concentrations. There were no significant associations to hospital admissions when higher pollution levels were prevalent. The analysis of all respiratory hospital admissions for all ages in the entire country (Netherlands) produced a statistically significant association for both 1-h and 24-h periods (100 µg/m^3). Increment: 100 µg/m^3 increment. All respiratory, Amsterdam 24-h avg 15-64 yrs RR 0.944 (0.864, 1.032) lag 2 RR 0.915 (0.809, 1.035) lag 0-3 >65 yrs RR 1.046 (0.965, 1.134) lag 2 RR 1.008 (0.899, 1.131) lag 0-3 1-h max 15-64 yrs RR 0.989(0.952, 1028) lag 2 RR 0.977 (0.927, 1.030) lag 0-3 >65 yrs RR 1.022 (0.985, 1060) lag 2 RR 1.010 (0.955, 1.068) lag 0-3 RR 0.941 (0.863, 1.026) lag 0-3 COPD, Amsterdam 24-h avg–all ages RR 0.907 (0.814, 1.011) lag 0 RR 0.948 (0.838, 1.072) lag 0-1 1-h max–all ages RR 0.978 (0.933, 1.026) lag 0 RR 0.995 (0.940, 1.053) lag 0-1 Asthma, Amsterdam 24-h avg–all ages RR 0.802 (0.696, 0.924) lag 1 RR 0.792 (0.654, 0.958) lag 0-3 1-h max–all ages RR 0.995 (0.942, 1.051) lag 0 All respiratory, Rotterdam 24-h avg 15-64 yrs RR 0.941 (0.855, 1.036) lag 1 RR 0.895 (0.787, 1.019) lag 0-2 >65 yrs 1977-1981 RR 1.027 (0.904, 1.165) lag 2 RR 1.011 (0.834, 1.227) lag 0-3 >65 yrs 1982-1984 RR 1.087 (0.890, 1.328) lag 0 RR 1.258 (0.926, 1.710) lag 0-3 >65 yrs 1985-1989 RR 1.045 (0.908, 1.204) lag 0 RR 0.968 (0.787, 1.190) lag 0-3 1-h max 15-64 yrs RR 0.989(0.953, 1025) lag 1 RR 0.965 (0.915, 1.018) lag 0-2 >65 yrs 1977-1981 RR 0.892 (0.842, 0.945) lag 0 RR 0.987 (0.907, 1.074) lag 0-3 >65 yrs 1982-1984 RR 1.005 (0.933, 1.081) lag 0 RR 1.062 (0.938, 1.202) lag 0-3 >65 yrs 1985-1989 RR 1.010 (0.955, 1.068) lag 0 RR 1.064 (0.992, 1.141) lag 0-1 COPD, Rotterdam 24-h avg–all ages RR 0.963 (0.874, 1.059) lag 2 RR 1.019 (0.887, 1.172) lag 0-3 1-h max–all ages RR 0.991 (0.955, 1.029) lag 2 RR 1.013 (0.953, 1.076) lag 0-3 All respiratory, Rotterdam 24-h avg 15-64 yrs RR 0.941 (0.855, 1.036) lag 1 RR 0.895 (0.787, 1.019) lag 0-2 >65 yrs 1977-1981 RR 1.027 (0.904, 1.165) lag 2

STUDY	METHODS	POLLUTANTS	FINDINGS
Spix et al. (1998) Multicity (London, Amsterdam, Rotterdam, Paris, Milan), Europe Period of Study: 1977 and 1991	Hospital Admissions Outcome(s) (ICD9): All respiratory (460-519); Asthma (493) Age groups analyzed: 15-64, 65+ Study design: Time-series Statistical analyses: Poisson regression following APHEA protocol. Pooled meta-analysis adjusted for heterogeneity Covariates: trend, seasonality, day of wk, holiday, temperature, humidity, unusual events (strikes, etc.) Lag: 1 to 3 days	SO_2 daily mean ($\mu g/m^3$) LondoN: 29 Amsterdam: 21 Rotterdam: 25 Paris: 23 MilaN: 66 NO_2, O_3, BS, TSP	Daily counts of adult respiratory admissions were not consistently associated with daily mean levels of SO_2. Heterogeneity between cities was likely due to the number of stations or temperature. Only hospital admissions for ≥ 65 yr olds were significantly associated with SO_2 in the warm season. Increment: 50 $\mu g/m^3$ All cities, yr round 15-64 yrs RR 1.009 (0.992, 1.025) Warm RR 1.01 (0.98, 1.04) Cold RR 1.01 (0.97, 1.07) ≥ 65 yrs RR 1.02 (1.005, 1.046) Warm RR 1.06 (1.01, 1.11) Cold RR 1.02 (0.99, 1.04) APHEA protocol pooled result from ≥65 yrs old from Europe All respiratory RR 1.02 (1.00, 1.05)
Sunyer et al. (1997) Multicity, Europe (Barcelona, Helsinki, Paris, London) Period of Study: 1986-1992	Hospital admissions/ED Visits Outcome(s) (ICD 9): Asthma (493) Age groups analyzed: < 15, 15-64 Study design: Time-series Statistical analyses: APHEA protocol, Poisson regression, GEE; meta-analysis Covariates: Humidity, temperature, influenza, soybean, Long-term trend, season, day of wk Season: Cool, Oct-Mar; Warm: Apr-Sep Lag: 0,1,2,3 and cumulative 1-3	24-h median (range) ($\mu g/m^3$) Barcelona: 41 (2, 160) Helsinki: 16 (3, 95) LondoN: 31 (9, 100) Paris: 23 (1, 219) # of stations: Barcelona: 3 LondoN: 4 Paris: 4 Helsinki: 8 NO_2 black smoke O_3	SO_2 alone or as part of a mixture was a factor that exacerbated asthma admissions. In 2-pollutant models with SO_2 and BS, the association of BS with SO_2 was attenuated for < 15 yr olds, compared to single-pollutant model associations. In addition, the association of NO_2 was also attenuated by the inclusion of SO_2. Increment: 50 $\mu g/m^3$ of 24-h avg for all cities combined. Asthma 15-64 yrs 0.997 (0.961, 1.034) lag 2 1.003 (0.959, 1.050) lag 0-3, cum < 15 yrs 1.075 (1.026, 1.126) lag 1 1.061 (0.996, 1.131) lag 2-3, cum 2-pollutant models: SO_2/Black smoke < 15 yrs 1.092 (1.031, 1.156) lag 0-1 SO_2/NO_2 < 15 yrs 1.075 (1.019, 1.135)
Sunyer et al. (2003) Multicity study (Birmingham (B), London (L), Milan (M), Netherlands (N), Paris (P), Rome (R) and Stockholm (S), Europe Period of Study: 1992 and 1997	Hospital admissions/ED Visits Outcome(s) (ICD 9): Asthma (493); COPD and Asthma (490-496); All respiratory (460-519) Age groups analyzed: All, 0-14 yrs; 16-64 yrs; ≥ 65 yrs Study design:Time-series Poisson regression with GAM following APHEA 2 protocol Covariates: temperature, humidity, Long-term trend, season Lag: 0, 1	SO_2 24-h avg and SD ($\mu g/m^3$) B 24.3 (12.7) L 23.6 (23.7) M 32.5 (37.5) N 8.5 (7.7) P 17.7 (12.5) R 9.8 (9.9) S 6.8 (6.2) PM_{10} (r = 0.64) CO (r = 0.53)	The magnitude of association with asthma across the seven cities was comparable to earlier studies of London, Helsinki and Paris. Exposure factors may be important. Children may spend greater time outdoors compared with adults. Pneumonia requires chronic exposure to produce inflammatory response and infection, whereas asthma is an acute response. Increment: 10 $\mu g/m^3$ Asthma 0-14 yrs 1.3% (0.4, 2.2) 15-64 yrs 0.0% (−0.9, 1.00) COPD and Asthma ≥ 65 yrs 0.6% (0.0, 1.2) All Respiratory ≥ 65 yrs 0.5% (0.1, 0.9) Asthma 0-14 yrs SO_2 + PM_{10}: −3.7% (p > 0.1) SO_2 + CO: −0.7% (p > 0.1)

STUDY	METHODS	POLLUTANTS	FINDINGS
Sunyer et al. (1991) Barcelona, Spain Period of Study: 1985-1986	ED Visits Outcome(s) COPD (ICD 9): 490-496 Age groups analyzed: > 14 Study design: Time-series # of Hospitals: 4 Statistical analyses: multivariate linear regression Covariates: Meteorology, season, day of wk Statistical package: Lag: 0 to 2 days	24-h avg (SD): 56.5 (22.5) $\mu g/m^3$ 98th: 114.3 Range: 17, 160 1-h max (SD): 141.9 (98.8) $\mu g/m^3$ 98th: 461.3 Range: 17, 160 Number of monitors: 14-720 BS, CO, NO_2, O_3	An incremental change of 25 $\mu g/m^3$ in SO_2 was correlated with an adjusted increase of 0.5 daily visits due to COPD. SO_2 and ER visits were more strongly correlated in warm weather. Even at 24-h avg levels less than 100 $\mu g/m^3$, effects of SO_2 were statistically significant for COPD admissions. Change in 24-h SO_2 daily ER $\mu g/m^3$ admissions P-value 150 0.55 < 0.01 100 0.7 < 0.01 72 0.7 0.04 52 0.41 > 0.05 39 −1.27 > 0.05 0.5 excess daily admissions per 25 $\mu g/m^3$ increment of SO_2.
Sunyer et al. (1993) Barcelona, Spain Period of Study: 1985-1989	ED Visits Outcome(s) (ICD 9): COPD (490-492; 494-496) Study design: Time-series Statistical analyses: Autoregressive linear regression Statistical package: Lag: 1,2	SO_2, 24-h Winter Tertiles ($\mu g/m^3$) < 40.4 40.4, 61 >61 Winter Tertiles ($\mu g/m^3$) < 28.1 28.1, 46.1 >46.1 BS	SO_2 concentrations were associated with the number of COPD ER admissions in the winter and summer. An increase of 25 $\mu g/m^3$ in SO_2 produced an adjusted change of ~6% and 9%, respectively, in the number of COPD emergencies in the winter and summer. Controlling for particulate matter resulted in a loss of significance. Co linearity of BS with SO_2 was observed. Effects were expressed as adjusted changes in daily COPD ER admissions based on an increment of 25 $\mu g/m^3$. Winter: 6% Summer: 9% Mean ER admissions for COPD (winter) were 15.8 (range 3, 34) and 8.3 (range 1, 24) in the summer.
Tenias et al. (1998) Valencia, Spain Period of Study: 1993-1995 Seasons: Cold: Nov-Apr Warm: May-Oct	ED Visits Outcome(s): Asthma ICD 9 Code(s): NR Age groups analyzed: > 14 Study design: Time-series N: 734 Statistical analyses: Poisson regression, APHEA protocol Covariates: seasonality, temperature, humidity, long-term trend, day of wk, holidays, influenza Season: Cold: Nov-Apr; Warm: May-Oct Dose-response investigated: Yes Lag: 0-3 days	24 h avg: 26.6 $\mu g/m^3$ 25th: 17.9 50th: 26.2 75th: 34.3 95th: 42.6 Cold: 31.7 Warm: 21.7 1-h max: 56.3 $\mu g/m^3$ 25th: 36.3 50th: 52.2 75th: 72.2 95th: 95.2 Cold: 64.6 Warm: 48.2 # of Stations: 2 24 h avg: O_3 (r = −0.431) NO_2 (24 h av) (r = 0.265) NO_2 (1-h) (r = 0.199) 1-h: O_3 (r = −0.304) NO_2 (24 h avg) (r = 0.261) NO_2 (1-h) (r = 0.201)	SO_2 showed the strongest correlation to asthma admissions during the warm mos. Multipollutant models showed that O_3 and black smoke had a small effect on the association between SO_2 and asthma ER visits while NO_2 greatly depressed these effects. It is likely that NO_2 was the dominant pollutant for respiratory outcomes. SO_2 was the “most vulnerable pollutant” to the presence of other pollutants. Increment: 10 $\mu g/m^3$ SO_2 24-h avg All yr 1.050 (0.973, 1.133) lag 0 Cold 1.032 (0.937, 1.138) lag 0 Warm 1.070 (0.936, 1.224) lag 0 SO_2 1-h max All yr 1.027 (0.998, 1.057) lag 0 Cold 1.018 (0.980, 1.057) lag 0 Warm 1.038 (0.990, 1.090) lag 0

STUDY	METHODS	POLLUTANTS	FINDINGS
Tenias et al. (2002) Valencia, Spain Period of Study: 1994-1995	ED Visits Outcome(s): COPD ICD 9 Code(s): NR Age groups analyzed: > 14 Study design: Time-series N: 1,298 # of Hospitals: 1 Statistical analyses: Poisson regression, APHEA protocol; basal models and GAM Covariates: Seasonality, annual cycles, temperature, humidity, day of wk, feast days Season: Cold, Nov-Apr; Warm, May-Oct Dose-response investigated: Yes Lag: 0-3 days	24 h avg: 26.6 μg/m^3 25th: 17.9 50th: 26.2 75th: 34.3 95th: 42.6 Cold: 31.7 Warm: 21.7 1-h max: 56.3 μg/m^3 25th: 36.3 50th: 52.2 75th: 72.2 95th: 95.2 Cold: 64.6 Warm: 48.2 BS (r = 0.687) NO_2 (r = 0.194) CO (r = 0.734) O_3 (r = −0.431)	SO_2 did not show any significant association with COPD ER visits for all seasons analyzed. SO_2 did not affect O_3 or CO association to ER admission for COPD when assessed together in the Multipollutant model. Possibility of a linear relationship between pollution and risk of emergency cases could not be ruled out. Increment: 10 μg/m^3. 24-h avg SO_2 All yr RR 0.971 (0.914, 1.031) lag 0 Cold, 24-h avg: RR 0.970 (0.905, 1.038) lag 0 Warm, 24-h avg: RR 0.982 (0.885, 1.090) lag 0 1-h max SO_2 All yr RR 0.981 (0.958, 1.027) lag 3 Cold, 24-h avg: RR 0.972 (0.945, 1.000) lag 3 Warm, 24-h avg: RR 1.003 (0.979, 1.056) lag 3
Thompson et al. (2001) Belfast, Northern Ireland Period of Study: 1993-1995	Hospital admissions/ED Visits Outcome(s): Asthma ICD 9 Code(s): NR Age groups analyzed: Children Study design: Time-series N: 1,044 Statistical analyses: Followed APHEA protocol, Poisson regression analysis Covariates: Season, long-term trend, temperature, day of wk, holiday Season: Warm (May-Oct); Cold (Nov-Apr) Statistical package: Stata Lag: 0-3	Warm Season SO_2 (ppb): Mean: 12.60; SD: 10.60; IQR: 6.0, 16.0 Cold Season SO_2 (ppb): Mean: 20.40; SD: 17.90; IQR: 11.0, 24.0 PM_{10} (r = 0.66) NO_2 (r = 0.82) NOx (r = 0.83) NO (r = 0.76) O_3 (r = −0.58) CO (r = 0.64) Benzene (r = 0.80)	This study found weak, positive associations for SO_2 and adverse respiratory outcomes in asthmatic children. SO_2 Increment: Per doubling (ppb) Lag 0 RR 1.07 (1.03, 1.11) Lag 0-1 RR 1.09 (1.04, 1.15) Lag 0-2 RR 1.08 (1.02, 1.15) Lag 0-3 RR 1.08 (1.01, 1.15) Warm only Lag 0-1 RR 1.11 (1.04, 1.19) Cold only Lag 0-1 RR 1.07 (1.00, 1.15) Adjusted for Benzene Lag 0-1 RR 0.99 (0.90, 1.09)
Tobías et al. (1999) Barcelona, Spain Period of Study: 1986-1989	ED Visits Outcome(s): Asthma ICD9: NR Age groups analyzed: > 14 Study design: Time-series Statistical analyses: Poisson regression, followed APHEA protocol Covariates: Temperature, humidity, long-term trend, season, day of wk Lag: NR	24-h avg SO_2 μg/m^3 Non-epidemic Days: 85.8 (62.4) Epidemic Days: 116.3 (79.3) BS NO_2 O_3	The study failed to find a significant association between SO_2 and asthma ED visits. ∃ x 104 (SE □ 104) using Std Poisson Without modeling asthma epidemics: 3.99 (4.14) Modeling epidemics with 1 dummy variable: 1.64 (2.76) Modeling epidemics with 6 dummy variables: 1.53 (2.75) Modeling each epidemic with dummy variable: 2.20 (2.65) ∃ □ 104 (SE □ 104) using Autoregressive Poisson Without modeling asthma epidemics: 6.99 (14.37) Modeling epidemics with 1 dummy variable: 1.68 (2.77) Modeling epidemics with 6 dummy variables: 1.72 (2.75) Modeling each epidemic with dummy variable: 2.85 (2.89)

STUDY	METHODS	POLLUTANTS	FINDINGS
Vigotti et al. (1996) Milan, Italy Period of Study: 1980-1989	Hospital Admissions Outcomes (ICD 9 codes): Respiratory disease (460-519). Age groups analyzed: 15-64 yrs and >64 yrs Study design: Time-series N: >73,000 Statistical analyses: APHEA protocol Covariates: Season: Cold season (Oct. to Mar) and Warm season (Apr to Sep) Lag: 0, cumulative 4 day (0-3)	24-h avg: 117.7 μg/m^3 Range: 3.0, 827.8 5th: 15.0 25th: 34.0 50th: 65.5 75th: 162.5 95th: 376.3 Winter:248.6 Range: 30.6, 827.8 5th: 78.8 25th: 138.5 50th: 216.0 75th: 327.8 95th: 527.0 Summer:30.5 Range: 3.0, 113.8 5th: 9.1 25th: 18.5 50th: 27.8 75th: 39.2 95th: 62.7 # of monitors: 4; r = 0.89, 0.91 TSP (r = 0.63)	The effect of single day or cumulative day exposure to SO_2 was more pronounced during the cool mos. Interaction between seasons was not significant. SO_2 did not interact with TSP. No differences were noted between age groups. There were increased, but not significant (borderline), risks for increased hospital admissions based on an increment change in SO_2 of 125 μg/m^3 in the winter. Increment: 100 μg/m^3 All respiratory 15-64 yrs All yr round: RR 1.05 (1.00, 1.10) lag 0 Warm: RR 1.04 (0.98, 1.11) lag 0 Cool: RR 1.06 (1.00, 1.13) lag 0 >64 yrs All yr: RR 1.04 (1.00, 1.09) lag 0 Warm: RR 1.02 (0.96, 1.08) lag 0 Cool: RR 1.05 (1.00, 1.11) lag 0
Walters et al. (1994) Birmingham, United Kingdom Period of Study: 1988-1990	Hospital Admissions Outcome(s) (ICD9): Asthma (493) and acute respiratory conditions (466, 480-486, 490-496) Study design:Time-series Statistical analyses: Least squares regression Covariates: Temperature, pressure, humidity Lag: 3 day moving avg.	SO_2 24-h mean (μg/m^3) All yr: 39.06 Max: 126.3 Spring: 42.9 Summer: 37.8 AutumN: 40.9 Winter: 34.2 BS	In 2-pollutant models BS remained significant but SO_2 was no longer associated significantly with admission. A 100 μg/m^3 increment in SO_2 might result in four (0-7) more asthma admissions and 15.5 (6-25) move respiratory admissions/day. Spring and autumn did not show associations with admissions for asthma or respiratory. Increment of 100 μg/m^3 Asthma Summer: 1.4% (−10, 39) lag 0 Winter: 2.7% (−0.8, 6.1) lag 0 All respiratory Summer: 5.9% (1.1, 10.6) lag 0 ($p < 0.02$) Winter: 18% (8.8, 26.8) lag 0 ($p < 0.0002$)
LATIN AMERICA			
Braga* et al. (1999) São Paulo, Brazil Period of Study: 10/1992-10/1993	Hospital Admissions Outcome(s) (ICD9): All respiratory (466, 480-486,491-492,496) Age groups analyzed: < 13 yrs Study design:Time-series N: 68,918 # of Hospitals: 112 Statistical analyses: Multiple linear regression models (least squares). Also used Poisson regression techniques. GLM and GAM using LOESS for smoothing. Covariates: Season, temperature, humidity, day of wk, Statistical package: SPSS, S-Plus Lag: 1,2,3,4,5,6,7 moving avgs	24-h avg 22.40 (9.90) μg/m^3 MiN: 6.4 Max: 69.6 # of monitors: 13 PM_{10} (r = 0.73) CO (r = 0.62) NO_2 (r = 0.53) O_3	SO_2 did not show a correlation with respiratory hospital admissions with any lag structure. Increment: 22.4 μg/m^3 0.12 (−0.04, 0.28) lag 0 0.18 (−0.00, 0.37) lag 0-1 0.19 (−0.01, 0.39) lag 0-2 0.18 (−0.04, 0.40) lag 0-3 0.18 (−0.05, 0.42) lag 0-4 0.12 (−0.13, 0.36) lag 0-5 0.08 (−0.18, 0.35) lag 0-6

STUDY	METHODS	POLLUTANTS	FINDINGS
Braga* et al. (2001) São Paulo, Brazil Period of Study: 1/93-11/97	Hospital Admissions Outcome(s) (ICD 9): All respiratory admissions (460-519) Age groups analyzed: 0-19, ≤ 2, 3-5, 6-13, 14-19 Study design: Time-series Statistical analyses: Poisson regression with GAM Covariates: Long-term trend, season, temperature, relative humidity, day of wk, holiday Statistical package: S-Plus 4.5 Lag: 0-6 moving avg	SO_2 Mean: 21.4 μg/m^3; SD: 11.2 IQR: 14.4 μg/m^3 Range: 1.6, 76.1 # of stations: 5-6 PM_{10} (r = 0.61) NO_2 (r = 0.54) CO (r = 0.47) O_3 (r = 0.17)	Children < 2 yrs were most susceptible to the effect of each pollutant. Pneumonia and bronchopneumonia were the main cause of hospital admissions (71%) in the < 2-yr-old group. Bronchitis/asthma were more important for the intermediate age groups. However, in all age groups the largest increase in admissions was caused by chronic disease in tonsils and adenoids. Multipollutant models rendered all pollutants except PM_{10} and SO_2 from significance. The effect of PM_{10} stayed relatively unchanged while SO_2 was reduced; however, it remained significant. Increment: μg/m^3 (IQR) All respiratory admissions < 2 yrs 5.9% (4.5, 7.4) 3-5 yrs 1.6% (−1.3, 4.4) 6-13 yrs 0.6% (−2.2, 3.5) 14-19 yrs 1.3% (−3.2, 5.8) All ages 4.5% (3.3, 5.8)
Farhat* et al. (2005) São Paulo, Brazil Period of Study: 1996-1997	Hospital Admissions/ED Visits Outcome(s) (ICD9): Lower Respiratory Disease (466, 480-5) Age groups analyzed: < 13 Study design: Time-series N: 4,534 # of Hospitals: 1 Statistical analyses: 1) Poisson regression and 2) GAM – no mention of more stringent criteria Covariates: Long-term trends, seasonality, temperature, humidity Statistical package: S-Plus Lag: 0-7 days, 2,3,4 day moving avg	24-h avg: Mean: 23.7 μg/m^3 SD: 10.0 Range: 3.4, 75.2 IQR: 12.5 # of Stations: 6 PM_{10} (r = 0.69) NO_2 (r = 0.66) CO (r = 0.49) O_3 (r = 0.28)	This study reports a significant effect of air pollution on respiratory morbidity, though several pollutants were associated with increased respiratory events, making it difficult to isolate a single agent as the main atmospheric contaminant. Increment: 12.5 μg/m^3 (IQR) Single-pollutant models (estimated from graphs): Pneumonia ~21% (4.8, 37) Asthma ~12% (−10, 38) Pneumonia multipollutant models: Adjusted for: PM_{10} 13.3 (−5.7, 32.3) 6-day avg NO_2 16.5 (−1.6, 34.6) 6-day avg CO 18.4 (0.5, 36.2) 6-day avg O_3 18.4 (0.5, 36.2) 6-day avg Multipollutant model 13.3 (−5.9, 32.6) 6-day avg Asthma multipollutant models: Adjusted for: PM_{10} 3.8 (−23.3, 31.0) 2-day avg NO_2 −1.2 (−27.4, 25.0) 2-day avg CO 6.2 (−18.8, 31.2) 2-day avg O_3 9.4 (−14.6, 33.5) 2-day avg Multipollutant model −0.5 (−27.7, 26.6) 2-day avg
Gouveia and Fletcher (2000) São Paulo, Brazil Period of Study: 11/92-9/94	Hospital Admissions Outcome(s) (ICD 9): All respiratory; Pneumonia (480-486); asthma or bronchitis (466, 490, 491, 493) Age groups analyzed: < 1; < 5 yrs Study design: Time-series Statistical analyses: Poisson regression Covariates: Long-term trend, season, temperature, relative humidity, day of wk, holiday, strikes in public transport or health services Season: Cool (May-Oct), Warm (Nov-Apr) Statistical package: SAS Lag: 0, 1, 2 days	24-h avg: Mean: 18.3 μg/m^3 SD: 9.0 Range: 3.2, 61.1 5th: 7.6 25th: 11.9 50th: 16.6 75th: 22.2 95th: 35.8 # of stations: 4 PM_{10} (r = 0.72) NO_2 (r = 0.37) CO (r = 0.65) O_3 (r = 0.08)	Current ambient air pollution concentrations have short-term adverse effects on children's respiratory morbidity assessed through admissions to hospitals. Increment: 27.1 μg/m^3 (90th – 10th) All Respiratory < 5 yrs RR 1.038 (0.983, 1.096) lag 1 < 5 yrs Cool RR 1.06 (0.99, 1.11) (estimated from graph) < 5 yrs Warm RR 0.98 (0.89, 1.07) (estimated from graph) Pneumonia < 5 yrs RR 1.024 (0.961, 1.091) lag 1 < 1 yr RR 1.071 (0.998, 1.149) lag 0 Asthma < 5 yrs RR 1.106 (0.981, 1.247) lag 2

STUDY	METHODS	POLLUTANTS	FINDINGS
Ilabaca et al. (1999) Santiago, Chile Period of Study: 2/1/95–8/31/96 Days: 578	ED Visits Outcome(s) (ICD9): Upper respiratory illness (460-465, 487); Lower respiratory illness (466, 480-486, 490-494, 496, 519.1, 033.9); Pneumonia (480-486) Age groups analyzed: < 15 Study design: Time-series # of Hospitals: 1 Statistical analyses: Poisson regression Covariates: Long-term trend, season, day of wk, temperature, humidity, influenza epidemic Season: Warm (Sep-Apr), Cool (May-Aug) Lag: 0-3 days	24-h avg SO_2 ($\mu g/m^3$) Warm: Mean: 14.9 MediaN: 13.2 SD: 8.8 Range: 1.9, 60.2 5th: 5.6 95th: 32.0 Cool: Mean: 31.8 MediaN: 28.2 SD: 18.4 Range: 5.6, 92.1 5th: 9.4 95th: 75.2 # of stations: 4 Warm: NO_2 (r = 0.6556) O_3 (r = 0.1835) PM_{10} (r = 0.6687) $PM_{2.5}$ (r = 0.5764) Cool: NO_2 (r = 0.7440) O_3 (r = 0.1252) PM_{10} (r = 0.7337) $PM_{2.5}$ (r = 0.6874)	SO_2 was related to the number of respiratory ED visits, but because of the high correlation between contaminants, it is difficult to establish independent health effects. These results support the fact that exposure to air pollution mixtures may decrease immune functions and increase the risk for respiratory infections among children. Increment: IQR All respiratory Cool Lag 2 IQR: RR 1.0289 (1.0151, 1.0428) Lag 3 IQR: RR 1.0374 (1.0236, 1.0513) Lag avg 7 IQR: RR 1.0230 (1.0086, 1.0377) Warm Lag 2 IQR: RR 1.0029 (0.9860, 1.0200) Lag 3 IQR: RR 1.0108 (0.9937, 1.0282) Lag avg 7 IQR: RR 1.0108 (0.9756, 1.0473) Upper respiratory Cool Lag 2 IQR: RR 1.0584 (1.0394, 1.0778) Lag 3 IQR: RR 1.0513 (1.0324, 1.0706) Lag avg 7 IQR: RR 1.0316 (1.0120, 1.0515) Warm Lag 2 IQR: RR 1.0061 (0.9850, 1.0277) Lag 3 IQR: RR 1.0130 (0.9916, 1.0349) Lag avg 7 IQR: RR 0.9815 (0.9390, 1.0260) Pneumonia Cool Lag 2 IQR: RR 1.0164 (0.9757, 1.0587) Lag 3 IQR: RR 1.0342 (0.9938, 1.0762) Lag avg 7 IQR: RR 1.0291 (0.9850, 1.0751) Warm Lag 2 IQR: RR 1.1010 (1.0404, 1.1653) Lag 3 IQR: RR 1.0248 (0.9669, 1.0862) Lag avg 7 IQR: RR 1.2151 (1.0771, 1.3709)
Lin et al. (1999) São Paulo, Brazil Period of Study: May 1991-Apr 1993 Days: 621	ED Visits Outcome(s): Respiratory disease, Upper respiratory illness, Lower respiratory illness, Wheezing ICD 9Code(s): NR Age groups analyzed: < 13 Study design: Time-series # of Hospitals: 1 Statistical analyses: Gaussian and Poisson regression Covariates: Long-term trend, seasonality, day of wk, temperature, humidity Lag: 5-day lagged moving avgs	SO_2 $\mu g/m^3$: Mean: 20 SD: 8 Range: 4, 60 Number of stations: 3 NO_2 (r = 0.38) CO (r = 0.56) PM_{10} (r = 0.73) O_3 (r = 0.21)	The results of this study demonstrate a significant association between the increase in emergency visits for all respiratory illness, especially URI, and SO_2 levels. Increment: 10 $\mu g/m^3$ All respiratory illness SO_2 alone RR 1.079 (1.052, 1.107) 5-day moving avg $SO_2 + PM_{10} + O_3 + NO_2 + CO$ RR 0.938 (0.900, 0.977) Lower respiratory illness SO_2 alone RR 1.052 (0.984, 1.125) 5-day moving avg $SO_2 + PM_{10} + O_3 + NO_2 + CO$ RR 0.872 (0.783, 0.971) Upper respiratory illness SO_2 alone RR 1.075 (1.044, 1.107) 5-day moving avg $SO_2 + PM_{10} + O_3 + NO_2 + CO$ RR 0.951 (0.906, 0.999) Wheezing SO_2 alone RR 1.034 (0.975, 1.096) 5-day moving avg $SO_2 + PM_{10} + O_3 + NO_2 + CO$ RR 0.908 (0.824, 1.002)

STUDY	METHODS	POLLUTANTS	FINDINGS
Martins* et al. (2002) São Paulo, Brazil Period of Study: 5/96-9/98	ED Visits Outcome(s) (ICD10): Chronic Lower Respiratory Disease (CLRD) (J40-J47); includes chronic bronchitis, emphysema, other COPDs, asthma, bronchiectasia Age groups analyzed: >64 Study design: Time-series N: 712 # of Hospitals: 1 Catchment area: 13,163 total ER visits Statistical analyses: Poisson regression and GAM – no mention of more stringent criteria Covariates: Weekdays, time, min temperature, relative humidity, daily number of non-respiratory emergency room visits made by elderly Statistical package: S-Plus Lag: 2-7 days and 3 day moving avgs	SO_2 24-h avg ($\mu g/m^3$): 18.7, SD: 10.6 Range: 2.0, 75.2 IQR: 15.1 $\mu g/m^3$ # of Stations: 13 O_3 (r = 0.28) NO_2 (r = 0.67) PM_{10} (r = 0.72) CO (r = 0.51)	The results of the study show a significant association between SO_2 and CLRD among the elderly. Increment: IQR of $\mu g/m^3$ Percent increase: 17.5 (5.0, 23.0) lag 3-day moving avg (estimated from graph) Single-pollutant model ∃ = 0.0140 (0.0056) Multipollutant model (with ozone) ∃ = 0.0104 (0.0059)
ASIA			
Agarwal et al. (2006) Safdarjung area of south Deli Period of Study: 2000-2003	Hospital Admissions Outcome(s) (ICD9): COPD, asthma and emphysema Study design: time-series Statistical Analysis: Performed Kruskal-Wallis one way analysis of variance by rank, chi-square analysis. Statistical package: SPSS Age groups analyzed: all Covariates: Temperature-min and maximum, relative humidity at 0830 and 1730 h and wind speed N: NR # Hospitals: 1 Lag: none	Mean, SD Quarter 1: 16.7, 5.5 Quarter 2: 13.6, 2.6 Quarter 3: 12.8, 3.1 Quarter 4: 14.3, 2.8 NO_2 SPM RSPM	SO_2 was found to be in “low” category the entire time, so no analysis could be performed

STUDY	METHODS	POLLUTANTS	FINDINGS
Chew et al. (1999) Singapore Period of Study: 1990-1994	Hospital Admissions/ED Visits Outcome(s) (ICD 9): Asthma (493) Age groups analyzed: 3-12, 13-21 Study design: Time-series N: 23,000 # of Hospitals: 2 Statistical analyses: Linear regression, GLM Covariates: variables that were significantly associated with ER visits were retained in the model Statistical package: SAS/STAT, SAS/ETS 6.08 Lag: 1, 2 days avgs	24-h avg: 38.1 $\mu g/m^3$, SD: 21.8 Range: 3.0, 141.0 # of Stations: 15 NO_2 O_3 TSP	SO_2 was positively correlated to daily ER visits and hospitalization for asthma in children (3-12 yrs), but not adolescents. The association of ER visits with SO_2 persisted after standardization for meteorological and temporal variables. An adjusted increase in 2.9 ER visits for every 20 $\mu g/m^3$ increase in ambient SO_2 levels with a lag of 1 was observed. The increased number of ER visits/day for each quartile are listed below: Q1: < 9 Q2: 10-12 Q3: 13-16 Q4: > 16 Categorical analysis (via ANOVA) p-value and Pearson correlation coefficient (r) using continuous data comparing daily air pollutant levels and daily number of ER visits Age Group: 3-12 13-21 Lag 0 r = 0.04 r = 0.05 p < 0.001 p = 0.086 Lag 1 r = 0.10 r = 0.06 p < 0.001 p = 0.016 Lag 2 r = 0.08 r = 0.07 p < 0.001 p = 0.019
Hwang and Chan (2002) Taiwan Period of Study: 1998	ED Visits Outcome(s) (ICD 9): Lower Respiratory Disease (LRD) (466, 480-6) including acute bronchitis, acute bronchiolits, pneumonia Age groups analyzed: 0-14, 15-64, ≥ 65, all ages Study design: Time-series Catchment area: Clinic records from 50 communities Statistical analyses: Linear regression, GLM Covariates: temperature, dew point temperature, season, day of wk, holiday Lag: 0,1,2 days and avgs	24-h avg: 5.4 ppb, SD: 3.0 Range: 1.5, 16.9 NO_2 PM_{10} O_3 CO No correlations for individual-pollutants.	Colinearity of pollutants prevented use of multipollutant models Increment: 10% change in SO_2 (natural avg) which is equivalent to 2.4 ppb. NOTE: The percent change is for the rate of clinic use NOT for relative risk for adverse effect. Increased clinic visits for lower respiratory disease (LRD) by age group 0-14 yrs Lag 0 0.5% (0.3, 0.6) 15-64 yrs Lag 0 0.7% (0.5, 0.8) ≥65 yrs Lag 0 0.8% (0.6, 1.1) All ages Lag 0 0.5% (0.4, 0.7)
Ko et al. (2007b) Hong Kong 2000-2005	Hospital Admissions Outcome(s) (ICD9): Asthma Study design: Retrospective ecological study Statistical Analysis: Generalized additive models with Poisson distribution. Age groups analyzed: All Covariates: N: 69,716 # Hospitals: 15 Lag: 0-5 days	Mean, SD ($\mu g/m^3$) Whole yr: 18.8, 13.1 < 20 °C: 18.0, 10.0 ≥20 °C: 19.1, 14.1 NO_2 PM_{10} $PM_{2.5}$ O_3	SO_2 had a non-significant effect on respiratory admissions. Relative Risk (95% CI) Lag 0: 1.004 (0.998, 1.011) Lag 1: 1.000 (0.994, 1.007) Lag 2: 0.999 (0.993, 1.006) Lag 3: 1.002 (0.998, 1.008) Lag 4: 1.004 (0.997, 1.010) Lag 5: 0.997 (0.990, 1.003) Lag 0,1: 1.003 (0.996, 1.011) Lag 0,2: 1.003 (0.994, 1.011) Lag 0,3: 1.004 (0.994, 1.014) Lag 0-4: 1.007 (0.996, 1.017) Lag 0-5: 1.004 (0.993, 1.016)

STUDY	METHODS	POLLUTANTS	FINDINGS
Ko et al. (2007a) Hong Kong 2000-2004	Hospital Admissions Outcome(s) (ICD9): COPD Study design: Retrospective ecological study Statistical Analysis: Poisson distribution Age groups analyzed: All ages Covariates: Autocorrelation and overdispersion were corrected N: 119,225 # Hospitals: 15 Lag: 0-5 days	15.0 µg/m^3 SD: 11.6 NO_2 PM_{10} O_3 $PM_{2.5}$	Positive association with hospital admission for acute exacerbations of COPD. Relative Risk (95% CI) Lag 0: 1.007 (1.001, 1.014) Lag 1: 0.991 (0.981, 1.001) Lag 2: 0.992 (0.985, 1.000) Lag 3: 1.006 (0.999, 1.013) Lag 4: 1.004 (0.998, 1.011) Lag 5: 1.004 (0.997, 1.010) Lag 0-1: 0.998 (0.991, 1.006) Lag 0-2: 0.993 (0.985, 1.001) Lag 0-3: 0.998 (0.989, 1.007) Lag 0-4: 1.001 (0.991, 1.010) Lag 0-5: 1.004 (0.994, 1.014)
Lee* et al. (2002) Seoul, Korea Period of Study: 12/1/97-12/31/99 Days: 822	Hospital Admissions Outcomes (ICD 10): Asthma (J45–J46) Age groups analyzed: < 15 Study design: Time-series N: 6,436 Statistical analyses: Poisson regression, log link with GAM Covariates: Time, day of wk, temperature, humidity Season: Spring (Mar-May), Summer (Jun-Aug), Fall (Sep-Nov), Winter (Dec-Feb) Lag: 0-2 days cumulative	24-h SO_2 (ppb) Mean: 7.7 SD: 3.3 5th: 3.7 25th: 5.1 50th: 7.0 75th: 9.5 95th: 14.3 # of stations: 27 NO_2 (r = 0.723) O_3 (r = −0.301) CO (r = 0.812) PM_{10} (r = 0.585)	This study reinforces the possible role of SO_2 on asthma attacks, although it should be interpreted with caution because the effect estimates are close to the null and because results in the multipollutant models are inconsistent. Increment: 14.6 ppb (IQR) Asthma SO_2 RR 1.11 (1.06, 1.17) lag 0-2 SO_2 + PM_{10} RR 1.08 (1.02, 1.14) lag 0-2 SO_2 + NO_2 RR 0.95 (0.88, 1.03) lag 0-2 SO_2 + O_3 RR 1.12 (1.06, 1.17) lag 0-2 SO_2 + CO RR 0.99 (0.92, 1.07) lag 0-2 SO_2 + O_3 + CO + PM_{10} + NO_2 RR 0.949 (0.868, 1.033)
Lee et al. (2006) Hong Kong, China Period of Study: 1997-2002 Days: 2,191	Hospital Admissions Outcome(s) (ICD 9): Asthma (493) Age groups analyzed: ≤18 Study design: Time-series N: 26,663 Statistical analyses: Semi-parametric Poisson regression with GAM (similar to APHEA 2) Covariates: Long-term trend, temperature, relative humidity, influenza, day of wk, holiday Statistical package: SAS 8.02 Lag: 0-5 days	SO_2 24-h Mean: 17.7 µg/m^3, SD: 10.7 IQR: 11.1 µg/m^3 25th: 10.6 50th: 15.2 75th: 21.7 # of stations: 9-10 PM_{10} (r = 0.37) $PM_{2.5}$ (r = 0.47) NO_2 (r = 0.49) O_3 (r = −0.17)	Absence of an association of SO_2 with asthma admissions was attributed to low ambient SO_2 levels during the study period due to restrictions on sulfur content in fuel. Increment: 11.1 µg/m^3 (IQR) Asthma Single-pollutant model Lag 0 −1.57% (−2.87, −0.26) Lag 1 −1.77% (−3.06, −0.46) Lag 2 −1.15% (−2.42, 0.14) Lag 3 0.82% (−0.45, 2.11) Lag 4 1.40% (0.13, 2.69) Lag 5 1.46% (0.19, 2.74) Multipollutant model–including PM, NO_2, and O_3 0.81% (−0.75, 2.4) lag 5 Other lags NR

STUDY	METHODS	POLLUTANTS	FINDINGS
Lee et al. (2007) Kaohsiung, Taiwan 1996-2003	Hospital Admissions Outcome(s) (ICD9): COPD (490-492, 494, and 496) identified by records from the National Health Insurance (NHI) program Study design: Case-crossover Statistical Analysis: Conditional logistic regression Statistical package: SAS Age groups analyzed: All ages Covariates: Adjustment for temperature and humidity N: 25,108 # Hospitals: 63 Lag: Cumulative lag up to 2 days	24-h avg (ppb): 9.49 Range: 0.92, 31.33 PM_{10} NO_2 CO O_3	All pollutants, except SO_2, were significantly associated with COPD hospital admissions on warm days, while on cold days all pollutants were found to be significantly associated. In two pollutant models, CO and O_3 were significantly associated with each of the other pollutants on warm days, and on cool days, only NO_2 was significantly associated with all pollutants. Odds Ratio (95% CI), Single-pollutant model (per 5.79 ppb SO_2) ≥ 25 °C 1.024 (0.973, 1.077) < 25 °C 1.190 (1.093, 1.295) Odds Ratio (95% CI), Co-pollutant model (per 5.79 ppb SO_2) ≥ 25 °C SO_2 + PM_{10}: 1.002 (0.951, 1.054) SO_2 + NO_2: 0.979 (0.926, 1.034) SO_2 + CO: 0.929 (0.876, 0.985) SO_2 + O_3: 1.057 (1.004, 1.113) < 25 °C SO_2 + PM_{10}: 1.043 (0.952, 1.143) SO_2 + NO_2: 0.767 (0.689, 0.855) SO_2 + CO: 1.004 (0.915, 1.103) SO_2 + O_3: 1.198 (1.100, 1.304)
Tanaka et al. (1998) Kushiro, Japan Period of Study: 1992-1993	ED Visits Outcome(s): Asthma Age groups analyzed: 15-79 Study design: Time-series N: 102 # of Hospitals: 1 Statistical analyses: Poisson regression Covariates: temperature, vapor pressure, barometric pressure, relative humidity, wind velocity, wind direction at maximal velocity Statistical package: NR	SO_2 24-h avg 3.2 (2.4) ppb in fog 3.7 (1.9) ppb in fog free days Max SO_2 24-h avg < 11 ppb NO_2 (r = NR) SPM (TSP); r = O_3; r = NR	The results reveal that ED visits by atopic subjects increased on low SO_2 days. This observation is inconsistent with most air pollution epidemiology, as high levels of air pollutants have conventionally been linked with asthma exacerbation. Increment: 5 ppb Nonatopic OR 1.18 (0.96, 1.46) Atopic OR 0.78 (0.66, 0.93)
Tsai et al. (2006) Kaohsiung, Taiwan Period of Study: 1996-2003 Days: 2922	Hospital Admissions Outcome(s) (ICD 9): Asthma (493) Study design: Case-crossover N: 17,682 Statistical analyses: Conditional logistic regression Covariates: Temperature, humidity Season: Warm (≥ 25 °C); Cool (< 25 °C) Statistical package: SAS Lag: 0-2 days Cumulative	SO_2 24-h Mean: 9.49 ppb Range: 0.92, 31.33 25th: 6.37 50th: 8.94 75th: 12.16 # of stations: 6 PM_{10} NO_2 O_3 CO	Positive associations were observed between air pollutants and hospital admissions for stroke. In single-pollutant models SO_2 was not associated with either PIH or IS. The season did not affect these associations. SO_2 was also not significant in 2-pollutant models. Increment: 5.79 ppb (IQR) Seasonality Single-pollutant model >25 °C 1.018 (0.956, 1.083) lag 0-2 < 25 °C 1.187 (1.073, 1.314) lag 0-2 Dual-pollutant model Adjusted for PM_{10} >25 °C 0.993 (0.932, 1.058) lag 0-2 < 25 °C 1.027 (0.921, 1.146) lag 0-2 Adjusted for CO >25 °C) 0.910 (0.847, 0.978) lag 0-2 < 25 °C 1.036 (1.027, 1.046) lag 0-2 Adjusted for NO_2 >25 °C 0.967 (0.903, 1.035) lag 0-2 < 25 °C 0.735 (0.646, 0.835) lag 0-2 Adjusted for O_3 >25 °C 1.055 (0.990, 1.123) lag 0-2 < 25 °C 1.195 (1.080, 1.323) lag 0-2

STUDY	METHODS	POLLUTANTS	FINDINGS
Wong et al. (1999) Hong Kong, China Period of Study: 1994-1995	Hospital Admissions Outcome(s) (ICD 9): All respiratory admissions (460-6, 471-8, 480-7, 490-6); Asthma (493), COPD (490-496), Pneumonia (480-7) Age groups analyzed: 0-4, 5-64, ≥ 65, all ages # of Hospitals: 12 Study design:Time-series Statistical analyses: Poisson regression (followed APHEA protocol) Covariates: Trend, season, day of wk, holiday, temperature, humidity Statistical package: SAS 8.02 Lag: days 0-3 cumulative	Median 24-h SO_2: 17.05 µg/m^3 Range: 2.74, 68.49 25th: 12.45 75th: 25.01 # of stations: 7, r = O_3 SO_2 PM_{10}	Adverse respiratory effects of SO_2 were noted at low concentrations. Results for respiratory outcomes were attributed to the elderly population. This was also true for the other pollutants. Therefore, it is difficult to be certain that the effects were due mainly to SO_2. Pair-wise comparisons in multipollutant models showed significant interactions of $PM_{2.5}$, NO_2, and O_3. Increment = 10 µg/m^3 Overall increase in admissions: 1.013 (1.004, 1.021) lag 0 Respiratory relative risks (RR) 0-4 yrs: 1.005 (0.991, 1.018) lag 0 5-64 yrs: 1.008 (0.996, 1.021) lag 0 >65 yrs: 1.023 (1.012, 1.036) lag 0 Asthma: 1.017 (0.998, 1.036) lag 0 COPD: 1.023 (1.011, 1.035) lag 0 Pneumonia: 0.990 (0.977, 1.004) lag 4
Wong et al. (Wong et al., 2001) Hong Kong, China Period of Study: 1993-1994	Hospital Admissions Outcome(s) (ICD 9): Asthma (493) Age groups analyzed: ≤ 15 N: 1,217 # of Hospitals: 1 Study design: Time-series Statistical analyses: Poisson regression (followed APHEA protocol) Covariates: Season, temperature, humidity Season: Summer (Jun-Aug), Autumn (Sep-Nov), Winter (Dec-Feb), Spring (Mar-May) Lag: 0,1,2,3,4,5 days; and cumulative 0-2 and 0-3 days.	24-h avg SO_2 Mean: 12.2 µg/m^3 SD: 12.9 Range: 0, 98 µg/m^3 AutumN: 10.6 (9.6) Winter: 10.0 (7.5) Spring: 9.6 (8.8) Summer: 18.5 (19.5) # of stations: 9 PM_{10} NO_2	SO_2 levels were found to be the highest during the summer. There were consistent and statistically significant associations between asthma admission and increased daily levels of SO_2. No associations were noted in the spring or winter. No significant associations were found between hospital admissions and day of the wk, humidity, temperature or atmospheric pressure. Total admissions were limited to one hospital. Increment: 10 µg/m^3 Asthma All yr: RR 1.06 p = 0.004 AutumN: NR Winter: NR Spring: NR Summer: NR

STUDY	METHODS	POLLUTANTS	FINDINGS
Wong et al. (2002a)* London England and Hong Kong Period of Study: LondoN: 1992-1994 Hong Kong: 1995-1997 Days: 1,096	Hospital Admissions Outcome(s) (ICD 9): All respiratory admissions (460-519); asthma (493) Age groups analyzed: 15-64, 65+, all ages Study design: Time-series Statistical analyses: APHEA protocol, Poisson regression with GAM Covariates: Long-term trend, season, influenza, day of wk, holiday, temperature, humidity, thunderstorms Season: Cool, Oct-Mar; Warm: Apr-Sep Dose-Response Investigated?: Yes Statistical package: S-Plus Lag: 0, 1, 2, 3, 4 days, 0-1 cum. avg.	24-h SO_2 µg/m^3 Hong Kong Mean: 17.7 Warm: 18.3 Cool: 17.2 SD: 12.3 Range: 1.1, 90.0 10th: 6.2 50th: 14.5 90th: 32.8 London Mean: 23.7 Warm: 22.2 Cool: 25.3 SD: 12.3 Range: 6.2, 113.6 10th: 13.2 50th: 20.6 90th: 38.1 Hong Kong $PM_{2.5}$ (r = 0.30) NO_2 (r = 0.37) O_3 (r = −0.18) London $PM_{2.5}$ (r = 0.64) NO_2 (r = 0.71) O_3 (r = −0.25)	Similar non-statistically significant associations between asthma hospital admissions and SO_2 were found in both cities. The association between respiratory hospital admissions and SO_2 showed significance in the cold season in Hong Kong and on an all yr basis. Respiratory hospital admissions were not significantly associated with SO_2 in Britain. In the 2-pollutant model the association between respiratory hospital admission and SO_2 in London was insignificant, and remained insignificant after adjusted for the second pollutants. In Hong Kong, the positive association of SO_2 was most affected by NO_2, losing statistical significance. The positive association remained robust when adjusted for O_3, and a slight decrease in association after adjusted for $PM_{2.5}$. Increment: 10 µg/m^3 Asthma, 15-64 yrs Hong Kong ER −0.1 (−2.4, 2.2) lag 0-1 ER −1.5 (−3.4, 0.5) lag Warm: ER 1.5 (−1.5, 4.6) lag 0-1 Cool: ER −2.0 (−5.4, 1.4) lag 0-1 London ER 0.7 (−1.0, 2.5) lag 0-1 ER 2.1 (0.7, 3.6) lag 3 Warm: ER −1.4 (−4.7, 1.9) lag 0-1 Cool: ER 1.6 (−0.5, 3.8) lag 0-1 Respiratory 65+ yrs Hong Kong ER 1.8 (0.9, 2.6) lag 0-1 ER 1.7 (1.0, 2.4) lag 0 Warm: ER 1.1 (0.0, 2.2) lag 0-1 Cool: ER 2.7 (1.4, 4.0) lag 0-1 +O_3 ER 1.9 (1.1, 2.8) lag 0-1 +$PM_{2.5}$ ER 1.2 (0.3, 2.2) lag 0-1 +NO_2 ER 0.3 (−0.7, lag 1.4) lag 0-1 London ER 0.2 (−0.6, 1.1) lag 0-1 ER 1.2 (0.5, 2.0) lag 3 Warm: ER 1.3 (−0.5, 3.1) lag 0-1 Cool: ER −0.3 (−1.3, 0.8) lag 0- +O_3 ER 0.5 (−0.4, 1.5) lag 0-1 +$PM_{2.5}$ ER 1.2 (0.3, 2.2) lag 0-1 +NO_2 ER 0.5 (−0.7, 1.7)lag 0-1
Yang and Chen (2007) Taipei, Taiwan Period of Study: 1996-2003	Hospital Admissions Outcome(s) (ICD9): COPD (490-492, 494, and 496) identified by records from the National Health Insurance (NHI) program Study design: Case-crossover Statistical Analysis: Conditional logistic regression Statistical package: SAS Age groups analyzed: All ages Covariates: Adjustments for weather variables, day of the wk, seasonality, and long-term time trends N: 46,491 # Hospitals: 47 Lag: Cumulative lag up to 2 days	24-h avg (ppb): 4.33 Range: 0.15, 17.82 25th: 2.67 50th: 3.90 75th: 5.46 PM_{10} NO_2 CO O_3	In single-pollutant models, all pollutants, except SO_2, significantly associated with COPD hospital admissions on warm days (≥20 °C). On cold days (< 20 °C), only SO_2 was significantly associated with COPD hospital admissions. In multi-pollutant models, NO_2 and O_3 were significantly associated with each pollutant on warm days. Odds Ratio (95% CI), Single-pollutant model (per 2.79 ppb SO_2) ≥ 20 °C: 1.006 (0.970, 1.043) < 20 °C: 1.071 (1.015, 1.129) Odds Ratio (95% CI), Co-pollutant model (per 2.79 ppb) ≥ 20 °C SO_2 + PM_{10}: 0.909 (0.872, 0.949 SO_2 + NO_2: 0.835(0.798, 0.873) SO_2 + CO: 0.920(0.884, 0.958) SO_2 + O_3: 0.978(0.943, 1.015) < 20 °C SO_2 + PM_{10}: 1.067 (0.997, 1.141) SO_2 + NO_2:1.147 (1.072, 1.227) SO_2 + CO: 1.140 (1.066, 1.219)

*Default GAM
+Did not report correction for over-dispersion
APHEA: Air Pollution and Health: a European Approach

Table F-3. Associations of short-term exposure to SO_2 with cardiovascular morbidity in field/panel studies.

STUDY	METHODS	POLLUTANTS	FINDINGS
UNITED STATES			
Dockery et al. (2005) Boston, MA Period of Study: Jul 1995-Jul 2002	Cohort study of 203 cardiac patients with implanted cardioverter defibrillators. Patients were followed for an avg of 3.1 yrs from 1995-2002 to assess the role of air pollution on the incidence of ventricular arrhythmias. The association of arrhythmic episode-days and air pollutions analyzed with logistic regression using GEE with random effects. Model adjusted for patient, season, min temperature, mean humidity, day of the wk, and previous arrhythmia within 3 days. Only effects of 2-day running mean of air pollution concentration reported.	48-h avg SO_2; MediaN: 4.9 ppb 25th%: 3.3 ppb 75%: 7.4 ppb 95%: 12.8 ppb Copollutants: $PM_{2.5}$ BC SO_4^{2-} PN NO_2 CO O_3	No statistically significant association between any of the air pollutant and ventricular arrhythmias when all events were considered. However, ventricular arrhythmias within 3 days of a prior event were statistically significant with SO_2, $PM_{2.5}$, BC, NO_2, CO, and marginally with SO_4^{2-}, but not with O_3 or PN. CO, NO_2, BC, and $PM_{2.5}$ correlated, thus it was impossible to differentiate the independent effects. Since the increased risk of ventricular tachyarrhythmia was associated with air pollution observed among patients with a recent tachyarrhythmia, it was suggested that air pollution acts in combination with cardiac electrical instability to increase risk of arrhythmia. For IQR (4.0 ppb) increase in 48-h mean SO_2: All events: OR = 1.04 (0.94, 1.14), p = 0.28. Prior arrhythmia event < 3 Days: 1.30 (95% CI: 1.06, 1.61), p = 0.013. Prior arrhythmia event >3 Days: 0.98 (0.87, 1.11) p = 0.78
Gold et al. (2000) Boston, MA Jun-Sep Period of Study: 1997	Panel study on 21 active Boston residents aged 53-87 yrs to investigate the association between short-term changes in ambient air pollution and short-term changes in cardiovascular function. Participants observed up to 12 times from June to Sep 1997 (163 observations made in total). Protocol involved 25 mins per wk of continuous ECG monitoring, that included 5 mins of rest, 5 mins of standing, 5 mins of exercise outdoors, 5 mins of recovery, and 20 cycles of slow breathing. Fixed effects models adjusted for time-varying covariates and individuals traits.	24-h avg mean 3.2 ppb Range: 0, 12.6 ppb IQR: 3.0 ppb Copollutants: $PM_{2.5}$ $PM_{10-2.5}$ O_3 NO_2 CO	In single-pollutant models, 24-h mean SO_2 associated with reduced heart rate in the first rest period but not overall. Associations weaker for shorter averaging periods. Association between SO_2 and heart rate not significant with the multipollutant model (SO_2 and $PM_{2.5}$). SO_2 not associated with r-MSSD. Heart rate, first rest period, mean 66.3 bpm, single-pollutant model, estimated effect (SE) −1.0 (0.5); % mean 1.5, p = 0.03. Heart rate, first rest period, mean 66.3 bpm Multipollutant model ($PM_{2.5}$ and SO_2): SO_2 estimated effect (SE) −0.8 (0.5); % mean 1.2, p = 0.09. $PM_{2.5}$ estimated effect (SE) −1.6 (0.7); % mean 2.5, p = 0.03. Overall heart rate, mean 74.9 bpm, Single-pollutant model estimated effect (SE) −0.5 (0.5), p = 0.30. Multipollutant model SO_2 estimated effect (SE) −0.2 (0.5), p = 0.6 $PM_{2.5}$ estimated effect (SE) −1.9 (0.7) p = 01% mean 2.6
Liao et al. (2004) Three locations in United States: Minneapolis, MN; Jackson, MS; Forsyth County, NC 1996-1998	Cross-sectional study of 6,784 cohort members of the Atherosclerosis Risk in Communities Study. Participants were 45-64 yrs of age; baseline clinical examinations conducted from 1987-1989. HRV data collected from 1996-1998. Air pollutants obtained form EPA AIRS for this same period. Resting, supine, 5-min beat-to-beat RR interval data were collected over a 4-h period. Multivariable linear regression models used to assess associations between pollutants measured 1-3 days prior to HRV measurements. Models controlled for age, ethnicity-center, sex, education, current smoking, BMI, heart rate, use of cardiovascular medication, hypertension, prevalent coronary heart disease, and diabetes.	Mean (SD) SO_2 measured 1 day prior to HRV measurement was 4 (4) ppb Copollutants: PM_{10} O_3 CO NO_2	Significant interaction between SO_2 and prevalence of coronary heart disease for low-frequency power analyses. SO_2 inversely associated with SD of normal R-R intervals and low-frequency power and positively associated with heart rate. SO_2 association with low-frequency power stronger among those with history of coronary heart disease. Effect size of PM_{10} larger than for gaseous pollutants. Log-transformed low-frequency power effect estimate and SE per 1 SD increment (4 ppb) SO_2 lag 1 day: Log transformed high-frequency power −0.024 (SE 0.016) Standard deviation of normal R-R intervals −0.532 (SE 0.270), p < 0.05=Heart rate: 0.295 (SE 0.130), p < 0.05. Prevalent CHD: −0.122 (SE 0.056), p < 0.01. No prevalent CHD −0.012 (SE 0.016)

STUDY	METHODS	POLLUTANTS	FINDINGS
Liao et al. (2005) United States 1996-1998	Cross-sectional survey 10,208 participants (avg age 54 yrs) from Atherosclerosis Risk in Communities (ARIC) study cohort to assess the association between criteria air pollutants and hemostatic and inflammatory markers. 57% of participants were female and 66% male. Used hemostatis/ inflammation variables collected during the baseline examination and air pollution data 1-3 days prior to the event. Used multiple linear regression models that controlled for age, sex, ethnicity-center, education, smoking, drinking status, BMI, history of chronic respiratory disease, humidity, seasons, cloud cover, and temperature. Also history of CVD and diabetes if not effect modifier in a particular model.	SO_2 mean (SD) 0.0005 (0.004) ppm Q1-3: 0.005 (0.003) ppm Q4: 0.006 (0.005) ppm Copollutants: PM_{10} CO NO_2 O_3	Significant curvilinear association between SO_2 witfactor VIII-C, WBC, and serum albumin. Curvilinear association indicated threshold effect Results shown in graph.
Luttmann-Gibson et al. (2006) Steubenville, OH 2000	Conducted a panel study during the summer and fall of 2000, which consisted of 32 subjects 54-90 yrs old living in Steubenville, OH. Used linear mixed models, fixed effects of pollution, age, gender, race, obesity, season, time of day, apparent temperature, and a first order autoregressive process for within-subject residuals to examine the relation between air pollution and log-transformed HRV parameters and heart rate.	24-h avg (ppb): 4.1 Copollutants: $PM_{2.5}$ SO_4^{2-} EC NO_2 O_3	Increasing concentrations of $PM_{2.5}$ and SO_4^{2-} in the previous day were both found to be associated with reduced HRV. No association was observed between increasing SO_2 concentrations in the previous day and HRV. % Change (95% CI) (per 4.3 ppb SO_2). Standard Deviation of Normal RR Intervals (SSDN) 0.7 (−1.0, 2.5). Differences Between Adjacent RR Intervals (r-MSSD) 0.5 (−2.8, 4.0). High-Frequency Power (HF) 1.7 (−4.9, 8.7). Low-Frequency Power (LF) 4.9 (−1.4, 11.5). Heart Rate (HR) 0.3 (−0.2, 0.8)
Metzger et al. (2007) Atlanta, GA 1993-2002	Collected information on 518 patients (6287 event-days) for ventricular tachyarrhythemic events over 10-yr period. Used GEE analysis, a case-crossover analysis, and a sensitivity analysis stratified on subject	15.5 ppb (±16.4) Copollutants: PM_{10} O_3 NO_2 CO $PM_{2.5}$	Little evidence of associations between ambient air quality measurements and ventricular tachyarrhythmic events. Odds ratio (95% CI) All events: 1.002 (0.968-1.037) Events resulting in cardiac pacing or defibrillatioN: 0.988 (0.936-1.042). Events resulting in defibrillatioN: 1.004 (0.911-1.105). Primary GEE model: 1.002 (0.968-1.037) Controlling for min temperature: 1.010 (0.976-1.046) Using an unconstrained distributed Lag: 0.996 (0.952-1.083). Warm Season: 1.029 (0.989-1.116). Cold Season: 0.986 (0.956-1.023)
Park et al. (2005) Greater Boston area, MA Nov 2000-Oct 2003	Cross-sectional study of effect of ambient air pollutants on heart rate variability (HRV) in 497 men who were in the Normative Aging Study and examined from Nov 2000 and Oct 2003. HRV measured between 0600 and 1300 h after resting for 5 mins. 4-h, 24-h, and 48-h moving avgs of air pollution matched to time of ECG measurement. Linear regression models included: age, BMI, fasting blood glucose, cigarette smoking, use of cardiac medications, room temp, season, and the lagged moving avg of apparent temp corresponding to the moving avg period for the air pollutant. Mean arterial blood pressure (MAP) and apparent temperature also included. Assessed modifying effects of hypertension, IHD, diabetes or use of cardiac/antihypertensive meds.	24-h avg SO_2 4.9 ppb SD: 3.4 Range: 0.95, 24.7 ppb Copollutants: $PM_{2.5}$ PNC BC NO_2 O_3 CO	No significant association between HRV and SO_2 for any of the averaging periods, but positive relationship. 4-h moving avg SO_2: (per 1 SD, 3.4 ppb SO_2) Log10 SDNN: 2.3 (−1.7, 6.4) Log10 HF:5.6 (−4.9, 17.3) Log10 LF: 2.2 (−5.9, 11.1) Log10 (LF:HF): −3.2 (−10.1, 4.2)

STUDY	METHODS	POLLUTANTS	FINDINGS
Peters et al. (2000a) Eastern Massachusetts, U.S. 1995-1997	Pilot study to test hypothesis that patients with implanted cardioverter defibrillators would experience potentially life-threatening arrhythmias associated with air pollution episodes. Records detected arrhythmias and therapeutic interventions downloaded from the implanted defibrillator. Mean age of patients 62.2 yrs. 100 patients followed for over 3 yrs for 63,628 person-days. 33 patients with any discharges and 6 patients with 10 or more events. Data analyzed by logistic regression models using fixed effects models with individual intercepts for each patient. Model controlled for trend, season, meteorologic conditions, and day of week. Evaluated air pollutants on same day, lags 1, 2, and 3 days, and 5-day mean.	24-h avg SO_2: 7 ppb MediaN: 5 ppb Max: 87 ppb Copollutants: PM_{10} $PM_{2.5}$ BC CO O_3 NO_2	No association between increased defibrillator discharges and SO_2. 33 patients with at least 1 defibrillator discharge Odds Ratio (95% CI) Lag 0 0.76 (0.48, 1.21); Lag 1 0.91 (0.60, 1.37) Lag 2 0.89 (0.59, 1.34); Lag 3 1.09 (0.78, 1.52) 5-day mean 0.85 (0.50, 1.43) 6 patients with at least 10 discharges Odds Ratio (95% CI) Lag 0 0.72 (0.40, 1.31); Lag 1 0.77 (0.44, 1.37) Lag 2 1.01 (0.63, 1.61); Lag 3 1.08 (0.72, 1.62) 5-day mean 0.75 (0.38, 1.47)
Peters et al. (2001) Greater Boston area, MA Jan 1995-May 1996	Case cross over Study design used to investigate association between air pollution and risk of acute myocardial infarctions in 772 patients (mean age 61.6 yrs) with MI as part of the Determinants of Myocardial Infarction Onset Study. For each subject, one case period was matched to 3 control periods, 24 h apart. Used conditional logistic regression models that controlled for season, day of wk, temperature, and relative humidity.	24-h avg SO_2: 7 ppb SD: 7 ppb 1-h avg SO_2: 7 ppb SD: 10 ppb Copollutants: $PM_{2.5}$, PM_{10}, $PM_{10-2.5}$, BC O_3, CO, NO_2	SO_2 not statistically associated with risk of onset of MI. Limitation of study is only 1 air pollution monitoring site available. OR for 2-h avg SO_2 and 24-h avg SO_2 estimated jointly: 2 h per 2 ppb increase SO_2 Unadjusted: 1.00 (0.87, 1.14) Adjusted: 0.96 (0.83, 1.12) 24 h per 2 ppb increase Unadjusted: 0.92 (0.71, 1.20) Adjusted: 0.91 (0.67, 1.23)
Rich et al. (2005) Boston, MA Jul 1995-Jul 2002	Case cross-over design used to evaluate association between ventricular arrhythmias detected by implantable cardioverter defibrillators and air pollution. Same study population as Dockery et al. (2005): 203 patients with ICD and residential zip codes within 40 km of central particle monitoring site. Analyses conducted on 84 subjects with confirmed ventricular arrhythmias during the follow-up. Case periods defined by time of each confirmed arrhythmic event. Control periods (3-4 per case) selected by matching on weekday and hour of the day within the same calendar mo. Used conditional logistic regression that controlled for temperature, dew point, barometric pressure, and a frailty term for each subject. ORs presented for IQR increase in mean concentration and averaging time. Moving avg of concentrations considered: lags 0-2, 0-6, 0-23, and 0-47 h.	1-h avg SO_2: MediaN: 4.3 ppb 25th %: 2.6 75th %: 7.5 Max: 71.6 24-h avg SO_2: MediaN: 4.8 25th %: 3.2 75th %: 7.3 Max: 31.4 Copollutants: $PM_{2.5}$ BC NO_2 CO O_3	An IQR increase in the 24-h moving avg SO_2 (4.1 ppb) marginally associated with a 9% increased risk of ventricular arrhythmia and an increased risk with 48-h moving avg. There was no risk associated with 24-h moving avg after controlling for $PM_{2.5}$ cases that had a prior ventricular arrhythmia within 72-h had greater risk associated with SO_2 compared to those without a recent event, suggesting that risk is greater among cases with more irritable or unstable myocardium. Odds ratios- single-pollutant model 0-2-h lag (per 4.7 ppb) 1.07 (0.97, 1.18) 0-6-h lag (per 4.5 ppb) 1.09 (0.98, 1.20) 0-23-h lag (per 4.1 ppb) 1.09 (0.97, 1.22) 0-47-h lag (per 4.0 ppb) 1.17 (1.02, 1.34) Odds ratios- 2-pollutant model: SO_2 and $PM_{2.5}$ Per 4.1 ppb SO_2: 1.00 (0.84, 1.20). SO_2 and O_3 Per 4.1 ppb SO_2: 1.12 (0.99, 1.27). Per 4.1 ppb increase SO_2 Prior arrhythmia event < 3 Days: 1.20 (1.01, 1.44). Prior arrhythmia event >3 Days: 0.96 (0.83, 1.10)
Rich et al. (2006b) Boston, MA 1995-2002	Case-crossover study consisting of 203 individuals with implantable cardioverter defibrillators (ICDs) implanted between Jun 1995 and Dec 1999. Used conditional logistic regression, which included variables for mean pollutant concentration in the hour of the arrhythmia, and natural splines for mean temperature, dew point, and barometric pressure in the 24 h before the arrhythmia. The regression analyses were run for each pollutant individually to examine the association between increasing pollutant levels and paroxysmal atrial fibrillation episodes (PAF).	Max 24-h avg (ppb): 31.4 Max 1-h max (ppb): 71.6 Copollutants: $PM_{2.5}$ BC NO_2 CO O_3	Ozone was significantly associated with PAF in the hour preceding the arrhythmia, but the effect was not significant when analyzing the preceding 24-h. Increasing levels of $PM_{2.5}$, NO_2, and BC resulted in non-significant positive associations with PAF. SO_2 was not associated with PAF. Odds Ratio (per 4.9 ppb SO_2): 1.02 (0.81, 1.28) lag 0 h Odds Ratio (per 4.1 ppb SO_2): 0.99 (0.71, 1.39) lag 0-23-h

STUDY	METHODS	POLLUTANTS	FINDINGS
Rich et al. (2006a) St. Louis, Missouri May 2001-Dec 2002	Case-crossover design study of 56 patients with implantable cardioverter defibrillators. Subjects ranged from 20 to 88 yrs (mean 63). Case period defined by time of confirmed ventricular arrhythmia. Control periods matched on weekday and hour of the day within the same calendar mo. Used conditional logistic regression model that included mean of the previous 24-h temperature, relative humidity, barometric pressure, mean pollutant concentration in the 24 h before the arrhythmia. Model also included a frailty term for each subject.	599 days 25^{th} %: 2 ppb 50^{th} %: 4 ppb 75^{th} %: 7 ppb Daily IQR: 5 ppb Case/control IQR: 5 ppb Copollutants: $PM_{2.5}$, EC, OC, NO_2 , CO, O_3	Statistically significant increase in risk of ventricular arrhythmias associated with each 5 ppm increase in 24-h moving avg SO_2. OR for ventricular arrhythmia associated with IQR increase 6-h moving avg SO_2 per 4 ppb: 1.04 (95% CI: 0.96, 1.12) 12-h moving avg SO_2 per 5 ppb: 1.17 (95% CI: 1.04, 1.30) 24-h moving avg SO_2 per 5 ppb: 1.24 (95% CI: 1.07, 1.44) 48-h moving avg SO_2 per 4 ppb: 1.15 (95% CI: 1.00, 1.34)
Sarnat et al. (2006) Steubenville, OH 2000	Panel study consisting of 32, non-smoking older adults approximately 53-90 yrs old. Electrocardiograms (ECGs) and questionnaires regarding symptoms were administered on a weekly basis. Used a logistic mixed effects regression to examine the association between increasing air pollutant concentrations and supraventricular ectopy (SVE) and ventricular ectopy (VE).	1-day avg SO_2 24-h avg (ppb): 10.4 (8.3) Range: 1.8, 58.3 5-day moving avg 24-h avg (ppb): 10.7 (5.5) Range: 2.4, 31.3 Copollutants: $PM_{2.5}$, EC, O_3, NO_2, SO_4^{2-}, CO	$PM_{2.5}$ was significantly associated with SVE, whereas, SO_4^{2-} and O_3 were marginally associated in models including 5-day moving avg pollutant concentrations. However, no pollutants were found to be associated with VE in similar models. Overall, subjects that reported previous cardiovascular conditions (e.g., myocardial infarction and hypertension) were found to be more susceptible to SVE due to increasing air pollutant concentrations. Odds Ratio (per 5.4 ppb SO_2) 5-day moving avg SVE: 1.04 (0.78, 1.39) VE: 1.28 (0.85, 1.92)
Schwartz et al. (Schwartz et al., 2005) Boston, MA 12 wks during the summer of 1999	Panel study of 28 subjects (aged 61-89 yrs) to examine association between summertime air pollution and HRV. Subjects examined once a wk up to 12 wks and HRV measured for approximately 30 mins. Analyses used hierarchical models that controlled for baseline medical condition, smoking history, day of wk and hour of day, indicator variable for whether subjects had taken their medication before they came, temperature and time trend.	24-h avg SO_2: 25th %: 0.017 ppm 50th %: 0.020 ppm 75th %: 0.54 ppm Copollutants: O_3 NO_2 CO $PM_{2.5}$ BC	No significant association with SO_2 Percentage change in HRV associated with IQR (0.523 ppm) increase in SO_2 SDNN (ms) 0.4 (−1.3 to 2.1) RMSSD (ms) 1.4 (−2.6 to 5.5) PNN50 (ms) 3.8 (−12.1 to 22.5) for 1-h avg SO_2 SDNN (ms) 0.4 (−4.2 to 5.1) for 24-h avg SO_2 RMSSD (ms) −0.3 (−1.3 to 0.8) PNN50 (%) −0.2 (20.9 to 17.6) LFHFR 2.9 (−4.9 to 11.4)
Sullivan et al. (2004) King County, Washington 1988-1994	Case-crossover study of 5,793 confirmed cases of acute MI. Data was analyzed using simple descriptive analyses and Pearson's correlation coefficient.	9 ppb Range: 0-38 ppb Copollutants: $PM_{2.5}$ PM_{10} CO	Increases in SO_2 were not associated with MI after adjusting for relative humidity and temperature Averaging time, Odds Ratio (95% CI) (per 10 ppb SO_2) 1-h: 0.97 (0.94, 1.01) 2 h: 0.98 (0.95, 1.01) 4 h: 0.99 (0.96, 1.03) 24 h: 1.0 (0.95, 1.06)
Tolbert et al. (2007) Atlanta, GA 1993-2004	ED Visits Outcome(s) (ICD9): Cardiovascular (410-414, 427, 428, 433-437, 440, 443-445, 451-453); Respiratory (493, 786.07, 786.09, 491, 492, 496, 460-465, 477, 480-486, 466.1, 466.11, 466.19) Study design: Time-series Statistical Analysis: Poisson Generalized Linear Model (GLM). Statistical package: SAS Age groups analyzed: All ages Covariates: Adjustment for day-of-wk, hospital entry, holidays, time, temperature, dew point temperature # Hospitals: 41 N: 238,360 (Cardiovascular) 1,072,429 (Respiratory) Lag(s): 3-day moving avg	1-h max (ppb): 14.9 Range: 1.0, 149.0 10th: 2.0 25th: 4.0 75th: 20.0 90th: 35.0 Copollutants: PM_{10},$PM_{2.5}$, O_3 NO_2, CO, SO_4^{2-} Total Carbon OC, EC Water-Soluble Metals Oxygenated Hydrocarbons	In single pollutant models, O_3, PM_{10}, CO, and NO_2 significantly associated with ED visits for respiratory outcomes. Relative Risk (95% CI) (per 16.0 ppb SO_2) 1.003 (0.997, 1.009)

STUDY	METHODS	POLLUTANTS	FINDINGS
Wheeler et al. (2006) Atlanta, Georgia 1999-2000	30 individuals with myocardial infarction or COPD were administered a questionnaire and an HRV protocol. Linear mixed-effect models were used to analyze the data.	Mean: 1.9 ppb Copollutants: $PM_{2.5}$, EC, O_3 CO, NO_2	No association with SO_2
CANADA			
Rich et al. (2004) Vancouver, British Columbia, Canada Feb-Dec 2000	Case-crossover analysis used to investigate association between air pollution and cardiac arrhythmia in 34 patients (aged 15-85 yrs, mean 62) with implantable cardioverter defibrillators. Study included only patients who experienced at least 1 ICD discharge during the study period. Control days were 7 days before and 7 days after day of ICD discharge. Conditional logistic regression analyses were stratified by individual.	24-h avg: 2.6 ppb SD: 1.3 ppb IQR: 1.6 ppb Copollutants: $PM_{2.5}$, EC, OC SO_4^{2-}, PM_{10}, CO NO_2, O_3	No statistically significant association between SO_2 and implantable cardioverter defibrillator discharges. However, when an analysis was stratified by season, OR for SO_2 were higher in the summer compared to winter. No quantitative results provided. Results shown in graph.
Vedal et al. (2004) Vancouver, British Columbia, Canada 1997-2000	Retrospective, longitudinal panel study of 50 patients, aged 12-77 yrs with implantable cardioverter defibrillators. Total of 40,328 person-days over 4-yr period. GEE used to assess associations between short term increases in air pollutants and implantable cardioverter defibrillator discharges. Models controlled for temporal trends, meteorology, and serial autocorrelation.	24-h mean (SD) SO_2: 2.4 (1.2) ppb Range: 0.3, 8.1 ppb MediaN: 2.2 ppb 25th percentile: 1.5 75th percentile: 3.1 Copollutants: PM_{10} O_3 NO_2 CO	Concluded that in general no consistent effect of air pollution on cardiac arrhythmias in this population. There were no statistically significant associations between SO_2 and cardiac arrhythmias at any lag day, but positive associations at lag 2. When analysis was restricted to only patients who had at least 2 arrhythmias per yr over their period of observation (N: 16), a positive and significant association was seen with SO_2 at 2 days lag. When analysis was restricted to patients averaging 3 or more arrhythmias per yr (N: 13), there was no significant association, but a positive association was seen at 2 days lag. When stratified by season, SO_2 effects were in the in the positive direction in the winter, but in the negative direction in the summer. Authors noted results may be due to chance because of multiple comparisons or SO_2 may be surrogate for some other factor. Summer analysis: significant negative association with SO_2 at lag days 2 and 3 (data not shown). When stratified to patients with 2 or more arrhythmia event-days per yr, significant negative associations observed with SO_2 at lag of 3 days. Winter analysis: significant positive effect of SO_2 at 3 days lag (data not shown). If restricted to patients with at least 2 arrhythmias per yr, a significant positive association was seen at lags 2 and 3 days. When restricted to patients with 3 or more arrhythmia event days per yr, positive associations observed for SO_2 at lags of 2 and 3 days. No quantitative results, but % change in arrhythmia event-day rate for each SD increase in pollution concentration on log scale provided in figures.
EUROPE			
Beger et al. (2000) Erfurt, Germany Oct 2000-Apr 2001	Prospective panel study of 57 non-smoking men, of which 74% are ex-smokers, with coronary heart disease aged 52-76 yrs old. Subjects underwent 24-h electrocardiogram (ECG) recordings and analysis once every 4 wks. Associations analyzed using Poisson and linear regression modeling, for supraventricular and ventricular tachycardia, respectively, adjusting for trend, weekday, and meteorologic data.	24-h avg (SD) ($\mu g/m^3$): 4.1 (1.8) Range: 3.0, 11.7 Copollutants: Ultrafine Particles Accumulation Mode Particles $PM_{2.5}$ PM_{10} NO_2 CO NO	UFP, ACP, $PM_{2.5}$, and NO_2 associated with increased risk for supraventricular tachycardia and ventricular tachycardia at almost all lags. The majority of statistically significant associations was observed in the previous 24-71-h and with the 5-day moving avg. Associations were not observed for increasing concentrations of SO_2. Relative Risk (per 1.5 $\mu g/m^3$ SO_2) Supraventricular Extrasystoles 0.92 (0.77, 1.09) lag 0. 0.98 (0.86, 1.12) lag 0-23-h 1.04 (0.93, 1.16) lag 24-47 h. 1.14 (0.98, 1.34) lag 48-71-h 0.95 (0.83, 1.09) lag 72-95-h. 1.01 (0.80, 1.27) lag 5-d avg Ventricular Extrasystoles −2.1 (−6.1, 2.1) lag 0. −1.8 (−6.1, 2.7) lag 0 – 23-h −0.1 (−4.4, 4.4) lag 24 – 47 h. 4.5 (−0.4, 9.5) lag 48-71-h −2.2 (−6.4, 2.3) lag 72-95-h. −1.2 (−7.5, 5.5) lag 5-d avg
Henrotin et al. (2007) Dijon, France 1994-2004	Bi-directional case-crossover design to examine association between air pollutant and ischaemic stroke onset (2078 cases).	Mean: 6.9 $\mu g/m^3$ SD: 7.5 MiN: 0 Max: 65 Copollutants: SO_X, O_3, CO PM_{10}	SO_2 not significantly associated with occurrence of strokes Odds Ratio (95% CI) Ischaemic stroke: D0: 0.978 (0.868, 1.103). D-1: 0.978 (0.863, 1.108) D-2: 1.015 (0.902, 1.143). D-3: 1.003 (0.892, 1.127) Hemorrhagic stroke: D0: 1.099 (0.815, 1.483). D-1: 1.014 (0.747, 1.376) D-2: 0.961 (0.712, 1.297). D-3: 0.954 (0.729, 1.248)

STUDY	METHODS	POLLUTANTS	FINDINGS
Ibald-Mulli et al. (2001) Augsburg, Germany 1984-85, 1987-88	Retrospective analysis of 2607 subjects (25-64 yrs, subset of the participants of first and second MONICA survey who had valid electrocardiograms recordings in both surveys and blood pressure measurements). Used regression models for repeated measures that controlled for age, current smoking, and cardiovascular medication, BMI, total and high density lipoprotein cholesterol, temp, RH, and barometric pressure.	24-h avg SO_2 ($\mu g/m^3$) 1984-1985: Mean: 60.2 SD: 47.4 Range: 13.0, 238.2 follow up 1987-1988 Mean: 23.8 SD: 12.3 Range: 5.6, 71.1 Copollutants: TSP, CO	SO_2 and TSP associated with increases in systolic blood pressure. In the multipollutant model with TSP, the effect of TPS remained significant, but the SO_2 effect was substantially reduced. No clear association between SO_2 and CO and diastolic blood pressure was observed. Same day concentrations: mean change in systolic blood pressure per 5th to 95th percentile increase in SO_2 (per 80 $\mu g/m^3$) Same day concentrations (per 80 $\mu g/m^3$): Men (N: 1339): 0.96 (0.07, 1.85) Women (N: 1268): 0.96 (−0.46, 1.49) Men and womeN: 0.74 (0.08, 1.40) 5-day avgs: Mean change in systolic blood pressure per 5th to 95th percentile increase in SO_2 (per 75 $\mu g/m^3$) MeN: 0.97 (0.09, 1.85). WomeN: 1.23 (0.23, 2.22) Men and womeN: 1.07 (0.41, 1.73) 2-pollutant model. Men and womeN: 0.23 (−0.50, 0.96)
Peters et al. (1999) Augsburg, Germany Winter 1984-1985 Winter 1987-1988	Retrospective analysis on subsample of 2,681 subjects (25-64 yrs) of the MONICA cohort who had valid electrocardiogram readings from both surveys and no acute infections. GEE for clusters used to assess association between heart rate and air pollution. Analyses adjusted for temperature, relative humidity, and air pressure.	24-h avg SO_2 ($\mu g/m^3$) Winter 1984-85 Outside episode: Mean: 48.1 SD: 23.1 Range: 13, 103 Winter 1984-85 During episode: Mean: 200.3 SD: 26.6 Range: 160, 238 Winter: 1987-88 Mean: 23.6 SD: 12.2 Range: 6, 71 Copollutants: CO, TSP	Increases in SO_2 concentrations associated with increases in heart rate Mean change in heart rate per 5th to 95th percentile SO_2 Same day concentrations (per 80 $\mu g/m^3$ SO_2) MeN: 1.02 (0.41, 1.63) WomeN: 1.07 (0.41, 1.73) Men and womeN: 1.04 (0.60, 1.49) 5-day avg (per 75 $\mu g/m^3$ SO_2) MeN: 1.29 (0.68, 1.90) WomeN: 1.26 (0.57, 1.95) Men and womeN: 1.28 (0.82, 1.74)
Ruidavets et al. (2005) Toulouse, France 1995-1997	Cross-sectional survey of 863 randomly chosen adults (35-65 yrs) living in Toulouse (MONICA center) to examine the relationship between resting heart rate and air pollution. Resting heart rate was measured twice in a sitting position after a five minute rest. Used polytomous logistic regression models with quintiles of RHR. Final model controlled for sex, physical activity, systolic blood pressure, cardiovascular drug use, CRP, relative humidity, and season mos.	Mean SO_2: 13.3 (7.5) $\mu g/m^3$ Range: 1.3, 47.7 $\mu g/m^3$ Copollutants: NO_2, O_3	Marginally significant association between SO_2 and RHR in Q5 compared with Q1. No association with SO_2 at 1, 2, or 3 days lag. OR based on daily levels of $_{SO2}$. OR for resting heart rate = 1.19 (95% CI: 1.02, 1.39) in 5th quintile (>75 bpm) compared to first quintile (< 60 bpm) for 5 $\mu g/m^3$ increase in SO_2 same day 0 am-12 pm. OR for resting heart rate 1.14 (95% CI: 1.01 to 1.30) in 5th quintile (>75 bpm) compared to first quintile (< 60 bpm) for 5$\mu g/m^3$ increase in SO_2 same day 12 am-12 pm Not-significant associations not listed
LATIN AMERICA			
Holguin et al. (2003) Mexico City, Mexico Feb 8 to Apr 30, 2000	Panel study of 34 nursing home residents (60-96 yrs) to assess association between heart rate variability and air pollution. Heart rate variability measured every alternate day for 3 mos. Thirteen of the subjects had hypertension. Used GEE models that controlled for age and avg heart rate during HRV measurement.	24-h mean SO_2 (ppb). Mean: 24 SD: 12 Range: 6, 85 Copollutants: Indoor $PM_{2.5}$ Outdoor $PM_{2.5}$ O_3, NO_2, CO	SO_2 not related to heart rate variability on the same day or lag 1 day Change in HRV per 10 ppb Beta Coefficient (95% CI) HRV-HF −0.003 (−0.035, 0.035) HRV-LF −0.004 (−0.004, 0.003) HRV-LF/HF 0.012 (−0.060, 0.082)

Table F-4. Associations of short-term exposure to SO_2 with emergency department visits and hospital admissions for cardiovascular diseases.

STUDY	METHODS	POLLUTANTS	EFFECTS
UNITED STATES			
Gwynn et al. (2000) New York (Buffalo; Rochester) 1988-1990	Hospital Admissions Outcome(s) (ICD9): Respiratory (466, 480-486), Circulatory (401-405, 410-417), Total (minus 800) from Statewide Planning and Research Cooperative System (SPARCS) Study design: Time-series Statistical Analysis: Loess fits of temperature and relative humidity Age groups analyzed: All ages Covariates: Adjustments for weather Lag(s): 0, 3	24-h avg (ppb): 12.2 Range: 1.63, 37.7 H^+ SO_4^{2-} PM_{10} Filled PM_{10} O_3 CO NO_2 CoH	∃= 0.000245 (0.000917) t = 0.27 Relative Risk (per 7 ppb SO_2) 1.002
Koken et al. (2003) Denver, United States Period of Study: Jul and Aug, 1993-1997, N: 310 days	Outcome(s) (ICD9): Acute MI 410.00-410.92; Atherosclerosis 14.00-414.05; Pulmonary Heart Failure 416.0-416.9; Dysrhythmia 427.0-427.9; CHF 428.0. Discharge data from Agency for Healthcare Research and Quality (AHRQ) database. Age group analyzed: 65+ yrs Study populatioN: 60,000 Covariates : Seasonal adjustment not needed. Adjustment for temperature, dew point temperature made. Study design: Time-series Statistical Analysis: GLMs to analyze frequency of admissions as a function of exposure. GEEs to estimate parameters in Poisson regression models, adjusting for overdispersion. Lag(s): 0-4 day	SO_2 24-h avg (ppb) Mean (SD): 5.7 (2.94) MiN: 0.4 25th: 3.8 50th: 5.3 75th: 7.2 Max: 18.9 O_3 (r = −0.10) CO (r = 0.21) PM_{10} (r = 0.36) NO_2 (r = 0.46)	Effects were reported as percent change in hospitalizations based on an increment of 3.4 ppb. Single-pollutant model Dysrhythmia 8.9% (−0.34, 18.93) lag 0, adjusted for gender but not temperature SO_2 was found to be associated with cardiac dysrhythmia but not other outcomes. No association was observed for PM or NO_2 with the outcomes.
Low et al. (2006) New York City, NY Period of Study: 1995-2003, 3287 days	Outcome(s) (ICD): Ischemic stroke 433-434; Undetermined stroke 436; monitored intake in 11-hospitals (ER or clinic visits). Excluded stroke patients admitted for rehabilitation. Study design: Time-series Statistical Analysis: Autoregressive integrated moving avg (ARIMA) models Software package: SAS	SO_2 24-h avg (ppm) Mean (SD): 0.009124 MiN: 0 25th: 0.005 MediaN: 0.009 75th: 0.014 Max: 0.096 PM_{10} (0.042) NO_2 (0.33) CO (0.303) Pollen (0.085)	At the highest concentration of SO_2 (96 ppb) in New York city over the study period the expected increase in strokes would be 0.857 visits on the day of the event. Each 1000 ppb (1 ppm) SO_2 would produce an additional 8.878 visits (SE 4.471) (p = 0.0471) for stroke.

STUDY	METHODS	POLLUTANTS	EFFECTS
Metzger et al. (2004) Atlanta, GA Period of Study: Jan 1993-Aug 31 2000, 4 yrs	Outcome(s): IHD 410-414; AMI 410; Dysrhythmias 427; cardiac arrest 427.5; congestive heart failure 428; peripheral and cerebrovascular disease 433-437, 440, 443-444, 451-453; atherosclerosis 440; stroke 436. ED visits from billing records. N: 4,407,535 visits, 37 CVD visits/days # Hospitals: 31 Age groups analyzed: adults ≥ 19, elderly 56+ Statistical Analysis: Poisson regression, GLM. Sensitivity analyses using GEE and GAM (strict convergence criteria) Covariates: long-term trends, mean and dew point temp, relative humidity (cubic splines) Statistical Software: SAS Season: Warm, Apr 15-Oct 14, Cool, Oct 15-Apr 14. Lag(s): 0-3 days	SO_2 1-h max (ppb) MediaN: 11.0 10th-90th Range: 2.0 to 39 ppb PM_{10} (0.20) O_3 (0.19) NO_2 (0.34) CO (0.26) $PM_{2.5}$ (0.17) $PM_{10-2.5}$ (0.21) Ultrafine (0.24) Multipollutant models used. All models specified a priori.	Results presented for RR of an incremental increase in SO_2 of 20 ppb (a priori lag 3 day moving avg). All CVD: 1.007 (0.993, 1.022) Dysrhythmia: 1.001 (0.975, 1.028) CHF: 0.992 (0.961, 1.025) IHD: 1.007 (0.981, 1.033) PERI: 1.028 (0.999, 1.059) Finger wounds 1.007 (0.998, 1.026) Single day lag models presented graphically. No multipollutant models run for SO_2 since association was not observed in single-pollutant models.
Michaud et al. (2004) Hilo, Hawaii Period of Study: 1997-2001, N: 1385 days	Outcome(s) (ICD9): Cardiac 410-414, 425-429, Emergency visits, primary diagnosis. Study design: Time-series Statistical Analysis: Exponential regression, autocorrelation assessed by regressing square root of number of ED visits on covariates (Durbin-Watson statistic). Newey-West procedure also conducted for assessment of autocorrelation. Covariates: Temperature, humidity, interaction between SO_2 and PM Lag(s): 1-3 days	SO_2 (all hourly measurements) (ppb) Mean (SD): 1.92 (12.2) MiN: 0 Max: 447 Daily SO_2 (12am-6am) (ppb) Mean (SD): 1.97 (7.12) MiN: 0 Max: 108.5 PM	Effects were presented as relative risk based on an increment of 10 ppb and the 24-h avg SO_2 concentration. Cardiac 0.92 (0.85, 1.00) lag 3 No associations of cardiac ER visits with VOG (SO_2-acidic aerosols) observed.
Moolgavkar (2000)* Cook County IL, Los Angeles County, CA, Maricopa County, AZ 1987-1995	Outcome(s) (ICD9): CVD 390-429; Cerebrovascular disease 430-448. Hospital admissions from CA department of health database. Age groups analyzed: 20-64, 65+ yrs Study design: Time-series N: 118 CVD admissions/days # Hospitals: NR Statistical Analysis: Poisson regression, GAM Covariates: Adjustment for day of wk, long-term temporal trends, relative humidity, temperature Statistical package: SPLUS Lag: 0-5 days	SO_2 24-h avg (ppb) Cook County: MiN: 0.5; Q1: 4 MediaN: 6; Q3: 8 Max: 36 LA County: MiN: 0; Q1: 1 MediaN: 2; Q3: 4 Max: 16 Maricopa County: MiN: 0; Q1: 0.5 MediaN: 2; Q3: 4 Max: 14 PM_{10} (0.11, 0.42) $PM_{2.5}$ (0.42) (LA only) CO (0.35, 0.78) NO_2 (0.02, 0.74) O_3 (−0.37, 0.01)	Results reported for percent change in hospital admissions per 10 ppb increase in SO_2. T statistic in parentheses. CVD, 65+: Cook County 4.0 (6.1), lag 0 3.1 (4.5), lag 0, 2-pollutant model (CO) 1.0 (1.4), lag 0, 2-pollutant model (NO_2) LA County 14.4 (15.2), lag 0 −2.5 (−1.6), lag 0, 2-pollutant model (CO) 7.7 (5.7), lag 0, 2-pollutant model (NO_2) Maricopa County 7.4 (4.5), lag 0 3.0 (1.8), lag 0, 2-pollutant model (CO) 3.9 (1.5), lag 0, 2-pollutant model (SO_2) Cerebrovascular Disease, 65+: Cook County 3.1 (3.3) LA County 6.5 (4.9) Lags 1-5 also presented. Effect size generally diminished with increasing lag time. Increase in hospital admissions (10.3 for CVD and 9.0 for cerebrovascular) also observed for the 20-64 age group.

STUDY	METHODS	POLLUTANTS	EFFECTS
Moolgavkar (2003a) Cook County IL, Los Angeles County, CA, Maricopa County, AZ 1987-1995	Outcome(s) (ICD9): CVD 390-429; Cerebrovascular disease 430-448 was not considered in the reanalysis. Hospital admissions from CA department of health database. Age groups analyzed: 20-64, 65+ yrs Study design: Time-series N: 118 CVD admissions/day # Hospitals: NR Statistical Analysis: Poisson regression, GAM with strict convergence criteria (10-8), GLM using natural splines Covariates: Adjustment for day of wk, long-term temporal trends, relative humidity, temperature Statistical package: SPLUS Lag: 0-5 days	See original analysis (Moolgavkar, 2000) above. See original analysis (Moolgavkar, 2000) above.	Use of stringent criteria in GAM did not alter results substantially. However, increased smoothing of temporal trends attenuated results for all gases and effect size diminished with increasing lag. Results reported for incremental increase of 10 ppb SO_2. Estimated coefficient and T statistic in parentheses. GLM with 100 df (LA County) 13.67 (11.82), lag 0 6.44 (5.23), lag 1 0.23 (0.18), lag 2
Morris et al. (1995) U.S. (Chicago, Detroit, LA, Milwaukee, NYC, Philadelphia) Period of Study: 1986-1989, 4 yrs	Outcome(s) (ICD9): CHF 428. Daily Medicare hospital admission records. Study design: Time-series Statistical analyses: GLM, negative binomial distribution Age groups analyzed: ≥ 65 yrs Covariates: Temperature, indicator variables for mo to adjust for weather effects and seasonal trends, day of wk, yr Statistical software: S-PLUS Lag(s): 0-7 days	SO_2 1-h max (ppm) Mean (SD) LA: 0.010 (0.005) Chicago: 0.025 (0.011) Philadelphia: 0.029 (0.015) New York: 0.032 (0.015) Detroit: 0.025 (0.013) HoustoN: 0.018 (0.009) Milwaukee: 0.017 (0.013) NO_2 O_3 CO Correlations of SO_2 with other pollutants strong.	Results reported for RR of admission for CHF associated with an incremental increase in SO_2 of 0.05 ppm. CHF: LA: 1.60 (1.41, 1.82) Chicago: 1.05 (1.00, 1.10) Philadelphia: 1.01 (0.96, 1.06) New York: 1.04 (1.01, 1.08) Detroit: 1.00 (0.95, 1.06) HoustoN: 1.07 (0.97, 1.17) Milwaukee: 1.07 (0.99, 1.15) RR diminished in multipollutant (4 copollutants) models for all cities.
Peel et al. (Peel et al., 2007) Atlanta, GA Period of Study: Jan 1993-Aug 2000	Outcome(s) (ICD9): IHD 410-414; dysrhythmia 427; CHF 428; peripheral vascular and cerebrovascular disease 433-437, 440, 443, 444, 451-453. Computerized billing records for ED visits. Comorbid conditions: Hypertension 401-405; diabetes 250; dysrhythmia 427, CHF 428; atherosclerosis 440; COPD 491, 492, 496; pneumonia 480-486; upper respiratory infection 460-465, 466.0; asthma 493, 786.09. # Hospitals: 31 N: 4,407,535 visits Study design: Case-crossover and time-series. CVD outcomes among susceptible groups with comorbid conditions. Statistical analyses: Conditional logistic regression and Poisson GLM. Covariates: Cubic splines for temperature and humidity included in models. Time independent variables controlled through design. Statistical Software: SAS Lag(s): 3 day avg, lagged 0-2 day	SO_2 1-h max (ppb) Mean (SD): 16.5 (17.1) 10th: 2 90th: 39 PM_{10} O_3 NO_2 CO	Results expressed as OR for association of CVD admissions with a 20 ppb incremental increase in SO_2. Case-Crossover: All CVD 1.009 (0.995,1.024), 0-2 avg IHD 1.013 (0.988, 1.039), 0-2 avg Dysrhythmia 1.003 (0.975, 1.031), 0-2 avg Peripheral and Cerebrovascular 1.024 (0.993, 1.055), 0-2 avg CHF 0.993 (0.961, 1.026), 0-2 avg Time-series: Odds Ratio (95% CI) (per 20 ppb SO_2) All cardiovascular disease: 1.007 (0.993, 1.022) Ischemic heart disease: 1.007 (0.981, 1.003) Dysrhythmia: 1.001 (0.975, 1.028) Peripheral and cerebrovascular disease: 1.028 (0.999, 1.059) Congestive heart failure: 0.992 (0.961, 1.025) Effect modification by comorbid conditions was not observed.

STUDY	METHODS	POLLUTANTS	EFFECTS
Schwartz and Morris (1995)* Detroit, MI Period of Study: 1986-1989	Outcome(s) (ICD9): IHD 410-414; CHF 428; Dysrhythmia 427. Medicare data, diagnosis at discharge. Study design: Time-series Statistical Analysis: Poisson regression, GAM Age groups analyzed: 65+ yrs Covariates: Adjustments for long-term patterns, temperature, humidity, days of the wk, holidays, viral infections, etc. Lag(s): 0-3, cumulative up to 3 days	SO_2 24-h avg (ppb): Mean: 25.4 IQR: 18 ppb Q2: 15 Q3: 33 # Stations: 6 PM_{10} (0.42) CO (0.23) O_3 (0.15)	Effects were expressed as relative risk based on an increment of 18 ppb. IHD 1.014 (1.003, 1.026) lag 0, single-pollutant 1.009 (0.994, 1.023), 2-pollutant model with PM_{10} CHF 1.002 (0.978, 1.017), single-pollutant model Risks for dysrhythmia were NR for SO_2.
Schwartz (1997) * Tuscon, AZ Period of Study: Jan 1988-Dec 1990	Outcome(s) (ICD9): CVD 390-429. Ascertained from hospital discharge records. Study design: Time-series Statistical Analysis: Poisson regression, GAM Age groups analyzed: 65+ Covariates: Long-term and seasonal trends, day of the wk, temperature, dew point, Statistical software: S-PLUS	SO_2 24-h avg (ppb) Mean: 4.6 ppb IQR: 3.9 ppb 10th: 0.7 Q2: 2.0 MediaN: 3.4 Q3: 5.9 90th: 10.1 PM_{10} (0.095) NO_2 (0.482) CO (0.395) O_3 (−0.271)	Results were expressed as percent change based on an increment of 3.9 ppb. 0.14% (−1.3%, 1.6) No other statistically significant associations for cardiovascular outcomes were observed.
Tolbert et al. (2007) Atlanta, GA 1993-2004	ED Visits. Outcome(s) (ICD9): Cardiovascular (410-414, 427, 428, 433-437, 440, 443-445, 451-453); Respiratory (493, 786.07, 786.09, 491, 492, 496, 460-465, 477, 480-486, 466.1, 466.11, 466.19). Study design: Time-series Statistical Analysis: Poisson Generalized Linear Model (GLM). Statistical package: SAS Age groups analyzed: All ages. Covariates: Adjustment for day-of-wk, hospital entry, holidays, time, temperature, dew point temperature # Hospitals: 41. N: 238,360 (Cardiovascular); 1,072,429 (Respiratory). Lag(s): 3-day moving avg	1-h max (ppb): 14.9 Range: 1.0, 149.0 PM_{10} $PM_{2.5}$ O_3 NO_2 CO Sulfate Total Carbon Organic Carbon EC Water-Soluble Metals Oxygenated Hydrocarbons	Relative Risk (95% CI) (per 16.0 ppb SO_2) 1.003 (0.994, 1.011)
Wellenius et al. (2005b) Birmingham, Chicago, Cleveland, Detroit, Minneapolis, New Haven, Pittsburgh, Seattle Period of Study: Jan 1986-Nov 1999 (varies slightly depending on city)	Outcome(s) IS, primary diagnosis of acute but ill-defined cerebrovascular disease or occlusion of the cerebral arteries; HS, primary diagnosis of intracerebral hemorrhage. ICD codes not provided. Hospital admissions ascertained from the Centers for Medicare and Medicaid Services. Cases determined from discharge data were admitted from the ER to the hospital. N IS: 155,503 N HS: 19,314 Study design: Time-stratified Case-crossover. Control days chosen such that they fell in same mo and same day of wk. Design controls for seasonality, time trends, chronic and other slowly varying potential confounders. Statistical Analysis: 2-stage hierarchical model (random effects), conditional logistic regression for city effects in the first stage Software package: SAS Covariates: Lag(s): 0-2, unconstrained distributed lags	SO_2 24 h avg (ppb) 10th: 2.17 25th: 3.57 MediaN: 6.22 75th: 10.26 90th: 16.17 SO_2 data not available for Birmingham, AL PM_{10} (0.39) CO, NO_2	Results reported for percent increase in stroke admissions for an incremental increase in SO_2 equivalent to one IQR (6.69). Ischemic Stroke: 1.35 (0.43, 2.29), lag 0 Hemorrhagic Stroke: 0.68 (−1.77, 3.19) Multipollutant models not run.

STUDY	METHODS	POLLUTANTS	EFFECTS
Wellenius et al. (2005a) Allegheny County, PA (near Pittsburgh) Period of Study: Jan 1987-Nov 1999	Outcome(s): CHF 428. Cases are Medicare patients admitted from ER with discharge of CHF Study design: Case-crossover, control exposures same mo and day of wk, controlling for season by design. Statistical Analysis: Conditional logistic regression N: 55,019 admissions, including repeat admissions, 86% admitted ≤ 5 times Age groups analyzed: 65+ yrs (Medicare recipients) Covariates: Temperature and pressure. Effect modification by age, gender, secondary diagnosis arrhythmias, atrial fibrillation, COPD, hypertension, type 2 diabetes, AMI within 30 days, angina pectoris, IHD, acute respiratory infection. Statistical software: SAS Lag(s): 0-3	SO_2 24-h avg (ppb): Mean (SD): 14.78 (9.88) 5th: 3.98 25th: 7.70 MediaN: 12.24 75th: 18.98 95th: 33.93 # Stations: 10 PM_{10} (0.51) CO (0.54) NO_2 (0.52) O_3 (−0.19)	Effects were reported as percent change based on an increment of 11 ppb. CHF, single-pollutant models: 2.36 (1.05, 3.69) lag 0, or 2.14 (0.95, 3.35) lag 0 after adjusted to an increment of 10 ppb. CHF, 2-pollutant models: 1.35 (−0.27, 2.99), SO_2 with PM_{10} 0.10 (−1.35, 1.57), SO_2 with CO 0.68 (−0.82, 2.21), SO_2 with NO_2 2.02 (0.68, 3.37), SO_2 with O_3
CANADA			
Burnett et al. (1997a) * Metropolitan Toronto (Toronto, North York, East York, Etobicoke, Scarborough, York), Canada Period of Study: 1992-1994, 388 days, summers only	Outcome(s) (ICD9): IHD 410-414; Cardiac Dysrhythmias 427; Heart failure 428. All Cardiac 410-414, 427, 428. Obtained from hospital discharge data. PopulatioN: 2.6 Million residents Study design: Time-series Age groups analyzed: All # Hospitals: NR Statistical Analysis: Relative risk regression models, GAMs. Covariates: Adjusted for long- term trends, seasonal and subseasonal variation, day of the wk, temperature, dew point Season: Summer only Dose response: Figures presented Lag: 1-4 days	SO_2 daily 1-h max (ppb): Mean: 7.9 CV: 64 MiN: 0 25th percentile: 4 50th percentile: 7 75th percentile: 11 Max: 26 # of Stations: 4-6 (Results are reported for additional metrics including 24-h avg and daytime avg (day) H^+ (0.45) SO_4 (0.42) TP (0.55) FP (0.49) CP (0.44) COH (0.50) O_3 (0.18) NO_2 (0.46) CO (0.37)	Effects were expressed as relative risk based on an increment of 7.00 ppb (IQR). T ratio in parentheses. All cardiac disease Single-pollutant model 1.041 (2.66), daily max over 4 days, lag 0 Multipollutant model w/ SO_2, O_3, NO_2 Of 7.72 excess hospital admissions, 2.8% attributed to SO_2. Objective of study was to evaluate the role of particle size and chemistry on cardiac and respiratory diseases.
Burnett et al. (1999) * Metropolitan Toronto (Toronto, North York, East York, Etobicoke, Scarborough, York), Canada Period of Study: 1980-1995, 15 yrs	Outcome(s) (ICD9): IHD 410-414; Cardiac Dysrhythmias 427; Heart failure 428; All cardiac 410-414, 427, 428; Cerebrovascular Disease obtained from hospital discharge data 430-438; Peripheral Circulation Disease 440-459. PopulatioN: 2.13-2.42 million residents Study design: Time-series Statistical Analysis: GAMs to estimate log RR per unit changes, stepwise regression used to select min number of air pollutants in multipollutant models. Covariates: Long-term trends, seasonal variation, day of wk, temperature, and humidity. Statistical package: S-PLUS Lag(s): 0-2 days	SO_2 daily avg (ppb) Mean: 5.35 5th percentile: 0 25th percentile: 1 50th percentile: 4 75th percentile: 8 95th percentile: 17 Max: 57 Multiple day avgs used in models $PM_{2.5}$ (0.50) $PM_{10-2.5}$ (0.38) PM_{10} (0.52) CO (0.55) SO_2 (0.55) O_3 (−0.04)	Effects were reported as % change based on an increment of 5.35 ppb. Single-pollutant model Dysrhythmias 0.8% (−0.3, 1.9) Cerebrovascular 0.04% (−0.7, 0.8) CHF 1.93% (0.9, 2.9) IHD 2.32% (1.6, 3.1) Attributed percent increase in admissions for SO_2 were determined from multipollutant models. IHD Attributed percent increase: 0.95% Authors note SO_2 effects could be largely explained by other variables in the pollution mix as demonstrated by the multipollutant model.

STUDY	METHODS	POLLUTANTS	EFFECTS
Fung et al. (2005) Windsor, Ontario, Canada Period of Study: Apr 1995-Jan 2000	Outcome(s) (ICD9): CHF 428; IHD 410-414; dysrhythmias 427 and all cardiac. Hospital admissions from Ontario Health Insurance Plan records. Study design: Time-series Statistical Analysis: GLM N: 11,632 cardiac admission, 4.4/day for 65+ age group Age groups analyzed: 65+, < 65 yrs Statistical Software: SPLUS Lag(s): lag 0, 2, 3 day avg	SO_2 1-h max (ppb) Mean (SD): 27.5 (16.5) MiN: 0 Max: 129 IQR: 19.3 ppb CO (0.16) O_3 (−0.02) PM_{10} (0.22) NO_2 (0.22)	Effects were expressed as percent change of cardiac disease hospital admissions based on an increment of 19.3 ppb. Single-pollutant model: < 65 yrs 2.3% (−1.8, 6.6) lag 0 3.9% (−1.5, 9.6) lag 0-1 3.4% (−3.0, 10.1) lag 0-2 ≥ 65 yrs 2.6% (0.0, 5.3) lag 0 4.0% (0.6, 1.6) lag 0-1 5.6% (1.5, 9.9) lag 0-2 Inclusion of particulate matter and adjustment for meteorological variables did not change the association between SO_2 and cardiac hospitalization.
Stieb et al. (2000) * Saint John, New Brunswick Canada Period of Study: July 1992-Mar 1996	Outcome(s): Angina pectoris; MI; dysrhythmia/conduction disturbance; CHF; All Cardiac. ED Visits collected prospectively. Study design: Time-series Statistical analyses: Poisson regression, GAM N: 19,821 ER visits # Hospitals: 2 Lag(s): 1-8 days	SO_2 24-h avg (ppb) Mean (SD): 6.7 (5.6) 95th: 18 Max: 60 SO_2 max (ppb) Mean (SD): 23.8 (21.0) 95th: 62 Max: 161 CO (0.31) H_2S (−0.01) O_3 (−0.02) NO_2 (0.41) PM_{10} (0.36) $PM_{2.5}$ (0.31) H^+ (−0.24) SO_4 (0.26) COH (0.31)	Results reported for percent change in admissions based on a single-pollutant model for incremental increase in NO_2 equivalent to one IQR (8.9 ppb) Cardiac visits (p-value in parentheses): 4.9 (0.002), 1 day avg, lag 8, all yr 2.8 (0.067), 5 day avg, lag 6, May-Sept Multi-pollutant models: 4.9, (1.7, 8.2), 1 day avg, lag 8, all yr (O_3) Lags 0-10 presented graphically. All but lag 8 in single-pollutant model approximately null.
Villeneuve et al. (2006) Edmonton, Canada Period of Study: Apr 1992-Mar 2002	Outcome(s) (ICD9): Acute ischemic stroke 434, 436; hemorrhagic stroke 430, 432; transient ischemic attach (TIA) 435; Other 433, 437, 438. ED visits supplied by Capital Health. N: 12,422 Stroke Visits Catchment area: 1.5 million people Study design: Case-crossover, exposure index time compared to referent time. Time independent variables controlled in the design. Index and referent day matched by day of wk. Statistical Analysis: Conditional logistic regression, stratified by season and gender. Covariates: Temperature and humidity Statistical software: SAS Season: Warm: Apr-Sep; Cool: Oct-Mar. Lag(s): 0, 1, 3 day avg	SO_2 24 h avg ppb: All yr Mean (SD): 2.6 (1.9) MediaN: 2.0 25th: 1.0 75th: 4.0 IQR: 3.0 Summer Mean (SD): 2.1 (1.6) MediaN: 2.0 25th: 1.0 75th: 3.0 IQR: 2 Winter Mean (SD): 3.1 (2.0) MediaN: 3.0 25th: 2.0 75th: 4.0 IQR: 2.0 Correlation between SO_2 and other pollutants (all yr): NO_2 (0.42) CO (0.41) O_3 (−0.25) $PM_{2.5}$ (0.22) PM_{10} (0.19)	Effects were reported as odds ratios based on an increment of 3 ppb. Acute Ischemic stroke, ≥ 65 yrs All yr OR 1.05 (0.99,1.11) lag 0 Warm OR 1.11 (1.01, 1.22) lag 0 Cold OR 1.00 (0.93, 1.09) lag 0 Effect stronger among males Hemorrhagic stroke, ≥ 65 yrs All yr: 0.98 (0.90, 1.06), lag 0 Cold: 0.94 (0.84, 1.05), lag 0 Warm: 1.03 (0.90, 1.17) Effect stronger among males Transient Cerebral Ischemic Attack, ≥ 65 yrs All yr: 1.06 (1.00, 1.12), lag 0 Cold: 1.03 (0.95, 1.11), lag 0 Warm OR 1.11 (1.02, 1.22) lag 0 2-pollutant models presented graphically. Association of SO_2 with Acute Ischemic stroke diminished with inclusion of CO and NO_2.

STUDY	METHODS	POLLUTANTS	EFFECTS
EUROPE			
Anderson et al. (Anderson et al., 2001)* West Midlands conurbation, UK Period of Study: 1994-1996, N: 832 days	Outcome(s) (ICD9): All CVD 390-459; cardiac disease 390-429; IHD 410-414; stroke 430-438. Emergency admissions counted. Catchment area: 2.3 million Age groups analyzed: 0-14, 15-64, ≥ 65. Study design: Time-series, APHEA 2 methods Statistical analyses: GAMs for modeling non-liner dependence of some variables. Covariates: Adjusted for effects of seasonal patterns, temperature and humidity, influenza episodes, day of wk and holidays. Software package: S-PLUS Season: Interaction by warm and cool season investigated. Lag(s): 0-3 days	SO_2 24-h avg (ppb) Mean (SD): 7.2 (4.7) MiN: 1.9 10th: 3.3 MediaN: 5.8 90th: 12.3 Max: 59.8 # of Stations: 5 sites PM_{10} (0.55) $PM_{2.5}$ (0.52) $PM_{2.5-10}$ (0.31) BS (0.50) SO_4 (0.19) NO_2 (0.52) O_3 (-0.22)	Results reported for % change in admissions, increment = 9 ppb (10th-90th). All CVD all ages −0.4 (−2.2, 1.5), mean lags 0 + 1 Cardiac all ages: 0.7 (−1.3, 2.8), mean lags 0 + 1 IHD ≥ 65 yrs 1.5 (−2.5, 5.6), mean lags 0 + 1 Stroke ≥ 65 yrs −5.1 (−9.6, −0.4), mean lags 0 + 1
Atkinson et al. (Atkinson et al., 1999a) London, England Period of Study: 1992-1994, N: 1,096 days	Outcome(s) (ICD9): All CVD 390-459; IHD 410-414. Emergency admissions obtained from the Hospital Episode Statistics (HES) database (complaints). Ages groups analyzed: 0-14 yrs, 15-64 yrs, 0-64 yrs, 65+ yrs, 65-74 yrs, 75+ yrs Study design: Time-series, hospital admission counts N: 189,109 CVD admissions Catchment area: 7 million residing in 1,600 Km^2 area of Thames basin. Statistical analyses: APHEA protocol, Poisson regression Covariates: Adjusted long-term seasonal patterns, day of wk, influenza, temperature, humidity (compared alternative methods for modeling meteorological including linear, quadradic, piece-wise, spline) Season: Warm season Apr-Sep, cool season remaining mos, interactions between season investigated Dose response investigated: Yes, bubble charts presented Statistical package: SAS Lag: 0-3 Dose response: Bubble plots presented	SO_2 24 h avg (ppb): Mean: 21.2 SD: 7.8 MiN: 7.4 10th: 13 MediaN: 19.8 90th: 31 Max: 82.2 10th-90th percentile: 11.2 # of Stations: 3, results averaged across stations PM_{10} CO SO_2 O_3 BS Correlations of SO_2 with CO, NO_2, O_3, BS ranged from 0.5-0.6 Correlation of SO_2 with O_3 negative	Results reported for % change in admissions, increment 10th-90th percentile (11.2 ppb). All CVD, all ages 1.57 (0.22, 2.93), lag 0 All CVD, 0-64 yrs 2.44 (0.3, 4.63), lag 0 All CVD, 65+ 1.72 (0.15, 3.32), lag 0 IHD, 0-64 yrs −2.03 (−5.35, 0.91), lag 2 IHD, 65+ 3.10 (0.61, 5.65), lag 0 Effect size and significance diminished in models containing SO_2 and BS.

STUDY	METHODS	POLLUTANTS	EFFECTS
Ballester et al. (2001) * Valencia, Spain Period of Study: 1992-1996	Outcome(s) (ICD9): All CVD 390-459; heart diseases 410-414, 427, 428; cerebrovascular diseases 430-438. Admissions from city registry – discharge codes used. Study design: Time-series N: 1080 CVD admissions # of Hospitals: 2 Catchment area: 376,681 inhabitants of Urban Valencia Statistical analyses: Poisson regression, GAM, APHEA/ Spanish EMECAM protocol. Both Linear and nonparametric model, including a loess term was fitted, departure from linearity assess by comparing deviance of both models. Covariates: Long-term trend and seasonality, temperature and humidity, weekdays, flu, special events, air pollution. Season: Hot season May to Oct; Cold season Nov to Apr Statistical package: SAS Lag: 0-4	24 h avg ($\mu g/m^3$): Mean: 25.6 SD: NR MiN: 4.4 Max: 68.4 mediaN: 25 # of Stations: 14 manual, 5 automatic Correlation among stations: 0.3-0.62 for BS, 0.46-0.78 for gaseous pollutants CO (0.74) NO_2 (0.22) O_3 (−0.35) BS (0.63)	Results expressed as relative risk, increment of 10 $\mu g/m^3$. All CVD 1.0302 (1.0042, 1.0568), lag 2 Heart disease 1.0357 (1.0012, 1.0714), lag 2 Cerebrovascular disease 1.0378 (0.9844 to 1.0940), lag 5 Digestive diseases 1.0234 (0.9958, 1.0518), lag 1 All CVD, hottest semester 1.050 (1.010, 1.092), lag 2 Effect size for all CVD and cerebrovascular disease diminished in 2-pollutant models.
Ballester et al. (2006) Multicity, SpaiN: Barcelona, Bilbao, Castellon, Gijon, Huelva, Madrid, Granada, Oviedo, Seville, Valencia, Zaragoza Period of Study: 1995/1996-1999, N: 1,096 days	Outcome(s) (ICD9): All CVD 390-459; Heart diseases 410-414,427,428. Emergency admission from hospital records. Discharge data used. Study design: Time-series, meta-analysis to pool cities N: Daily mean admissions reported by city. Statistical analyses: Poisson regression and GAM, with stringent convergence criteria, meta-analysis with random effect model. Tested linearity by modeling pollutant in linear and non-linear way (spline smoothing). Linear model provided best results 55% of time but used in all cases to facilitate comparability. Covariates: Temperature, humidity and influenza, day of wk unusual events, seasonal variation and trend of the series Season: Hot: May to Oct; Cold: Nov to Apr Statistical package: S-PLUS Lag: 0-3	SO_2 24-h avg ($\mu g/m^2$) Mean, 10th, 90th Barcelona: 15.5, 6.6, 27.9 Bilbao: 18.6, 10.2, 29.3 Cartagena: 27.1, 14.6, 40.8 CastelloN: 7.7, 3.8, 12.7 GijoN: 29.4, 10.3, 52.4 Granada: 19.1, 8.8, 31.5 Huelva: 11.9, 4.5, 22.6 Madrid: 21.8, 8.7, 41.8 Oviedo: 40.9, 16.3, 75.5 Pamplona: 7.6, 1.8, 17.0 Seville: 9.6, 5.6, 14.6 Valencia: 16.6, 9.4, 24.4 Vigo: 9.3, 2.6, 18.2 Zaragoza: 9.3, 2.0, 19.9 # of Stations: Depends on the city Correlation among stations: Correlations between SO_2 stations within cities poor. CO (0.58) O_3 (−0.03) NO_2 (0.46) BS (0.24) TSP (0.31) PM_{10} (0.46) Correlations reported are the median for all cities.	Results reported for % change in admissions, increment 10 ($\mu g/m^3$). All cardiovascular 1.33% (0.21, 2.46) lag 0-1 Heart diseases 1.72% (0.50, 2.95) lag 0-1 Single day lags presented graphically. Effect size decreased with increasing lag. Multi-pollutant results presented graphically. Control for CO and particulates diminished SO_2 effects.

STUDY	METHODS	POLLUTANTS	EFFECTS
D'Ippoliti et al. (2003) Rome, Italy Period of Study: Jan 1995- June 1997	Outcome(s) (ICD): AMI 410 (first episode). Computerized hospital admission data. Study design: Case-crossover, time stratified, control days within same mo falling on the same day. Statistical analyses: Conditional logistic regression, examined homogeneity across co-morbidity categories N: 6531 cases Age groups analyzed: 18-64 yrs, 65-74 yrd, ≥ 75 Season: Cool: Oct-Mar; Warm: Apr-Sep Lag(s): 0-4 day, 0-2 day cum avg Dose Response: OR for increasing quartiles presented and p-value for trend.	SO_2 24 h avg (µg/m^3) All yr: Mean (SD): 9.5 (6.0) 25th: 5.4 50th: 8.2 75th: 12.6 IQR: 7.2 Cold season: Mean (SD): 12.7 (6.5) Warm Season: Mean (SD): 88.3 (15.4) # Stations: 5 TSP (0.29) NO_2 (0.37) CO (0.56)	Results reported as odds ratios for increment equal to one IQR (7.2 µg/m^3). AMI Quartile I (referent) Quartile II 0.987 (0.894, 1.089), lag 0-2 Quartile III 1.008 (0.892, 1.140), lag 0-2 Quartile IV 1.144 (0.991, 1.321), lag 0-2 Results at various lags NR for SO_2.
Llorca et al. (2005) Torrelavega, Spain Period of Study: 1992-1995	Outcome(s) (ICD): CVD (called cardiac in paper) 390-459. Emergency admissions, excluding nonresidents. Obtained admissions records from hospital admin office. Study design: Time-series Statistical analyses: Poisson regression, APHEA protocol Covariates: Rainfall, temperature, wind speed direction N: 18,137 admissions Statistical software: STATA Lag(s): NR	SO_2 24 h avg µg/m^3: Mean (SD): 13.3 (16.7) TSP (−0.40) NO_2 (0.588) SH_2 (0.957) NO (0.544)	Results expressed as rate ratios. Increment = 100 µg/m^3. Cardiac admissions, single-pollutant model 0.94 (0.84, 1.05) Five-pollutant model 1.09 (0.83, 1.42) All cardiorespiratory admissions, single-pollutant model RR 0.98 (0.89, 1.07) Five-pollutant model 0.98 (0.80, 1.21)
Poloniecki et al. (1997) London, UK Period of Study: Apr, 1987-Mar 1994, 7 yrs	Outcome(s): All CVD 390-459; MI 410; Angina pectoris 413; other IHD 414; ARR 427; congestive heart failure 428; cerebrovascular disease 430-438. Hospital Episode Statistics (HES) data on emergency hospital admissions. Study design: Time-series N: 373, 556 CVD admissions Statistical analyses: Poisson regression with GAM, APHEA protocol Covariates: Long-term trends, seasonal variation, day of wk, influenza, temperature and humidity. Season: Warm, Apr-Sep; Cool, Oct-Mar Lag: 0-1	$SO_2$24 h avg ppb: MiN: 0 10%: 2 MediaN: 6 90%: 21 Max: 1 Black Smoke CO 24 h avg NO_2 24 h avg O_3 8 h Correlations between pollutants high but not specified	Effects were expressed as relative risk based on an increment of 19 ppb (10th-90th percentile). Single-pollutant models (lag 0-1) MI: 1.0326 (1.0133, 1.0511) Angina: 1.0133 (0.9907, 1.0383) IHD: 0.9944 (0.9651, 1.0239) ARR: 1.0181 (1.0000, 1.0448) CHF: 1.0057 (0.9846, 1.0258) Cerebrovascular: 1.0019 (0.9837, 1.0189) All circulatory: 1.0248 (1.0062, 1.0444) MI, 2-pollutant models, cool season 1.0399 (1.0171, 1.0628), SO_2 only 1.0285 (1.0019, 1.0571), SO_2 with NO_2 1.0380 (1.0057, 1.0704), SO_2/CO 1.0285 (1.0019, 1.0552), SO_2/BS 1.0476 (1.0209, 1.0742), SO_2 with O_3 In the warm season no significant associations were observed in 2-pollutant models..
Prescott et al. (1998) * Edinburgh, UK Period of Study: Oct 1992-Jun 1995	Outcome(s) (ICD9): Cardiac and cerebral ischemia 410-414, 426-429, 434-440. Extracted from Scottish record linkage system. Study design: Time-series Statistical Analysis: Poisson, log linear regression models Age groups analyzed: < 65, 65+ yrs Covariates: Seasonal and weekday variation, temperature, and wind speed. Lag(s): 0, 1, 3 day moving avg	NO_2 24 h avg ppb Mean (SD): 8.3 (5.6) Range: 1-50 90th-10th Percentile = 12 ppb O_3, 24 h avg PM, 24 h avg NO_2, 24 h avg	CO, 24 h avg Correlations NR. Results reported as % increase in admissions, increment 10 ppb. All CVD, ≤ 65 yrs 4.9 (−1.0, 11.1), 3 day moving avg All CVD, ≥ 65 yrs −3.7 (−12.4, 5.9), 3 day moving avg

STUDY	METHODS	POLLUTANTS	EFFECTS
Sunyer et al. (2003) Europe (Birmingham, London, Milan, Paris, Rome, Stockholm, the Netherlands) 1990-1996	Hospital Admissions Outcome(s) (ICD9): Cardiovascular diseases (390-429); IHD (410-413); stroke (430-438) Study design: Time-series Statistical Analysis: Poisson autoregression with GAM Age groups analyzed: All ages Covariates: Trend, seasonal patterns, meteorological factors Lag(s): 0 + 1	24-h median ($\mu g/m^3$): Birmingham: 19 LondoN: 21 MilaN: 18 Netherlands: 9 Paris: 15 Rome: 9 Stockholm: 5 PM_{10} BS NO_2 O_3	% increase in Hospital Admissions (95% CI) (per 10 $\mu g/m^3$ SO_2) Cardiovascular All ages: 0.7 (0.3, 1.1) >65: 0.7 (0.3, 1.2) IHD < 65: 0.6 (0.2, 1.1) >65: 1.2 (0.8, 1.6) IHD after adjustment for CO, NO_2, BS < PM_{10} < 65: 0.7 (0.1, 1.3) >65: −1.4 (−8.0, 6.0) Stroke >65: 0.0 (−0.5, 0.5)
Yallop et al. (2007) London, England Period of Study: Jan 1998-Oct 2001, > 1400 days	Outcome(s): Acute pain in Sickle Cell Disease (HbSS, HbSC, HbS/∃0, thalassaemia, HbS/∃+). Admitted to hospital for at least one night. Study design: Time-series Statistical analyses: Cross-correlation function N: 1047 admissions Covariates: No adjustment made in analysis, discussion includes statement that the effects of weather variables and copollutants are inter-related. Statistical package: SPSS Lag(s): 0-2 days Dose response: quartile analysis, graphs presented, ANOVA comparing means across quartiles.	NR O_3 CO NO NO_2 PM_{10}	No association for SO_2
AUSTRALIA			
Jalaludin et al. (2006) Sydney, Australia Period of Study: Jan 1997-Dec 2001	Outcome(s) (ICD9): All CVD 390-459; cardiac disease 390-429; IHD 410-413; and cerebrovascular disease or stroke 430-438; Emergency room attendances obtained from health department data. Age groups included: 65+ Study design: Time-series, multicity APHEA2 Protocol. Statistical Analysis: GAM (with appropriate convergence criteria) and GLM Models. Only GLM presented. Lag: 0-3 Covariates: Daily avg temperature and daily relative, humidity, long-term trends, seasonality, weather, day of wk, public school holidays, outliers and influenza epidemics. Dose response: quartile analysis Season: Separate analyses for warm (Nov-Apr) and cool periods (May-Oct).	SO_2 24 h avg avg (ppb) Mean (SD): 1.07 (0.58) MiN: 0.09 25th: 0.64 MediaN: 1.01 75th: 1.39 Max: 3.94 IQR: 0.75 # of Stations: 14 BS (0.21) PM_{10} (0.37) O_3 (0.454) NO_2 (0.52) CO (0.46)	Effects were presented as percent change based on an increment of 0.75 ppb. Single-pollutant model: All CVD, all yr 1.33% (0.24, 2.43) lag 0 Cardiac: 1.62% (0.33, 2.93) lag 0 IHD: 1.12% (−0.84, 3.12) lag 0 Stroke: −1.41% (−3.67, 0.90) lag 0 Cool Season All cardiovascular: 2.15% (0.84, 3.46) lag 0 Cardiac: 2.48% (0.94, 4.04) lag 0 IHD: 2.49% (0.13, 4.91) lag 0 Stroke: −0.19% (−2.90, 2.60) lag 0 Warm Season All cardiovascular: 0.06% (−1.48, 1.62) lag 0 Cardiac: 0.38% (−1.37, 2.16) lag 0 IHD: −0.47% (−3.08, 2.22) lag 0 Stroke: −2.74% (−5.92, 0.55) lag 0 Results for lags 0-3 presented. In general, effect size diminished with increasing lag. Effects of SO_2 on all CVD were diminished with inclusion of PM and CO (graphically presented.)

STUDY	METHODS	POLLUTANTS	EFFECTS
Petroeschevsky et al. (2001) Brisbane, Australia Period of Study: Jan 1987-Dec 1994, 2,922 days	Outcome(s) (ICD9): CVD 390-459. Hospital admissions, non-residents excluded. Study design: Time-series Statistical analyses: Poisson regression, APHEA protocol, linear regression and GEEs Age groups analyzed: 15-64, 65+ Covariates: Temperature, humidity, rainfall. Long-term trends, season, flu, day of wk, holidays. Dose response: Quintile analysis. Statistical software: SAS Lag(s): lag 0-4, 3 day avg, 5 day avg	SO_2 24-h avg (pphm) Summer: Mean, min, max 0.39, 0.0, 1.63 Fall: Mean, min, max 0.42, 0.01, 3.55 Winter: Mean, min, max 0.48, 0.0, 2.08 Spring: Mean, min, max 0.37, 0.0, 6.02 Overall: Mean, min, max 0.41, 0.0, 3.55 SO_2 1-h max (pphm) Summer: Mean, min, max 0.78, 0.0, 5.5 Fall: Mean, min, max 0.93, 0.05, 5.95 Winter: Mean, min, max 1.13, 0.0, 6.68 Spring: Mean, min, max 0.84, 0.0, 6.01 Overall: Mean, min, max 0.92, 0.0, 6.68 BSP O_3 NO_2	Effects were expressed as relative risk based on an increment of 10 ppb and the 24-h avg SO_2 concentrations. All CVD 15 to ≥ 65 yrs 1.028 (0.987, 1.070) lag 0 15 to 64 yrs 1.081 (1.010, 1.158) lag 0 ≥ 65 yrs 1.038 (0.988, 1.091) lag 1 Non-significant increasing risk for CVD in those 15-64 by quintile of SO_2 concentration observed.
ASIA			
Chan et al. (2006) * Taipai, Taiwan Period of Study: Apr 1997-Dec 2002, 2090 days	Outcome(s) (ICD9): Cerebrovascular disease 430-437; stroke 430-434; hemorrhagic stroke 430-432; ischemic stroke 433-434. Emergency admission data collected from National Taiwan University Hospital. Ages groups analyzed: age >50 included in study Study design: Time-series N: 7341 Cerebrovascular admissions among those >50 yrs old Catchment area: Statistical analyses: Poisson regression, GAMs used to adjust for non-linear relation between confounders and ER admissions. Covariates: Time trend variables: yr, mo, and day of wk, daily temperature difference, and dew point temperature. Linearity: Investigated graphically by using the LOESS smoother. Lag: 0-3, cumulative lag up to 3 days	SO_2 24-h avg (ppb): Mean: 4.3 SD: 2.4 MiN: 0.4 Max: 17.1 IQR: 3.1 ppb # of Stations: 16 Correlation among stations: NR PM_{10} (0.59) $PM_{2.5}$ (0.51) CO (0.63) NO_2 (0.64) O_3 (0.51)	Results reported for OR for association of emergency department admissions with an IQR increase in SO_2 (3.1 ppb) Cerebrovascular: 1.008 (0.969, 1.047), lag 0 Stroke: 0.991 (0.916, 1.066), lag 0 Ischemic stroke: 1.044 (0.966, 1.125), lag 0 Hemorrhagic stroke: 0.918 (0.815, 1.021), lag 0 No significant associations for SO_2 reported. Lag 0 shown but similar null results were obtained for lags 0-3. 2-pollutant models to adjust for copollutants but not for SO_2, which was not associated with health outcomes.
Chang et al. (2005) Taipei, Taiwan Period of Study: 1997-2001, 5 yrs	Outcome(s) (ICD9): CVD 410-429. Daily clinic visits or hospital admission from computerized records of National Health Insurance. Discharge data. Source populatioN: 2.64 Million N: 40.8 admissions/day, 74,509/5 yrs # Hospitals: 41 Study design: Case-crossover, referent day 1 wk before or after index day Statistical analyses: Conditional logistic regression. Covariates: Same day temperature and humidity. Season: warm/cool (stratified by temperature cutpoint of 20 °C) Lag(s): 0-2 days	SO_2 24-h avg (ppb) Mean: 4.32 MiN: 0.15 25th: 2.74 MediaN: 3.95 75th: 5.49 Max: 14.57 IQR: 2.75 # of Stations: 6 CO O_3 NO_2 PM_{10} Correlations NR.	Effects were expressed as odds ratios based on an increment of 2.75 ppb. Warm (≥ 20 °C) 0.967 (0.940, 0.995) Cool (< 20 °C) 1.015 (0.965, 1.069) In 2-pollutant models with (PM_{10}, NO_2, CO, or O_3) the effect of SO_2 was attenuated for both temperature ranges such that it was negatively associated with CVD. ≥ 20 °C: 0.874 (0.77, 0.880), w/ PM_{10} < 20 °C: 0.986 (0.928, 1.048), w/ PM_{10} ≥ 20 °C: 0.826 (0.798, 0.854), w/ NO_2 < 20 °C: 0.922 (0.865, 0.984), w/ NO_2 ≥ 20 °C: 0.903 (0.876, 0.931), w/ CO < 20 °C: 0.960 (0.901, 1.022), w/ CO ≥ 20 °C: 0.953 (0.926, 0.981), w/ O_3 < 20 °C: 1.014 (0.963, 1.067), w/ O_3

STUDY	METHODS	POLLUTANTS	EFFECTS
Lee et al. (2003) Seoul, Korea Period of Study: Dec 1997-Dec 1999, 822-days, 184 days in summer	Outcome(s) (ICD10): IHD: Angina pectoris 120; Acute or subsequent MI 121-123; other acute IHD 124. Electronic medical insurance data used. Study design: Time-series Statistical methods: Poisson regression, GAM with strict convergence criteria. Age groups analyzed: all ages, 64+ Covariates: Long-term trends LOESS smooth, temperature, humidity, day of wk. Season: Presented results for summer (Jun, Jul, Aug) and entire period. Lag(s): 0-6	SO_2 24 h avg (ppb): 5th: 3.7 10th: 5.1 MediaN: 7.0 75th: 9.5 95th: 14.3 Mean (SD): 7.7 (3.3) IQR: 4.4 All yr NO_2 (0.72) O_3 (−0.30) CO (0.81) PM_{10} (0.59) Warm season NO_2 (0.79) O_3 (−0.56) CO (0.41) PM_{10} (0.61)	Results reported for RR of IHD hospital admission for an incremental increase in SO_2 equivalent to one IQR (4.4 ppb). Single-pollutant model: Entire season- IHD All ages 0.96 (0.92, 0.99) lag 3 ≥ 64 yrs 0.95 (0.90, 1.01) lag 3 Summer- IHD All ages 1.09 (0.96, 1.24) lag 3 ≥ 64 yrs 1.32 (1.08, 1.62) lag 3 2-pollutant model: Entire season; SO_2 and PM_{10} ≥ 64 yrs 0.98 (0.94, 1.03) lag 3
Tsai et al. (2003) Kaohsiung, Taiwan Period of Study: 1997-2000	Outcome(s) (ICD9): All cerebrovascular 430-438; SHS 430; PIH 431-432; IS 433-435; Other 436-438. Ascertained from National Health Insurance Program computerized admissions records. Study design: Case-crossover Statistical Analysis: Conditional logistic regression. N: 23,179 stroke admissions # Hospitals: 63 Statistical software: SAS Season: Warm (≥ 20 °C); Cool (< 20 °C). Lag(s): 0-2, cumulative lag up to 2 previous days	SO_2 (ppb) MiN: 1.25 25th: 6.83 MediaN: 9.76 75th: 13.00 Max: 26.80 Mean: 10.08 # StatioN: 6 PM_{10} SO_2 CO O_3	Results reported as OR for the association of admissions with an incremental increase of SO_2 equivalent to the IQR of 6.2 ppb PIH admissions Warm: 1.06 (0.95, 1.18), lag 0-2 Cool: 0.85 (0.58, 1.26), lag 0-2 IS admissions: Warm: 1.06 (1.00, 1.13), lag 0-2 Cool: 1.11 (0.83, 1.48), lag 0-2 2-pollutant models: PIH 0.91 (0.80, 1.03) w/ NO_2 IS 0.93 (0.87, 1.00) w/ NO_2 PIH 0.94 (0.83, 1.06), w/ CO IS 0.94 (0.88, 1.02), w/ CO PIH 1.08 (0.96, 1.20) w/ O_3 IS 1.08 (1.01, 1.15) w/ O_3 PIH 0.99 (0.88, 1.11) w/ PM IS 1.01 (0.95-1.08) w/ PM
Wong et al. (1999) Hong Kong, China Period of Study: 1994-1995	Outcome(s) (ICD9): CVD: 410-417, 420-438, 440-444; CHF 428; IHD 410-414; Cerebrovascular Disease 430-438. Hospital admissions through ER departments via Hospital Authority (discharge data). Study design: Time-series Statistical analyses: Poisson regression, APHEA protocol # Hospitals: 12 Covariates: Daily temperature, relative humidity day of wk, holidays, influenza, long-term trends (yr and seasonality variables). Interaction of pollutants with cold season examined. Season: Cold (Dec-Mar) Lag(s): 0-3 days	SO_2 24-h avg ($\mu g/m^3$) Mean: 20.2 IQR: 10 PM_{10} SO_2 O_3	Results reported for RR associated with incremental increase in NO_2 equal to 10 $\mu g/m^3$. All CVD, All ages 1.016 (1.006, 1.026) lag 0-1 All CVD, 5-65 yrs 1.004 (0.989, 1.020) lag 0-1 All CVD, >65 yrs 1.021 (1.010, 1.032) lag 0-1 CHF 1.036 (1.013, 1.059) lag 0 IHD 1.010 (0.995, 1.025) lag 0-1 Cerebrovascular 0.990 (0.978, 1.002) lag 3 2-pollutant model results not presented for SO_2

STUDY	METHODS	POLLUTANTS	EFFECTS
Wong et al. (2002a)* Hong Kong, London Period of Study: 1995-1997 (Hong Kong), 1992-1994 (London)	Outcome(s) (ICD9): Cardiac disease 390-429; IHD 410-414. Patients admitted to hospitals from emergency departments, out patient departments or directly to inpatient wards. Statistical Analysis: Poisson regression, GAMs Covariates: Smooth functions of time, temperature, humidity (up to 3 days before admission) day of wk, holidays and unusual events. Statistical software: S-PLUS Season: Warm/cold Lag(s): 0-3, cumulative 0-1	SO_2 24-h avg ($\mu g/m^3$) Hong Kong Mean, all yr: 17.7 (12.3) Mean, warm: 18.3 Mean, cold: 17.2 MiN: 1.1 10th: 6.2 50th: 14.5 90th: 32.8 Max: 90 London Mean, all yr: 23.7 (12.3) Mean, warm: 22.2 Mean, cold: 25.3 Min 6.2 10th: 13.2 50th: 20.6 90th: 38.1 Max: 113.6 Hong Kong NO_2 (0.37) PM_{10} (0.30) O_3 (−0.18) London NO_2 (0.71) PM_{10} (0.64) O_3 (−0.25)	Effects expressed as % change, increment was 10 $\mu g/m^3$ Cardiac (all ages) Hong Kong All yr: 2.1% (1.3, 2.8) lag 0-1 Warm: 1.0% (0.0, 2.0) lag 0-1 Cold: 1.9% (1.2, 2.7) lag 0-1 London All yr: 1.6% (1.0, 2.2) lag 0-1 Warm: 0.6% (−0.6, 1.7) lag 0-1 Cold: 1.9% (1.2, 2.7) lag 0-1 IHD (all ages) Hong Kong All yr: 0.1% (−1.1, 1.2) lag 0-1 Warm: −0.6% (−2.0, 0.8) lag 0-1 Cold: 1.0% (−0.8, 2.8) lag 0-1 London All yr: 1.7% (0.8, 2.6) lag 0-1 Warm: 1.0% (−0.6, 2.6) lag 0-1 Cold: 2.0% (0.9, 3.1) lag 0-1 Multipollutant model Cardiac (all ages) Hong Kong SO_2 alone 2.1% (1.3, 2.8) SO_2 with NO_2 1.4% (0.4, 2.3) SO_2 with O_3 2.1% (1.4, 2.9) SO_2 with PM_{10} 2.0% (1.1, 2.8) London SO_2 1.6% (1.0, 2.2) SO_2 with NO_2 1.4% (0.6, 2.3) SO_2 with O_3 1.6% (0.9, 2.2) SO_2 with PM_{10} 2.2% (1.2, 3.2)
Yang et al. (2004) Kaohsiung, Taiwan Period of Study: 1997-2000	Outcome(s) (ICD9): All CVD: 410-429 * (All CVD typically defined to include ICD9 codes 390-459) N: 29,661 Study design: Case-crossover Statistical Analysis: Poisson Time-series regression models, APHEA protocol # of Hospitals: 63 Season: Authors indicate not considered because the Taiwanese climate is tropical with no apparent seasonal cycle Covariates: Stratified by warm (≥ 25°) and cold (< 25°) days, temperature, and humidity measurements included in the model Statistical package: SAS Lag: 0-2 days	SO_2 24-h avg (ppb) MiN: 1.25 25%: 6.83 50%: 9.76 75%: 13.00 Max: 26.80 Mean: 10.08 # of Stations: 6 Correlation among stations: NR PM_{10} CO SO_2 O_3 8 2-pollutant models used to adjust for copollutants Correlations NR	OR's for the association of one IQR (17.08 ppb) increase in SO_2 with daily counts of CVD hospital admissions are reported All CVD (ICD9: 410-429), one-pollutant model ≥ 25°: 0.999 (0.954, 1.047) < 25°: 1.187 (1.092, 1.291) All CVD (ICD9: 410-429), 2-pollutant models Adjusted for PM_{10}: ≥ 25°: 0.961 (0.917, 1.008) < 25°: 1.048 (0.960, 1.145) Adjusted for NO_2: ≥ 25°: 0.921 (0.875, 0.969) < 25°: 0.711 (0.641, 0.789) Adjusted for CO: ≥ 25°: 0.831 (0.785, 0.879) < 25°: 0.996 (0.910, 1.089) Adjusted for O_3: ≥ 25°: 1.034 (0.987, 1.084) < 25°: 1.194 (1.098, 1.299)
MIDDLE EAST			
Hosseinpoor et al. (2005) Tehran, Iran Period of Study: Mar 1996-Mar 2001, 5 yrs	Outcome(s) (ICD9): Angina pectoris 413. Primary discharge diagnosis from registry databases or records. Study design: Time-series Statistical methods: Poisson regression # Hospitals: 25 Covariates: Long-term trends, seasonality, temperature, humidity, holiday, post-holiday, day of wk. Lag(s): 0-3	SO_2 24-h avg ($\mu g/m^3$) Mean (SD): 73.74 (33.30) MiN: 0.30 25th: 48.23 MediaN: 74.05 75th: 98.64 Max: 499.26 NO_2 CO O_3 PM_{10} Correlations NR	Results reported for relative risk in hospital admissions per increment of 10 $\mu g/m^3$ SO_2. Angina 0.99995 (0.99397, 1.00507), lag 1 In a multipollutant model only CO (lag 1) was significantly associated with angina pectoris related hospital admissions.

Table F-5. Associations of short-term exposure to SO_2 with mortality.

STUDY	METHODS	POLLUTANTS	OUTCOME	FINDINGS
META ANALYSIS				
Stieb et al. (2002; reanalysis 2003) meta-analysis of estimates from various countries.	The lags and multiday averaging used varied Meta-analysis of time-series study results.	24-h avg ranged from 0.7 ppb (San Bernardino) to 75 ppb (Shenyang) "Representative" concentratioN: 9.4 ppb Copollutants: PM_{10}, O_3, NO_2, CO	All cause	Single-pollutant model (29 estimates): 1.0% (0.6, 1.3) Multipollutant model estimates (10 estimates): 0.9% (0.3, 1.4)
UNITED STATES				
Chock et al. (2000) Pittsburgh, PA 1989-1991	Lags: 0, 1, 2, 3 Poisson GLM. Time-series study. Numerous results	Mean NR Copollutants: PM_{10}, O_3, NO_2, CO; 2-, 5-, and 6-pollutant models	All cause; age < 74 yrs; age 75+ yrs	All cause: Age 0-74 yrs: Lag 1: 0.7% (−0.7, 2.2) Age 75+ yrs: Lag 1: −0.2% (−1.6, 1.3)
De Leon et al. (2003) New York City 1985-1994	Lags: 0 or 1 Poisson GAM with Stringent convergence Criteria; Poisson GLM. Time-series study.	24-h avg: 15 ppb Copollutants: PM_{10}, O_3, NO_2, CO; 2-pollutant models	Circulatory and cancer with and without contributing respiratory causes	Gaseous pollutants results were given only in figures. Circulatory: Age < 75 yrs: ~2% Age 75+ yrs: ~2%
Dockery et al. (1992) St. Louis, MO and Eastern Tennessee 1985-1986	Lag: 1 Poisson with GEE. Time-series study.	24-h avg: St. Louis: 9 ppb Eastern Tennessee: 5 ppb Copollutants: PM_{10}, $PM_{2.5}$, SO_4^{2-}, H+, O_3, NO_2	All cause	All cause: St. Louis, MO: 0.8% (−1.7, 3.2) Eastern Tennessee: 0.4% (−0.4, 1.1)
Gamble (1998) Dallas, TX 1990-1994	Lag: 0 Poisson GLM. Time-series study.	24-h avg: 3 ppb Copollutants: PM_{10}, O_3, NO_2, CO; 2-pollutant models	All cause; respiratory; cardiovascular	All cause: −0.8% (−3.8, 2.4) Respiratory: −1.0% (−5.8, 4.1) Cardiovascular: −0.5% (−11.4, 11.8)
Gwynn et al. (2000) Buffalo, NY	Lag: 0, 1, 2, 3 Poisson GAM with Default convergence criteria. Time-series study.	24-h avg: 12 ppb Copollutants: PM_{10}, CoH, SO_4^{2-}, O_3, NO_2, CO, H+	All cause; respiratory; circulatory	All cause: Lag 0: −0.1% (−1.8, 1.7) Circulatory: Lag 3: 1.3% (−2.9, 5.6) Respiratory: Lag 0: 6.4% (−2.5, 16.2)
Kelsall et al. (1997) Philadelphia, PA 1974-1988	Lag: 0 (AIC presented for 0 through 5) Poisson GAM.	24-h avg: 17 ppb Copollutants: TSP, CO, NO_2, O_3	All cause; respiratory; cardiovascular	All cause: Single-pollutant: 0.8% (0.3, 1.4) With all other pollutants: 0.8% (0.1, 1.6)
Kinney and Özkaynak (1991) Los Angeles County, CA 1970-1979	Lag: 1 OLS (ordinary least squares) on high-pass filtered variables. Time-series study.	24-h avg: 15 ppb Copollutants: KM (particle optical reflectance), Ox, NO_2, CO; multipollutant models	All cause; respiratory; circulatory	All cause: Exhaustive multipollutant model: 0.0% (−1.1, 1.2)
Klemm and Mason (2000); Klemm et al. (2004) Atlanta, GA Aug 1998-Jul 2000	Lag: 0-1 Poisson GLM using quarterly, monthly, or biweekly knots for temporal smoothing. Time-series study.	1-h max: 19 ppb Copollutants: $PM_{2.5}$, $PM_{10-2.5}$, EC, OC, SO_4^{2-}, NO_3−, O_3, NO_2, CO	All cause; respiratory; cardiovascular; cancer; other; age < 65 yrs; age 65+ yrs	All cause - Age 65+ yrs: Quarterly knots: 4.7% (−2.6, 12.5) Monthly knots: 3.4% (−4.1, 11.5) Bi-weekly knots: 1.0% (−6.7, 9.3)

STUDY	METHODS	POLLUTANTS	OUTCOME	FINDINGS
Klemm et al. (2004) Georgia (Fulton; DeKalb counties) 1998-2000	Lags: 2-day avg (avg of lag 0 and lag 1) Poisson with GLM. Time-series study.	1-h max (ppb): 19.4 (13.42) Copollutants: $PM_{2.5}$, Coarse mass, O_3, NO_2, CO, Acid, Ultrafine surface area, Ultrafine count, EC, Organic carbon, SO_4,Oxygenated hydrocarbons, Nonmethane hydrocarbons, NO_3	All-cause	≥ 65 yrs old Quarterly knots (SE) ∃ = 0.00115 (0.00092) t = 1.24 Monthly knots (SE) ∃ = 0.00084 (0.00096) t = 0.87 Biweekly knots (SE) ∃ = 0.00024 (0.00101) t = 0.24
Lipfert et al. (2000a) Seven counties in Philadelphia, PA area 1991-1995	Lag: 0-1 Linear with 19-day weighted avg Shumway filters. Time-series study. Numerous results.	24-h avg: 8 ppb 1-h max: 18 ppb Copollutants: PM_{10}, $PM_{2.5}$, PM_{10}-2.5, SO42−, other PM indices, O_3, NO_2, CO; 2-pollutant models	All cause; respiratory; cardiovascular; all ages; age 65+ yrs; age < 65 yrs; various subregional boundaries	All-cause: Philadelphia: 0.7% (p > 0.05)
Lippmann et al. (2000); reanalysis Ito, (2003) Detroit, MI 1985-1990 1992-1994	Lags: 0, 1, 2, 3, 0-1, 0-2, 0-3 Poisson GAM, reanalyzed with stringent convergence criteria; Poisson GLM. Numerical SO_2 risk estimates were not presented in the re-analysis. Time-series study.	24-h avg: 1985-1990: 10 ppb 1992-1994: 7 ppb Copollutants: PM_{10}, $PM_{2.5}$, PM_{10}-2.5, SO42−, H+, O_3, NO_2, CO; 2-pollutant models	All cause; respiratory; circulatory; cause-specific	Poisson GAM: All cause: 1985-1990: Lag 1: 0.5% (−1.5, 2.4) 1992-1994: Lag 1: 1.1% (−1.4, 3.6)
Mar et al.(2000; reanalysis in 2003) Phoenix, AZ. 1995-1997	Lags: 0 for all cause; 0, 1, 2, 3, 4 for cardiovascular Poisson GAM with default convergence criteria (only cardiovascular deaths were reanalyzed in 2003). Time-series study.	24-h avg: 3.1 ppb Copollutants: $PM_{2.5}$, PM_{10}, PM_{10}-2.5, CO, NO_2, O_3, and selected trace elements, ions, EC, OC, TOC, and factor analysis components	All cause, cardiovascular	Poisson GAM: All cause: Lag 0: 11.2% (−1.5, 25.6) Poisson GLM: Cardiovascular: Lag 1: 7.4% (−13.1, 32.6)
Moolgavkar et al. (1995) Philadelphia, PA 1973-1988.	Lag: 1 Poisson GLM. Time-series study.	24-h avg: Spring: 17 ppb Summer: 16 ppb Fall: 18 ppb Winter: 25 ppb Copollutants: TSP, O_3; 2-pollutant models	All cause	All yr: 1.3% (0.8, 1.8) Spring: 1.7% (0.6, 2.9) Summer: 0.9% (−0.7, 2.5) Fall: 1.3% (0.0, 2.6) Winter: 2.0% (0.9, 3.0)
Moolgavkar (2000; reanalysis 2003a) Cook County, IL; Los Angeles County, CA; and Maricopa County, AZ 1987-1995	0, 1, 2, 3, 4, 5 Poisson GAM with default convergence criteria in the original Moolgavkar (2000); GAM with stringent convergence criteria and GLM with natural splines in the 2003 re-analysis. The 2000 analysis presented total death risk estimates only in figures.	24-h avg median: Cook County: 6 ppb Los Angeles: 2 ppb Maricopa County: 2 ppb $PM_{2.5}$, PM_{10}, O_3, NO_2, CO; 2- and 3-pollutant models	Cardiovascular; cerebrovascular; COPD	GLM (re-analysis): Cook County: All-cause: Lag 1: 2.6% (1.4, 3.8) Cardiovascular: Lag 1: 2.9% (1.0, 4.8) Los Angeles: Cardiovascular: Lag 1: 5.9% (3.0, 9.0)
Moolgavkar (2003b) Cook County, IL and Los Angeles County, CA 1987-1995	Lags: 0, 1, 2, 3, 4, 5 Poisson GAM with default convergence criteria. Time-series study.	24-h avg median: Cook County: 6 ppb Los Angeles: 2 ppb Copollutants: $PM_{2.5}$, PM_{10}, O_3, NO_2, CO; 2-pollutant models	All cause; cardiovascular	All cause: Cook County: Single-pollutant: Lag 1: 2.6% (1.5, 3.7) With PM_{10}: Lag 1: 1.9% (0.6, 3.2) Los Angeles: Single-pollutant: Lag 1: 6.9% (5.4, 8.4) With $PM_{2.5}$: Lag 1: 7.6% (3.4, 12.0)

STUDY	METHODS	POLLUTANTS	OUTCOME	FINDINGS
Samet et al. (2000a; 2000b); reanalysis Dominici et al. (2003) 90 U.S. cities (58 U.S.cities with SO_2 data) 1987-1994	Lags: 0, 1, 2 Poisson GAM, reanalyzed with stringent convergence criteria; Poisson GLM. Time-series study.	24-h avg ranged from 0.4 ppb (Riverside) to 14.2 ppb (Pittsburgh) Copollutants: PM_{10}, O_3, NO_2, CO; multipollutant models	All cause; cardiopulmonary	Posterior means: All cause: Single-pollutant: Lag 1: 0.6% (0.3, 1.0) With PM_{10} and NO_2: Lag 1: 0.4% (−0.6, 1.4)
Schwartz (1991) Detroit, MI 1973-1982	Lags: 0, 1, 0-1 Poisson GEE. Time-series study.	24-h avg: 12 ppb Copollutants: TSP (predicted from extinction coefficient); 2-pollutant models	All cause	Poisson regression coefficient Single-pollutant: Lag 1: 0.863 (SE = 0.323) With TSP: Lag 1: 0.230 (SE = 0.489) (Though SO_2 levels were reported in ppb, these coefficients must have been for SO_2 in ppm.)
Schwartz (2000) Philadelphia, PA 1974-1988	Lag: 0 Poisson GAM model in 15 winter and 15 summer periods. The second stage regressed the TSP and SO_2 risk estimates on SO_2/TSP relationships.	24-h avg summer mean declined from 20 ppb in 1974 to 9 ppb in 1988; winter mean declined from 35 ppb in 1974 to 17 in 1988 Copollutants: TSP, extinction coefficient	All cause	Single-pollutant: 2.3% (1.6, 3.0) With TSP: 0.4% (−2.2, 3.1)
Schwartz (2004) 14 U.S. cities that had daily PM_{10} data	Lag: 1 Case-crossover design, estimating PM_{10} risks by matching by the levels of gaseous pollutants.	24-h avg median ranged from 2.2 ppb (Spokane, WA) to 39.4 ppb (Pittsburgh, PA) Copollutants: PM_{10} risk estimates computed, matched by the levels of SO_2, CO, NO_2, and O_3	All cause	SO_2 risk estimates not computed. PM_{10} risk estimates showed the largest risk estimate when matched for SO_2.
CANADA				
Burnett et al. (2004) 12 Canadian cities 1981-1999	Lag: 1 Poisson GLM. Time-series study.	24-h avg ranged from 1 ppb (Winnipeg) to 10 ppb (Halifax) Copollutants: $PM_{2.5}$, PM_{10}-2.5, O_3, NO_2, CO	All cause	Single-pollutant: 0.7% (0.3, 1.2) With NO_2: 0.4% (0.0, 0.8)
Burnett et al. (1998a) 11 Canadian cities 1980-1991	Lags: 0, 1, 2, 0-1, 0-2 examined but the best lag/averaging for each city chosen Poisson GAM with default convergence criteria. Time-series study.	24-h avg ranged from 1 ppb (Winnipeg) to 11 ppb (Hamilton) Copollutants: O_3, NO_2, CO	All cause	Single-pollutant: 3.4% (2.0, 4.7) With all gaseous pollutants: 2.6% (1.3, 3.9)
Burnett et al. (1998) Toronto 1980-1994	Lags: 0, 1, 0-1 Poisson GAM with default convergence criteria. Time-series study.	24-h avg: 5 ppb Copollutants: O_3, NO_2, CO, TSP, COH, estimated PM_{10}, estimated $PM_{2.5}$	All cause	Single-pollutant: Lag 0: 1.0% (0.3, 1.8) With CO: Lag 0: 0.6% (−0.4, 1.5)
Goldberg et al. (2003) Montreal, Quebec 1984-1993	Lags: 0, 1, 0-2 Poisson GLM with natural splines. Time-series study.	24-h avg: 6 ppb Copollutants: $PM_{2.5}$, coefficient of haze, SO42−, O_3, NO_2, CO	Congestive heart failure (CHF) as underlying cause of death versus those classified as having CHF 1 yr prior to death	CHF as underlying cause of death: Lag 1: −0.1% (−8.9, 9.6) Having CHF 1 yr prior to death: Lag 1: 5.4% (1.3, 9.5)
Vedal et al. (2003) Vancouver, British Columbia 1994-1996	Lags: 0, 1, 2 Poisson GAM with stringent convergence criteria. Time-series study. By season.	24-h avg: 3 ppb Copollutants: PM_{10}, O_3, NO_2, CO	All cause; respiratory; cardiovascular	Results presented in figures only. All cause: Summer: Lag 0: ~3% Winter: Lag 1: ~1%

STUDY	METHODS	POLLUTANTS	OUTCOME	FINDINGS
Villeneuve et al. (2003) Vancouver, British Columbia 1986-1999	Lags: 0, 1, 0-2 Poisson GLM with natural splines. Time-series study.	24-h avg: 5 ppb Copollutants: $PM_{2.5}$, PM_{10}, PM_{10}-2.5, TSP, coefficient of haze, SO42−, O_3, NO_2, CO	All cause; respiratory; cardiovascular; cancer; socioeconomic status	All yr: All cause: Lag 1: 1.7% (−1.1, 4.5) Cardiovascular: Lag 1: 1.1% (−3.1, 5.4) Respiratory: Lag 1: 8.3% (0.6, 16.6)
EUROPE				
Anderson et al. (1996) London, England 1987-1992	Lag: 1 Poisson GLM. Time-series study.	24-h avg: 11 ppb Copollutants: BS, O_3, NO_2; 2-pollutant models	All cause; respiratory; cardiovascular	All cause: 1.0% (0.0, 2.0) Respiratory: 1.7% (−1.3, 4.9) Cardiovascular: 0.2% (−1.4, 1.8)
Anderson et al. (2001) West Midlands region, England 1994-1996	Lag: 0-1 Poisson GAM with default convergence criteria. Time-series study.	24-h avg: 7 ppb Copollutants: PM_{10}, $PM_{2.5}$, PM_{10}-2.5, BS, SO42−, O_3, NO_2, CO	All cause; respiratory; cardiovascular	All cause: −0.2% (−2.5, 2.1) Respiratory: −2.2% (−7.4, 3.2) Cardiovascular: −0.2% (−3.5, 3.1)
Ballester et al. (2002) 13 Spanish cities 1990-1996	Lags: 0-1 for 24-h avg SO_2; 0 for 1-h max SO_2 Poisson GAM with default convergence criteria. Time-series study.	24-h avg SO_2 ranged from 2.8 ppb (Sevilla) to 15.6 ppb (Oviedo) Copollutants: TSP, BS, PM_{10}	All cause, cardiovascular, respiratory	All cause: Lag 0-1: 1.4% (0.2, 2.7) Cardiovascular: Lag 0-1: 1.4% (−0.4, 3.3) Respiratory: Lag 0-1: 3.5% (1.0, 6.0)
Biggeri et al. (2005) 8 Italian cities Period variable between 1990-1999	Lag: 0-1 Poisson GLM. Time-series study.	24-h avg ranged from 2 ppb (Verona) to 14 ppb (Milan) Copollutants: O_3, NO_2, CO, PM_{10}	All cause; respiratory; cardiovascular	All cause: 4.1% (1.1, 7.3) Respiratory: 7.4% (−3.6, 19.6) Cardiovascular: 4.9% (0.4, 9.7)
Bremner et al. (1999) London, England 1992-1994	Lags: Selected best from 0, 1, 2, 3, (all cause); 0, 1, 2, 3, 0-1, 0-2, 0-3 (respiratory, cardiovascular) Poisson GLM. Time-series study.	24-h avg: 7 ppb Copollutants: BS, PM_{10}, O_3, NO_2, CO; 2-pollutant models	All cause; respiratory; cardiovascular; all cancer; all others; all ages; age specific (0-64, 65+, 65-74, 75+ yrs)	All cause: Lag 1: 1.6% (−0.5, 3.7) Respiratory: Lag 2: 4.8% (−0.2, 10.0) Cardiovascular Lag 1: 1.3% (−1.7, 4.3)
Clancy et al. (2002) Dublin, Ireland 1984-1996	NA Comparing standardized mortality rates for 72 mos before and after the ban on coal sales in Sep 1990.	24-h avg: 1984-1990: 11.7 ppb 1990-1996: 7.7 ppb Copollutants: BS	All cause, cardiovascular, and respiratory	BS mean declined by a larger percentage (70%) than SO_2 (34%) between the two periods. All cause death rates reduced by 5.7% (4, 7); respiratory deaths by 15.5% (12, 19); cardiovascular deaths by 10.3% (8, 13).
Dab et al. (1996) Paris, France 1987-1992	Lag: 1 Poisson autoregressive. Time-series study.	24-h avg: 10 ppb 1-h max: 21 ppb Copollutants: BS, PM_{13}, O_3, NO_2, CO	Respiratory	Lag 1: 2.3% (−0.9, 5.5)
Díaz et al. (1999) Madrid, Spain 1990-1992	Lag: 1 Autoregressive OLS regression. Time-series study.	24-h avg: Levels NR. Copollutants: TSP, O_3, NO_2, CO	All cause; respiratory; cardiovascular	Only significant regression coefficients were shown, but description of the table was not clear enough to derive risk estimates.
Fischer et al. (2003) The Netherlands 1986-1994	Lags: 0-6 Poisson GAM with default convergence criteria. Time-series study.	24-h avg mediaN: 3.5 ppb Copollutants: PM_{10}, BS, O_3, NO_2, CO	All-cause, cardiovascular, COPD, and pneumonia in age groups < 45, 45-64, 65-74, 75+	Cardiovascular: Age < 45 yrs: 4.3% (−4.6, 13.9) Age 45-64 yrs: −0.5% (−3.6, 2.7) Age 65-74 yrs: 1.6% (−0.8, 4.2); Age 75+ yrs: 2.8% (1.3, 4.3)

STUDY	METHODS	POLLUTANTS	OUTCOME	FINDINGS
Garcia-Aymerich et al. (2000) Barcelona, Spain 1985-1989	Selected best averaged lag Poisson GLM. Time-series study.	Levels NR. Copollutants: BS, O_3, NO_2	All cause; respiratory; cardiovascular; general population; patients with COPD	All cause: General population: Lag 0-3: 4.4% (2.3, 6.5) COPD patients: Lag 0-2: 2.6% (−5.0, 10.7) Respiratory: General populatioN: Lag 0-1: 3.5% (−0.6, 7.8) COPD patients: Lag 0-2: 2.3% (−8.9, 15.0) Cardiovascular: General populatioN: Lag 0-3: 5.1% (2.3, 8.0) COPD patients: Lag 0-2: 2.0% (−11.5, 17.5)
Hoek et al. (2002) Rotterdam, the Netherlands 1983-1991	Lag: 1 Poisson GAM with default convergence criteria. Time-series study.	24-h avg median: 7.7 ppb Copollutants: TSP, BS, Fe, O_3, CO	All cause	Single-pollutant:1.5% (0.0, 3.0) With TSP and O_3: 0.5% (−1.2, 2.3)
Hoek et al. (2000; reanalysis Hoek, 2003) The Netherlands: Entire country, four urban areas 1986-1994	Lag: 1, 0-6 Poisson GAM, reanalyzed with stringent convergence criteria; Poisson GLM. Time-series study.	24-h avg mediaN: 3.5 ppb in the Netherlands; 5.6 ppb in the four major cities Copollutants: PM_{10}, BS, SO_4^{2-}, NO_3-, O_3, NO_2, CO; 2-pollutant models	All cause; COPD; pneumonia; cardiovascular	Poisson GLM: All cause: Lag 1: 1.3% (0.7, 1.9) Lag 0-6: 1.8% (0.9, 2.7) With BS: 1.1% (−0.3, 2.4) Cardiovascular: Lag 0-6: 2.7% (1.3, 4.1) COPD: Lag 0-6: 3.6% (−0.3, 7.7) Pneumonia: Lag 0-6: 6.6% (1.2, 12.2)
Hoek et al. (2001; reanalysis Hoek, 2003) The Netherlands 1986-1994	Lag: 0-6 Poisson GAM, reanalyzed with stringent convergence criteria; Poisson GLM. Time-series study.	24-h avg mediaN: 3.5 ppb in the Netherlands; 5.6 ppb in the four major cities Copollutants: PM_{10}, O_3, NO_2, CO	Total cardiovascular; myocardial infarction; arrhythmia; heart failure; cerebrovascular; thrombosis-related	Poisson GLM: Total cardiovascular: 2.7% (1.3, 4.1) Myocardial infarctioN: 0.8% (−1.2, 2.8) Arrhythmia: 2.3% (−3.9, 8.8) Heart failure: 7.1% (2.6, 11.7) Cerebrovascular: 4.4% (1.4, 7.5) Thrombosis-related: 9.6% (3.1, 16.6)
Katsouyanni et al. (1997) 12 European cities Period of Studys vary by city, ranging from 1977 to 1992	“Best” lag variable across cities from 0 to 3 Poisson autoregressive. Time-series study.	24-h avg median of the median across the cities was 14 ppb, ranging from 5 ppb (Bratislava) to 26 ppb (Cracow) Copollutants: BS, PM_{10}	All cause	All cities: 1.1% (0.9, 1.4) Western cities: 2.0% (1.2, 2.8) Central eastern cities: 0.5% (−0.4, 1.4)

STUDY	METHODS	POLLUTANTS	OUTCOME	FINDINGS
Keatinge and Donaldson (2006) London 1991-2002	Lags: Mean of 0, −1, −2 Graphic analysis and GAM. Time-series study.	24-h avg: Levels NR Copollutants: O_3, PM_{10}	All-cause	Relative Risk for a 10^6 Increase in Mortality (per 10 ppb SO_2) SO_2 + Temp: 3.1 (0.6, 5.5) SO_2 + Temp + Acclim.: 2.2 (−0.1, 4.6) SO_2 + Temp + Acclim. + Acclim. □ Temp: 2.5 (0.2, 4.8) SO_2 + Temp + Acclim. + Acclim. □ Temp + SuN: 2.3 (−0.03, 4.5) SO_2 + Temp + Acclim. + Acclim. □ Temp + Sun + Wind: 1.6 (−0.7, 3.8) SO_2 + Temp + Acclim. + Acclim. □ Temp + Sun + Wind + Abs. Humidity: 1.7 (−0.6, 3.9) SO_2+ Temp + Acclim. + Acclim. □ Temp + Sun + Wind+ Abs. Humidity + RaiN: 1.8 (−0.4, 4.1) SO_2 + Temp. + Abs. Humidity: 2.5 (0.03, 4.9)
Kotesovec et al. (2000) Northern Bohemia, Czech Republic 1982-1994	Lags: 0, 1, 2, 3, 4, 5, 6, 0-6 Poisson GLM, time-series study	24-h avg: 34.9 ppb Copollutants: TSP	All cause, cardiovascular (only age = < 65 presented), cancer	All cause: Lag 1: 0.1% (−0.1, 0.4)
Le Tertre et al. (2002) Bordeaux , Le Havre, Lille, Lyon, Marseille, Paris, Rouen, Strasbourg, France Period of Study varies by city, ranging from 1990-1995	Lags: 0-1 Poisson GAM with default convergence criteria. Time-series study.	24-h avg ranged from 3 ppb (Bordeaux) to 9 ppb (Rouen) Copollutants: BS, O_3, NO_2	All cause; respiratory; cardiovascular	8-city pooled estimates: All cause: 2.0% (1.2, 2.9) Respiratory: 3.2% (0.1, 6.3) Cardiovascular: 3.0% (1.5, 4.5)
Michelozzi et al. (1998) Rome, Italy 1992-1995	Lags: 0, 1, 2, 3, 4 Poisson GAM with default convergence criteria. Time-series study.	24-h avg: 5.7 ppb Copollutants: PM_{13}, NO_2, O_3, CO	All-cause	Lag 1: −2.0% (−4.4, 0.5); (negative estimates at all lags examined)
Peters et al. (2000) NE Bavaria, Germany 1982-1994 Coal basin in Czech Republic 1993-1994	Lags: 0, 1, 2, 3 Poisson GLM. Time-series study.	24-h avg: Czech Republic: 35 ppb Bavaria, Germany: 14 ppb Copollutants: TSP, PM_{10}, O_3, NO_2, CO	All cause; respiratory; cardiovascular; cancer	Czech Republic: All cause: Lag 1: 0.8% (−0.2, 1.8) Bavaria, Germany: All cause: Lag 1: 0.3% (−0.3, 0.9)
Pönkä et al. (1998) Helsinki, Finland 1987-1993	Lags: 0, 1, 2, 3, 4, 5, 6, 7 Poisson GLM. Time-series study.	24-h avg median: 3.5 ppb Copollutants: TSP, PM_{10}, O_3, NO_2	All cause; cardiovascular; age < 65 yrs, age 65+ yrs	No risk estimate presented for SO_2. PM_{10} and O_3 were reported to have stronger associations.
Prescott et al. (1998) Edinburgh, Scotland 1992-1995	Lag: 0 Poisson GLM. Time-series study.	24-h avg: 1981-1995: 15 ppb 1992-1995: 8 ppb Copollutants: BS, PM_{10}, O_3, NO_2, CO; 2-pollutant models	All cause; respiratory; cardiovascular; all ages; age < 65 yrs; age 65+ yrs	Results presented as figures only. Essentially no associations in all categories. Very wide confidence intervals.
Rahlenbeck and Kahl (1996) East Berlin, Germany 1981-1989	Lags: 0, 1, 2, 3, 4, 5 OLS, with log of SO_2, Time-series study.	24-h avg: 61.9 ppb “SP” (beta absorption)	All cause	Single-pollutant: Lag 1: 4.4% (0, 8.7); With SP: Lag 1: 2.9% (−2.7, 8.5)

STUDY	METHODS	POLLUTANTS	OUTCOME	FINDINGS
Roemer and van Wijinen (2001) Amsterdam, the Netherlands 1987-1998	Lags: 1, 2, 0-6 Poisson GAM with default convergence criteria (only one smoother). Time-series study.	24-h avg: Background sites: 3.1 ppb Traffic sites: 4.2 ppb Copollutants: BS, PM_{10}, O_3, NO_2, CO	All cause	Total population using background sites: Lag 1: 2.6% (−0.6, 5.8) Traffic population using background sites: Lag 1: 0.6% (−6.9, 8.6) Total population using traffic sites: Lag 1: 2.4% (−0.3, 5.1)
Saez et al. (1999) Barcelona, Spain 1986-1989	Lags: 0-1 Poisson with GEE. Time-series study.	Levels NR. Copollutants: BS, O_3, NO_2,	Asthma mortality; age 2-45 yrs	RR = 1.9 (0.7, 4.4)
Saez et al. (2002) Seven Spanish cities Variable periods of study between 1991 and 1996	Lags: 0-3 Poisson GAM with default convergence criteria. Time-series study.	Values for SO_2 NR. Copollutants: O_3, PM, NO_2, CO	All cause; respiratory; cardiovascular	Risk estimates for SO_2 was NR. Including SO_2 in regression model did not appear to reduce NO_2 risk estimates.
Spix and Wichman (1996) Koln, Germany 1977-1985	Lags: 0, 1, 0-3 Poisson GLM. Time-series study.	24-h avg: 15 ppb 1-h max: 32 ppb Copollutants: TSP, PM_7, NO_2	All-cause	Lag 1: 0.8% (0.2, 1.4)
Sunyer et al. (2002) Barcelona, Spain 1986-1995	Lags: 0-2 Conditional logistic (case-crossover)	24-h avg median: 6.6 ppb Copollutants: PM_{10}, BS, NO_2, O_3, CO, pollen	All cause, respiratory, and cardiovascular mortality in a cohort of patients with severe asthma	Odds ratio: Patients with 1 asthma admission: All cause: 14.8% (−19.8, 64.4) Patients with more than 1 asthma adm: All cause: 50.4% (−48.6, 340.4) Patients with more than 1 asthma or COPDadm: All cause: 20.2% (−17.5, 75.0) NO_2 and O_3 were more strongly associated with outcomes than SO_2.
Sunyer et al. (1996) Barcelona, Spain 1985-1991	Selected best single-day lag Autoregressive Poisson. Time-series study.	24-h avg median: Summer: 13 ppb Winter: 16 ppb Copollutants: BS, NO_2, O_3	All cause; respiratory; cardiovascular; all ages; age 70+ yrs	All yr, all ages: All cause: Lag 1: 3.5% (1.9, 5.1) Respiratory: Lag 0: 3.5% (−0.2, 5.0) Cardiovascular: Lag 1: 2.2% (0.5, 3.9)
Verhoeff et al. (1996) Amsterdam, the Netherlands 1986-1992	Lags: 0, 1, 2 Poisson GLM. Time-series study.	24-h avg: 4.5 ppb Copollutants: BS, PM_{10}, O_3, CO; multipollutant models	All cause; all ages; age 65+ yrs	Single-pollutant: Lag 1: 1.4% (−1.4, 4.2) With BS: −3.7% (−8.1, 0.9)
Zeghnoun et al. (2001) Rouen and Le Havre, France 1990-1995	Lags: 0, 1, 2, 3, 0-3 Poisson GAM with default convergence criteria. Time-series study.	24-h avg: RoueN: 10 ppb Le Havre: 12 ppb Copollutants: NO_2, BS, $PM_{13,}$ O_3	All cause; respiratory; cardiovascular	All cause: RoueN: Lag 1: 2.3% (−1.1, 5.9) Le Havre: Lag 1: 1.1% (−0.3, 2.5)
Zmirou et al. (1996) Lyon, France 1985-1990	Lags: Selected best from 0, 1, 2, 3 Poisson GLM. Time-series study.	24-h avg: 16 ppb Copollutants: PM_{13}, NO_2, O_3	All cause; respiratory; cardiovascular; digestive	All cause: Lag 0: 3.4% (1.4, 5.4) Respiratory: Lag 3: 2.8% (0.9, 4.8) Cardiovascular:Lag 0-3: 4.5% (2.0, 7.0)

STUDY	METHODS	POLLUTANTS	OUTCOME	FINDINGS
Zmirou et al. (1998) 10 European cities Period of Studys vary by city, ranging from 1985-1992	Lags: 0, 1, 2, 3, 0-1, 0-2, 0-3 (best lag selected for each city) Poisson GLM. Time-series study.	24-h avg: Cold Season: Ranged from 12 ppb (London) to 87 ppb (Milan) ppb Warm Season: Ranged from 5 ppb (Bratislava) to 21 ppb (Cracow) in warm season Copollutants: BS, TSP, NO_2, O_3	Respiratory; cardiovascular	Western cities: Respiratory: 2.8% (1.7, 4.0) Cardiovascular: 2.3% (0.9, 3.7) Central eastern cities: Respiratory: 0.6% (−1.1, 2.3) Cardiovascular: 0.6% (0.0, 1.1)
LATIN AMERICA				
Borja-Aburto et al. (1998) SW Mexico City 1993-1995	Lags: 0, 1, 2, 3, 4, 5, and multiday avg. Poisson GAM with default convergence criteria (only one smoother). Time-series study.	24-h avg: 5.6 ppb Copollutants: $PM_{2.5}$, O_3, NO_2; 2-pollutant models	All cause; respiratory; cardiovascular; other; all ages; age >65 yrs	SO_2 risk estimates NR. $PM_{2.5}$ and O_3 were associated with mortality.
Borja-Aburto et al. (1997) Mexico City 1990-1992	Lags: 0, 1, 2 Poisson iteratively weighted and filtered least-squares method. Time-series study.	24-h avg median: 5.3 ppb TSP, O_3 CO; 2-pollutant models	All cause; respiratory; cardiovascular; all ages; age < 5 yrs; age >65 yrs	All-cause: Lag 0: 0.2% (−1.1, 1.5) Cardiovascular: Lag 0: 0.7% (−1.6, 3.0) Respiratory: Lag 0: −1.0% (−5.0, 3.2)
Cakmak et al. (2007) 7 Chilean urban centers 1997-2003	Lags: 0, 1, 2, 3, 4, 5, 0-5 Poisson GLM with random effects between cities. Time-series study.	24-h avg ranged from 9.12 ppb (Las Condes) to 64.06 ppb (Independencia) Population-weighted avg concentratioN: 14.08 ppb Copollutants: PM_{10}, O_3, CO	All cause; respiratory; cardiovascular; all ages; age < 65 yrs; age 65-74 yrs; age 75-84 yrs; age 85+ yrs	All cause: All ages: Single-pollutant: Lag 1: 4.0% (2.4, 5.6) Lag 0-5: 6.5% (4.5, 8.5) Multipollutant: Lag 1: 3.2% (1.3, 5.1) < 65 yrs: Lag 0-5: 3.0% (0.6, 5.5) 65-74 yrs: Lag 0-5: 5.1% (1.2, 9.1 75-84 yrs: Lag 0-5: 7.8% (4.1, 11.6) 85+ yrs: 7.8% (4.2, 11.5) Warm Season: Lag 0-5: 7.2% (4.1, 10.3) Cool Season: Lag 0-5: 3.0% (-0.4, 6.5)
Cifuentes et al. (2000) Santiago, Chile 1988-1966	Lags: 1-2 Poisson GAM with default convergence criteria; Poisson GLM. Time-series study.	24-h avg: 18.1 ppb Copollutants: $PM_{2.5}$, PM_{10}-2.5, CO, NO_2, O_3	All cause	Poisson GLM: Single-pollutant: Lag 1-2: 0.2% (−0.9, 1.3) With other pollutants: Lag 1-2: −0.6% (−1.7, 0.5)
Conceição et al. (2001) São Paulo, Brazil 1994-1997	Lag: 2 Poisson GAM with default convergence criteria. Time-series study.	24-h avg: 7.4 ppb Copollutants: PM_{10}, CO, O_3	Child mortality (age under 5 yrs)	Single-pollutant: Lag 2: 17.0% (7.0, 28.0); With all other pollutants: Lag 2: 13.7% (−1.1, 30.8)
Loomis et al. (1999) Mexico City 1993-1995	Lags: 0, 1, 2, 3, 4, 5, 3-5 Poisson GAM with default convergence criteria. Time-series study.	24-h avg: 5.6 ppb Copollutants: $PM_{2.5}$, O_3	Infant mortality	SO_2 risk estimates NR. $PM_{2.5}$ and O_3 were associated with mortality.
Ostro et al. (1996) Santiago, Chile 1989-1991	Lag: 0 OLS, Poisson. Time-series study.	1-h max: 60 ppb Copollutants: PM_{10}, O_3, NO_2; 2-pollutant models	All cause	Lag 0: 0.7% (−0.3, 1.7)

STUDY	METHODS	POLLUTANTS	OUTCOME	FINDINGS
Pereira et al. (1998) São Paulo, Brazil 1991-1992	Lag: 0 Poisson GLM. Time-series study.	24-h avg: 6.6 ppb Copollutants: PM_{10}, O_3, NO_2, CO	Intrauterine mortality	Single-pollutant model: 11.5% (−0.3, 24.7) With other pollutants: 8.6% (−8.7, 29.3)
Saldiva et al. (1994) São Paulo, Brazil 1990-1991	Lags: 0-2 OLS of raw or transformed data. Time-series study.	24-h avg: 6.0 ppb Copollutants: PM_{10}, O_3, NO_2, CO; multipollutant models	Respiratory; age < 5 yrs	−1.0% (−47.1, 45.1)
Saldiva et al. (1995) São Paulo, Brazil 1990-1991	Lag: 0-1 OLS; Poisson with GEE. Time-series study.	24-h avg: 6.5 ppb Copollutants: PM_{10}, O_3, NO_2, CO; 2-pollutant models	All cause; age 65+ yrs	Single-pollutant: 8.5% (1.3, 15.6) With other pollutants: −3.1% (−13.0, 6.9)
ASIA				
Ha et al. (2003) Seoul, Korea 1995-1999	Lag: 0 Poisson GAM with default convergence criteria. Time-series study.	24-h avg: 11.1 ppb Copollutants: PM_{10}, O_3, NO_2, CO	All cause; respiratory; postneonatal (1 mo to 1 yr); age 2-64 yrs; age 65+	All cause: Postneonates: 11.3% (4.0, 19.1) Age 65+ yrs: 3.2% (3.1, 3.3)
Hong et al. (2002) Seoul, Korea 1995-1998	Lag: 2 GAM with default convergence criteria. Time-series study.	24-h avg (ppb): 12.1 (7.4) Copollutants: $PM_{10,}$ NO_2 CO, O_3	Stroke	% increase (per 5.7 ppb SO_2) 2.9% (0.8, 5.0) lag 2 Stratified by PM_{10} (MediaN: 47.4 μg/m^3) <Med: 1.3% ≥ Med: 3.8%
Hong et al. (2002) Seoul, Korea 1995-1998	Lag: 2 Poisson GAM with default convergence criteria. Time-series study.	24-h avg: 12.1 ppb Copollutants: PM_{10}, O_3, NO_2, CO	Acute stroke mortality	5.2% (1.4, 9.0)
Kwon et al. (2001) Seoul, Korea 1994-1998	Lag: 0 Poisson GAM with default convergence criteria; case-crossover analysis using conditional logistic regression.	24-h avg: 13.4 ppb Copollutants: PM_{10}, O_3, NO_2, CO	Mortality in a cohort of patients with congestive heart failure	Odds ratio in general populatioN: 1.0% (−0.1, 2.1) Congestive heart failure cohort: 6.9% (−3.4, 18.3)
Lee et al. (2000) Seoul, Korea 2000-2004	Lag: 1 GAM with stringent convergence criteria. Time-series study.	24-h avg (ppb): 5.20 (2.17) Copollutants: PM_{10}, CO, NO_2, O_3	Non-accidental	% Increase (per 3.06 ppb SO_2) 2.7 (1.8, 3.5) lag 1
Lee et al. (1999) Seoul and Ulsan, Korea 1991-1995	Lags: 0-2 Poisson with GEE. Time-series study.	1-h max: Seoul: 26 ppb UlsaN: 31 ppb Copollutants: TSP, O_3	All cause	Seoul: 1.5% (1.1, 1.9) UlsaN: 1.0% (−0.2, 2.2)
Lee and Schwartz (1999) Seoul, Korea 1991-1995	Lags: 0-2 Conditional logistic regression. Case-crossover with bidirectional control sampling.	1-h max: 26 ppb Copollutants: TSP, O_3	All cause	Two controls, ± 1 wk: 0.3% (−0.5, 1.0) Four controls, ± 2 wks: 1.0% (0.3, 1.6)
Lee et al. (2000) 7 Korean cities 1991-1997	Lags: 0-1 Poisson GAM with default convergence criteria. Time-series study.	24-h avg SO_2 ranged from 12.1 ppb (Kwangju) to 31.4 ppb (Taegu) Copollutants: TSP, NO_2, O_3, CO	All cause	Single-pollutant : Lag 0-1 : 0.6% (0.3, 0.8) Multipollutant : Lag 0-1 : 0.6% (0.2, 0.9)

STUDY	METHODS	POLLUTANTS	OUTCOME	FINDINGS
Qian et al. (2007) Wuhan, China 2000-2004	Lag: 0 Poisson GAM with stringent convergence criteria. Time-series study.	24-h avg ($\mu g/m^3$): 44.1 (25.3) Copollutants: PM_{10} NO_2 O_3	Non-accidental, cardiovascular, stroke, cardiac, respiratory, cardiopulmonary	Mean % change (per 10 $\mu g/m^3$ SO_2) Non-accidental All Ages: 0.01 (−0.46, 0.47) < 65: −0.55 (−1.33, 0.23) ≥ 65: 0.22 (−0.32, 0.76) Cardiovascular All Ages: 0.20 (−0.45, 0.86) < 65: −0.63 (−1.96, 0.72) ≥ 65: 0.41 (−0.31, 1.14) Stroke All Ages: −0.27 (−1.04, 0.51) < 65: −1.35 (−3.01, 0.33) ≥ 65: 0.01 (−0.87, 0.88) Cardiac All Ages: 0.88 (−0.22, 1.99) < 65: 0.29 (−2.11, 2.75) ≥ 65: 1.01 (−0.18, 2.21) Respiratory All Ages: 1.13 (−0.28, 2.56) < 65: −0.59 (−4.24, 3.19) ≥ 65: 1.36 (−0.05, 2.80) Cardiopulmonary All Ages: 0.29 (−0.33, 0.92) < 65: −0.80 (−2.07, 0.49) ≥ 65: 0.53 (−0.15, 1.20)
HEI International Scientific Oversight Committee (2004) East Asian cities.	The lags and multi-day averaging used in varied Meta-analysis of time-series study results	The levels of SO_2 in these Asian cities were generally higher than those in the U.S. or Canadian cities, with more than half of these studies reporting the mean SO_2 levels higher than 10 ppb. Copollutants considered varied across studies.	All-cause	The estimates were found to be heterogeneous across 11 studies. Random-Effects Estimate: 1.49% (95% CI: 0.86, 2.13); Fixed-Effects Estimate: 1.01% (95% CI: 0.73, 1.28).
Tsai et al. (2003) Kaohsiung, Taiwan 1994-2000	Lags: 0-2 Conditional logistic regression. Case-crossover analysis.	24-h avg: 11.2 ppb Copollutants: PM_{10}, NO_2, O_3, CO	All cause; respiratory; cardiovascular; tropical area	Odds ratios: All cause: 1.1% (−4.4, 6.8) Respiratory: 3.5% (−17.6, 29.9) Cardiovascular: 2.4% (−9.1, 15.4)
Venners et al. (2003) Chonqing, China 1995	Lags: 0, 1, 2, 3, 4, 5 Poisson GLM, time-series study	24-h avg: 74.5 ppb Copollutants:$PM_{2.5}$	All cause, cardiovascular, respiratory, cancer, and other	All cause: Lag 2: 1.1% (−0.1, 2.4) Cardiovascular: Lag 2: 2.8% (0.4, 5.2) Respiratory: Lag 2: 3.0% (0.4, 5.7)

STUDY	METHODS	POLLUTANTS	OUTCOME	FINDINGS
Venners et al. (2003) Chongqing, China 1995	Lags: 0, 1, 2, 3, 4, 5 Robust Poisson regression. Time-series study.	24-h avg ($\mu g/m^3$): 213.0 Copollutants: $PM_{2.5}$	Total (Non-accidental), Cardiovascular, Respiratory, Cancer, Other	Relative Risk (95% CI) Total (per 100 $\mu g/m^3$ SO_2) 1.01 (0.96, 1.06) lag 0 1.03 (0.98, 1.08) lag 1 1.04 (1.00, 1.09) lag 2 1.04 (0.99, 1.08) lag 3 1.01 (0.96, 1.05) lag 4 1.01 (0.97, 1.06) lag 5 All Yr-Lag 2 (per 100 $\mu g/m^3$ SO_2) Total: 1.04 (1.00, 1.09) Respiratory: 1.11 (1.02, 1.22) Cardiovascular: 1.10 (1.02, 1.20) Cancer: 1.02 (0.93, 1.28) Other: 1.03 (0.97, 1.10) 6 mos (Jan-Jun)-Lag 2 (per 100 $\mu g/m^3$ SO_2) Total: 1.08 (1.02, 1.14) Respiratory: 1.16 (1.04, 1.29) Cardiovascular: 1.23 (1.11, 1.17) Cancer: 0.95 (0.70, 1.29) Other: 1.08 (0.99, 1.14) All Yr (Excluding high-mortality days)-Lag 2 (per 100 $\mu g/m^3$ SO_2) Total: 1.02 (0.97, 1.07) Respiratory: 1.07 (0.98, 1.18) Cardiovascular: 1.05 (0.96, 1.14) Cancer: 1.06 (0.82, 1.35) Other: 1.00 (0.93, 1.07) All Yr-Lag 3 (per 100 $\mu g/m^3$ SO_2) Total: 1.04 (0.99, 1.08) Respiratory: 1.00 (0.91, 1.10) Cardiovascular: 1.20 (1.11, 1.30) Cancer: 0.94 (0.74, 1.18) Other: 0.99 (0.85, 1.06) 6 mos (Jan-Jun)-Lag 3 (per 100 ug/m^3 SO_2) Total: 1.01 (0.96, 1.07) Respiratory: 0.97 (0.87, 1.09) Cardiovascular: 1.18 (1.07, 1.30) Cancer: 1.02 (0.76, 1.37) Other: 0.96 (0.88, 1.04) All Yr (Excluding high-mortality days)-Lag 3 (per 100 $\mu g/m^3$ SO_2) Total: 1.03 (0.99, 1.08) Respiratory: 1.01 (0.92, 1.12) Cardiovascular: 1.20 (1.10, 1.30) Cancer: 0.90 (0.70, 1.17) Other: 0.97 (0.90, 1.04)
Wong et al. (2001) Hong Kong 1995-1997	Lags: 0, 1, 2 Poisson GAM with default convergence criteria. Time-series study.	24-h avg: Warm Season: 6.4 ppb Cool Season: 6.0 ppb Copollutants: PM_{10}, O_3, NO_2; 2-pollutant models	All cause; respiratory; cardiovascular	All cause: Lag 1: 3.2% (1.1, 5.3) Respiratory: Lag 0: 5.3% (2.2, 8.6) Cardiovascular: Lag 1: 4.3% (1.1, 7.5)

STUDY	METHODS	POLLUTANTS	OUTCOME	FINDINGS
Wong et al. (2002b) Hong Kong 1995-1998	Lags: 0, 1, 2, 0-1, 0-2 Poisson GLM. Time-series study.	24-h avg: 29 ppb Copollutants: PM_{10}, O_3, NO_2; 2-pollutant models	Respiratory; cardiovascular; COPD; pneumonia and influenza; ischemic heart disease; cerebrovascular	Respiratory: Lag 0-1: 2.6% (0.2, 5.1) Cardiovascular: Lag 0-1: 1.2% (−1.0, 3.5)
Yang et al. (2004) Taipei, Taiwan 1994-1998	Lags: 0-2 Conditional logistic regression. Case-crossover analysis.	24-h avg: 5.5 ppb Copollutants: PM_{10}, NO_2, O_3, CO	All cause; respiratory; cardiovascular; subtropical area	Odds ratios: All cause: −0.5% (−7.0, 6.6) Respiratory: −1.8% (−23.1, 25.3); Cardiovascular: −3.4% (−15.2, 10.0)
AUSTRALIA				
Simpson et al. (1997) Brisbane, Australia 1987-1993	Lag: 0 Autoregressive Poisson with GEE. Time-series study.	24-h avg: 4.2 ppb 1-h max: 9.6 ppb Copollutants: PM10, bsp, O3, NO2, CO	All cause; respiratory; cardiovascular	All cause: All yr: Lag 0: −2.8% (−2.7, 8.6) Summer: Lag 0: 2.8% (−8.3, 15.2) Winter: Lag 0: 2.8% (−3.9, 9.8)

Table F-6. Associations of long-term exposure to SO_2 with respiratory morbidity.

STUDY	METHODS	POLLUTANT	RESULTS
UNITED STATES AND CANADA			
Dockery et al. (1996) 18 sites in U.S. 6 sites in Canada	Study of the respiratory health effects of acid aerosols in 13,369 white children aged 8 to 12 yrs old from 24 communities in the United States and Canada between 1988 and 1991. Information was gathered by questionnaire and a pulmonary function.	SO_2 mean 4.8 ppm SD 3.5 Range 0.2, 12.9	With the exception of the gaseous acids (nitrous and nitric acid), none of the particulate or gaseous pollutants, including SO_2, were associated with increased asthma or any asthmatic symptoms. Stronger associations with particulate pollutants were observed for bronchitis and bronchitic symptoms. Odds Ratio (95% CI) for 12.7 ppb range of SO_2 pollution Asthma 1.05 (057, 1.93) Attacks of Wheeze 1.07 (0.75, 1.55) Persistent Wheeze 1.19 (0.80, 1.79) Any asthmatic symptoms 1.16 (0.80, 1.68) Bronchitis 1.56 (0.95, 2.56) Chronic cough 1.02 (0.66, 1.58) Chronic phlegm 1.55 (1.01, 2.37) Any Bronchitic symptoms 1.29 (0.98, 1.71)

STUDY	METHODS	POLLUTANT	RESULTS
Dockery et al. (1989) Watertown, MA; St. Louis, MO; Portage, WI; Kingston-Harriman, TN; Steubenville, OH; Topeka, KS 1980-1981 school yr	Cross-sectional assessment of the association between air pollution and chronic respiratory health of 5,422 (10-12 yrs) white children examined in the 1980-1981 school yr. Children were part of the cohort of children in the Six Cities Study of Air pollution and Health. Symptoms were analyzed using logistic regression that included sex, age, indicators of parental education, maternal smoking, indicator for gas stove, and an indicator for city. Respiratory symptoms investigated were bronchitis, chronic cough, chest illness, persistent wheeze, asthma. The logarithm of pulmonary function was fitted to a multiple linear regression model that included sex, sex-specific log of height, age, indicators of parental education, maternal smoking, a gas stove indicator, and city indicator. Annual means of the 24 h avg air pollutant concentration for the 12 mos preceding the examination of each child was calculated for each city.	Daily mean concentrations, averaging hourly concentrations for each day with at least 18 hourly values Portage: 4.2 ppb Topeka: 3.5 Watertown: 10.5 Kingston: 6.5 St. Louis: 13.5 Steubenville: 27.8	No significant associations between SO_2 and any pulmonary function measurements. No significant association between SO_2 and symptoms. Relative odds and 95% CI between most/least polluted cities: Bronchitis: 1.5 (0.4, 5.8) Chronic cough: 1.8 (0.3, 12.5) Chest illness: 1.5 (0.4, 5.9) Persistent wheeze: 0.9 (0.4, 1.9) Asthma: 0.6 (0.3, 1.2) Reference symptoms: Hay fever: 0.6 (0.2, 1.7) Ear ache: 1.2 (0.3, 5.3) Nonrespiratory illness: 1.0 (0.6, 1.5) Analysis stratified by asthma or persistent wheeze bronchitis No wheeze or asthma 1.5 (0.5, 4.3) Yes wheeze or asthma 2.0 (0.3, 14.3) Chronic cough No wheeze or asthma 2.4 (0.5, 11.7) Yes wheeze or asthma 1.9 (0.1, 44.1) Chest illness No wheeze or asthma 1.5 (0.4, 5.6) Yes wheeze or asthma 1.9 (0.3, 13.0)
Euler et al. (1987) California, USA	Cross-sectional study of 7,445 (25 yrs or older) Seventh-Day Adventists who lived in their 1977 residential areas (Los Angeles and it border counties, San Francisco, and San Diego) for at least 10 yrs to determine the effect of long-term cumulative exposure to ambient levels of TSP and SO_2 on COPD symptoms. Study population is subgroup of NCI-funded ASHMOG study that enrolled 36,805 Seventh-Day Adventists in 1974. Each participant's cumulative exposure to the pollutant exceeding 4 different threshold levels were estimated using moly residence ZIP code histories and interpolated dosages from state monitoring stations. Participants completed a questionnaire on respiratory symptoms, smoking history, occupational history, and residence history.	None provided	Study reported that SO_2 exposure was not associated with symptoms of COPD until concentrations exceeded 4 ppm. The correlation coefficient of SO_2 (above 4 ppm) with TSP (above 200 $\mu g/m^3$) the highest exposure levels for these two pollutants was 0.30; thus, the authors believed that it was possible to separate the effects of SO_2 from TSP. Multiple regressions used in the analysis. No significant effect at exposures levels below 4 ppm or above 8 ppm. Relative risk estimate (based on 1,003 cases) SO_2 exposure above 2 ppm during 11 yrs of study 2000 h/yr: 1.09 1000 h/yr : 1.04 500 h/yr: 1.03 SO_2 exposure above 4 ppm 500 h/yr : 1.18 250 h/yr: 1.09 100 h/yr: 1.03 SO_2 above 8 ppm 60 h/yr: 1.07 30 h/yr: 1.03 15 h/yr: 1.02 SO_2 above 14 ppm 10 h/yr: 1.03 5 h/yr: 1.01 1 h/yr: 1.00
Goss et al. (2004) U.S. nationwide 1999-2000	Cohort study of 18,491 cystic fibrosis patients over 6 yrs of age who were enrolled in the Cystic Fibrosis Foundation National Patient Registry in 1999 and 2000. Mean age of patients was 18.4 yrs; 92% had pancreatic insufficiency. Air pollution from the Aerometric Information Retrieval System linked with patient's home ZIP code. Air pollutants studied included O_3, NO_2, SO_2, CO, PM_{10}, and $PM_{2.5}$. Health endpoints of interest were pulmonary exacerbations, lung function, and mortality. However, study did not have enough power to assess the outcome of mortality. Logistic regression and polytomous regression models that adjusted for sex, age, weight, race, airway colonization, pancreatic function, and insurance status were used.	Mean (SD): 4.91 (2.6) ppb MediaN: 4.3 ppb IQR: 2.7-5.9 ppb	With the single-pollutant model, no significant association between SO_2 and pulmonary exacerbations. Odds ratio per 10 ppb increase in SO_2: 0.83 (95% CI: 0.71, 1.01), p = 0.068 No clear association between pulmonary function and SO_2. No effect estimates provided.

STUDY	METHODS	POLLUTANT	RESULTS
McDonnell et al. (1999) California, U.S. 1973-1992	Prospective study (over 15 yrs) of 3,091 nonsmokers aged 27-87 yrs that evaluated the association between long-term ambient O_3 exposure and the development of adult-onset asthma. Cohort consisted of nonsmoking, non-Hispanic white, California Seventh Day Adventists who were enrolled in 1977 in the AHSMOG study. Logistic regression used to assess the association between the 1973-1992 mean 8-h avg ambient O_3 concentration and the 1977-1992 incidence of doctor-told asthma. Levels of PM_{10}, NO_2, and SO_4 were measured but no effect estimates were given.	Mean: SO_2 6.8 µg/m^3 Range: 0.0-10.2 µg/m^3 Correlation coefficient r = 0.25 with O_3	No significant positive association between SO_2 and asthma for males or females. Addition of a second pollutant to the O_3 model for the male subjects, did not result in a decrease of more than 10% in the magnitude of the regression coefficient for O_3, and for the females addition did not cause the coefficient for O_3 to become significantly positive
Schwartz (1989) United States 1976-1980	Cross-sectional study using data from the Second National Health and Nutrition Examination Survey (NHANES II) to examine the relation between air pollution and lung function growth in 4,300 children and youths 6-24 yrs old. A two-staged analysis was performed that consisted of (1) regression equations including factors known to affect lung function and (2) a regression of the residuals of the first regression on air pollution.	Annual percentiles (ppm): 10th: 0.0060 25th: 0.0106 50th: 0.0131 75th: 0.0159 90th: 0.0193	The study did not find an association between SO_2 and any of the lung function growth measurements (i.e., FVC, FEV1, and Peak flow).
EUROPE			
Ackermann-Liebrich et al. (1997) 8 communities in Switzerland Aarau, Basel, Davos, Geneva, Lugano, Montana, Payerne, and Wald 1991-1993	Cross-sectional population based study of 9,651 adults (18-60 yrs) in 8 areas in Switzerland (SAPALDIA), to evaluate the effect of long-term exposure of air pollutants on lung function. Examined the effects of SO_2, NO_2, O_3, TSP, and PM_{10}. Participants were given a medical exam that included questionnaire data, lung function tests, skin prick testing, and end-expiratory CO concentration. Subjects had to reside in the area for at least 3 yrs to be in the study.	Mean SO_2 in 1991 (µg/m^3) Mean: 11.7 SD: 7.1 Range: 2.5, 25.5	Mean values of SO_2, PM_{10}, and NO_2 were significantly associated with reduction in pulmonary function. SO_2 was correlated with Pm^3_0 (r = 0.78), PM_{10} (r = 0.93) and NO_2 (r = 0.86). Authors stated that the association with SO_2 disappeared after controlling for PM_{10} but no data was shown. Regression coefficients and 95% CI in healthy never smokers (per 10 µg/m^3 increase in annual avg SO_2) FVC: −0.0325 (−0.0390, −0.0260) FEV_1: −0.0125 (−0.0192,−0.0058)
Braun-Fahrlander et al. (1997) 10 communities in Switzerland Anieres, Bern, Biel, Geneva, Langnau, Lugano, Montana, Payerne, Rheintal, Zurich 1992-1993	Cross-sectional study of 4,470 children (6-15 yrs) living in 10 different communities in Switzerland to determine the effects of long term exposure to PM_{10}, NO_2, SO_2, and O_3 on respiratory and allergic symptoms and illnesses. Part of the Swiss Study on Childhood Allergy and Respiratory Symptoms with Respect to Air Pollution (SCARPOL).	Annual mean SO_2 (µg/m^3) Lugano: 23 Geneva: 13 Zurich: 16 BerN: 11 Anieres: 4 Biel: 15 Rheintal: 8 Langnau: NA Payerne: 3 MontaN: 2	This study reported that the annual mean SO_2, PM_{10}, and NO_2 were positively and significantly associated with prevalence rates of chronic cough, nocturnal dry cough, and bronchitis and conjunctivitis symptoms. Strongest association found with PM_{10}. However, there was no significant association between SO_2 and asthma or allergic rhinitis. Adjusted relative odds between the most/least polluted community 2-23 µg/m^2 (0.8, 8.8 ppb) Chronic cough: 1.57 (1.02, 2.42) Nocturnal dry cough: 1.66 (1.16, 2.38) Bronchitis: 1.48 (0.98, 2.24) Wheeze: 0.88 (0.54, 1.44) Asthma (ever): 0.74 (0.45, 1.21) Sneezing during pollen Season: 1.07 (0.67, 1.70) Hay fever: 0.84 (0.55, 1.29) Conjunctivitis symptoms: 1.74 (1.22, 2.46) Diarrhea: 1.02 (0.75, 1.39)
Charpin et al. (1999) Etang de Berre area of France: Arles, Istres, Port de Bouc, Rognac-Velaux, Salon de Provence, Sausset, Vitrolles Jan-Feb 1993	Cross-sectional cohort study of 2,073 children (10-11 yrs) from 7 communities in France (some with the highest photochemical exposures in France) to test the hypothesis that atopy is greater in towns with higher photochemical pollution levels. Mean levels of SO_2, NO_2, and O_3 were measured for 2 mos in 1993. Children tested for atopy based on skin prick test (house dust mite, cat dander, grass pollen, cypress pollen, and Alternaria). To be eligible for the study, subjects must have resided in current town for at least 3 yrs. Questionnaire filled out by parents that included questions on socioeconomic status and passive smoking at home. Two-mo mean level of air pollutants used in logistic regression analysis.	24-h mean (SD) SO_2 (µg/m^3) Arles: 29.7 (15.5) Istres: 23.8 (12.7) Port de Bouc: 32.3 (24.5) Rognanc-Velaux: 39.5 (21.8) Salon de Provence: 17.3 (11.6) Sausset: 29.0 (28.7) Vitrolles : 57.4 (32.0)	Study did not demonstrate any association between air pollution and atopic status of the children living in the seven communities, some with high photochemical exposures. A limitation of study is that authors did not consider short-term variation in air pollution and did not have any indoor air pollution measurements.

STUDY	METHODS	POLLUTANT	RESULTS
Frischer et al. (2001) Nine communities in Austria Sep-Oct 1997	Cross-sectional cohort study of 877 children (mean age 11.2 yrs) living in 9 sites with different O_3 exposures. Urinary eosinophil protein U-EPX) measured as a marker of eosinophil activation. U-EPX determined from a single spot urine sample analyzed with linear regression models.	½-h avg SO_2: 30-day mean 2.70 ppb IQR 2.1 ppb	No significant association between SO_2 and U-EPX Regression coefficient and SE −10.57 (0.25) per ppb SO_2
Frischer et al. (1999) Nine communities in Austria 1994-1996	Longitudinal cohort study of 1150 children (mean age 7.8 yrs) to investigate the long-term effects of O_3 on lung growth. Children were followed for 3 yrs and lung function was recorded biannually, before and after summertime. The dependant variables were change in FVC, FEV_1, and MEF_{50}. The 9 sites were selected to represent a broad range of O_3 exposures. GEE models adjusted for baseline function, atopy, gender, site, environmental tobacco smoke exposure, season, and change in height. Other pollutants studied included PM_{10}, SO_2, and NO_2.	Annual mean SO_2 (ppb) in 1994 AmstetteN: 3.75 St. ValentiN: 3.00 Krems: 3.75 HeidenreichsteiN: 4.13 Ganserndorf: 5.63 Mistelbach: 5.25 Wiesmath: 6.00 Bruck: 4.88 Pollau: 2.25	No consistent association observed between lung function and SO_2, NO_2 and PM_{10}. A negative effect estimate was observed during the summer and a positive estimate during the winter. Change in lung function (per ppb SO_2): FEV_1 (mL/day): Summer: −0.018 (0.004), p < 0.001 Winter : 0.003 (0.001), p < 0.001 FVC (mL/day): Summer: −0.009 (0.004), p = 0.02 Winter: 0.002 (0.001), p = 0.03 MEF_{50} (mL/s/day): Summer: −0.059 (0.010), p < 0.001 Winter: 0.003 (0.003), p = 0.26
Frye et al. (2003) Zerbst, Hettstedt, Bitterfeld,East Germany 1992-93, 1995-1996, 1998-1999	Three consecutive cross-sectional surveys of children (11-14 yrs) from three communities in East Germany. Parents of 3,155 children completed a questionnaire on symptoms. Lung function tests performed on 2,493 children. Study excluded children if they lived for less than 2 yrs in current home and if their previous home was more than 2 km away. The log-transformed lung function parameters were used as the response variables in a linear regression analysis that controlled for sex, height, season of examination, lung function equipment, parental education, parental atopy, and environmental tobacco smoke. Used avg of annual means of pollutants 2 yrs preceding each survey.	Used avg of annual means of pollutants 2 yrs preceding health measurement High of 113 μg/m^3 (in Bitterfeld) to a low of 6 μg/m^3. (Pollution values only described in figure)	The annual mean TSP declined from 79 to 25 μg/m^3 and SO_2 from 113 to 6 μg/m^3 and the mean FVC and FEV_1 increased from 1992-1993 to 1998-1999. Study concluded that reduction of air pollution in a short time period may improve children's lung function. Percent change of lung function for a 100-μg/m^3 decrease in SO_2 2 yrs before the investigation (N: 1,911) FVC: 4.9 (0.7, 9.3) FEV_1: 3.0 (−1.1, 7.2) FEV_1/FVC: −1.5 (−3.0, 0.1)
Garcia-Marcos et al. (1999) Cartagena, Spain winter 1992	A total of 340 children (10-11 yrs) living in and attending schools within a polluted and a relatively nonpolluted area were included in this study which aimed to establish the relative contribution socioeconomic status, parental smoking, and air pollution on asthma symptoms, spirometry, and bronchodilator response. Parents completed questionnaire on respiratory symptoms and risk factors including, living in polluted area, maternal smoking, paternal smoking, number of people living in the house, proximity to heavy traffic roads. Spirometry was performed before and after an inhaled 0.2 mg fenoterol was delivered to determine bronchodilator response. Bronchodilator response was considered positive if the FVC after fenoterol was increased by at least 10% or PEF by 12%. Logistic regression included as independent variables all the risk factors.	Annual mean SO_2 (μg/m^3) Polluted areas 75 μg/m^3 Nonpolluted areas: 20 μg/m^3	This study found that living in the polluted areas reduced the risk of a positive bronchodilator response (RR = 0.61, p = 004).

STUDY	METHODS	POLLUTANT	RESULTS
Gokirmak et al. (2003) Malatya, Turkey	Study on occupational exposure to SO_2 in apricot sulfurization workers that investigated the role of oxidative stress resulting exposure to high concentrations of SO_2 on bronchoconstriction. Forty workers (mean age: 28 yrs, range 16-60 yrs) who have been working in apricot sulfurization for 20-25 days each yr and 20 controls (mean age: 29 yrs, range 17-42) who had no SO_2 exposure participated in the study. Activities of antioxidant enzymes (glutathione peroxidase (GSH-Px), superoxide dismutase (SOD) and catalase) malondialdehyde (MDA) concentrations (marker of lipid peroxidation), and pulmonary function test measured in subjects.	SO_2 conc ranged from 106.6 to 639.2 ppm in 9 apricot farms. Mean conc around sulfurization chamber: 324.1 (35.1) ppm	SOD, GSH-Px, and catalase activities were lower and malondialdehyde concentrations were higher in the apricot sulfurization workers compared to controls. Pulmonary function decreased after SO_2 exposure among the apricot sulfurization workers. Authors concluded that occupational exposure to high concentrations of SO_2 enhances oxidative stress and that lipid peroxidation may be a mechanism of SO_2 induced bronchoconstriction. Apricot sulfurization workers vs. controls Mean (SD) SOD (U/mL): 2.2 (0.6) vs. 3.2 (0.7) U/m , $p < 0.0001$ Glutathione peroxidase (U/mL): 0.6 (0.3) vs. 1.1 (0.3), $p < 0.0001$ Catalase (L/L): 107.6 (27.4) vs. 152.6 (14.3), $p < 0.0001$ MDA (nmol/L): 4.1 (0.9) vs. 1.9 (5.3) , $p < 0.0001$ Before vs. after SO_2 exposure among apricot sulfurization workers Mean (SD) FVC (% predicted) 88 (17) vs. 84 (16) , $p < 0.001$ FEV_1 (% predicted) 98 (14) vs. 87 (14), $p < 0.001$ FEVV1/FVC: 92 (7) vs. 86 (9), $p < 0.001$ FEF25-75% (% predicted) 108 (19) vs. 87 (23) , $p < 0.001$
Heinrich et al. (2002) Reunified Germany Bitterfeld, Hettstedt, Zerbst 1992-1993, 1995-1996, 1998-1999	Three cross-sectional surveys of children (5-14 yrs) from 3 areas that were formerly part of East Germany to investigate the impact of declines in TSP and SO_2 on prevalence of nonallergic respiratory disorders in children. Study excluded children if they lived for less than 2 yrs in current home and if their previous home was more than 2 km away. GEE used for analysis.	SO_2 concentration in $\mu g/m^3$ Yr /Zerbst/Bitterf/ Hettst 1991/78/113/ 84 1992/ 58/ 75/ 46 1993/ 42/ 60/ 49 1994/ 29/ 35/ 38 1995/ 21/ 30/ 26 1996 25 24 25 1997/ 13/ 13/ 13 1998/ 8/ 9/ 6	Study found that SO_2 exposure was significantly associated with prevalence of bronchitis, frequent colds, and febrile infections. While results are reported as risk for an increase in air pollutant, the respiratory health of children improved with declines in TSP and SO_2. Authors concluded that exposure to combustion-derived air pollution is causally related to nonallergic respiratory health in children. Odds ratio and 95% CI: (per 100 $\mu g/m^3$ in 2 yr mean SO_2) All children: Bronchitis: 2.72 (1.74, 4.23) Otitis media: 1.42 (0.94, 2.15) Sinusitis: 2.26 (0.85, 6.04) Frequent colds: 1.81 (1.23, 2.68) Febrile infections: 1.76 (1.02, 3.03) Cough in morning: 1.10 (0.73, 1.64) Shortness of breath: 1.31 (0.84, 2.03) Children without indoor exposures (living in damp houses with visible molds, ETS in the home, gas cooking emissions, and contact with cats) Bronchitis: 4.26 (2.15, 8.46) Otitis media: 1.43 (0.73, 2.81) Sinusitis: 2.95 (0.52, 16.6) Frequent colds: 2.29 (1.15, 4.54) Febrile infections: 1.75 (0.78, 3.91) Cough in morning: 1.00 (0.38, 2.64) Shortness of breath: 2.07 (0.90, 4.75)

STUDY	METHODS	POLLUTANT	RESULTS
Herbarth et al. (2001) East Germany 1993-1997	Meta-analysis of three cross-sectional studies: (1) Study on Airway Diseases and Allergies among Kindergarten Children (KIGA), (2) the Leipzig Infection, Airway Disease and Allergy Study on School starters (LISS), and (3) KIGA-IND, which was based on the KIGA design but conducted in 3 differentially polluted industrial areas. A total of 3,816 children participated in the three studies. Analysis of data from parent-completed questionnaires to determine the effect of life time exposure to SO_2 and TSP on the occurrence of acute bronchitis. Total lifetime exposure burden corresponds to the exposure duration from birth to time of the study. The LISS study was divided in to LISS-U for the urban area and LISS-R for the rural area. Logistic regression analysis used that adjusted for predisposition in the family (mother or father with bronchitis), ETS, smoking during pregnancy or in the presence of the pregnant women.	Avg lifetime exposure burden of SO_2 (µg/m^3) KIGA: 142 LISS: 48 LIISS: R 47 KIGA-IND: 59	This study found the highest bronchitis prevalence in the KIGA cohort and the lowest in the LISS cohort, which is consistent with the SO_2 concentrations in these cohorts. Study found a correlative link between SO_2 and bronchitis (R = 0.96, p < 0.001) but not TSP (R = 0.59). Results of study suggest that SO_2 may be a more important factor than TSP in the occurrence of bronchitis in these study areas. Odds ratio for bronchitis adjusted for parental predisposition, smoking, and lifetime exposure to SO_2 and TSP (2-pollutant model). SO_2: 3.51 (2.56, 4.82) TSP: 0.72 (0.49, 1.04)
Hirsch et al. (1999) Dresden, Germany	Cross sectional study to relate the prevalence of respiratory and allergic diseases in childhood to measurements of outdoor air pollutants. 5,421 children ages 5-7 yrs and 9-11 yrs were evaluated by questionnaires, skin-prick testing, venipuncture for (Ig)E, lung function, and bronchial challenge test.	Mean (µg/m^3): 48.3 Range: 29.0-69.3 25-75 percentile 42.7-54.3	Sox was positively associated with current morning cough but not with bronchitis. Prevalence odds ratio (95% CI) for symptoms within past 12 mos, +10 µg/m^3: Wheeze: Atopic 103 (0.79, 1.35) µg/m^3 Nonatopic 1.36 (1.01, 1.84) Morning Cough: Atopic 1.22 (0.92, 1.61) Nonatopic 1.32 (1.07, 1.63) Prevalence odds ratio (95% CI) for doctor's diagnosis, +10 µg/m^3: Asthma Atopic 1.07 (0.79, 1.45) Nonatopic 1.35 (1.00, 1.82) Bronchitis Atopic 1.04 (0.87, 1.25) Nonatopic 0.99 (0.88, 1.12)
Horak et al. (2002) Eight communities in Austria 1994-1997	Longitudinal cohort study that continued the work of Frischer et al. (1999) by adding one more yr of data and analyzing the effects of PM_{10} in addition to SO_2, NO_2, and O_3. At the beginning of the study 975 children (mean age 8.11 yrs) were recruited for the study, but only 80.6% of the children performed all 6 lung function tests (twice a yr). The difference for each lung function parameter between two subsequent measures was divided by the days between measurements and presents as difference per day (dpd) for that parameter. 860 children were included in the GEE analysis that controlled for sex, atopy, passive smoking, initial height, height difference, site, and initial lung function.	Seasonal mean SO_2 µg/m^3: Winter: Mean: 16.8 Range: 7.5, 37.4 Summer: Mean : 6.9 µg/m^3 Range: 3.1, 11.7	Moderate correlation between PM_{10} and SO_2 in the winter (r = 0.52). In a one-pollutant model for SO_2, long term seasonal mean concentration of SO_2 was had a positive association with FVC dpd and FEV_1 dpd in the winter, but no effect on MEF_{25-75} dpd. In a two-pollutant model with PM_{10}, wintertime SO_2 had a positive association with FEV_1 dpd. Single-pollutant model FVC dpd: Summer: 0.009, p = .336 Winter: 0.006, p = .009 FEV_1 dpd: Summer : 0.005, p = 0.576 Winter: 0.005, p = 0.013 MEF_{25-75}: Summer: 0.015, p = 0.483 Winter: 0.003, p = 0.637 Two-pollutant model: SO_2 + PM_{10} FVC dpd: Summer: 0.008, p = 0.395 Winter: 0.004, p = 0.225 FEV_1 dpd: Summer : 0.010 (0.271) Winter: 0.007 (0.025) MEF_{25-75} dpd: Summer : 0.037, p = 0.086 Winter: 0.007, p = 0.429

STUDY	METHODS	POLLUTANT	RESULTS
Jedrychowski et al. (1999) Krakow, Poland 1995 (Mar-Jun) and 1997 (Mar-Jun)	Cohort prospective study consisting of 1,001 preadolescent children (9 yrs old) from two areas of Krakow, Poland. The study examined lung function growth using FVC and FEV1 measurements taken in 1995 and then again two yrs later, 1997. Used a two-stage analysis that consisted of (1) multivariate linear regression analyses to determine body variables that are significant predictors of lung function growth, and then (2) multivariate logistic regression to examine the relation between air pollution and lung function growth.	Annual avg: City Center (μg/m^3): 43.87 (32.69) Control Area (μg/m^3): 31.77 (21.93)	The study did not provide individual estimates for SO_2.
Koksal et al. (2003) Malatya, Turkey	Study on occupational exposure to high concentrations of SO_2 on respiratory symptoms and pulmonary function on apricot sulfurization workers. Apricot sulfurization workers (N: 69) from 15 apricot farms who have been working in sulfurization of apricots for 20-25 days a yr during each summer were recruited for the study. Subjects rated symptoms (itchy eyes, runny nose, stuffy nose, itchy or scratchy throat, cough, shortness of breath, phlegm, chest pain, and fever) before during and 1-h after each exposure.	SO_2 conc ranged from 106.6 to 721.0 ppm	SO_2 exposure at high concentrations increased symptoms of itchy eyes, shortness of breath, cough, running and/or stuffy nose, and itchy or scratchy throat during exposure ($p < 0.05$). Inhalation of high concentrations of SO_2 for 1-h caused significant decreases in pulmonary function. Difference in pulmonary function measured before and after exposure: FVC (L) 0.16 (0.42), $p < 0.05$ FEV_1 (L) 0.39 (0.36), $p < 0.001$ FEV_1/FVC: 5.22 (6.75), $p < 0.001$ PEF (L/s) 1.39 (1.06), $p < 0.001$ $FEF_{25-75\%}$ (L/s) 0.82 (0.70), $p < 0.001$
Kopp et al. (2000) Ten communities in Austria and SW Germany	Longitudinal cohort study of 797 children (mean age 8.2 yrs) from 2nd and 3rd grades of 10 schools in Austria and SW Germany to assess the effects of ambient O_3 on lung function in children over a 2-summer period. Study also examined the association between avg daily lung growth and SO_2, NO_2, and PM_{10}. Each child performed 4 lung function tests during spring 1994 and summer 1995. ISAAC questionnaire used for respiratory history. Linear regression models used to assess effect of air pollutants on FVC and FEV_1, which were surrogates of lung growth.	Mean SO_2 (95% CI) ppb Apr-Sep 1994 AmstetteN: 3.7 (0.7, 3.9) St ValentiN: 2.6 (1.5, 5.2) Krems: 3.7 (0.7, 7.5) VillingeN: 0.7 (0 , 3.0) HeindenreichsteiN: 3.7, (0.7, 7.5) Ganserndorf: 3.7 (0.7, 11.2) Mistelbach: 3.7 (0.7, 7.5) Wiesmath: 6.3 (3.4, 9.4) Bruck: 1.5 (0.7, 4.1) Freudenstadt: 0.7 (0, 3.0) Oct 1994-Mar 1995 AmstetteN: 3.7 (0.7, 7.5) St ValentiN: 3.0 (1.1, 9.4) Krems: 3.7 (0.7, 11.0) VillingeN: 1.9 (0 , 3.0) HeindenreichsteiN: 3.7 (0.7, 15.0) Ganserndorf: 3.7 (0.7, 22.5) Mistelbach: 3.7 (0.7, 22.5) Wiesmath: 2.23 (0.7, 10.1) Bruck: 15 (1.1, 7.9) Freudenstadt: 1.57 (0.4, 5.3) Apr-Sep 1995 AmstetteN: 3.7 (0.7, 3.8) St ValentiN: 2.6 (1.1, 6.8) Krems: 3.7 (0.5, 3.8) VillingeN: 0.7 (0 , 2.6) HeindenreichsteiN: 0.7 (0.5, 0.9) Ganserndorf: 3.7 (0.7, 7.5) Mistelbach: 3.7 (0.7, 7.5) Wiesmath: 7.5 (0.7, 14.9) Bruck: 3.7 (0.4, 4.9) Freudenstadt: 0.7 (0, 3.4)	Lower FVC and FEV_1 increases observed in children exposed to high ambient O_3 levels vs. those exposed to lower levels in the summer. This study found no effect of SO_2 and PM_{10} on FVC increase during the summer of 1995 and winter 1994/1995, however, SO_2 was negatively associated with FVC during the summer of 1994. Change in FVC (per ppb SO_2) Summer 1994: −0.044, $p = 0.006$ Winter 1994/95: 0.007, $p = 0.243$ Summer 1995: 0.045, $p = 0.028$

STUDY	METHODS	POLLUTANT	RESULTS
Kramer et al. (1999) East and West Germany 1991 to 1995	Repeated cross-sectional studies between 1991 and 1995 on 7-yr-old children in East Germany and between 1991 and 1994 in West Germany. Comparison of prevalence of airway diseases and allergies in East and West Germany during the first five yrs after reunification. A total of 19,090 children participated in the study. Logistic regression used to assess the effect of SO_2 and TSP on airway diseases and allergies. Analysis performed on 14,144 children with information on all covariates of interest.	East Germany 2-yr avg concentration ranged from 45 to 240 µg/m^3 West Germany 2-yr avg concentration ranged from 18-33	All infectious airway diseases and irritation of the airway was associated with either SO_2 or TSP in East Germany in 1991. The decrease of pollution between 1991 and 1995 had a favorable effect on the prevalence of these illnesses. SO_2 was significantly associated with more than 5 colds in the last 12 mos, tonsillitis, dry cough in the last 12 mos, and frequent cough in 1991-1995. Odds ratio and 95% CI: (per 200 µg/m^3 SO_2) in East Germany areas, 1991-1995 for children living at least 2 yrs in the areas, adjusted for time trend: Infectious airway diseases Pneumonia ever diagnosed: 1.17 (0.85, 1.62) Bronchitis ever diagnosed: 0.85 (0.68, 1.05) $5 colds in last 12 mos: 1.55 (1.18, 2.04) Tonsillitis in the last 12 mos: 1.89 (1.49, 2.39) Dry cough in the last 12 mos: 1.46 (1.12, 1.91) Frequent cough ever: 2.51 (1.79. 3.53) Allergic diseases and symptoms: Irritated eyes in the last 12 mos: 1.06 (0.66, 1.70) Irritated nose in the last 12 mos: 1.26 (0.96, 1.66) Wheezing ever diagnosed: 0.68 (0.46, 1.01) Bronchial asthma ever diagnosed: 2.73 (1.24, 6.04) Hay fever ever diagnosed: 0.60 (0.24, 1.52) Eczema ever diagnosed: 0.87 (0.65, 1.18) Allergy ever diagnosed: 0.93 (0.67, 1.29)
Liebhart et al. (2007) Poland (Bialystok, Bydgoszcz, Gdansk, Krakow, Lublin, Lodz, Poznan, Rabka, Warszawa, Wroclaw, Zabrze) 1998-1999	The Polish Multicentre Study of Epidemiology of Allergic Diseases (PMSEAD), which consisted of a cohort of 16,238 individuals aged 3-80 yrs old from 33 areas in 11 regions of Poland. Asthma diagnosis was determined through household questionnaires. Conducted multivariate and univariate logistic regression analyses to examine the prevalence of and risk factors for asthma.	Range (µg/m^3): 4.0-35.0	In multivariate logistic regression models, black smoke was found to be a significant risk factor for asthma for both children and adults. SO_2 was found to be a significant risk factor for asthma in both children and adults, but only in a univariate logistic regression. Adjusted Odds Ratio (95% CI) Univariate logistic regression ChildreN: 1.34 (1.04, 1.72) Adults: 1.19 (1.02, 1.38) Multivariate logistic regression ChildreN: 1.20 (0.91, 1.59) Adults: 1.01 (0.85, 1.20)
Kohlhammer et al. (2007) Hettstedt, Germany 1992-1999	Three repeated cross-sectional studies of 5,360 children ages 5-14 examining health impacts (lifetime pneumonia) of social and environmental factors	---	No relationship between SO_2 and pneumonia was observed.
Penard-Morand et al. (2006) Six communities in France: Bordeaux, Clermont-Ferrand, Creteil, Marseille, Strasbourg and Reims Mar 1999-Oct 2000	Cross-sectional study of 4,901 children (9-11 yrs) form 108 randomly selected schools in 6 cities to assess the association between long-term exposure to background air pollution (NO_2, SO_2, PM_{10}, O_3) and atopy and respiratory outcomes. Analysis restricted to children who had lived at least the last 3 yrs in their house at the time of the examination. Analysis used three yr avgd air pollutant concentrations at the children's schools. Parents completed questionnaire on respiratory and allergic disorders (asthma, allergic rhinitis (AR), and atopic dermatitis) and children underwent examination that included a skin prick test to assess allergic sensitization, evidence of visible flexural dermatitis and measure of exercise-induced bronchial reactivity (EIB).	Estimated 3-yr avg concentrations at 108 schools Low conc: 4.6 µg/m^3 (Range: 1.3, 7.4), High conc: 9.6 µg/m^3 (range 7.7, 13.7)	Increased concentrations of SO_2 were significantly associated with an increased risk of EIB, lifetime asthma and lifetime AR. Past yr wheeze and asthma were also associated with SO_2. In a two-pollutant model with PM_{10}, significant associations were observed between SO_2 and EIB and past yr wheeze. Odds ratio and 95% CI (per 5 µg/m^3 SO_2) EIB: 1.39 (1.15, 1.66), $p < 0.001$ Flexural dermatitis: 0.86 (0.73, 1.02), $p < 0.10$ Past yr wheeze: 1.23 (1.0, 1.51), $p < 0.05$ Past yr asthma: 1.28 (1.00, 1.65), $p < 0.01$ Past yr rhinoconjunctivitis: 1.05 (0.89, 1.24) Past yr atopic dermatitis: 1.01 (0.86, 1.18) Lifetime asthma: 1.19 (1.00, 1.41), $p < 0.10$ Lifetime allergic rhinitis: 1.16 (1.01, 1.32), $p < 0.05$ Lifetime atopic dermatitis: 0.93 (0.82, 1.05) Two-pollutant model with PM_{10} EIB: 1.46 (1.12, 1.90) Past yr wheeze: 1.45 (1.09, 1.93)

STUDY	METHODS	POLLUTANT	RESULTS
Pikhart et al. (2001) Czech Republic, Poland, 1993-1994	Part of the small-area variation in air pollution and health (SAVIAH) study to assess long-term effects of air pollution on respiratory outcomes. Analysis on data from two centers of the multicenter study: Prague, Czech Republic, and Poznan, Poland. Both cities had wide variation in air pollution levels. Parents/guardians of 6,959 children (7-10 yrs) completed a questionnaire about the socioeconomic situation of the family, type of housing, family history of atopy, parental smoking, family composition, and health of the child. SO_2 was measured at 80 sites in Poznan and 50 sites in Prague during 2-wk campaigns. From these data GIS was used to estimate pollutant concentrations at a small area level. Logistic regression used to assess effect of air pollution on the prevalence of respiratory outcomes.	Mean SO_2 ($\mu g/m^3$) Prague: 83.9 Range: 65.8-96.6 PoznaN: 79.7 Range: 44.2-140.2	SO_2 levels (mean of home and school) were associated with the prevalence of wheezing/whistling in the past 12 mos. There was a marginal association between SO_2 and lifetime prevalence of wheezing and physician diagnosed asthma. Fully adjusted model controlled for age, gender, maternal education, number of siblings, dampness at home, heating and cooking on gas, maternal smoking, and family history of atopy and center. Authors noted SO_2 is strongly spatially correlated with particles in the Czech Republic and probably Poland, so SO_2 may be proxy for exposure to other pollutants. Not other pollutants measured in study. Odds ratio (per 50 $\mu g/m^3$) SO_2 Wheezing/whistling in past 12 mos: 1.32 (1.10, 1.57) Wheezing/whistling ever: 1.13 (0.99, 1.30) Asthma ever diagnosed by doctor: 1.39 (1.01, 1.92) Dry cough at night: 1.06 (0.89, 1.27)
Ramadour et al. (2000) Seven towns in SE France Jan-Feb 1993	Cross-sectional cohort study of 2,445 children (age 13-14 yrs) who had lived for at least 3 yrs in their current residence to compare the levels of O_3, SO_2, and NO_2 to the prevalence rates of rhinitis, asthma, and asthmatic symptoms. Some of the communities had the heaviest photochemical exposure in France. Subjects completed ISAAC survey of asthma and respiratory symptoms. Analysis conducted with logistic regression models that controlled for family history of asthma, personal history of early -life respiratory diseases, and SES. Also performed simple univariate linear regressions.	Mean (SD) $\mu g/m^3$ of SO_2 during 2-mo period Port de Bouc: 32.3 (24.5) Istres: 23.8 (12.7) Sausset: 29.0 (28.7) Rognanc-Velaux: 39.5 (21.8) Vitrolles: 57.4 (32.0) Arles: 29.7 (15.5) SaloN: 17.3 (11.6)	Study found no relationship between mean levels of SO_2, NO_3, or O_3 and rhinitis ever, 12-mo rhinitis, rhinoconjunctivitis, and hay fever or asthmatic symptoms. Simple regression analyses of respiratory outcomes vs. mean SO_2 levels in the 7 towns indicated that nocturnal dry cough was associated with mean SO_2 levels (r = 0.891). Potential confounding across towns.
Soyseth et al. (1995) Ardal and Laerdal, Norway winter seasons 1989-92	Cross-sectional study of 529 children (aged 7-13 yrs) to determine whether exposure to SO_2 during infancy is related to the prevalence of bronchial hyperresponsiveness (BHR). A sulfur dioxide emitting aluminum smelter is present in Ardal, but there is no air polluting industry in Laerdal. Parents filled out questionnaire regarding family history of asthma, type of housing, respiratory symptoms and parent's smoking habits. Spirometry was performed on each child and bronchial hyperactivity was determined by methacholine challenge or reversibility test. Skin prick test done to assess atopy. Also examined, the effects of fluoride.	Median SO_2 37.1 $\mu g/m^3$ at ages 0-12 mos 37.9 $\mu g/m^3$ at ages 13-36 mos	This study found that the risk of BHR was associated with SO_2 exposure at 0-12 mos Odds ratio for BHR (per 10 $\mu g/m^3$ SO_2) for various ages at exposure 0-12 mos: 1.62 (1.11, 2.35) 13-36 mos: 1.40 (0.90, 2.21) 37-72 mos: 1.19 (0.77, 1.82) 73-108 mos: 1.19 (0.63, 2.22)
Studnicka et al. (1997) Austria (8 nonurban communities) 1991-1993	Longitudinal study of 843 children 7 yrs old from 8 nonurban Austrian communities. A logistic regression was used to examine the association between SO_2 concentrations and asthma and respiratory symptoms by comparing low, regular, and high SO_2 communities with very low SO_2 communities.	**Range:** Jan. 1991-Dec. 1993 (ppb): 6.0 (Krems), 12.0 (Mistel. and Gäns)	SO_2 was significantly associated with bronchial asthma in the last 12 mos and positively associated with parent-reported “ever asthma” when comparing low SO_2 concentration communities with very low SO_2 communities. Adjusted Prevalence Odds Ratio Wheeze last 12 mos Low: 0.68. Regular: 0.88. High: 0.42 Cough apart from colds last 12 mos Low: 0.75. Regular: 0.85. High: 0.72 Bronchitis last 12 mos Low: 0.21. Regular: 0.45. High: 0.56 Bronchial asthma last 12 mos Low: 2.35. Regular: 0.22. High: 0.33 Parent-reported “ever asthma” Low: 1.70. Regular: 0.23. High: 0.67

STUDY	METHODS	POLLUTANT	RESULTS
von Mutius et al. (1995) Leipzig, East Germany, Oct 1991-Jul 1992	The effects of high to moderate levels of air pollution (SO_2, NO_X, and PM) on the incidence of upper respiratory were investigated in 1,500 schoolchildren (9-11 yrs) in Leipzig, East Germany. Logistic regression models controlled for paternal education, passive smoke exposure, number of siblings, temperature, and humidity.	During winter mos, SO_2 daily max concentrations ranged from 40-1283 $\mu g/m^3$. During high pollution period, mean concentration of SO_2 was 188 $\mu g/m^3$ and during low pollution mean was 57 $\mu g/m^3$.	The daily mean values of SO_2 and NO_x were significantly associated with increased risk of developing upper respiratory illnesses during the high concentration period. In the low concentration period, only NO_x daily mean values were associated with increased risks. In a two-pollutant model with PM, similar estimates to the single-pollutant model were obtained, thus collinearity of data may not account for the effects of high mean concentrations of SO_2. Odds ratio and 95% CI: (did not indicate per what level of SO_2 increase) Daily mean SO_2 High period: 1.72 (1.19, 2.49) Low period: 1.40 (0.95, 2.07) Daily max SO_2 High period: 1.26 (0.80, 1.96) Low period: 0.99 (0.66, 1.47)

STUDY	METHODS	POLLUTANT	RESULTS
LATIN AMERICA			
Solé et al. (2007) São Paulo, Brazil (São Paulo West (SPW), São Paulo South (SPS), Santo André (SA), Curitiba (CR), Porto Alegre (PoA))	Cohort of 16,209 adolescents (13-14 yrs old) from the 21 centers involved in the International Study of Asthma and Allergies in Childhood (ISAAC). Each participant was given a questionnaire to identify various allergy-related symptoms that occurred in the last 12 mos. The relationship between affirmative answer to a question, socioeconomic status, and air pollutants was analyzed by the Spearman correlation coefficient. The location with the lowest level of a specific air pollutant was defined as the reference and the risk of an affirmative answer to a question was presented as an odds ratio for each location.	NR	In the analysis of the risk of allergy-related symptoms due to SO_2 levels in relation to the center with the lowest annual mean SO_2 concentrations SPW was significantly associated with every symptom. Other significant associations were observed in SA for current wheezing; in CR for rhinitis and rhinoconjunctivitis; and in PoA for current wheezing, nighttime cough, rhinitis, and eczema. Odds Ratio (95% CI)-Reference Center: São Paulo South (SPS) Current Wheezing SPW: 1.21 (1.08, 1.38) SA: 1.31 (1.16, 1.48) CR: 1.02 (0.90, 1.15) PoA: 1.68 (0.85, 1.10) Severe Asthma SPW: 2.01 (1.56, 2.60) SA: 1.04 (0.78, 1.40) CR: 1.08 (0.81, 1.42) PoA: 1.01 (1.29, 2.20) Nighttime Cough SPW: 1.14 (1.03, 1.26) SA: 0.94 (0.85, 1.04) CR: 0.93 (0.84, 1.02) PoA: 1.25 (0.91, 1.12) Rhinitis Last Yr SPW: 1.14 (1.02, 1.27) SA: 1.05 (0.94, 1.18) CR: 1.71 (1.54, 1.90) PoA: 1.36 (1.12, 1.40) Rhinoconjunctivitis SPW: 1.78 (1.55, 2.04) SA: 1.15 (0.99, 1.33) CR: 1.50 (1.31, 1.72) PoA: 1.48 (1.18, 1.57) Severe Rhinitis SPW: 1.50 (1.32, 1.71) SA: 1.08 (0.94, 1.24) CR: 1.52 (1.34, 1.73) PoA: 0.97 (1.30, 1.69) Eczema SPW: 1.40 (1.17, 1.68) SA: 1.00 (0.83, 1.21) CR: 0.88 (0.72, 1.06) PoA: 1.40 (0.80, 1.18) Flexural Eczema SPW: 2.00 (1.58, 2.52) SA: 0.95 (0.73, 1.24) CR: 1.02 (0.79, 1.31) PoA: 2.41 (1.09, 1.80) Severe Eczema SPW: 2.58 (1.94, 3.44) SA: 0.92 (0.65, 1.30) CR: 0.71 (0.50, 1.02) PoA: NR (1.80, 3.22)
ASIA			
Ho et al. (2007) Taiwan 1995-1996	Survey of 69,367 children ages 12-15 by questionnaire. The max likelihood estimation was carried out with Fisher's scoring algorithm and GEE.	NR	SO_2 not significant in both genders. However, SO_2 showed a reversal effect on monthly asthma attack rate. (Authors state that this reversal effect could be caused by the interaction of sulfur dioxide with the lowest 5% monthly temperature avg)

STUDY	METHODS	POLLUTANT	RESULTS
Hwang et al. (2005) Taiwan 2001	A cross-sectional study consisting of 32,672 Taiwanese school children aged 6-15 yrs old. Using a modified Chinese version of the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire collected information on each participant's health, environmental exposures, and other variables. A two-stage hierarchical model consisting of logistic and linear regression analyses was used to account for, in the first stage, variation among subjects, and, in the second stage, variation among municipalities.	2000 (ppb): 3.53 (2.00)	Increased annual levels of NO_X, CO, and O_3 were associated with an increased risk of childhood asthma levels. In both single- and co-pollutant models SO_2 was not found to be associated with the risk of asthma. Odds Ratio (95% CI) (per 10 ppb SO_2) Single-pollutant model 0.874 (0.729, 1.054) Two-pollutant model NO_X + SO_2: 0.724 (0.545, 0.963) CO + SO_2: 0.689 (0.542, 0.875) SO_2 + O_3: 0.826 (0.674, 1.014)
Peters et al. (1996) Hong Kong (Kwai Tsing; Southern) 1989-1991	Cohort of 3,521 children from two districts in Hong Kong with good and poor air quality prior to the 1990 legislation to reduce fuel sulfur levels. Analyses consisted of multivariate methods using logistic regression along with generalized estimating equations (GEE) to examine the effect of legislation implemented to reduce fuel sulfur levels on respiratory health.	Annual avg ($\mu g/m^3$) Southern 1989: 11 1990: 8 1991: 7 Kwai Tsing 1989: 111 1990: 67 1991: 23	SO_2 emissions were reduced by 80% after institution of the legislation. The study does not provide effect estimates for individual pollutants.
Wang et al. (1999) Taiwan (Kaohsiung; Pintong) 1995-1996	A cross-sectional study consisting of 165,173 high school students aged 11-16 yrs old residing in the communities of Kaohsiung and Pintong in Taiwan from Oct 1995 to Jun 1996. Used a video and questionnaire developed by the International Study of Asthma and Allergies in Childhood (ISAAC). The association between air pollution and asthma was examined using logistic regression. In addition, the study performed a multiple logistic regression to examine the independent effects of risk factors of asthma after adjusting for age, sex, parents' education, and area of residence. The multiple logistic regression included pollutant concentrations to examine the combined effect.	Median: 1996 (ppm): 0.013	In the univariate analysis, increasing concentrations of TSP, SO_2, NO_2, CO, O_3, and airborne dust were all found to be significantly associated with asthma. These univariate estimates are associated with concentrations above a cutoff (i.e., the median concentrations of each pollutant). In the multivariate analysis increasing concentrations of TSP, NO_2, CO, O_3, and airborne dust were significantly associated with asthma. Odds Ratio (95% CI) (per 0.013 ppm SO_2) Univariate analysis ≥ 0.013 ppm: 1.05 (1.02, 1.09) Adjusted Odds Ratio (95% CI) Multivariate analysis 0.98 (0.95, 1.02)
MIDDLE EAST			
Dubnov et al. (2007) Israel (Hadera, Pardes-Hanna) 1996 and 1999	Cohort of 1,492 schoolchildren (7-14 yrs old) living near a major coal-fired power station. Subjects underwent pulmonary function tests (PFT) for forced vital capacity (FVC) and forced expiratory volume during the first second (FEV1) to examine the association between pulmonary function and long-term exposure to air pollution. Using stepwise multiple regression (SMR) and ordinary leas squares regression (OLS) examined the multiplicative effect of NO_X and SO_2 on pulmonary function.	1996 and 1999 avg (SD) (ppm): 12.9 (11.3)	Using an integrated concentration value (ICV), which equals the product of NO_X concentration and SO_2 concentration when both concentrations individually exceed the half-hour reference level, found significant associations between exposure to air pollution and decrements in pulmonary function. All Children NOX □ SO_2 ΔFVC (%) ∃ = −0.004, p < 0.001 ΔFEV_1 (%) ∃ = −0.004, p < 0.001 Children in zone of highest concentration of air pollution NOX □ SO_2 ΔFVC (%) ∃ = −0.005, p < 0.001 ΔFEV_1(%) ∃ = −0.005, p < 0.001
AFRICA			
Houssaini et al. (2007) Morocco	Cross-sectional study of 1,318 children with a mean age of 12 yrs. Used a questionnaire and medical diagnosis/reporting for asthma, and evaluated using Student's t-test, Chi-square, odds ratios, and Cochran-Armitage tests.	Annual Avg: 2000-2001: 60.2 $\mu g/m^3$ 2001-2002: 50.2 $\mu g/m^3$ 2002-2003: 49.6 $\mu g/m^3$ 2003-2004: 36.8 $\mu g/m^3$	Significant prevalence for respiratory diseases, asthma, and infectious disease, when combined with TSP.

Table F-7. Associations of long-term exposure to SO_2 with lung cancer incidence and mortality.

STUDY	METHODS	POLLUTANTS	CONCLUSIONS
UNITED STATES			
Abbey et al. (1999) Three California air basins: San Francisco, South Coast (Los Angeles and eastward), San Diego 1977-1992	Prospective cohort study of 6,338 nonsmoking non- Hispanic white adult members of the Adventist Health Study followed for all cause, cardiopulmonary, nonmalignant respiratory, and lung cancer mortality. Participants were aged 27-95 yrs at enrollment in 1977. 1,628 (989 females, 639 males) mortality events followed through 1992. All results were stratified by gender. Used Cox proportional hazards analysis, adjusting for age at enrollment, past smoking, environmental tobacco smoke exposure, alcohol use, education, occupation, and body mass index. Analyzed mortality from all natural causes, cardiopulmonary, nonmalignant respiratory, and lung cancer.	Mean SO_2 Levels: 24-h avg SO_2: 5.6 ppb Copollutants: PM_{10} SO_4 O_3 NO_2	Lung cancer mortality showed large risk estimates for most of the pollutants in either or both sexes, but the number of lung cancer deaths in this cohort was very small (12 for female and 18 for male) Generally wide confidence intervals (relative to other U.S. cohort studies). Adjusted Mortality Relative Risk (95% CI) (per 3.72 ppb SO_2) Lung Cancer Males: 1.99 (1.24, 3.20) Females: 3.01 (1.88, 4.84)
Krewski et al. (2000)	Re-analysis and sensitivity analysis of Dockery et al. (1993) Harvard Six Cities study.	Mean SO_2 Levels: 24-h avg SO_2 ranged from 1.6 (Topeka) to 24.0 (Steubenville) ppb Copollutants: Fine Particles, Sulfates	SO_2 showed positive associations with lung cancer deaths (1.03 (95% CI: 0.91, 1.16)), but in this dataset, SO_2 was highly correlated with $PM_{2.5}$ (r = 0.85), sulfate (r = 0.85), and NO_2 (r = 0.84)
EUROPE			
Beelen et al. (2008) The Netherlands 1987-1996.	Cohort study on diet and cancer with 120,852 subjects who were followed from 1987 to 1996. BS, NO_2, SO_2, and $PM_{2.5}$ and traffic-exposure estimates were analyzed. Cox regression model adjusted for age, sex, smoking, and area-level socioeconomic status.	Mean SO_2 Levels: Mean: 4.8 ppb, with a range of 1.5 to 11.8 ppb. Copollutants: $PM_{2.5}$ BS NO_2	Traffic intensity on the nearest road was not associated with exposure SO_2. Background SO_2 levels were not associated with lung cancer mortality. Adjusted RR (per 20 $\mu g/m^3$ SO_2) 1.00 (0.79, 1.26)
Filleul et al. (2005) Seven French cities 1975-2001	Cohort study of 14,284 adults who resided in 24 areas from seven French cities when enrolled in the PAARC survey (air pollution and chronic respiratory diseases) in 1974. Daily measurements of SO_2, TSP, black smoke, NO_2, and NO were made in 24 areas for three yrs (1974-1976). Cox proportional hazards models adjusted for smoking, educational level, BMI, and occupational exposure. Models were run before and after exclusion of six area monitors influenced by local traffic as determined by the NO/NO_2 ratio >3.	Mean SO_2 Levels: 24-h avg SO_2 ranged from 17 mg/m^3 ("Area 3" in Lille) to 85 mg/m^3 ("Area 3" in Marseille) in the 24 areas in seven cities during 1974-1976. Median levels during 1990-1997 ranged from 8.5 mg/m^3 (Bordeaux) to 23.4 mg/m^3 (Rouen) in the five cities where data were available. Copollutants: TSP Black Smoke NO_2 NO	The authors noted that inclusion of air monitoring data from stations directly influenced by local traffic could overestimate the mean population exposure and bias the results. It should be noted that the table describing air pollution levels in Filleul et al.'s report indicates that the SO_2 levels in these French cities declined markedly from 1974-1976 and 1990-1997 period, by a factor of 2 to 3, depending on the city, whereas NO_2 levels between the two periods were variable, increased in some cities, and decreased in others. These changes in air pollution levels over the study period complicate interpretation of reported risk estimates. Relative Risk (95% CI) for lung cancer mortality (per 10 mg/m^3 multi-year average) All 24 areas: 0.99 (0.92, 1.07) 18 areas:1.00 (0.91, 1.11)

STUDY	METHODS	POLLUTANTS	CONCLUSIONS
Nafstad et al. (2003) Oslo, Norway 1972-1998	Retrospective study associating cardiovascular risk factors to a national cancer register among 16,209 men ages 10-49 yrs. Survival analyses and Cox proportional hazards regression were used to estimate associations.	Estimated for each person each yr from 1974 to 1998 Five-yr median average levels SO_2 participants home address, 1974-1978: 9.4 µg/m^3 (range 0.2 to 55.8) Median levels within the quartiles: 2.5 µg/m^3 6.2 µg/m^3 14.7 µg/m^3 31.3 µg/m^3 Copollutants: NO_X	Adjusted risk ratios (95% CI) of developing lung cancer: Model 1: 0-9.99 µg/m^3: Ref 10-19.99 µg/m^3: 1.05 (0.81, 1.35) 20-29.99 µg/m^3: 0.95 (0.72, 1.27) 30+ µg/m^3: 1.06 (0.79, 1.43) Model 2: Per 10 µg/m^3: 1.01 (0.94, 1.08) Adjusted risk ratios (95% CI) of developing non-lung cancer Model 1: 0-9.99 µg/m^3: Ref. 10-19.99 µg/m^3: 1.07 (0.96, 1.19) 20-29.99 µg/m^3: 0.90 (0.80, 1.02) 30+ µg/m^3: 0.98 (0.86, 1.10) Model 2: Per 10 µg/m^3: 0.99 (0.96, 1.02)
Nafstad et al. (2004) Oslo, Norway 1972-1998	Cohort study of 16,209 Norwegian men 40-49 yrs of age living in Oslo, Norway, in 1972-1973. Data from the Norwegian Death Register were linked with estimates of avg yearly air pollution levels at the participants' home addresses from 1974 to 1998. NO_X, rather than NO_2 was used. Exposure estimates for NO_X and SO_2 were constructed using models based on the subject's address, emission data for industry, heating, and traffic, and measured concentrations. Addresses linked to 50 of the busiest streets were given an additional exposure based on estimates of annual avg daily traffic. Cox proportional-hazards regression was used to estimate associations between exposure and total and cause-specific mortality, adjusting for age strata, education, occupation, smoking, physical activity level, and risk groups for cardiovascular diseases	Mean SO_2 Levels: The yearly avg of 24-h avg SO_2 were reduced with a factor of 7 during the study period from 5.6 ppb in 1974 to 0.8 ppb in 1995. Copollutants: NO_X	SO_2 did not show any associations with lung cancer, e.g., 1.00 (0.93, 1.08) per 10 µg/m^3 increase mortality in SO_2. No association was also observed when including SO_2 in the model as a categorical variable. Note the very low levels of SO_2.
Nyberg et al. (2000) Stockholm County, Sweden Jan 1, 1985-Dec 31, 1990	Case-control study of men 40-70 yrs, with 1,042 cases of lung cancer and 1,274 controls, to evaluate the suitability of an indicator of air pollution from heating.	Annual levels computed for each yr between 1950 and 1990, but not provided herein NO_X/NO_2	Little effect of SO_x in any time window, but highest correlations in early yrs. SO_X RR (CI 95%) from heating (per 10 µg/m^3) for 30-yr avg < 41.30 µg/m^3: 1 ≥ 41.30 to < 52.75: 1.06 (0.83, 1.35) ≥ 52.75 to < 67.14: 0.98 (0.77, 1.24) ≥ 67.14 to < 78.20: 0.90 (0.68, 1.19) ≥ 78.20: 1.00 (0.73, 1.37) SO_X RR (CI 95%) from heating (per 10 µg/m^3) for 10-yr avg < 66.20 µg/m^3: 1 ≥ 66.20 to < 87.60: 1.16 (0.91, 1.47) ≥ 87.60 to < 110.30: 1.00 (0.79, 1.27) ≥ 110.30 to < 129.10: 0.92 (0.70, 1.21) ≥ 129.10: 1.21 (0.89, 1.66)

Table F-8. Associations of long-term exposure to SO_2 with prenatal and neonatal outcomes.

STUDY	METHODS	POLLUTANTS	FINDINGS
UNITED STATES			
Bell et al. (2007) Connecticut and Massachusetts Period of Study: 1999-2002	Outcome(s): LBW Study design: Case-control N: 358,504 live singleton births Statistical Analysis: Linear models and logistic regression Covariates: Gestational length, prenatal care, type of delivery, child's sex, birth order, weather, yr, and mother's race, education, marital status, age, and tobacco use.	Gestational exposure (ppb) Mean: 4.7 SD: 1.2 IQR: 1.6 Copollutants: NO_2 CO PM_{10} $PM_{2.5}$	No relationship between gestational exposure to SO_2 and birth weight. First trimester exposure to SO_2 was associated with low birth weight. No statistical difference n the effect estimates of SO_2 for infants of black and white mothers. Increment: 1.6 ppb (IQR) Change in birth weight: Entire pregnancy: −0.9 g (−4.4, 2.6) Black mother: 1.2 (−6.5, 8.8) White mother: −1.4 (−5.1, 2.3) 1st trimester: −3.7 to −3.3 grams LBW: OR 1.003 (0.961, 1.046)
Gilboa et al. (2005) Seven Texas Counties Period of Study: 1997-2000	Outcome(s): Selected birth defects Study design: Case-control N: 4,570 cases and 3,667 controls Statistical Analysis: Logistic regression Covariates: Maternal education, maternal race/ethnicity, season of conception, plurality, maternal age, maternal illness Statistical package: SAS vs. 8.2	Levels NR Copollutants PM_{10} O_3 NO_2 CO	When the fourth quartile of exposure was compared with the first, SO_2 was associated with increased risk of isolated ventricular septal defects. Inverse associations were noted for SO_2 and risk of isolated atrial septal defects and multiple endocardial cushion defects. Aortic artery and valve defects < 1.3 ppb: 1.00 1.3 to < 1.9: NA 1.9 to < 2.7: 1.06 (0.34, 3.29) ≥ 2.7: 0.83 (0.26, 2.68) Atrial septal defects < 1.3 ppb: 1.00 1.3 to < 1.9: 1.22 (0.79, 1.88) 1.9 to < 2.7: 0.76 (0.47, 1.23) ≥ 2.7: 0.42 (0.22, 0.78) Pulmonary artery and valve defects < 1.3 ppb: 1.00 .3 to < 1.9: 0.63 (0.23, 1.74) 1.9 to < 2.7: 0.93 (0.36, 2.38) ≥ 2.7: 1.07 (0.43, 2.69) Ventricular septal defects < 1.3 ppb: 1.00 1.3 to < 1.9: 1.02 (0.68, 1.53) 1.9 to < 2.7: 1.13 (0.76, 1.68) ≥ 2.7: 2.16 (1.51, 3.09) Conotruncal defects < 1.3 ppb: 1.00 1.3 to < 1.9: 0.71 (0.46, 1.09) 1.9 to < 2.7: 0.71 (0.46, 1.09) ≥ 2.7: 0.58 (0.37, 0.91) Endocardial cushion and mitral valve defects < 1.3 ppb: 1.00 1.3 to < 1.9: 0.89 (0.50, 1.61) 1.9 to < 2.7: 0.89 (0.49, 1.62) ≥ 2.7: 1.18 (0.68, 2.06) Cleft lip with or without cleft palate < 1.3 ppb: 1.00 1.3 to < 1.9: 0.79 (0.52, 1.20) 1.9 to < 2.7: 0.95 (0.64, 1.43) ≥ 2.7: 0.75 (0.49, 1.15) Cleft palate < 1.3 ppb: 1.00 1.3 to < 1.9: 0.89 (0.40, 1.97) 1.9 to < 2.7: 1.49 (0.72, 3.06) ≥ 2.7: 1.22 (0.56, 2.66)

STUDY	METHODS	POLLUTANTS	FINDINGS
Lipfert et al. (2000b) United States 1990	Mortality Outcome(s): SIDS Study design: Cohort Statistical Analysis: Three logistic regression analyses to examine the relation between annual avg air pollutant values and various infant mortality endpoints (i.e., all causes, SIDS, respiratory, and other causes Statistical package: NR Age groups analyzed: 0-1 Covariates: Altitude, degree days (°F), median income (U.S. $), population density Lag(s): N/A		In a model that included states that lacked data on maternal education and smoking along with various personal and ecological variables, SO_2 was not found to be a significant predictor of SIDS mortality in infants with birth weights >2,500 g. ∃ = −0.0118 (0.0094) Mean Risk (95% CI) 0.95 (0.87, 1.03)
Maisonet et al. (2001) 6 Northeastern cities of U.S. Period of Study: 1994-1996	Outcome(s): Term LBW Study design: Case-control N: 89,557 live singleton births Statistical Analysis: Logistic regression models linear regression models Covariates: Maternal age, race, season of the yr, smoking and alcohol use during pregnancy, firstborn, gender, marital status, and previous terminations, prenatal care (ordinal variable), weight gain, and gestational age Stratified by race/ethnicity Statistical package: STATA	Exposure distribution (< 25th, 25th to < 50th, 50th to < 75th, 75th to < 95th, ≥ 95th) First trimester: < 7.09, 7.090 to 8.906, 8.907 to 11.969, 11.970 to 18.447, ≥18.448 Second trimester: < 6.596, 6.596 to 8.896, 8.897 to 11.959, 11.960 to 18.275, ≥ 18.276 Third trimester: < 5.810, 5.810 to 8.453, 8.454 to 11.777, 11.778 to 18.134, ≥ 18.135 Copollutants: CO PM_{10}	This study provides evidence of an increased risk for term LBW in relation to increased ambient air levels of SO_2 at concentrations well below the established standards. Higher risk estimates among whites when stratified by race/ethnicity First trimester: < 25th: Referent 25th-50th: 1.04 (0.88, 1.23) 50th-75th: 1.04 (0.94, 1.15) 75th-95th: 0.98 (0.81, 1.17) > 95th: 0.88 (0.73, 1.07) Increment (10 ppm): 0.98 (0.93, 1.03) Second trimester: 25th-50th: 1.18 (1.12, 1.25) 50th-75th: 1.12 (1.07, 1.17) 75th-95th: 1.13 (1.05, 1.22) > 95th: 0.87 (0.80, 0.95) Increment (10 ppm): 1.01 (0.93, 1.10) Third trimester: 25th-50th: 1.04 (0.92, 1.18) 50th-75th: 1.02 (0.87, 1.18) 75th-95th: 1.04 (0.84, 1.28) > 95th: 1.06 (0.76, 1.47) Increment (10 ppm): 1.01 (0.86, 1.20)
Sagiv et al. (2005) 4 Pennsylvania counties Period of Study: 1997-2001	Outcome(s): Pre-term birth Study design: Time-series N: 187,997 births Study design: Poisson-regression models Covariates: Long-term trends, copollutants, temperature, dew point temperature, and day of wk. Lag: Daily lags ranging from 1-7 days	Mean SO_2 Levels: 6-wk Mean: 7.9 ± 3.5 ppb (Range: 0.8, 17), MediaN: 8.1 Daily Mean: 7.9 ± 6.2 (Range: 0, 54.1), MediaN: 6.4 Copollutants: PM_{10}; r = 0.46 CO NO_2	This study found an increased risk for preterm delivery during the last 6 wks of pregnancy with exposure to SO_2. Increment: 15 ppb Mean: 6-wk SO_2: RR = 1.15 (1.00, 1.32) < 4.9 ppb: Referent 4.9 to 8.1 ppb: 1.02 (0.97, 1.06) 8.1 to 10.6 ppb: 1.04 (0.98, 1.10) 10.6 to 17.0 ppb: 1.06 (0.99, 1.14) Mean: Daily SO_2: RR = 1.07 (0.99, 1.15) lag 3
CANADA			
Dales et al. (2004) 12 Canadian cities Period of Study: 1984-1999	Outcome(s): SIDS Study design: Time-series N: 1556 SIDS deaths Statistical Analysis: Random effects regression model Covariates: Temperature, humidity, barometric pressure, season Lag: 0-5 days	Mean SO_2 Levels: 24-h avg: 5.51 ppb IQR: 4.92 Copollutants: CO NO_2 O_3 PM_{10} $PM_{2.5}$ $PM_{10-2.5}$	SIDS was associated with air pollution, with the effects of SO_2 seeming to be independent of sociodemographic factors, temporal trends, and weather. Increment: 4.92 ppb (IQR) Increase in SIDS incidence: 8.49%; p = 0.0079 lag 1

STUDY	METHODS	POLLUTANTS	FINDINGS
Dales et al. (2006) 11 Canadian cities Period of Study: 1986-2000	Outcome(s): Hospitalization for respiratory disease in the neonatal period Study design: Time-series N: 9,542 Statistical Analysis: Random effects regression model; Poisson using fixed- or random-effects model Covariates: Fay of wk, temperature, humidity, pressure Lag: 0-5 days Statistical package: S-PLUS vs. 6.2	Mean SO_2 Levels: 24-h avg: 4.3 ppb IQR: 3.8 Copollutants: NO_2; r = 0.20, 0.67 CO; r = 0.19, 0.66 O_3; r = −0.41, 0.13 PM_{10}; r = −0.09, 0.61 SO_4	This study detected a significant association for respiratory disease among neonates and gaseous air pollutants. Increment: 3.8 ppb (IQR) Increase in neonatal respiratory hospital admissions: SO_2 alone: 2.06% (1.04, 3.08) Multipollutant model: 1.66% (0.63, 2.69) Multipollutant model restricted to days with PM_{10} measures: 1.41% (0.35, 2.47)
Dugandzic et al. (2006) Nova Scotia, Canada Period of Study: 1988-2000	Outcome(s): Term LBW Study design: Retrospective cohort study N: 74,284 term, singleton births Statistical Analysis: Logistic regression models Covariates: Maternal age, parity, prior fetal death, prior neonatal death, and prior low birth weight infant, smoking during pregnancy, neighborhood family income, infant gender, gestational age, weight change, and yr of birth. Statistical package: SAS vs. 8.0	Mean: SO_2 10 ppb MediaN: 10 25th%: 7 75th%: 14 Max: 38 Copollutants: O_3 PM_{10}	In the analyses unadjusted for birth yr, first trimester exposures in the highest quartile for SO_2 associated with increased risk of LBW. After adjusting for birth yr, RR attenuated and not statistically significant. There was a linear concentration-response effect with increasing levels of SO_2 during the first trimester. First Trimester 25th-50th: 0.96 (0.73, 1.28) 51st-75th: 1.18 (0.88, 1.58) >75th: 1.36 (1.04, 1.78) Increment (7 ppb): 1.20 (1.05, 1.38) Second Trimester 25th-50th: 1.12 (0.86, 1.46) 51st-75th: 1.13 (0.85, 1.50) >75th: 1.04 (0.79, 1.37) Increment (7 ppb): 0.99 (0.87, 1.13) Third Trimester 25th-50th: 1.04 (0.80, 1.34) 51st-75th: 0.85 (0.63, 1.15) >75th: 0.88 (0.67, 1.15) Increment (7 ppb): 0.93 (0.81, 1.06)
Liu et al. (2003) Vancouver, Canada Period of Study: 1986-1998	Outcomes: Preterm birth, LBW, IUGR Study design: Case-control N: 229,085 singleton live births Statistical Analysis: Multiple logistic regressions Covariates: Maternal age, parity, infant sex, gestational age or birth weight and season of birth	24-h avg: 4.9 ppb, 5th: 1.5 25th: 2.8 50th: 4.3 75th: 6.3 95th: 10.5 100th: 30.5 1-h max: 13.4 ppb, 5th: 4.3 25th: 7.8 50th: 11.7 75th: 16.8 95th: 28.3 100th: 128.5 Copollutants: NO_2 (r = 0.61) CO (r = 0.64) O_3 (r = −0.35)	LBW and IUGR were associated with maternal exposure to SO_2 during the first mo of pregnancy and preterm birth was associated with SO_2 during the last mo. These results were robust to adjustment for copollutants. Increment: 5 ppb Low birth weight First mo: OR 1.11 (1.01, 1.22) Last mo: OR 0.98 (0.89, 1.08) Preterm birth First mo: OR 0.95 (0.88, 1.03) Last mo: OR 1.09 (1.01, 1.19) IUGR First mo: OR 1.07 (1.01, 1.13) Last mo: OR 1.00 (0.94, 1.06) First trimester: OR 1.07 (1.00, 1.14) Second trimester: 0.98 (0.91, 1.04) Third trimester: 1.03 (0.96, 1.10)

STUDY	METHODS	POLLUTANTS	FINDINGS
Liu et al. (2006) Calgary, Edmonton and Montreal, Canada Period of Study: 1986-2000	Outcome(s): IUGR Study design: Case-control N: 386,202 singleton live births Statistical Analysis: Multiple logistic regression Covariates: Maternal age, parity, infant sex, season of birth, city of residence	24-h avg: 3.9 ppb, 25% 2.0 ppb 50% 3.0 ppb 75% 5.0 ppb 95% 10.0 ppb 1-h max: 10.8 ppb, 25% 5.0 ppb 50% 8.6 ppb 75% 14.0 ppb 95% 28.0 ppb Copolllutants: NO_2 (r = 0.34) CO (r = 0.21) O_3 (r = −0.30) $PM_{2.5}$ (r = 0.44)	IUGR did not increase with maternal exposure to SO_2. Risk decreased during first 3 mos. Increment: 3.0 ppb ORs estimated from graph: 1st mo: OR ~0.966 (0.94, 0.99) 2nd mo: OR ~0.97 (0.95, 0.995) 3rd mo: OR ~0.97 (0.95, 0.995) 1st trimester: OR ~0 .96 (0.93, 0.99)
Bobak et al. (2000) Czech Republic Period of Study: 1990-1991	Outcomes: LBW, preterm birth Study design: Case-control N: 108,173 live singleton births Statistical Analysis: Logistic regression Covariates: Temperature, humidity, day of wk, season, residential area, maternal age, gender Statistical package: STATA	Mean trimester exposures 25th: 17.5 μg/m^3 50th: 32.0 μg/m^3 75th: 55.5 μg/m^3 Copollutants: TSP; r = 0.68 0.73 NO_X; r = 0.53, 0.63	LBW and preterm birth were associated with maternal exposure to SO_2, though the association between SO_2 and LBW was explained to a large extent by low gestational age. Increment: 50 μg/m^3 LBW (adjusted for sex, parity, maternal age group, education, marital status, and nationality, and mo of birth) 1st trimester: 1.20 (1.11, 1.30) 2nd trimester: 1.14 (1.06, 1.22) 3rd trimester: 1.14 (1.06, 1.23) LBW (also adjusted for gestational age) 1st trimester: 1.01 (0.88, 1.17) 2nd trimester: 0.95 (0.82, 1.10) 3rd trimester: 0.97 (0.85, 1.10) Preterm birth (AOR) 1st trimester: 1.27 (1.16, 1.39) 2nd trimester: 1.25 (1.14, 1.38) 3rd trimester: 1.24 (1.13, 1.36) Reduction in mean birth weight: 1st trimester: 1.4 g (5.9, 16.9)
LATIN AMERICA			
Gouveia et al. (2004) São Paulo, Brazil Period of Study: 1997	Outcome(s): LBW Study design: Case-control N: 179,460 live singleton births Statistical Analysis: Logistic regression with GAM Covariates: Gender, gestational age, maternal age, maternal education, antenatal care, parity, delivery method Statistical package: S-Plus 2000	Annual Mean: SO_2 (μg/m^3) Mean: 19.6 SD: 10.3 Range: 3.4, 56.9 Jan-Mar: 22.3 (7.7) Apr-June: 28.1 (10.1) Jul-Aug: 17.9 (8.7) Oct-Dec: 10.3 (3.9) Copollutants: PM_{10} CO NO_2 O_3	First and second trimester exposures to SO_2 had a significant association with birth weight, though in different directions. When air pollutants were divided into quartiles and the lowest quartile was used as the referent exposure category, SO_2 during the second trimester was marginally associated with low birth weight. Increment: 10 μg/m^3 Reduction in birth weight First trimester: −24.2 g (−55.5, 7.1) Second trimester: 33.7 g (1.6, 65.8) Third trimester: 9.7 g (−25.6, 44.9) First trimester: 2nd: 0.902 (0.843, 0.966) 3rd: 0.911 (0.819, 1.013) 4th: 0.906 (0.793, 1.036) Second trimester: 2nd: 0.986 (0.922, 1.053) 3rd: 1.005 (0.904, 1.117) 4th: 1.017 (0.883, 1.173) Third trimester: 2nd: 1.203 (0.861, 1.68) 3rd: 1.225 (0.872, 1.722) 4th: 1.145 (0.749, 1.752)

STUDY	METHODS	POLLUTANTS	FINDINGS
EUROPE			
Mohorovic (2004) Labin, Istra, Croatia Period of Study: 1987-1989	Outcomes: LBW and preterm delivery Study design: Cross-sectional N: 704 births Statistical Analysis: Multiple correlation analyses, factor analyses, chi-square Statistical package: DBASE IV, SPSS	Monthly ground levels of SO_2: Range: 34.1, 252.9 µg/m^3	The results show an association between SO_2 exposure at the end of the first and second mo of pregnancy and a negative correlation between length of gestations and lower birth weight of newborns. Correlation coefficients: 1st mo: Gestation length: −0.09, p = 0.008 Birthweight: −0.08, p = 0.016 2nd mo: Gestation length: −0.08, p = 0.016 Birthweight: −0.07, p = 0.026 3rd mo: Gestation length: −0.04, p = 0.147 Birthweight: −0.04, p = 0.135 6th mo: Gestation length: −0.02, p = 0.266 Birthweight: −0.04, p = 0.151 Whole pregnancy: Gestation length: −0.09, p = 0.007 Birthweight: −0.04, p = 0.153 Weekly avg during whole pregnancy: Gestation length: −0.05, p = 0.086 Birthweight: −0.06, p = 0.069
Pereira et al. (1998) São Paulo, Brazil Period of Study: 1991-1992	Outcome(s): Intrauterine mortality Study design: Time-series Statistical Analysis: Poisson regression models Covariates: Mo, day of wk, min daily temperature, relative humidity Lag: 2 to 14 days	24-h avg SO_2: 18.90 (8.53) mg/m^3 Range: 3.80, 59.70 Copollutants: PM_{10}; r = 0.45 NO_2; r = 0.41 O_3; r = 0.17 CO; r = 0.24	SO_2 exhibited a marginal association with intrauterine mortality, but only when Poisson regression was employed. A concentration-response relationship was found. Estimated regression coefficients and standard errors: SO_2 alone: 0.0038 (0.0020) SO_2 + NO_2 + CO + PM_{10} + O_3: 0.0029 (0.0031)
ASIA			
Ha et al. (2001) Seoul, Korea Period of Study: 1996-1997	Outcome(s): LBW Study design: Case-control N: 276,763 Statistical Analysis: Logistic regression, GAM Covariates: Gestational age, maternal age, parental education level, infant's birth order, gender	24-h avg: 1st trimester: 25th: 10.0 ppb 50th: 13.2 ppb.75th: 16.2 ppb 3rd trimester:25th: 8.4 ppb 50th: 12.2 ppb.75th: 16.3 ppb Copollutants: CO; r = 0.83. NO_2; r = 0.70 TSP; r = 0.67. O_3; r = −0.29	Ambient SO_2 concentrations during the first trimester of pregnancy were associated with LBW Increment: 1st trimester: 6.2 ppb; 3rd trimester: 7.9 ppb 1st trimester: RR 1.06 (1.02, 1.10) 3rd trimester: RR 0.93 (0.88, 0.98) Reduction in birth weight: 8.06 g (5.59, 10.53)
Lee et al. (2003) Seoul, Korea Period of Study: 1996-1998	Outcome(s): Term LBW Study design: N: 388,105 full-term singleton births Statistical Analysis: GAM Covariates: Infant sex, birth order, maternal age, parental education level, time trend, and gestational age.	Avg concentration (ppb) Mean: 12.1 SD: 7.4 Range: 3, 46 25th: 6.8 50th: 9.8 75th: 15.6 Copollutants: PM_{10}; r = 0.78, 0.85 CO; r = 0.79, 0.86 NO_2; r = 0.75, 0.76	Second trimester exposures to SO_2 as well as during the entire pregnancy were associated with LBW. Reduction in birth weight was 14.6 g for IQR increase in SO_2 in the second trimester. When the exposure for each mo of pregnancy was evaluated separately, SO_2 exposure during 3 to 5 mos of pregnancy associated with LBW. Increment: 8.8 ppb (IQR) First trimester: 1.02 (0.99, 1.06) Second trimester: 1.06 (1.02, 1.11) Third trimester: 0.96 (0.91, 1.00) All trimesters: 1.14 (1.04, 1.24)

STUDY	METHODS	POLLUTANTS	FINDINGS
Leem et al. (2006) Incheon, Korea Period of Study: 2001-2002	Outcome(s): Preterm delivery Study design: N: 52,113 singleton births Statistical Analysis: Log-binomial regression Covariates: Maternal age, parity, sex, season, maternal education, paternal education	Mean:SO_2 Concentrations by trimester: 1st trimester: MiN: 7.86 µg/m^3 25th: 17.61. 50th: 22.74 75th: 45.85. Max: 103.96 3rd trimester: MiN: 6.55 µg/m^3 25th: 17.03. 50th: 25.62 75th: 46.53. Max: 103.15 Copollutants: NO_2; r = 0.54. CO; r = 0.31 PM_{10}; r = 0.13	This study found the highest SO_2 concentrations during the first trimester to be significantly associated with elevated risks of preterm delivery. 1st trimester: 7.86 to 17.61 µg/m^3: referent 17.62 to 22.74: 1.13 (0.99, 1.28) 22.75 to 45.85: 1.13 (0.98, 1.30) 45.86 to 103.96: 1.21 (1.04, 1.42) 3rd trimester: 6.55 to 17.03 µg/m^3: referent 17.04 to 25.62: 0.87 (0.76, 1.01) 25.63 to 46.53: 0.97 (0.83, 1.13) 46.54 to 103.15: 1.11 (0.94, 1.31)
Lin et al. (2004) Kaohsiung and Taipei, Taiwan (1995-1997) Kaohsiung and Taipei, Taiwan (1995-1997)	Outcome(s): LBW Study design: Case-control N: 92,288 live births Statistical Analysis: Multiple logisistic regression Covariates: Gestational period, gender, birth order, maternal age, maternal education, season of birth	24-h avg: Kaohsiung Range: 10.07, 25.36 ppb Taipei: Range: 5.65, 9.33 ppb Copollutants: CO NO_2 O_3 PM_{10}	Few women living in Taipei were exposed to high levels of SO_2. In Kaohsiung, almost all women were exposed to high levels of SO_2. Women living in Kaohsiung had significantly higher risk of term LBW compared with women living in Taipei. OR for Kaoshiung births (compared to Taipei births) All births: OR: 1.13 (1.03, 1.24) Female births only: OR: 1.14 (1.01, 1.28)
Lin et al. (2004a) Kaohsiung and Taipei, Taiwan Period of Study: 1995-1997	Outcome(s): Term LBW Study design: Cohort N: 92,288 live births Statistical Analysis: Multiple logisistic regression Covariates: Gestational period, gender, birth order, maternal age, maternal education, season of birth	24-h avg: Kaohsiung Range: 10.07, 25.36 ppb Taipei: Range: 5.65, 9.33 ppb Copollutants: CO NO_2 O_3 PM10	This study found a 26% higher risk of term LBW delivery for mothers exposed to mean SO_2 concentrations exceeding 11.4 ppb during the entire pregnancy, as compared with mothers exposed to mean concentrations less than 7.1 ppb. Trimester specific analysis showed a significant association only for the third trimester. Lowest quartile of exposure = referent Entire pregnancy: 25th-75th: 1.16 (1.02, 1.33) >75th: 1.26 (1.04, 1.53) 1st trimester: 25th-75th: 1.02 (0.90, 1.16) >75th: 1.11 (0.94, 1.33) 2nd trimester: 25th-75th: 1.09 (0.96, 1.24) >75th: 1.17 (0.99, 1.37) 3rd trimester:25th-75th: 1.13 (0.99, 1.28) >75th: 1.20 (1.01, 1.41)
Wang et al. (1997) Four residential areas: Dongcheng, Xicheng, Cong-wen, Xuanwu Beijing, China Period of Study: 1988-1991	Outcome(s): Term LBW Study design: Cohort study N: 74,671 first parity live births Statistical Analysis: Multiple linear regression and logistic regression with GAM Covariates: Gestational age, residence, yr of birth, maternal age, and infant gender.	Mean pollution concentrations provided in graph TSP; r = 0.92	Exposure-response relationship between SO_2 during the third trimester of pregnancy and low birth weight. 3rd trimester: 9 to 18 µg/m^3 (reference) 18 to 55: 1.09 (0.94, 1.26) 55 to 146: 1.12 (0.97, 1.29) 146 to 239: 1.16 (1.01, 1.34) 239 to 308: 1.39 (1.22, 1.60) SO_2 as continuous variable: Odds ratio per 100 µg/m^3: 1.11 (1.06, 1.16)
Xu et al. (1995) Four residential areas: Dongchen, Xichen, Congwen, Xuanwu Beijing, China Period of Study: 1988	Outcome(s): Preterm delivery Study design: Prospective cohort study N: 25,370 singleton first live births Statistical Analysis: Multiple linear and logistic regression Covariates: Temperature, humidity, day of wk, season, residential area, maternal age, and gender of child.	2 monitors for SO_2: Dongcheng and Xicheng Dongcheng Annual Mean: 108 µg/m^3 SD: 141 µg/m^3) Xicheng annual Mean: 93 µg/m^3 (SD: 122 µg/m^3) Copollutants: TSP	Exposure response relationship between quar-tiles of SO_2 and crude incidence rates of pre-term birth. Dose dependent relationship between SO_2 and gestational age. The estimated reduced length of gestation was 0.075 wks or 12.6 h per 100/m^3 increase in SO_2. When TSP and SO_2 included in a multipollutant model, the effect of SO_2 was reduced by 32%. Effect on gestational age (wk) per 100 µg/m^3 regression coef and SE for lagged moving avg of SO_2. lag 0: −0.016 (0.021). lag 1: −0.022 (0.021) lag 6: −0.067 (0.024), p < 0.01 lag 7: −0.075 (0.024) , p < 0.01 lag 8: −0.075 (0.025), p < 0.01 OR for each quartile of SO_2 1st: 1.00. 2nd: 1.70 (1.15, 2.52) 3rd: 1.74 (1.03, 2.92). 4th: 1.58 (0.87, 2.86) Adjusted OR for preterm delivery: 1.21 (1.01, 1.46) per ln µg/m^3 increase in SO_2

STUDY	METHODS	POLLUTANTS	FINDINGS
Yang et al. (2003a) Kaohsiung, Taiwan Period of Study: 1995-1997	Outcome(s): Term LBW Study design: Case-control N: 13,396 first parity singleton live births Statistical Analysis: Multiple linear regression Covariates: Maternal age, season, marital status, maternal education, gender Statistical package: SAS	Mean: trimester exposure ($\mu g/m^3$) 1st trimester 33rd: 26.02. 67th: 36.07 2nd trimester 33rd: 25.76. 67th: 35.63 3rd trimester 33rd: 25.39. 67th: 36.96 Copollutants: PM_{10} r = 0.45, 0.46	A significant exposure-response relationship between maternal exposures to SO_2 and birth weight was found first trimester of pregnancy. Reduction in birth weight: 1st trimester: 33rd-67th: 3.68 g (−12.45, 19.21) >67th: 18.11 g (1.88, 34.34) Continuous: 0.52 g (0.09, 2.63) 2nd trimester: 33rd-67th: 1.78 g (−17.91, 14.35) >67th: 13.53 g (−2.62, 29.68) Continuous: 0.19 g (−0.78, 1.8) 3rd trimester: 33rd-67th: 0.43 g (−16.56, 15.70) >67th: 1.97 g (−18.24, 14.30) Continuous: 0.03 g (−1.21, 1.37)

Table F-9. Associations of long-term exposure to SO_2 with mortality.

STUDY	CONC.	METHOD	CONCLUSIONS
UNITED STATES			
Abbey et al. (1999) Three California air basins: San Francisco, South Coast (Los Angeles and eastward), San Diego 1977-1992	24-h avg SO_2: 5.6 ppb	Prospective cohort study of 6,338 nonsmoking non-Hispanic white adult members of the Adventist Health Study followed for all cause, cardiopulmonary, nonmalignant respiratory, and lung cancer mortality. Participants were aged 27-95 yrs at enrollment in 1977. 1,628 (989 females, 639 males) mortality events followed through 1992. All results were stratified by gender. Used Cox proportional hazards analysis, adjusting for age at enrollment, past smoking, environmental tobacco smoke exposure, alcohol use, education, occupation, and body mass index. Analyzed mortality from all natural causes, cardiopulmonary, nonmalignant respiratory, and lung cancer.	SO_2 was not associated with total (RR = 1.07 (95% CI: 0.92, 1.24) for male and 1.00 (95% CI: 0.88, 1.14) for female per 5 ppb increase in multiyear average SO_2), cardiopulmonary, or respiratory mortality for either sex. Lung cancer mortality showed large risk estimates for most of the pollutants in either or both sexes, but the number of lung cancer deaths in this cohort was very small (12 for female and 18 for male) Generally wide confidence intervals (relative to other U.S. cohort studies).
Beeson et al. (1998) Three California air basins: San Francisco, South Coast (Los Angeles and eastward), San Diego 1977-1992	24-h avg SO_2: 5.6 ppb	Prospective cohort study of 6,338 nonsmoking non-Hispanic white adult members of the Adventist Health Study aged 27-95 yrs at time of enrollment. 36 (20 females, 16 males) histologically confirmed lung cancers were diagnosed through 1992. Extensive exposure assessment, with assignment of individual long-term exposures to O_3, PM_{10}, SO_4^{2-}, and SO_2, was a unique strength of this study. All results were stratified by gender. Used Cox proportional hazards analysis, adjusting for age at enrollment, past smoking, education, and alcohol use.	Lung cancer incidence relative risk: Male: RR = 3.72 (95%CI: 1.91, 7.28); Female: RR = 2.78 (95%CI: 1.51, 5.12) per 5 ppb increase in SO_2 Case number very small (16 for male, 20 for female).
Dockery et al. (1993) Portage, WI; Topeka, KS; Watertown, MA; Harriman, TN; St. Louis, MO; Steubenville, OH 1974-1991.	24-h avg NO_2 ranged from 1.6 (Topeka) to 24.0 (Steubenville) ppb.	A prospective cohort study to study the effects of air pollution with main focus on PM components in six U.S. cities, which were chosen based on the levels of air pollution (Portage, WI, the least polluted to Steubenville, OH, the most polluted). Cox proportional hazards regression was conducted with data from a 14-to-16-yr follow-up of 8,111 adults in the six cities, adjusting for smoking, sex, BMI, occupational exposures, etc. $PM_{2.5}$ and sulfate were associated with these causes of deaths.	SO_2 result presented only graphically. Fine particles and sulfate showed better fit than SO_2.
Krewski et al. (2000) Re-analysis and sensitivity analysis of Dockery et al. (1993) study.	24-h avg NO2 ranged from 1.6 (Topeka) to 24.0 (Steubenville) ppb	Gaseous pollutants risk estimates were presented.	SO_2 showed positive associations with total (RR = 1.05 (95% CI: 1.02, 1.09) per 5 ppb increase in the average SO_2 over the study period), cardiopulmonary (1.05 (95% CI: 1.00, 1.10)), and lung cancer deaths (1.03 (95% CI: 0.91, 1.16)), but in this dataset, SO_2 was highly correlated with $PM_{2.5}$ (r = 0.85), sulfate (r = 0.85), and NO_2 (r = 0.84)

STUDY	CONC.	METHOD	CONCLUSIONS
Krewski et al. (2000); Jerrett et al. (2003); Krewski et al. (2003); Re-analysis/sensitivity analysis of Pope et al. (1995) study.	Multiyear avg of 24-h avg 9.3 ppb.	Re-analysis of Pope et al. (1995) study. Extensive sensitivity analysis with ecological covariates and spatial models to account of spatial pattern in the ACS data.	In the Jerret et al. reanalysis the relative risk estimates for total mortality was 1.06 (95% CI: 1.05, 1.07) per 5 ppb increase in the annual avg SO_2. In the spatial filtering model (this was the model that resulted in the largest reduction of SO_2 risk estimate when sulfate was included), the SO_2 total mortality risk estimate was 1.07 (95% CI: 1.03, 1.11) in the single-pollutant model and 1.04 (95% CI: 1.02, 1.06) with sulfate in the model. The risk estimates for $PM_{2.5}$ and sulfate were diminished when SO_2 was included in the models. In the sensitivity analysis conducted by Krewski et al. SO_2 was significantly associated with all-cause mortality in a single-pollutant model: 1.30 (1.23, 1.38). In the spatial analysis, SO_2 was found to be the only gaseous pollutant strongly associated with all-cause and cardiopulmonary disease mortality: Relative Risk (95% CI) (per 19.9 µg/m^3 Sulfates) Spatial Analysis, All-Cause Independent Observations Sulfates + SO_2: 1.05 (0.98, 1.12) Fine particles + SO_2: 1.03 (0.95, 1.13) Independent Cities Sulfates + SO_2: 1.13 (1.02, 1.25) Fine particles + SO_2: 1.14 (0.98, 1.32) Regional Adjustment Sulfates + SO_2: 1.10 (0.97, 1.24) Fine particles + SO_2: 1.11 (0.93, 1.33) Spatial Filtering Sulfates + SO_2: 1.05 (0.97, 1.14)
Lipfert et al. (2000a) 32 Veterans Administration hospitals nationwide in the U.S. 1976-2001	Mean of the 95th percentile of the 24-h avg SO_2 for 1997-2001 period: 15.8 ppb.	Update of the Lipfert et al. (2000a) study, with follow-up period extended to 2001. Study focused on the traffic density data. The county-level traffic density was derived by dividing vehicle-km traveled by the county land area. Because of the wide range of the traffic density variable, log-transformed traffic density was used in their analysis. They reported that traffic density was a better predictor of mortality than ambient air pollution variables, with the possible exception of O_3. The log-transformed traffic density variable was weakly correlated with SO_2 (r = 0.32) in this data set.	RR using the 1997-2001 air quality data period: 0.99 (95% CI: 0.97, 1.01) per 5 ppb increase; in a single-pollutant model. The 2-pollutant model with the traffic density variable: 0.99 (95% CI: 0.96, 1.01) per 5 ppb.
Lipfert et al. (2000b) 32 Veterans Administration hospitals nationwide in the U.S. 1997-2001	Mean of the 95th percentile of the 24-h avg SO_2 for 1999-2001 period: 16.3 ppb.	Update of the Lipfert et al. (2000a) study, examined $PM_{2.5}$ chemical constituents data. The analysis used county-level air pollution data for the period 1999-2001 and cohort mortality data for 1997-2001.	Traffic density was the most important predictor of mortality, but associations were also seen for EC, V, nitrate, and Ni. NO_2, ozone, and PM_{10} also showed positive but weaker associations. The risk estimate for SO_2 was essentially the same as that reported in the 2006a Lipfert et al. analysis (0.99 (95% CI: 0.96, 1.01) per 5 ppb) in a single-pollutant model. Multipollutant model results were not presented for SO_2.
Pope et al. (1995) U.S. nationwide 1982-1989	Not analyzed/ reported.	Investigated associations between long-term exposure to PM and the mortality outcomes in the American Cancer Society cohort. Ambient air pollution data from 151 U.S. metropolitan areas in 1981 were linked with individual risk factors in 552,138 adults who resided in these areas when enrolled in the prospective study in 1982. Death outcomes were ascertained through 1989. Cox proportional hazards model adjusted for smoking, education, BMI, and occupational exposures. $PM_{2.5}$ and sulfate were associated with total, cardiopulmonary, and lung cancer mortality, but not with mortality for all other causes.	Gaseous pollutants not analyzed.

STUDY	CONC.	METHOD	CONCLUSIONS
Pope et al. (2002) U.S. nationwide 1982-1998	24-h avg mean of 118 MSA's in1980: 9.7 ppb; mean of 126 MSA's during 1982-1998: 6.7 ppb.	Prospective cohort study of approximately 500,000 members of American Cancer Society cohort enrolled in 1982 and followed through 1998 for all cause, cardiopulmonary, lung cancer, and all other cause mortality. Age at enrollment was 30+ yrs. Air pollution concentrations in urban area of residence at time of enrollment assessed from 1982 through 1998. Other pollutants considered include TSP, PM_{15}, PM_{10}, $PM_{2.5}$, $PM_{15\text{-}2.5}$, SO_4^{2-}, SO_2, NO_2, and CO.	$PM_{2.5}$ was associated with total, cardiopulmonary, lung cancer mortality, but not with deaths for all other causes. SO_2 was associated with all the mortality outcomes, including all other causes of deaths. SO_2's risk estimate for total mortality was 1.03 (95% CI: 1.02, 1.05) per 5 ppb increase (1982-1998 average).Residential location was known only at enrollment to study in 1982. Thus, exposure misclassification possible.
Willis et al. (2003) Re-analysis/ sensitivity analysis of Pope et al. (1995) study.	Multiyear average of 24-h avg using MSA scales: 9.3 ppb; using county scales: 10.7 ppb.	Investigation of the effects of geographic scale over which the air pollution exposures are averaged. Exposure estimates were averaged over the county scale, and compared the original ACS results in which MSA scale average exposures were used. Less than half of the cohort used in the MSA-based study were used in the county scale based analysis because of the limited availability of sulfate monitors and because of the loss of subjects from the use of five-digit zip codes	In the analysis comparing the 2-pollutant model with sulfate and SO_2, they found that, in the MSA-scale model, the inclusion of SO_2 reduced sulfate risk estimates substantially (>25%), but not substantially (< 25%) in the county-scale model. In the MSA-level anlaysis (with 113 MSA's), SO_2 relative risk estimate was 1.04 (95% CI: 1.02, 1.06) per 5 ppb increase, with sulfate in the model. In the county-level anaysis (91 counties) with sulfate in the model, the corresponding estimate was smaller (RR = 1.02 [95% CI: 1.00, 1.05]). The correlation between covariates are different between the MSA-level data and county-level data.
Lipfert et al. (2000b; 2003) 32 Veterans Administration hospitals nationwide in the U.S. 1976-1996	SO_2 mean levels NR.	Cohort study of approximately 50,000 U.S. veterans (all males) diagnosed with hypertension. Mean age at recruitment was 51 yrs. Exposure to O_3 during four periods (1960-1974, 1975-1981, 1982-1988, 1989-1996) associated with mortality over three periods (1976-1981, 1982-1988, 1989-1996). Long-term exposures to TSP, PM_{15}, PM_{10}, $PM_{2.5}$, $PM_{15\text{-}2.5}$, SO_4^{2-}, NO_2, and CO also analyzed. Used Cox proportional hazards regression, adjusting for race, smoking, age, systolic and diastolic blood pressure, body mass index, and socioeconomic factors.	"SO_2 and Pb were considered less thoroughly. "The authors presented only qualitative results for SO_2 from the "Screening regressions" which indicated negatively significant risk estimate in the univariate model and non-significant positive estimate in the multivariate model.
CANADA			
Finkelstein et al. (2003) Ontario, Canada 1992-1999	24-h avg (ppb): 4.9 (1.0)	Cohort consisting of 5,228 people >40 yrs old that were referred for pulmonary function testing between 1985 and 1999. Within the cohort identified nonaccidental deaths that occurred from 1992 through 1999. Used air quality data for TSP from 1992-1994 and SO_2 for 1993-1995. Analyzed the association between TSP or SO_2 and socioeconomic status and mortality using a Cox proportional hazards model stratified by sex and 5-yr age groups.	Using the high income-low pollutant level as the reference the following results were reported for each of the mortality endpoints: Relative Risk (95% CI) All causes High income-high pollutant level: 1.35 (1.05, 1.73) Low income-low pollutant level: 1.64 (1.21, 2.24) Low income-high pollutant level: 2.40 (1.61, 3.58) Interaction with age group: 0.97 (0.95, 0.99) Cardiopulmonary causes High income-high pollutant level: 1.54 (1.13, 2.10) Low income-low pollutant level: 2.05 (1.45, 2.91) Low income-high pollutant level: 3.36 (2.12, 5.32) Interaction with age group: 0.95 (0.92, 0.97)
EUROPE			
Beelen et al. (2008) The Netherlands 1987-1996.	Cohort study on diet and cancer with 120,852 subjects followed from 1987 to 1996. BS, NO_2, SO_2, and $PM_{2.5}$ and traffic-exposure estimates were analyzed. Cox regression model adjusted for age, sex, smoking, and area-level socioeconomic status.	Mean SO_2 Levels: Mean: 4.8 ppb, with a range of 1.5 to 11.8 ppb. Copollutants: $PM_{2.5}$ BS NO_2	Traffic intensity on the nearest road was not associated with exposure SO_2. Background SO_2 levels were not associated with mortality. Adjusted RR (per 20 µg/m^3 SO_2) All cause: 0.97 (0.90,1.05) Cardiovascular: 0.94 (0.82, 1.06) Respiratory: 0.88 (0.64, 1.22)

STUDY	CONC.	METHOD	CONCLUSIONS
Elliott et al. (2007) Great Britain; 1966-1994 air pollution; 1982-1998 mortality in four periods.	24-h avg SO_2 levels declined from 41.4 ppb in 1966-1970 to 12.2 ppb in 1990-1994	A small area analysis of mortality rates in electoral ward, with the mean area of 7.4 km^2 and the mean population of 5,301 per electoral ward. Deaths rates were computed for four successive 4-yr periods from 1982 to 1994. The number of wards in these four periods ranged from 118 in the 1994-1998 period to 393 in the 1982-1986 period. Poisson model was fit to model observed deaths for each ward with a linear function for pollutant and random intercept, with and without adjustment for social deprivation.	They observed associations for both BS and SO_2 and mortality outcomes. The estimated effects were stronger for respiratory illness than other causes of mortality for the most recent exposure periods and most recent mortality period (pollution levels were lower). The adjustment for social deprivation reduced the risk estimates for both pollutants. The adjusted risk estimates for SO_2 for the pooled mortality periods using the most recent exposure windows were: 1.021 (95% CI: 1.018, 1.024) for all-cause; 1.015 (95% CI: 1.011, 1.019) for cardiovascular; and 1.064% (95% CI: 1.056, 1.072) for respiratory causes per 5 ppb increase in SO_2. The risk estimates for the most recent mortality period using the most recent exposure windows were larger.
Filleul et al. (2005) Seven French cities 1975-2001	24-h avg SO_2 ranged from 5.9 ppb ("Area 3" in Lille) to 29.7 ppb ("Area 3" in Marseille) in the 24 areas in seven cities during 1974-1976. Median levels during 1990-1997 ranged from 3.0 ppb (Bordeaux) to 8.2 ppb (Rouen) in the five cities where data were available.	Cohort study of 14,284 adults who resided in 24 areas from seven French cities when enrolled in the PAARC survey (air pollution and chronic respiratory diseases) in 1974. Daily measurements of SO_2, TSP, black smoke, NO_2, and NO were made in 24 areas for three yrs (1974-76). Cox proportional hazards models adjusted for smoking, educational level, BMI, and occupational exposure. Models were run before and after exclusion of six area monitors influenced by local traffic as determined by the NO/NO_2 ratio >3.	Before exclusion of the six areas, none of the air pollutants were associated with mortality outcomes. After exclusion of these areas, analyses showed associations between total mortality and TSP, BS, NO_2, and NO, but not SO_2 (1.01 (95% CI: 0.97, 1.06) per 5 ppb multi-yr average). From these results, the authors noted that inclusion of air monitoring data from stations directly influenced by local traffic could overestimate the mean population exposure and bias the results. It should be noted that the table describing air pollution levels in Filleul et al.'s report indicates that the SO_2 levels in these French cities declined markedly between 1974-76 and 1990-1997 period, by a factor of 2 to 3, depending on the city, whereas NO_2 levels between the two periods were variable, increased in some cities, and decreased in others. These changes in air pollution levels over the study period complicates interpretation of reported risk estimates.
Lepeule et al. (2006) Bordeaux, France 1988 – 1997	24-h avg ($\mu g/m^3$): 10.3 (6.6)	Identified 439 non-accidental deaths and 158 cardiorespiratory deaths from the Personnes Agées QUID (PAQUID) cohort. Used a Cox proportional hazards model with time dependent covariates to examine the association between black smoke (BS) and sulfur dioxide-strong acidity (SO_2-AF) and non-accidental and cardiorespiratory mortality.	Relative Risk (per 10 $\mu g/m^3$ SO_2-AF) Non-accidental Mortality 1.03 (0.86, 1.24) lag 0. 0.96 (0.88, 1.06) lag 1 0.96 (0.85, 1.09) lag 2. 1.03 (0.94, 1.12) lag 3 1.17 (0.99, 1.39) lag 4> 1.16 (0.86, 1.55) cumulative Cardiorespiratory mortality 0.84 (0.65, 1.10) lag 0. 1.06 (0.94, 1.19) lag 1 1.19 (1.03, 1.37) lag 2. 1.19 (1.03, 1.37) lag 3 1.07 (0.95, 1.19) lag 4. 0.85 (0.66, 1.10) lag 5 1.15 (0.75, 1.77) cumulative
Nafstad et al. (2004) Oslo, Norway 1972-1998.	The yearly averages of 24-h avg SO_2 were reduced with a factor of 7 during the study period from 5.6 ppb in 1974 to 0.8 ppb in 1995.	Cohort study of 16,209 Norwegian men 40-49 yrs of age living in Oslo, Norway, in 1972-1973. Data from the Norwegian Death Register were linked with estimates of average yrly air pollution levels at the participants' home addresses from 1974 to 1998. NO_X, rather than NO_2 was used. Exposure estimates for NO_X and SO_2 were constructed using models based on the subject's address, emission data for industry, heating, and traffic, and measured concentrations. Addresses linked to 50 of the busi-est streets were given an additional exposure based on estimates of annual average daily traffic. Cox proportional-hazards regression was used to estimate associations between exposure and total and cause-specific mortality, adjusting for age strata, education, occupation, smoking, physical activity level, and risk groups for cardiovascular diseases.	NO_x was associated with total, respiratory, lung cancer, and ischemic heart disease deaths. SO_2 did not show any associations with mortality (e.g., 0.97 (95% CI: 0.94, 1.01) per 5 ppb multi-yr average). The risk estimates presented for categorical levels of these pollutants showed mostly monotonic exposure-response relationships for NO_x, but not for SO_2. Note the very low levels of SO_2.

STUDY	CONC.	METHOD	CONCLUSIONS
Nafstad et al. (2003) Oslo, Norway 1972-1998	Yearly averages of 24-h avg. SO_2 reduced with a factor of 7 during study period from 5.6 ppb in 1974 to 0.8 ppb in 1995.	Lang cancer incidence was examined in the above cohort. During the follow-up period, 418 men developed lung cancer.	NO_x was associated with lung cancer incidence. SO_2 showed no association (1.01; [95% CI: 0.92, 1.12] per 5 ppb multi-yr average).

Table F-10. Associations of long-term exposure to SO_2 with lung cancer.

STUDY	METHODS	POLLUTANTS	CONCLUSIONS
UNITED STATES			
Abbey et al. (1999) Three California air basins: San Francisco, South Coast (Los Angeles and eastward), San Diego 1977-1992	Prospective cohort study of 6,338 nonsmoking non- Hispanic white adult members of the Adventist Health Study followed for all cause, cardiopulmonary, nonmalignant respiratory, and lung cancer mortality. Participants were aged 27-95 yrs at enrollment in 1977. 1,628 (989 females, 639 males) mortality events followed through 1992. All results were stratified by gender. Used Cox proportional hazards analysis, adjusting for age at enrollment, past smoking, environmental tobacco smoke exposure, alcohol use, education, occupation, and body mass index. Analyzed mortality from all natural causes, cardiopulmonary, nonmalignant respiratory, and lung cancer.	Mean SO_2 Levels: 24-h avg SO_2: 5.6 ppb Copollutants: PM_{10} SO_4 O_3 NO_2	Lung cancer mortality showed large risk estimates for most of the pollutants in either or both sexes, but the number of lung cancer deaths in this cohort was very small (12 for female and 18 for male) Generally wide confidence intervals (relative to other U.S. cohort studies). Adjusted Mortality Relative Risk (95% CI) (per 3.72 ppb SO_2) Lung Cancer Males: 1.99 (1.24, 3.20) Females: 3.01 (1.88, 4.84)
Krewski et al. (2000)	Re-analysis and sensitivity analysis of Dockery et al. (1993) Harvard Six Cities study.	Mean SO_2 Levels: 24-h avg SO_2 ranged from 1.6 (Topeka) to 24.0 (Steubenville) ppb Copollutants: Fine Particles, Sulfates	SO_2 showed positive associations with lung cancer deaths (1.03 [95% CI: 0.91, 1.16]), but in this dataset, SO_2 was highly correlated with $PM_{2.5}$ (r = 0.85), sulfate (r = 0.85), and NO_2 (r = 0.84)
EUROPE			
Beelen et al. (2008) The Netherlands 1987-1996.	Cohort study on diet and cancer with 120,852 subjects who were followed from 1987 to 1996. BS, NO_2, SO_2, and $PM_{2.5}$ and traffic-exposure estimates were analyzed. Cox regression model adjusted for age, sex, smoking, and area-level socioeconomic status.	Mean SO_2 Levels: Mean: 4.8 ppb, with a range of 1.5 to 11.8 ppb. Copollutants: $PM_{2.5}$ BS NO_2	Traffic intensity on the nearest road was not associated with exposure SO_2. Background SO_2 levels were not associated with lung cancer mortality. Adjusted RR (per 20 µg/m^3 SO_2) 1.00 (0.79, 1.26)
Filleul et al. (2005) Seven French cities 1975-2001	Cohort study of 14,284 adults who resided in 24 areas from seven French cities when enrolled in the PAARC survey (air pollution and chronic respiratory diseases) in 1974. Daily measurements of SO_2, TSP, black smoke, NO_2, and NO were made in 24 areas for three yrs (1974-1976). Cox proportional hazards models adjusted for smoking, educational level, BMI, and occupational exposure. Models were run before and after exclusion of six area monitors influenced by local traffic as determined by the NO/NO_2 ratio >3.	Mean SO_2 Levels: 24-h avg SO_2 ranged from 17 mg/m^3 ("Area 3" in Lille) to 85 mg/m^3 ("Area 3" in Marseille) in the 24 areas in seven cities during 1974-1976. Median levels during 1990-1997 ranged from 8.5 mg/m^3 (Bordeaux) to 23.4 mg/m^3 (Rouen) in the five cities where data were available. Copollutants: TSP Black Smoke NO_2 NO	The authors noted that inclusion of air monitoring data from stations directly influenced by local traffic could overestimate the mean population exposure and bias the results. It should be noted that the table describing air pollution levels in Filleul et al.'s report indicates that the SO_2 levels in these French cities declined markedly from 1974-1976 and 1990-1997 period, by a factor of 2 to 3, depending on the city, whereas NO_2 levels between the two periods were variable, increased in some cities, and decreased in others. These changes in air pollution levels over the study period complicate interpretation of reported risk estimates. Relative Risk (95% CI) for lung cancer mortality (per 10 mg/m^3 multi-year average). All 24 areas: 0.99 (0.92, 1.07). 18 areas:1.00 (0.91, 1.11)

STUDY	METHODS	POLLUTANTS	CONCLUSIONS
Nafstad et al. (2004) Oslo, Norway 1972-1998.	Cohort study of 16,209 Norwegian men 40-49 yrs of age living in Oslo, Norway, in 1972-1973. Data from Norwegian Death Register linked with estimates of avg yearly air pollution levels at the participants' home addresses from 1974 to 1998. NO_X, rather than NO_2 was used. Exposure estimates for NO_X and SO_2 were constructed using models based on the subject's address, emission data for industry, heating, and traffic, and measured concentrations. Addresses linked to 50 of the busiest streets were given an additional exposure based on estimates of annual avg daily traffic. Cox proportional-hazards regression was used to estimate associations between exposure and total and cause-specific mortality, adjusting for age strata, education, occupation, smoking, physical activity level, and risk groups for cardiovascular diseases	Mean SO_2 Levels: The yearly avg of 24-h avg SO_2 were reduced with a factor of 7 during the study period from 5.6 ppb in 1974 to 0.8 ppb in 1995. Copollutants: NO_X	SO_2 did not show any associations with lung cancer, e.g., 1.00 (0.93, 1.08) per 10 μg/m^3 increase mortality in SO_2. No association was also observed when including SO_2 in the model as a categorical variable. Note the very low levels of SO_2.

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