Integrated Science Assessment for Oxides of Nitrogen — Health Criteria

Annexes

EPA/600/R-08/072
July 2008

EPA
United States
Environmental Protection
Agency

July 2008
EPA/600/R-08/072

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Annexes

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

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Abbreviations and Acronyms

8-OHdG	8-hydroxy-2N-deoxyguanosine
5-HETE	5-hydroxyeicosatebrachoic
AA	arachidonic acid
ACP	accumulation mode particle
AHH	aryl hydrocarbon hydroxylase
ALT	alanine-amino-transferase
AM	alveolar macrophages
AMMN	N-nitroso-acetoxymethylmethylamine
AP	alkaline phosphatase
ARIC	Atherosclerosis Risk in Communities (Study)
AST	aspartate-amino-transferase
B[a]P	benzo[a]pyrene
BAL	bronchoalveolar lavage
BALF	bronchoalveolar lavage fluid
BC	black carbon
BHPN	N-bis(2-hydroxypropyl) nitrosamine
BLF	bronchial lavage fluid
bpm	beats per minute
bw	body weight
C	carbon or carbon black particles
CA	chromosome aberrations
CAT	catalase
CHD	coronary heart disease
CHF	congestive heart failure
Chol	cholesterol
CMD	count median diameter
CO	carbon monoxide
COPD	Chronic obstructive pulmonary disease
CRP	C-reactive protein
CVD	cardiovascular disease
CYP	Cytochrome P450
Dae	aerodynamic diameter
DEcCBP	DEP extract coated carbon black particles
DEN	diethylnitrosamine
DEP	diesel exhaust particles
DEP+C	diesel exhaust particle extract adsorbed to C
dG	2N-deoxyguanosine
DMBA	7, 12-dimethylbenzanthracene
DMSO	dimethyl sulfoxide
EC	elemental carbon
ED	emergency department

ELF	epithelial lining fluid
FHLC	fetal hamster lung cells
GAM	generalized additive models
γGCS	γ-glutamylcysteine synthetase
GPx	glutathione peroxidase
GPx	Se-dependent glutathione peroxidase
GPx	glutathione peroxidase
GRed	glutathione reductase
GS	glutathione synthetase
GSD	geometric standard deviation
GSH	glutathione
GSSG	glutathione disulfide
$GSSO_3H$	glutathione S-sulfonate
GST	glutathione-S-transferase
γGT	γ-glutamyl transpeptidase
HF	heart failure
HNO_2	nitrous acid
HNO_3	nitric acid
HP	hydrolyzed protein
HR	heart rate
HRV	heart rate variability
GT	γ-glutamyl transpeptidase
HVA-ICa	high-voltage activated calcium currents
ICAM-1	intercellular adhesion molecule
ICD	implantable cardioverter defibrillators
IgG	immunoglobulin
IHD	ischemic heart disease
IQR	interquartile range
LDH	lactate dehydrogenase
LOESS	locally estimated smoothing splines
LTB_4	leukotrine B4
MAD	median aerodynamic diameter
MI	myocardial infraction
MMAD	mass median aerodynamic density
MMD	mass median diameter
MN	micronuclei
MNPCE	micronucleated PCE
Mo	molybdenum
NADPH	nicotinamide adenie dinuclotide phosphate
NDMA	nitrosodimethylamine
NHANES III	Third National Health and Nutrition Examination Survey
NHLBI	National Heart, Lung, and Blood Institute
NMBzA	N-nitrosomethylbenzylamine
NO	nitric oxide

NO_2	nitrogen dioxide
NO_X	oxides of nitrogen; mono-nitrogent oxides (e.g. NO, NO_2)
NO_Y	total reactive nitrogen (all oxided forms of nitrogen) [Sum of NO_X and NO_Z)
NO_Z	other oxides of nitrogen (e.g. HNO_3 and PAN)
NR	Not Reported
O_3	ozone
OC	organic carbon
PAF	paroxysmal atrial fibrillation
PAH	polycyclic aromatic hydrocarbons
PAR	proximal alveolar region
PCE	polychromatic erythrocytes
PEC	pulmonary endocrine cells
PKA	cyclic AMP-dependent protein kinase A
PKI	synthetic peptide inhibitor of PKA
PL	phospholipids
$PM_{2.5}$	particulate matter particles equal to or smaller than 2.5 µm
PM_{10}	particulate matter particles between 2.5 µm and 10 µm
PNC	particle number concentration
ppb	parts per billion
ppm	parts per million
RBC	red blood cell or erythrocyte
RH	relative humidity
r-MSSD	root mean square successive difference (in heart period series) a time domain measurement of heart period variability
SCE	sister chromatid exchanges
SDNN	standard deviation of all normal-to-normal R-R intervals
SEPs	somatosensory-evoked potentials
SO_2	sodium dioxide
SOD	superoxide dismutase
SP-A	surfactant protein A
SPF	specific pathogen free
SPM	suspended particulate matter extract
SQCA	squamous cell carcinoma
SSO	seabuckthorn seed oil
SV40	simian virus 40
TBA	thiobarbituric acid
TBARS	thiobarbituric acid-reactive substance
TOC	potassium channel transient outward currents
TTX	tetrodotoxin
TTX-R	tetrodotoxin-resistant
TTX-S	tetrodotoxin-sensitive
TxB_2	thromboxane B2
UFP	ultafine particles
µm	micon, micrometer: 10^{-6} meter or (1/1000 of a millimeter)

$\dot{V}_E$	ventilation rate
VEPs	visual-evoked potentials
V_T	tidal volume
VWF	von Willibrand factor
W	tungsten
WBC	white blood cell

Annex 1. Framework for Review

This Integrated Science Assessment (ISA) presents a concise synthesis of the most policy-relevant science to form the scientific foundation for the review of the primary (health-based) National Ambient Air Quality Standards (NAAQS) for nitrogen dioxide (NO_2). The Annexes: (1) provide more details of the most pertinent scientific literature relative to the review of the NO_2 NAAQS in the areas of atmospheric sciences, air quality analyses, exposure assessment, dosimetry, controlled human exposure studies, toxicology, and epidemiology; and (2) focus on the key policy relevant questions and studies published since the last NAAQS review.

Annex AX1 details the methods used to identify and select studies; and frameworks for evaluating scientific evidence relative to causality determination. The overarching framework for evaluation of evidence for causality is outlined in Chapter 1 of this ISA, and this Annex provides supporting information for that framework, including excerpts from decision frameworks or criteria developed by other organizations.

Annex AX2 presents evidence related to the physical and chemical processes controlling the production, destruction, and levels of reactive nitrogen compounds in the atmosphere, including both oxidized and reduced species. Annex AX3 presents information on environmental concentrations, patterns, and human exposure to ambient oxides of nitrogen; however, most information relates to NO_2. Annex AX4 presents results from toxicological studies as well as information on dosimetry of oxides of nitrogen. Annex AX5 discusses results from controlled human exposure studies, and Annex AX6 presents evidence from epidemiologic studies. These Annexes include more detailed information on health or exposure studies that is summarized in tabular form, as well as more extensive discussion of atmospheric chemistry, source, exposure, and dosimetry information. Annex tables for health studies are generally organized to include information about (1) concentrations of oxides of nitrogen levels or doses and exposure times, (2) description of study methods employed, (3) results and comments, and (4) quantitative outcomes for oxides of nitrogen measures.

AX1.1. Literature Selection and Retrieval

Literature searches were conducted routinely to identify studies published since the last review. The review included publications from 1-2 years prior to the publication of 1993 AQCD for Oxides of Nitrogen (U.S. Environmental Protection Agency, 1993). Search strategies were iteratively modified in an effort to optimize the identification of pertinent publications. Additional papers were 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 public and CASAC during the external review process. Generally, only information that had undergone scientific peer review and had been published or accepted for publication was considered. The following sections briefly summarize criteria for selection of studies for this ISA.

The selection process for studies included in this ISA is shown in Figure AX1.1-1. Studies were evaluated by EPA staff and outside experts to determine if the studies merited inclusion. Criteria used for study selection are summarized below.

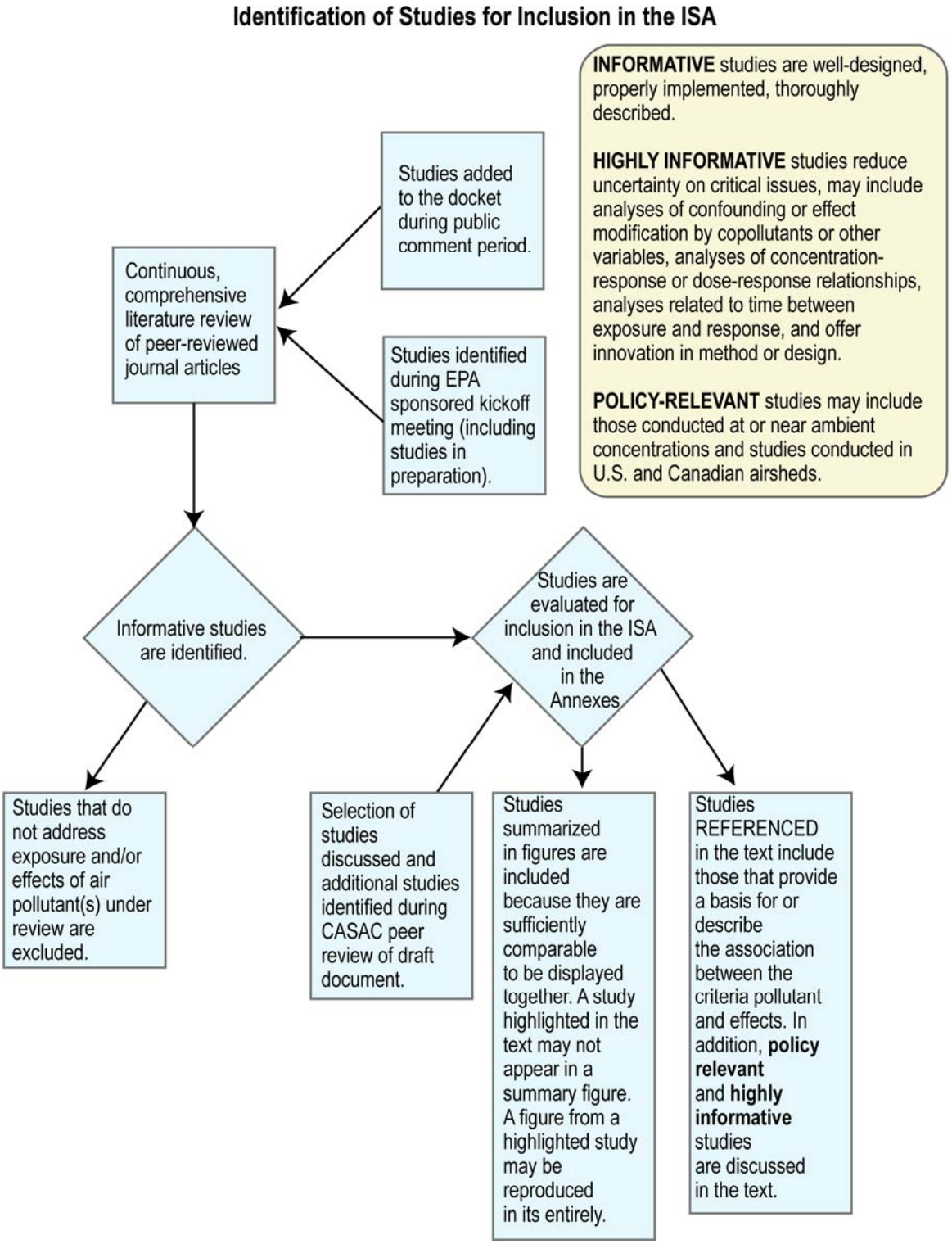


Figure AX1.1-1. Selection process for studies included in ISA.

AX1.1.1. General Criteria for Study Selection

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

- Are 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 NO_X?

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

AX1.1.2. Criteria for Selecting Epidemiology Studies

In selecting epidemiological studies, EPA considered whether a given study contained information on (1) associations with measured oxides of nitrogen concentrations using short- or long-term exposures at or near ambient levels of oxides of nitrogen, (2) health effects of specific oxides of nitrogen species or indicators related to oxides of nitrogen sources (e.g., motor vehicle emissions, 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 methodology issues (e.g., lag of effects, model specifications, thresholds, mortality displacement) related to interpretation of the health evidence. Among the epidemiological studies, particular emphasis was placed on those studies most relevant to the review of the NAAQS. Specifically, studies conducted in the United States or Canada were discussed in more detail than those from other geographical regions. Particular emphasis was placed on: (1) recent multicity studies that employ standardized analyses methods for evaluating effects of oxides of nitrogen and that provide overall estimates for effects based on combined analyses of information pooled across multiple cities, (2) new studies that provide quantitative effect estimates for populations of interest, and (3) studies that consider oxides of nitrogen as a component of a complex mixture of air pollutants.

Not all studies are accorded equal weight in the overall interpretive assessment of evidence regarding NO_2-associated health effects. Among well-conducted 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 produced 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 length of the study period and total number of events, and the variability of NO_2 exposures are important components 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 summarized, interpreted, and synthesized the most important studies and issues in the epidemiologic database pertaining to oxides of nitrogen exposure. For each study presented, the quality of the exposure and outcome data, as well as the quality of the statistical analysis methodology were discussed. The framework for evaluation of evidence is further described below.

AX1.1.3. Criteria for Selecting Toxicology Studies

Criteria for the selection of research evaluating animal toxicological or controlled human exposure studies included a focus on studies conducted within an order of a magnitude of ambient NO_2 concentrations and those studies that approximated expected human exposure conditions in terms of concentration and duration. Studies that elucidated 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 oxides of nitrogen is mainly limited to studies in which subjects are exposed to <5 ppm NO_2. For these controlled human exposures, emphasis is placed on studies that (1) investigate potentially susceptible populations such as asthmatics, particularly studies that compare responses in susceptible individuals with those in age-matched healthy controls; (2) address issues such as concentration-response or time-course of responses; (3) investigate exposure to NO_2 separately and in combination with other pollutants such as O_3 and SO_2; (4) include control exposures to filtered air; and (5) have sufficient statistical power to assess findings.

AX1.2. Guidelines for 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.

AX1.2.1. Surgeon General's Report: The Health Consequences of Smoking

The Surgeon General's Report (CDC, 2004) evaluates the health effects of smoking; it builds upon the first Surgeon General's report published in 1964 (USDEHW, 1964). It also updates the methodology for evaluating evidence that was first presented in the 1964 report. The 2004 report acknowledges the effectiveness of the previous methodology, but attempts 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 was important that scientific evidence was presented in a manner that conveyed 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 (USDHEW, 1964, p. 21).

This 2004 report created uniformly labeled conclusions that were used throughout the document. The following excerpts from the report included 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 (Institute of Medicine, 1999) to couch causal conclusions, and by IARC to classify carcinogenic substances (IARC, 1986). 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 (USDHEW, 1964, 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.

AX1.2.2. The EPA Guidelines for Carcinogen Risk Assessment

The EPA Guidelines for Carcinogen Risk Assessment, published in 2005 (U.S. Environmental Protection Agency, 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 a single integrative step after assessing all of the individual lines of evidence. Five standard descriptors are 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 recommended that a separate narrative be prepared on the weight of evidence and the descriptor. The Guidelines further recommended 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. Environmental Protection Agency, 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 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" (International Agency for Research on Cancer).

AX1.2.3. Improving Presumptive Disability Decision-Making Process for Veterans

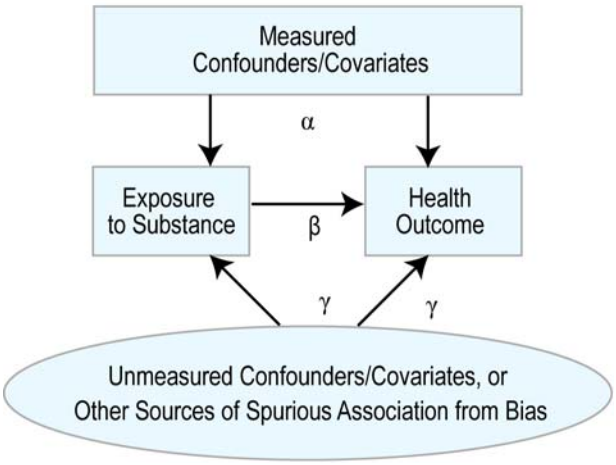
A recent publication by the Institute of Medicine (IOM) also provided the foundation for the causality framework adapted in this ISA (IOM, 2007). The Committee on Evaluation of the Presumptive Disability Decision-Making Process for Veterans was charged by the Veterans Association to describe how presumptive 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 included 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 AX1.2-1. 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 AX1.2-2 illustrates a belief state that might result when the evidence for causation is considered Sufficient.



Source: IOM (2007).

Figure AX1.2-1. Focusing on unmeasured confounders/covariates, or other sources of spurious association from bias.

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.

Again, using the Bayesian model to illustrate the idea of Equipoise and Above, Figure AX1.2-3 shows a posterior probability distribution that is an example of belief compatible with the category Equipoise and Above.

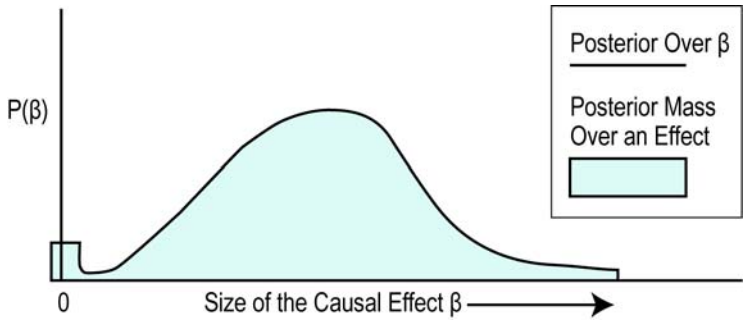
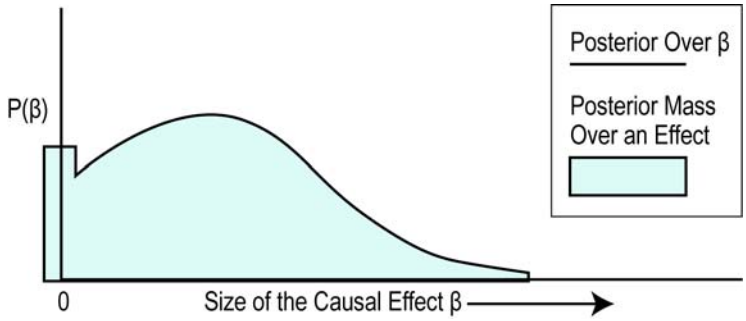
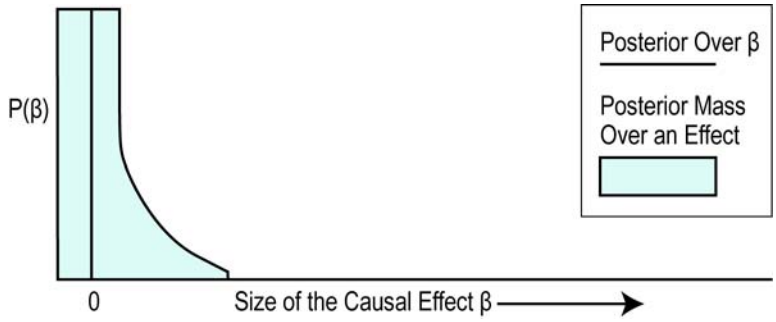


Figure AX1.2-2. Example posterior distribution for the determination of *Sufficient*.



Source: IOM (2007).

Figure AX1.2-3. Example posterior distribution for the determination of *Equipoise and Above*.



Source: IOM (2007).

Figure AX1.2-4. Example posterior distribution for the determination of *Against*.

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 AX1.2-4 then the scientific community should categorize the evidence as *Against* causation.

AX1.2.4. Formulation of Scientific Findings for Policy Purposes

The following guidelines in the form of questions were developed and published in 1991 by the National Acid Precipitation Assessment Program (NAPAP) Oversight Review Board for NAPAP 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?

> "<u>If this</u> [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.

AX1.2.5. IARC Cancer Guidelines for Scientific Review and Evaluation

The following is excerpted from the International Agency for Research on Cancer (IARC) 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.

AX1.2.6. 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) are 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 2. Atmospheric Chemistry of NO_X

AX2.1. Introduction

Nitrogen oxides (NO_X) along with volatile organic compounds (VOCs) including anthropogenic and biogenic hydrocarbons, aldehydes, etc. and carbon monoxide (CO) serve as precursors in the formation of ozone (O_3) and other elements of photochemical smog. Nitrogen dioxide is an oxidant and can further react to form other photochemical oxidants, in particular the organic nitrates, including peroxy acetyl nitrates (PAN) and higher PAN analogues. It can also react with toxic compounds such as polycyclic aromatic hydrocarbons (PAHs) to form nitro-PAHs, which may be even more toxic than the precursors.

The role of NO_X in O_3 formation was reviewed in Chapter 2 (Section 2.2) of the 2006 AQCD for Ozone and Other Photochemical Oxidants (U.S. Environmental Protection Agency, 2006), and in numerous texts (e.g., Seinfeld and Pandis, 1998; Jacob, 2000; Jacobson, 2002). Mechanisms for transporting O_3 precursors, the factors controlling the efficiency of O_3 production from NO_X, methods for calculating O_3 from its precursors, and methods for measuring NO_X were all reviewed in Section 2.6 of the 2006 O_3 AQCD. The main points from those discussions in the 2006 O_3 AQCD and updates, based on new materials will be presented here.

The overall chemistry of reactive nitrogen compounds in the atmosphere is summarized in Figure AX2.2-1 and is described in greater detail in the following sections. Nitrogen oxides are emitted primarily as NO with smaller quantities of NO_2. Emissions of NO_X are spatially distributed vertically with some occurring at or near ground level (e.g., mobile sources) and others aloft (e.g., electric generating utility (EGUs) stacks) as indicated in Figure AX2.2-1. Because of atmospheric chemical reactions, the relative abundance of different compounds contributed by different sources varies with location. Both anthropogenic and natural (biogenic) processes emit NO_X. In addition to gas phase reactions, multiphase processes are important for forming aerosol-phase pollutants, including aerosol NO_3^-.

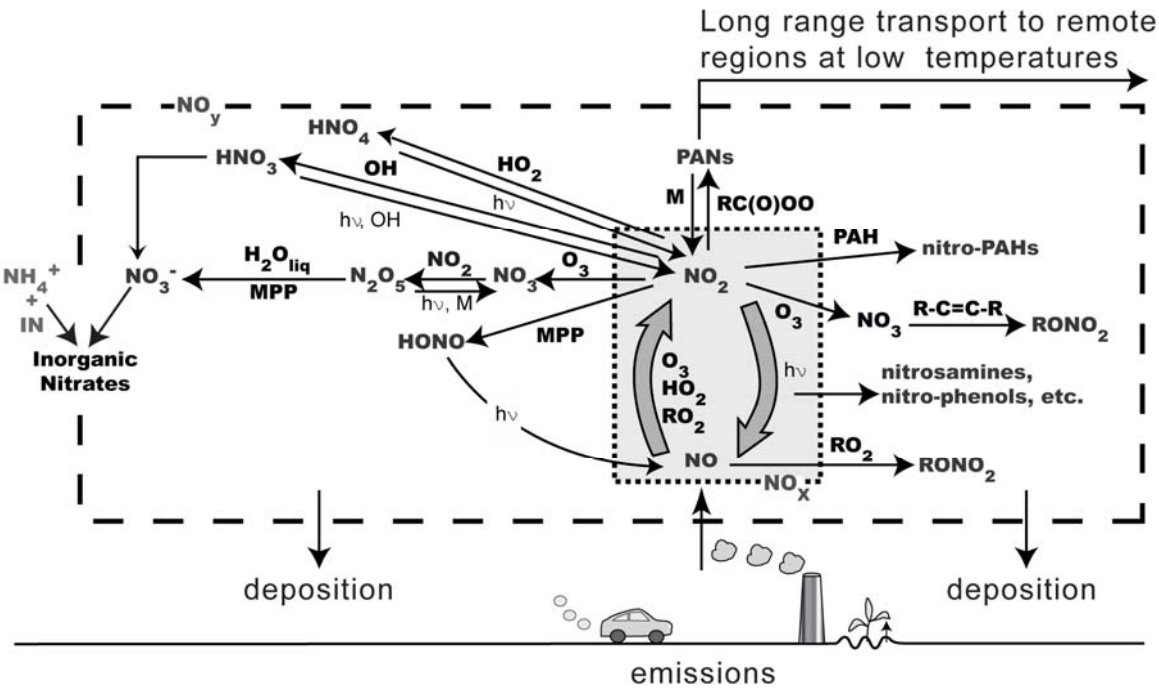


Figure AX2.2-1. Schematic diagram of the cycle of reactive nitrogen species in the atmosphere. MPP refers to multi-phase process; h< to a photon of solar energy.

AX2.2. Chemistry of NO_X in the Troposphere

AX2.2.1. Basic Chemistry

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

$$NO_2 + h\nu \rightarrow NO + O(^3P) \qquad \text{(AX2.2-1)}$$

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

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

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

NO and O_3 react to reform NO_2

$$NO + O_3 \rightarrow NO_2 + O_2 \qquad \text{(AX2.2-3)}$$

Reaction AX2.2-3 is responsible for O_3 decreases and NO_2 increases found near sources of NO (e.g., highways). The falloff of NO_2 from a road depends on wind speed and direction and the local structure of turbulent mixing, temperature (through the temperature dependence of Reaction AX2.2-3) and the amount of sunlight (through Reaction AX2.2-1). Oxidation of reactive VOCs leads to formation of reactive radical species that allow the conversion of NO to NO_2 without participation of O_3 as in Reaction AX2.2-3

$$NO \xrightarrow{HO_2,\ RO_2} NO_2 \qquad \text{(AX2.2-4)}$$

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

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

$$O_x = \sum(O(^3P) + O(^1D) + O_3 + NO_2) \qquad \text{(AX2.2-5)}$$

In much the same way, NO_X is sometimes referred to as "odd nitrogen". Hence, we see that production of O_X occurs by the schematic Reaction AX2.2-5, and that the sequence of reactions given by reactions AX2.2-1 through AX2.2-3 represents no net production of O_X. Definitions of species families and methods for constructing families are discussed in Jacobson (1999) and references therein. Other families that include nitrogen-containing species, and which will be referred to later in this chapter, are:

$$NO_z = \sum HNO_3 + HNO_4 + NO_3 + 2NO_2O_5 + PAN(CH_3CHO - OO - NO_2) + other\ organic\ nitrates + halogen\ nitrates + particulate\ nitrate)$$

$$NO_Y = NO_X + NO_Z + HONO;$$
$$and\ NH_X = NH_3 + NH_4^{\ +} \qquad \text{(AX2.2-6)}$$

In this equation, NO_Z refers to the sum of the oxidation products of NO_X.

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

$$NO_2 + O_3 \rightarrow NO_3 + O_2 \qquad \text{(AX2.2-7)}$$

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

$$NO_3 + hv \rightarrow NO + O_{2(10\%)} \qquad \text{(AX2.2-8a)}$$

$$NO_2 + O(^3P)_{(90\%)} \qquad \text{(AX2.2-8b)}$$

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

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

$$NO_3 + NO_2 \xleftrightarrow{M} N_2O_5 \qquad \text{(AX2.2-9)}$$

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

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

$$OH + NO_2 \xrightarrow{M} HNO_3 \qquad \text{(AX2.2-10)}$$

$$N_2O_5 \xrightarrow{H_20(1)} HNO_3 \qquad \text{(AX2.2-11)}$$

The gas-phase reaction of OH radical with NO_2 (Reaction AX2.2-11) initiates one of the major and ultimate removal processes for NO_X in the troposphere. This reaction removes OH and NO_2 radicals and competes with hydrocarbons for OH radicals in areas characterized by high NO_X concentrations, such as urban centers (see Section AX2.2.2). The timescale (τ) for conversion of NO_X to HNO_3 in the planetary boundary layer at 40 N latitude ranges from about 4 h in July to about 16 h in January. The corresponding range in τ at 25 N latitude is between 4 and 5 h, while at 50 N latitude, HNO_3 τ ranges from about 4 to 20 h (Martin et al., 2003). In addition to gas-phase HNO_3, Golden and Smith (2000) have shown on the basis of theoretical studies that pernitrous acid (HOONO) is also produced by the reaction of NO_2 and OH radicals. However, this channel of production most likely represents a minor yield approximately 15% at the surface (Jet Propulsion Laboratory, 2003).

Pernitrous acid will thermally decompose and can photolyze. Gas-phase HNO_3 formed from Reactions AX2.2-10 and AX2.2-11 undergoes wet and dry deposition to the surface, and uptake by ambient aerosol particles. Reaction AX2.2-10 limits NO_X τ to a range of hours to days. Geyer and Platt (2002) concluded that Reaction AX2.2-10 constituted about 10% of the removal of NO_X at a site near Berlin, Germany during spring and summer. However, other studies found a larger contribution to HNO_3 production from Reaction AX2.2-10. Dentener and Crutzen (1993) estimated 20% in summer and 80% of HNO_3 production in winter is from Reaction AX2.2-10. Tonnesen and Dennis (2000) found 16 to 31% of summer HNO_3 production was from Reaction AX2.2-10. The contribution of Reaction AX2.2-11 to HNO_3 formation is highly uncertain during both winter and summer. The importance of Reaction AX2.2-11 could be much higher during winter than during summer because of the much lower concentration of OH radicals and the enhanced stability of N_2O_5 due to lower temperatures and less sunlight. Note that Reaction AX2.2-11 proceeds as a heterogeneous reaction. Recent work in the northeastern United States indicates that this reaction proceeds at a faster rate in power plant plumes than in urban plumes (Brown et al., 2006a,b; Frost et al., 2006).

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

$$HNO_3 + h\nu \rightarrow OH + NO_2 \qquad \text{(AX2.2-12)}$$

and

$$HNO_3 + OH \rightarrow NO_3 + H_2O \qquad \text{(AX2.2-13)}$$

The lifetime of HNO_3 with respect to these two reactions is long enough for HNO_3 to act as a reservoir species for NO_X during long-range transport.

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

$$OH + NO \xrightarrow{M} HNO_2 \qquad \text{(AX2.2-14)}$$

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

$$HNO_2 + h\nu \rightarrow OH + NO \qquad \text{(AX2.2-15)}$$

Reaction AX2.2-15 is, however, a negligible source of HONO, which is formed mainly by multiphase processes (see Section AX2.2.3). At night, heterogeneous reactions of NO_2 in aerosols or at the earth's surface result in accumulation of HONO (Lammel and Cape, 1996; Jacob, 2000; Sakamaki et al., 1983; Pitts et al., 1984; Svensson et al., 1987; Jenkin et al., 1988; Lammel and Perner, 1988; Notholt et al., 1992a,b). Harris et al. (1982) suggested that photolysis of this HNO_2 at sunrise could provide an important early-morning source of OH radicals to drive O_3 formation.

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

$$HO_2 + NO_2 + M \rightarrow HNO_4 + M \qquad \text{(AX2.2-16)}$$

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

Although the lifetimes of HNO_4 and N_2O_5 are short (minutes to hours) during typical summer conditions, they can be much longer at the lower temperatures and darkness found during the polar night. Under these conditions, species such as PAN, HNO_3, HNO_4, and N_2O_5 serve as NO_X reservoirs that can liberate NO_2 upon the return of sunlight during the polar spring.

A broad range of organic nitrogen compounds can be directly emitted by combustion sources or formed in the atmosphere from NO_X emissions. Organic nitrogen compounds include the PANs, nitrosamines, nitro-PAHs, and the more recently identified nitrated organics in the quinone family. Oxidation of VOCs produces organic peroxy radicals (RO_2), as discussed in the 2006 AQCD for Ozone. Reaction of RO_2 radicals with NO and NO_2 produces organic nitrates ($RONO_2$) and peroxynitrates (RO_2NO_2)

$$RO_2 + NO \xrightarrow{M} RONO_2 \qquad \text{(AX2.2-17)}$$

$$RO_2 + NO_2 \xrightarrow{M} RO_2NO_2 \qquad \text{(AX2.2-18)}$$

Reaction (AX2.2-17) is a minor branch for the reaction of RO_2 with NO; the major branch involves NO_2 as in Reaction AX2.2-18. Note, however, that organic nitrate yields increase with carbon number (Atkinson, 2000).

The most important of these organic nitrates is PAN, the dominant member of the broader family of peroxyacylnitrates which includes peroxypropionyl nitrate (PPN) of anthropogenic origin and

peroxymethacrylic nitrate (MPAN) produced from isoprene oxidation. The PANs are formed by the combination reaction of acetyl peroxy radicals with NO_2

$$CH_3C(O)-OO + NO_2 \rightarrow CH_3C(O)OONO_2 \quad \text{(AX2.2-19)}$$

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

$$CH_3-C(O)H + h\nu \rightarrow CH_3-C(O) + H \quad \text{(AX2.2-20)}$$

$$CH_3-C(O)H + OH \rightarrow CH_3-C(O) + H_2O \quad \text{(AX2.2-21)}$$

Acetyl radicals then react with O_2 to yield acetyl peroxy radicals.

$$CH_3-C(O) + O_2 + M \rightarrow CH_3C(O)-OO + M \quad \text{(AX2.2-22)}$$

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

$$CH_3(CO)-OO + NO \rightarrow CH_3(CO)-O + NO_2 \quad \text{(AX2.2-23)}$$

and the acetyl-oxy radicals will then decompose

$$CH_3(CO)-O \rightarrow CH_3 + CO_2 \quad \text{(AX2.2-24)}$$

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

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

The peroxynitrates produced by AX2.2-19 are thermally unstable and most have very short lifetimes (less than a few minutes) owing to thermal decomposition back to the original reactants. They are thus not effective sinks of NO_X.

AX2.2.2. NO_X Concentrations and O_3 Formation

Ozone is unlike some other species whose rates of formation vary directly with the emissions of their precursors in that O_3 production ($P(O_3)$) changes nonlinearly with the concentrations of its precursors. At the low NO_X concentrations found in most environments ranging from remote continental areas to rural and suburban areas downwind of urban centers, the net production of O_3 increases with

increasing NO_X. At the high NO_X concentrations found in downtown metropolitan areas especially near busy streets and roadways and in power plant plumes, there is net destruction of O_3 by (titration) reaction with NO. Between these two regimes is a transition stage in which O_3 shows only a weak dependence on NO_X concentrations. In the high NO_X regime, NO_2 scavenges OH radicals which would otherwise oxidize VOCs to produce peroxy radicals, which in turn would oxidize NO to NO_2. In the low NO_X regime, VOC oxidation generates, or at least does not consume, free radicals, and O_3 production varies directly with NO_X. Sometimes the terms 'VOC-limited' and 'NO_X-limited' are used to describe these two regimes; also, the terms NO_X-limited and NO_X-saturated are used, e.g., by Jaeglé et al., 2001. The chemistry of OH radicals, which are responsible for initiating the oxidation of hydrocarbons, shows behavior similar to that for O_3 with respect to NO_X concentrations (Hameed et al., 1979; Pinto et al., 1993; Poppe et al., 1993; Zimmerman and Poppe, 1993). These considerations introduce a high degree of uncertainty into attempts to relate changes in O_3 concentrations to emissions of precursors. It should also be noted at the outset that in a NO_X-limited (or NO_X-sensitive) regime, O_3 formation is not insensitive to radical production or the flux of solar UV photons, just that O_3 formation is more sensitive to NO_X. For example, global tropospheric O_3 is sensitive to the concentration of CH_4 even though the troposphere is predominantly NO_X-limited.

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

Jacob et al. (1995) used a combination of field measurements and a chemical transport model (CTM) to show that the formation of O_3 changed from NO_X-limited to NO_X-saturated as the season changed from summer to fall at a monitoring site in Shenandoah National Park, VA. Photochemical production of O_3 generally occurs together with production of other species including HNO_3, organic nitrates, and hydrogen peroxide (H_2O_2). The relative rates of $P(O_3)$ and the production of other species varies depending on photochemical conditions and can be used to provide information about O_3-precursor sensitivity.

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

Trainer et al. (1993) suggested that the slope of the regression line between O_3 and NO_Z can be used to estimate the rate of $P(O_3)$ per NO_X ,also known as the O_3 production efficiency or OPE. Ryerson et al. (1998, 2001) used measured correlations between O_3 and NO_Z to identify different rates of O_3 production in plumes from large point sources.

Sillman (1995) and Sillman and He (2002) identified several secondary reaction products that show different correlation patterns for NO_X-limited conditions and NO_X-saturated conditions. The most

important correlations are for O_3 versus NO_Y, O_3 versus NO_Z, O_3 versus HNO_3, and H_2O_2 versus HNO_3. The correlations between O_3 and NO_Y, and O_3 and NO_Z are especially important because measurements of NO_Y and NO_X are widely available. Measured O_3 versus NO_Z (Figure AX2.2-2) shows distinctly different patterns in different locations. In rural areas and in urban areas such as Nashville, TN, O_3 shows a strong correlation with NO_Z and a relatively steep slope to the regression line. By contrast, in Los Angeles O_3 also increases with NO_Z, but the rate of increase of O_3 with NO_Z is lower and the O_3 concentrations for a given NO_Z value are generally lower.

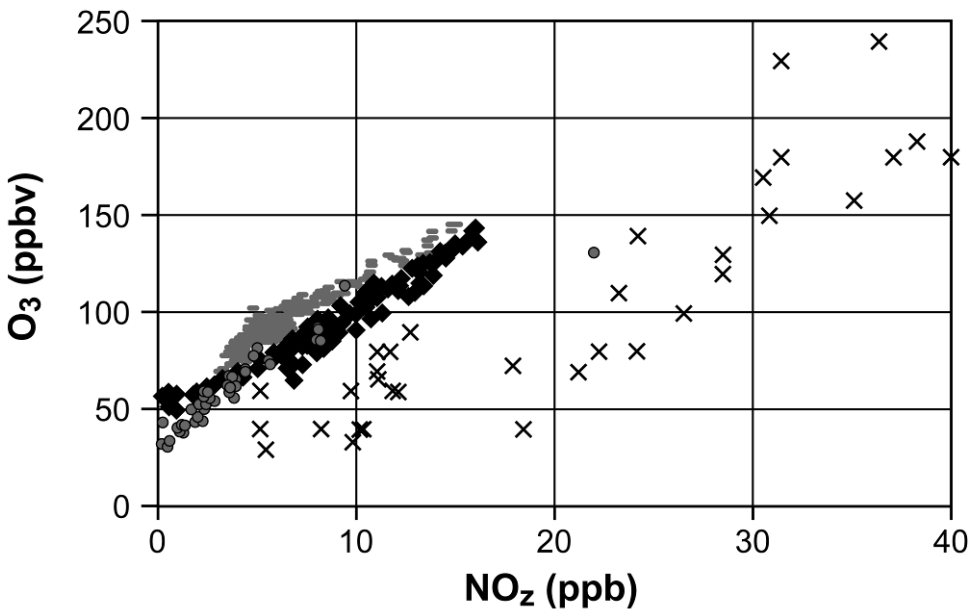


Figure AX2.2-2. Measured values of O_3 and NO_Z (NO_Y – NO_X). Measured during the afternoon at rural sites in the eastern United States (gray circle) and in urban areas and urban plumes associated with Nashville, TN (gray dash), Paris, FR (black diamond) and Los Angeles, CA (X)

The difference between NO_X-limited and NO_X-saturated regimes is also reflected in measurements of H_2O_2. Formation of H_2O_2 takes place by self-reaction of photochemically generated HO_2 radicals, so that there is large seasonal variation of H_2O_2 concentrations, and values in excess of 1 ppb are mainly limited to the summer months when photochemistry is more active (Kleinman, 1991). Hydrogen peroxide is produced in abundance only when O_3 is produced under NO_X-limited conditions. When the photochemistry is NO_X-saturated, much less H_2O_2 is produced. In addition, increasing NO_X tends to slow the formation of H_2O_2 under NO_X-limited conditions. Differences between these two regimes are also related to the preferential formation of sulfate during summer and to the inhibition of sulfate and hydrogen peroxide during winter (Stein and Lamb, 2003). Measurements in the rural eastern United States (Jacob et al., 1995), at Nashville (Sillman et al., 1998), and at Los Angeles (Sakugawa and Kaplan, 1989) show large differences in H_2O_2 concentrations likely due to differences in NO_X availability at these locations.

AX2.2.3. Multiphase Chemistry Involving NO_X

Recent laboratory studies on sulfate and organic aerosols indicate that the reaction probability γN_2O_5 is in the range of 0.01 to 0.05 (Kane et al., 2001; Hallquist et al., 2003; Thornton et al., 2003). Tie

et al. (2003) found that a value of 0.04 in their global model gave the best simulation of observed NO_X concentrations over the Arctic in winter.

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

Recent work in the Arctic has quantified significant photochemical recycling of NO_3^- to NO_X and attendant perturbations of OH chemistry in snow (Honrath et al., 2000; Dibb et al., 2002; Dominé and Shepson, 2002) which suggest the possibility that similar multiphase pathways could occur in aerosols. As mentioned above, NO_3^- is photolytically reduced to NO_2^- (Zafiriou and True, 1979) in acidic sea salt solutions (Anastasio et al., 1999). Further photolytic reduction of NO_2^- to NO (Zafiriou and True, 1979) could provide a possible mechanism for HNO_3 recycling. Early experiments reported production of NO_X during the irradiation of artificial seawater concentrates containing NO_3^- (Petriconi and Papee, 1972). Based on the above, HNO_3 recycling in sea salt aerosols is potentially important and warrants further investigation. Other possible recycling pathways involving highly acidic aerosol solutions and soot are reviewed by Jacob (2000).

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

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

Choi and Leu (1998) evaluated the interactions of HNO_3 on model black carbon soot (FW2), graphite, hexane, and kerosene soot. They found that HNO_3 decomposed to NO_2 and H_2O at higher HNO_3 surface coverages, i.e., $P(HNO_3) \geq 10^{-4}$ Torr. None of the soot models used were reactive at low HNO_3 coverages, at $P(HNO_3) = 5 \times 10^{-7}$ Torr or at temperatures below 220 K. They concluded that it is unlikely that aircraft soot in the upper troposphere/lower stratosphere reduces HNO_3.

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

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

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

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

AX2.2.4. Formation of Nitro-PAHs

Nitro-polycyclic aromatic hydrocarbons (nitro-PAHs) (see Figure AX2.2-3 for some example nitro-PAHs) are generated from incomplete combustion processes through electrophilic reactions of polycyclic aromatic hydrocarbons (PAHs) in the presence of NO_2 (International Agency for Research on Cancer [IARC], 1989; World Health Organization [WHO], 2003). Among combustion sources, diesel emissions have been identified as the major source of nitro-PAHs in ambient air (Bezabeh et al., 2003; Gibson, 1983; Schuetzle, 1983; Tokiwa and Ohnishi, 1986). Direct emissions of nitro-PAHs in PM vary with type of fuel, vehicle maintenance, and ambient conditions (Zielinska et al., 2004).

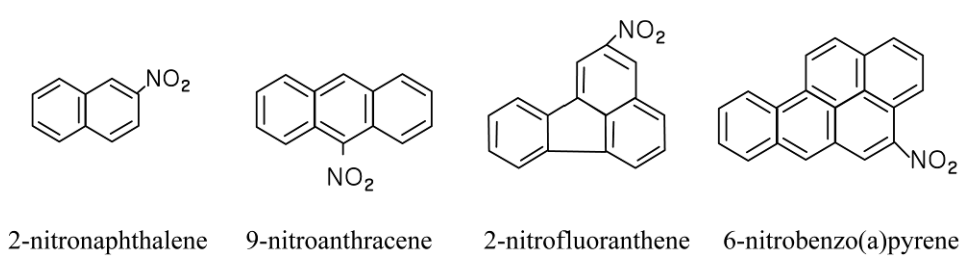


Figure AX2.2-3. Structures of same nitro-polycyclic aromatic hydrocarbons.

In addition to being directly emitted, nitro-PAHs can also be formed from both gaseous and heterogeneous reactions of PAHs with gaseous nitrogenous pollutants in the atmosphere (Arey et al., 1986, 1989, Arey, 1998; Perrini, 2005; Pitts, 1987; Sasaki et al., 1997; Zielinska et al., 1989). Different isomers of nitro-PAHs are formed through different formation processes. For example, the most abundant nitro-PAH in diesel particles is 1-nitropyene (1NP), followed by 3-nitrofluoranthene (3NF) and 8-nitrofluoranthene (8NF) (Bezabeh et al., 2003; Gibson, 1983; Schuetzle, 1983; Tokiwa and Ohnishi, 1986). However, in ambient particulate organic matter (POM), 2-nitrofluoranthene (2NF) is the dominant compound, followed by 1NP and 2-nitropyrene (2NP) (Arey et al., 1989; Bamford et al., 2003; Reisen and Arey, 2005; Zielinska et al., 1989), although 2NF and 2NP are not directly emitted from primary combustion emissions. The reaction mechanisms for the different nitro-PAH formation processes have been well documented and are presented in Figure AX2.2-4.

The dominant process for the formation of nitro-PAHs in the atmosphere is gas-phase reaction of PAHs with OH radicals in the presence of NO_X (Arey et al., 1986, Arey, 1998; Atkinson and Arey, 1994; Ramdahl et al., 1986; Sasaki et al., 1997). Hydroxyl radicals can be generated photochemically or at night through ozone-alkene reactions, (Finlayson-Pitts and Pitts, 2000). The postulated reaction mechanism of OH with PAHs involves the addition of OH at the site of highest electron density of the aromatic ring, for example, the 1-position for pyrene (PY) and the 3-position for fluoranthene (FL). This reaction is followed by the addition of NO_2 to the OH-PAH adduct and elimination of water to form the nitroarenes (Figure AX2.2-4) (Arey et al., 1986; Atkinson et al., 1990; Pitts, 1987). After formation, nitro-PAHs with low vapor pressures (such as 2NF and 2NP) immediately migrate to particles under ambient conditions (Fan et al., 1995; Feilberg et al., 1999). The second order rate-constants for the reactions of OH with most PAHs range from 10^{-10} to 10^{-12} cm^3/molecule/s at 298 K with the yields ranging from ~0.06 to ~5% (Atkinson and Arey, 1994). 2NF and 2NP have been found as the most abundant nitro-PAHs formed via reactions of OH with gaseous FL and PY, respectively, in ambient air.

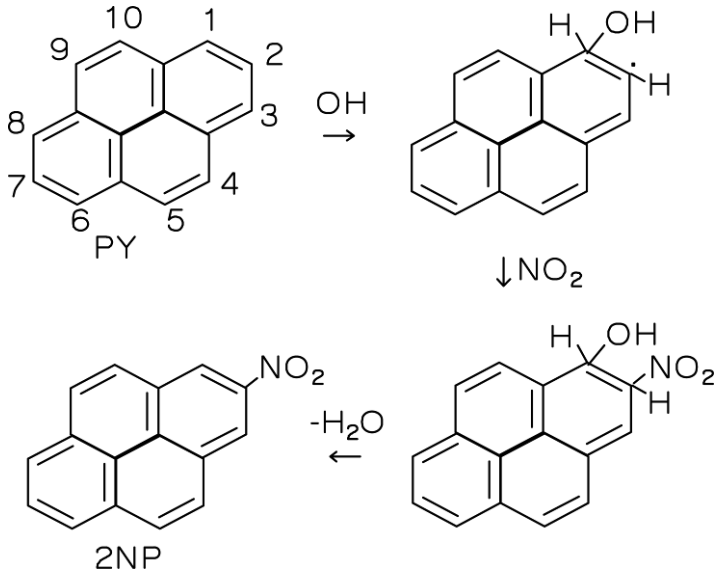


Figure AX2.2-4. Formation of 2-nitropyrene (2NP) from the reaction of OH with gaseous pyrene (PY).

The second important process for the formation of nitro-PAHs in the atmosphere is the nitration of PAHs by NO_3^- in the presence of NO_X at night (Atkinson et al., 1990; Atkinson and Arey, 1994; Sasaki et al., 1997). Nitrate radicals can be generated by reaction of ozone (O_3) with NO_2 in the atmosphere by Reaction AX2.2-25.

$$O_3 + NO_2 \rightarrow NO_3 + O_2 \qquad \text{(AX2.2-25)}$$

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

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

The third process of nitro-PAH formation in the atmosphere is nitration of PAHs by NO_2/N_2O_5 in the presence of trace amounts of HNO_3 in both gas and particle phases. This mechanism could be operative throughout the day and night (Pitts, 1983, 1985a,b; Grosjean et al., 1983; Ramdahl et al., 1984; Kamens et al., 1990). The formation of nitro-fluoranthenes was observed when adsorbed FL was exposed to gaseous N_2O_5, and the distribution of product NF isomers was 3- > 8- > 7- > 1- NF (Pitts et al., 1985a,b). The proposed mechanism for this reaction was an ionic electrophilic nitration by nitronium ion (NO_2^+). It was speculated that N_2O_5 became ionized prior to the reaction with FL (Zielinska et al., 1986). Only 1NP was observed for the reaction of PY with N_2O_5 on filters (Pitts et al., 1985b). Compared to the reactions of OH and NO_3, nitration of PAHs by NO_2/N_2O_5 is less important.

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

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

Esteve et al. (2006) examined the reaction of gas-phase NO_2 and OH radicals with various PAHs adsorbed onto model diesel particulate matter (SRM 1650a, NIST). Using pseudo second order rate coefficients, they derived lifetimes for conversion of the particle-bound PAHs to nitro-PAHs of a few days (for typical urban NO_2 levels of 20 ppb). They also found that the rates of reaction of OH with the PAHs were about four orders of magnitude larger than for the reactions involving NO_2. However, since the concentrations of NO_2 used above are more than four orders of magnitude larger than those for OH (10^6-10^7/cm^3), they concluded that the pathway involving NO_2 is expected to be favored over that involving OH radicals. Consistent with the importance of the gas-phase formation of NPAHS, both the mutagenic potency of PM and the content of NPAHs in PM vary by particle size, and are higher in the submicron size range (Xu and Lee, 2000; Kawanaka et al., 2004).

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

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

AX2.2.5. Multiphase Chemical Processes Involving NO_X and Halogens

Four decades of observational data on O_3 in the troposphere have revealed numerous anomalies not easily explained by gas-phase HO_X-NO_X photochemistry. The best-known example is the dramatic depletion of ground-level O_3 during polar sunrise due to multiphase catalytic cycles involving inorganic Br and Cl radicals (Barrie et al., 1988; Martinez et al., 1999; Foster et al., 2001). Other examples of anomalies in tropospheric O_3 at lower latitudes include low levels of O_3 (<10 ppb) in the marine boundary layer (MBL) and overlying free troposphere (FT) at times over large portions of the tropical Pacific (Kley et al., 1996), as well as post-sunrise O_3 depletions over the western subtropical Pacific Ocean (Nagao et al., 1999), the temperate Southern Ocean (Galbally et al., 2000), and the tropical Indian Ocean (Dickerson et al., 1999). The observed O_3 depletions in near-surface marine air are generally consistent with the model-predicted volatilization of Br_2, BrCl, and Cl_2 from sea salt aerosols through autocatalytic halogen "activation" mechanisms (e.g., Vogt et al., 1996; Von Glasow et al., 2002a) involving these aqueous phase reactions.

$$HOBr + Br^- + H^+ \rightarrow Br_2 + H_2O \qquad \text{(AX2.2-26)}$$

$$HOCl + Br^- + H^+ \rightarrow BrCl + H_2O \qquad \text{(AX2.2-27)}$$

$$HOCl + Cl^- + H^+ \rightarrow Cl_2 + H_2O \quad \text{(AX2.2-28)}$$

In polluted marine regions at night, the heterogeneous reaction

$$N_2O_5 + Cl^- \rightarrow ClNO_2 + NO_3^- \quad \text{(AX2.2-29)}$$

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

$$HNO_3 + Cl^- \rightarrow HCl + NO_3^- \quad \text{(AX2.2-30)}$$

and the corresponding shift in phase partitioning can accelerate the deposition flux to the surface of total NO_3 (Russell et al., 2003; Fischer et al., 2006). However, Pryor and Sorensen (2000) have shown that the dominant form of nitrate deposition is a complex function of wind speed. In polluted coastal regions where HCl from Reaction AX2.2-30 often exceeds 1 ppb, significant additional atomic Cl^- is produced via

$$HCl + OH \rightarrow Cl + H_2O \quad \text{(AX2.2-31)}$$

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

$$X + O_3 \rightarrow XO + O_2 \quad \text{(AX2.2-32)}$$

$$XO + HO_2 \rightarrow HOX + O_2 \quad \text{(AX2.2-33)}$$

$$HOX + h\nu \rightarrow OH + X \quad \text{(AX2.2-34)}$$

where (X = Br and Cl).

Formation of Br and Cl nitrates via

$$XO + NO_2 \rightarrow XNO_3 \quad \text{(AX2.2-35)}$$

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

$$XNO_3 + H_2O \rightarrow HOX + H^+ + NO_3^- \quad \text{(AX2.2-36)}$$

and

$$XNO_3 + Y^- \rightarrow XY + NO_3^- \quad \text{(AX2.2-37)}$$

(where Y = Cl, Br, or I) accelerates the conversion of NO_X to particulate NO_3^- and thereby contributes indirectly to net O_3 destruction (Sander et al., 1999; Vogt et al., 1999, Pszenny et al., 2004).

Most XNO_3 reacts via Reaction AX2.2-36 on sea salt whereas reaction AX2.2-37 is more important on sulfate aerosols. Partitioning of HCl on sulfate aerosols following Henry's Law provides Cl^- for Reaction AX2.2-37 to form BrCl. Product NO_3^- from both Reactions AX2.2-36 and AX2.2-37 partitions with the gas-phase HNO_3 following Henry's Law. Because most aerosol size fractions in the MBL are near equilibrium with respect to HNO_3 (Erickson et al., 1999; Keene et al., 2004), both sulfate and sea salt aerosol can sustain the catalytic removal of NO_X and re-activation of Cl and Br with no detectable change in composition. The photolytic reduction of NO_3^- in sea salt aerosol solutions recycles NO_X to the gas phase (Pszenny et al., 2004). Halogen chemistry also impacts O_3 indirectly by altering OH/HO_2 ratios through the steps of Reactions AX2.2-33 and AX2.2-34 (e.g., Stutz et al., 1999; Bloss et al., 2005).

In addition to O_3 destruction via Reaction AX2.2-32, atomic Cl oxidizes hydrocarbons (HCs) primarily via hydrogen abstraction to form HCl vapor and organic products (Jobson et al., 1994; Pszenny et al., 2006). The enhanced supply of odd-H radicals from HC oxidation leads to net O_3 production in the presence of sufficient NO_X (Pszenny et al., 1993). Available evidence suggests that Cl^- radical chemistry may be a significant net source for O_3 in polluted coastal/urban air (e.g., Tanaka et al., 2003; Finley and Saltzman, 2006).

An analogous autocatalyic O_3 destruction cycle involving multiphase iodine (I) chemistry also operates in the marine atmosphere (Alicke et al., 1999, Vogt et al., 1999; McFiggans et al., 2000; Ashworth et al., 2002). In this case, the primary source of I is believed to be either photolysis of CH_2I_2, other I-containing gases (Carpenter et al., 1999; Carpenter, 2003), or perhaps I_2 (McFiggans et al., 2004; Saiz-Lopez and Plane, 2004; McFiggans, 2005) emitted by micro-and macro flora. Sea salt and sulfate aerosols provide substrates for multiphase reactions that sustain the catalytic I-IO cycle. The IO radical has been measured by long-path (LP) and multi axis (MAX) differential optical absorption spectroscopy (DOAS) at Mace Head, Ireland; Tenerife, Canary Islands; Cape Grim, Tasmania; and coastal New England, USA. These studies have established that the IO radical has average daytime levels of about 1 ppt with maxima up to 7 ppt (e.g., Allan et al., 2000; Pikelnaya et al., 2006). Modeling suggests that up to 13% per day of O_3 in marine air may be destroyed via multiphase iodine chemistry (McFiggans et al., 2000). The reaction of IO with NO_2 followed by uptake of INO_3 into aerosols (analogous to Reactions AX2.2-32 through AX2.2-34) accelerates the conversion of NO_X to particulate NO_3^- and thereby contributes to net O_3 destruction. The reaction $IO + NO \rightarrow I + NO_2$ also influences NO_X cycling.

Most of the above studies focused on halogen-radical chemistry and related influences on NO_X cycling in coastal and urban air. However, available evidence suggests that similar chemical transformations proceed in other halogen-rich tropospheric regimes. For example, Cl, Br, and/or I oxides have been measured at significant concentrations in near-surface air over the Dead Sea, Israel, the Great Salt Lake, Utah (e.g., Hebestreit et al., 1999; Stutz et al., 1999, 2002; Zingler and Platt, 2005), and the Salar de Uyuni salt pan in the Andes mountains (U. Platt, unpublished data, 2006); high column densities of halogenated compounds have also been observed from satellites over the northern Caspian Sea (Wagner et al., 2001; Hollwedel et al., 2004). The primary source of reactive halogens in these regions is thought to be from activation along the lives of that in Reactions AX2.2-26 through AX2.2-28 involving concentrated salt deposits on surface evaporative pans. High concentrations of BrO have also been measured in volcanic plumes (Bobrowski et al., 2003, Gerlach, 2004). Although virtually unexplored, the substantial emissions of inorganic halogens during biomass burning (Lobert et al., 1999; Keene et al., 2006) and in association with crustal dust (Keene et al., 1999; Sander et al., 2003) may also support active halogen-radical chemistry and related transformations involving NO_X downwind of sources. Finally, observations from satellites, balloons, and aircraft indicate that BrO is present in the free troposphere at levels sufficient to significantly influence photochemistry (e.g., Von Glasow et al., 2004).

AX2.3. Transport of NO_X in the Atmosphere

Major episodes of high O_3 concentrations in the eastern United Sates and in Europe are associated with slow moving high-pressure systems. High-pressure systems during the warmer seasons are associated with subsidence, resulting in warm, generally cloudless conditions with light winds. The subsidence results in stable conditions near the surface, which inhibit or reduce the vertical mixing of O_3 precursors (NO_X, VOCs, and CO). Photochemical activity is enhanced because of higher temperatures and the availability of sunlight. However, it is becoming increasingly apparent that transport of O_3 and NO_X and VOC from distant sources can provide significant contributions to local [O_3] even in areas where there is substantial photochemical production. There are a number of transport phenomena occurring either in the upper boundary layer or in the free troposphere which can contribute to high O_3 values at the surface. These phenomena include stratospheric-tropospheric exchange (STE), deep and shallow convection, low-level jets, and the so-called "conveyor belts" that serve to characterize flows around frontal systems.

AX2.3.1. Convective Transport

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

AX2.3.2. Observations of the Effects of Convective Transport

The first unequivocal observations of deep convective transport of boundary layer pollutants to the upper troposphere were documented by Dickerson et al. (1987). Instrumentation aboard three research aircraft measured CO, O_3, NO, NO_X, NO_Y, and hydrocarbons in the vicinity of an active mesoscale convective system near the Oklahoma/Arkansas border during the 1985 PRE-STORM experiment. Anvil penetrations about 2 h after maturity found greatly enhanced mixing ratios inside the cloud of all of the aforementioned species compared with outside it. NO mixing ratios in the anvil averaged 3 to 4 ppb, with individual 3-min observations reaching 6 ppb; boundary layer NO_X was typically 1.5 ppb or less outside the cloud. Therefore, the anvil observations represent a mixture of boundary layer NO_X and NO_X contributed by lightning. Luke et al. (1992) summarized the air chemistry data from all 18 flights during PRE-STORM by categorizing each case according to synoptic flow patterns. Storms in the maritime

tropical flow regime transported large amounts of CO, O_3, and NO_Y into the upper troposphere with the midtroposphere remaining relatively clean. During frontal passages a combination of stratiform and convective clouds mixed pollutants more uniformly into the middle and upper levels.

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

Over remote marine areas, the effects of deep convection on trace gas distributions differ from those over moderately polluted continental regions. Chemical measurements taken by the NASA ER-2 aircraft during the Stratosphere-Troposphere Exchange Project (STEP) off the northern coast of Australia show the influence of very deep convective events. Between 14.5 and 16.5 km on the February 2-3, 1987 flight, chemical profiles that included pronounced maxima in CO, water vapor, and CCN, and minima of NO_Y, and O_3 (Pickering et al., 1993). Trajectory analysis showed that these air parcels likely were transported from convective cells 800-900 km upstream. Very low marine boundary layer mixing ratios of NO_Y and O_3 in this remote region were apparently transported upward in the convection. A similar result was noted in Central Equatorial Pacific Experiment (CEPEX) (Kley et al., 1996) and in Indian Ocean Experiment (INDOEX) (DeLaat et al., 1999) where a series of ozonesonde ascents showed very low upper tropospheric O_3 following deep convection. It is likely that similar transport of low-ozone tropical marine boundary layer air to the upper troposphere occurs in thunderstorms along the east coast of Florida. Deep convection occurs frequently over the tropical Pacific. Low-ozone and low-NO_X convective outflow likely will descend in the subsidence region of the subtropical eastern Pacific, leading to some of the cleanest air that arrives at the west coast of the United States.

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

AX2.3.3. Effects on Photolysis Rates and Wet Scavenging

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

Thunderstorm updraft regions, which contain copious amounts of water, are regions where efficient scavenging of soluble species can occur (Balkanski et al., 1993). NO_2 itself is not very soluble and therefore wet scavenging is not a major removal process for it. However, a major NO_X reservoir species, HNO_3 is extremely soluble. Very few direct field measurements of the amounts of specific trace gases that are scavenged in storms are available. Pickering et al. (2001) used a combination of model estimates of soluble species that did not include wet scavenging and observations of these species from the upper tropospheric outflow region of a major line of convection observed near Fiji. Over 90% of the NO_X in the outflow air appeared to have been removed by the storm; about 50% of CH_3OOH and about 80% of HCHO had been lost.

Convective processes and small-scale turbulence transport pollutants both upward and downward throughout the planetary boundary layer and the free troposphere. Ozone and its precursors (NO_X, CO, and VOCs) can be transported vertically by convection into upper part of the mixed layer on one day,

then transported overnight as a layer of elevated mixing ratios, perhaps by a nocturnal low-level jet, and then entrained into a growing convective boundary layer downwind and brought back to the surface.

Because NO and NO_2 are only slightly soluble, they can be transported over longer distances in the gas phase than can more soluble species which can be depleted by deposition to moist surfaces, or taken up more readily on aqueous surfaces of particles. During transport, they can be transformed into reservoir species such as HNO_3, PANs, and N_2O_5. These species can then contribute to local NO_X concentrations in remote areas. For example, it is now well established that PAN decomposition provides a major source of NO_X in the remote troposphere (Staudt et al., 2003). PAN decomposition in subsiding air masses from Asia over the eastern Pacific could make an important contribution to O_3 and NO_X enhancement in the United States (Kotchenruther et al., 2001; Hudman et al., 2004). Further details about mechanisms for transporting ozone and its precursors were described at length in the 2006 AQCD for Ozone.

AX2.4. Sources and Emissions of NO_X

NO_X has natural and anthropogenic sources. In Section AX2.4.1, interactions of NO_X with the terrestrial biosphere are discussed. Because of the tight coupling between processes linking emissions and deposition, they are discussed together. Additional sources are described in Section AX2.4.2. Field studies evaluating emissions inventories are discussed in Section AX2.4.2.4.

AX2.4.1. Interactions of NO_X with the Biosphere

NO_X affect vegetated ecosystems, and in turn the atmospheric chemistry of NO_X is influenced by vegetation. Extensive research on nitrogen inputs from the atmosphere to forests was conducted in the 1980s as part of the Integrated Forest Study, and is summarized by Johnson and Lindberg (1992). The following sections discuss sources of NO_X from soil, deposition of NO_X to foliage, reactions with biogenic hydrocarbons, and ecological effects of nitrogen deposition.

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

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

Several reactive nitrogen are species are deposited to vegetation, among them, HNO_3, NO_2, PAN, and organic nitrates. Deposition of HNO_3 appears to be relatively simple. Field observations based on concentration gradients and recently using eddy covariance demonstrate rapid deposition that approaches the aerodynamic limit (as constrained by atmospheric turbulence) in the Wesely (1989) formulation based

on analogy to resistance. Surface resistance for HNO_3 uptake by vegetation is negligible. Deposition rates are independent of leaf area or stomatal conductance, implying that deposition occurs to branches, soil, and leaf cuticle as well as internal leaf surfaces.

Deposition velocities (V_d) typically exceed 1 cm/s and exhibit a daily pattern controlled by turbulence characteristics such that midday maximum and lower values at night when there is stable boundary layer.

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

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

$$F=CV_d \tag{AX2.4-1}$$

$$V_d=(R_a+R_b=R_c)^{-1} \tag{AX2.4-2}$$

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

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

$$J=g_s(C_a-C_i) \tag{AX2.4-3}$$

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

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

$$J=g_s(C_a-C_i)=J_s(UV) \quad \text{(AX2.4-4)}$$

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

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

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

Formation of the hydroxyalkyl nitrates occurs following OH attack on VOCs. In some sense, this mechanism is just an alternate pathway for OH to react with NO_X to form a rapidly depositing species, because if VOC were not present, OH would be available to react with any NO_2 present to form HNO_3.

HNO_2 formation on vegetative surfaces at night has long been observed based on measurements of positive gradients (Harrison and Kitto, 1994). Surface reactions of NO_2 enhanced by moisture were proposed to explain these results. Production was evident at sites with high ambient NO_2; at low concentration, uptake of HONO exceeded the source. Daytime observations of HONO when rapid photolysis is expected to deplete ambient concentrations to very low levels implies a substantial source of photo-induced HONO formation at a variety of forested sites where measurements have been made. Estimated source strengths are 200-1800/ppt·h in the surface layer (Zhou et al., 2002a, 2003), which is about 20 times faster than all nighttime sources. HNO_2 sources could be important to OH/HO_2 budgets as HONO is rapidly photolyzed by sunlight to OH and NO. Additional evidence of light-dependent reactions to produce HONO comes from discovery of a HONO artifact in pyrex sample inlet lines exposed to ambient light. Either covering the inlet or washing it eliminated the HONO formation (Zhou et al., 2002b). Similar reactions might serve to explain observations of UV-dependent production of NO_X in empty foliar cuvettes that had been exposed to ambient air (Hari et al., 2003; Raivonen et al., 2003).

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

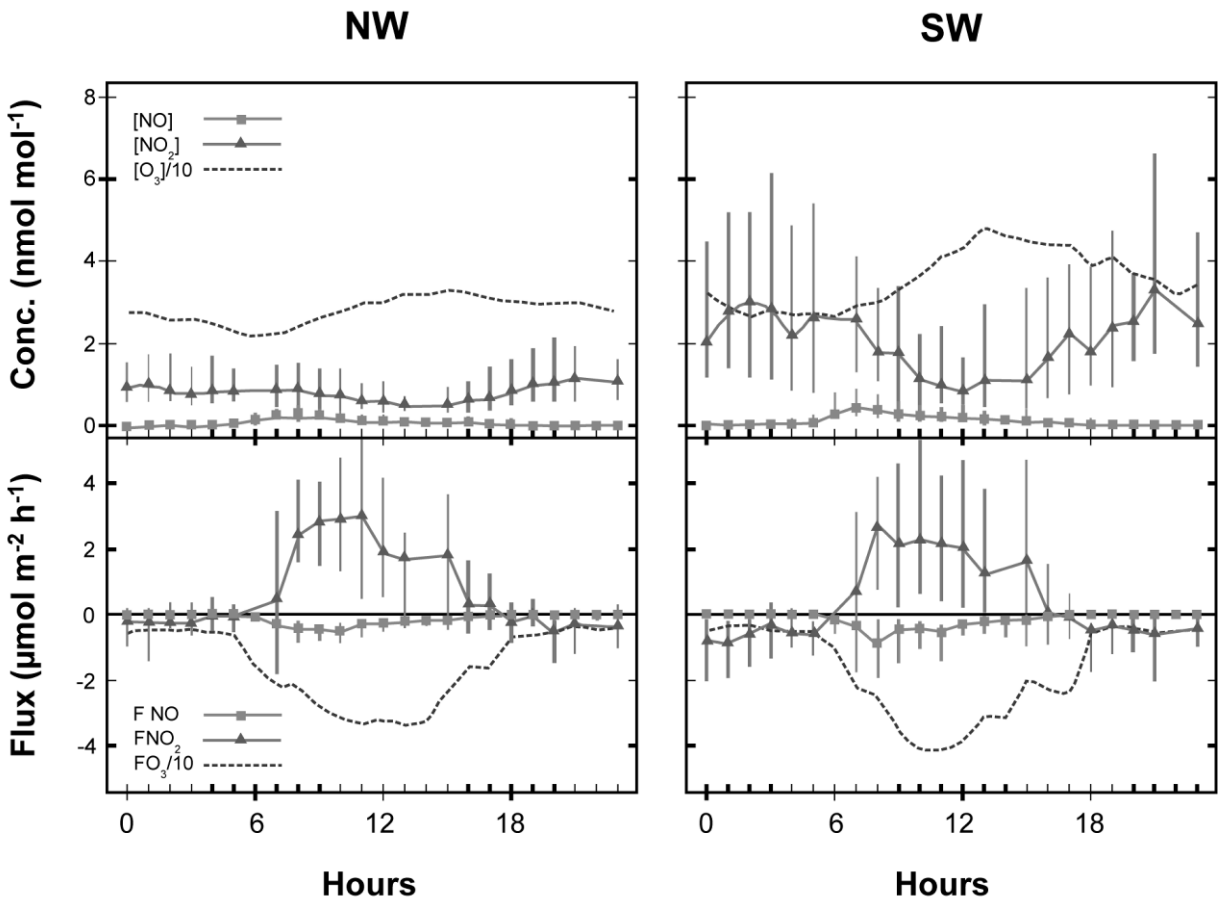
available amount of surface or surface-to-volume ratio can significantly influence the HONO production rates (Kaiser and Wu, 1977; Kleffmann et al., 1998; Svensson et al., 1987), which may explain the difference in the rates observed between laboratory and atmospheric measurements.

There is no consensus on a chemical mechanism for photo-induced HONO production. Photolysis of HNO_3 or NO_3^- absorbed on ice or in surface water films has been proposed (Honrath et al., 2002; Ramazan et al., 2004; Zhou et al., 2001, 2003); but alternative pathways include NO_2 interaction with organic surfaces such as humic substances (George et al., 2005; Stemmler et al., 2006). Note that either NO_3^- photolysis or heterogeneous reaction of NO_2 are routes for recycling deposited NO_X back to the atmosphere in an active form. NO_3 photolysis would return nitrogen that heretofore was considered irreversibly deposited, surface reactions between NO_2 and water films or organic molecules would decrease the effectiveness of observed NO_2 deposition if the HONO were re-emitted.

AX2.4.1.1. NO_2 and HNO_3 Flux Data from Harvard Forest

Harvard Forest is a rural site in central Massachusetts, where ambient NO_X, NO_Y, and other pollutant concentrations and fluxes of total NO_Y have been measured since 1990 (Munger et al., 1996). An intensive study in 2000 utilized a Tunable Diode Laser Absorption Spectrometer (TDLAS) to measure NO_2 and HNO_3. TDLAS has an inherently fast response, and for species such as NO_2 and HNO_3 with well-characterized spectra it provides an absolute and specific measurement. Absolute concentrations of HNO_3 were measured, and the flux inferred based on the dry deposition inferential method that uses momentum flux measurements to compute a deposition velocity and derives an inferred flux (Wesely and Hicks, 1977; Hicks et al., 1987). Direct eddy covariance calculations for HNO_3 were not possible because the atmospheric variations were attenuated by interaction with the inlet walls despite very short residence time and use of fluorinated silane coatings to make the inlet walls more hydrophobic. Nitrogen oxide response was adequate to allow both concentration and eddy covariance flux determination. Simultaneously, NO and NO_Y eddy covariance fluxes were determined with two separate O_3 chemiluminescence detectors, one equipped with a H_2-gold catalyst at the inlet to convert all reactive nitrogen compounds to NO. Additionally, the measurements include concentration gradients for NO, NO_2, and O_3 over several annual cycles to examine their vertical profiles in the forest canopy.

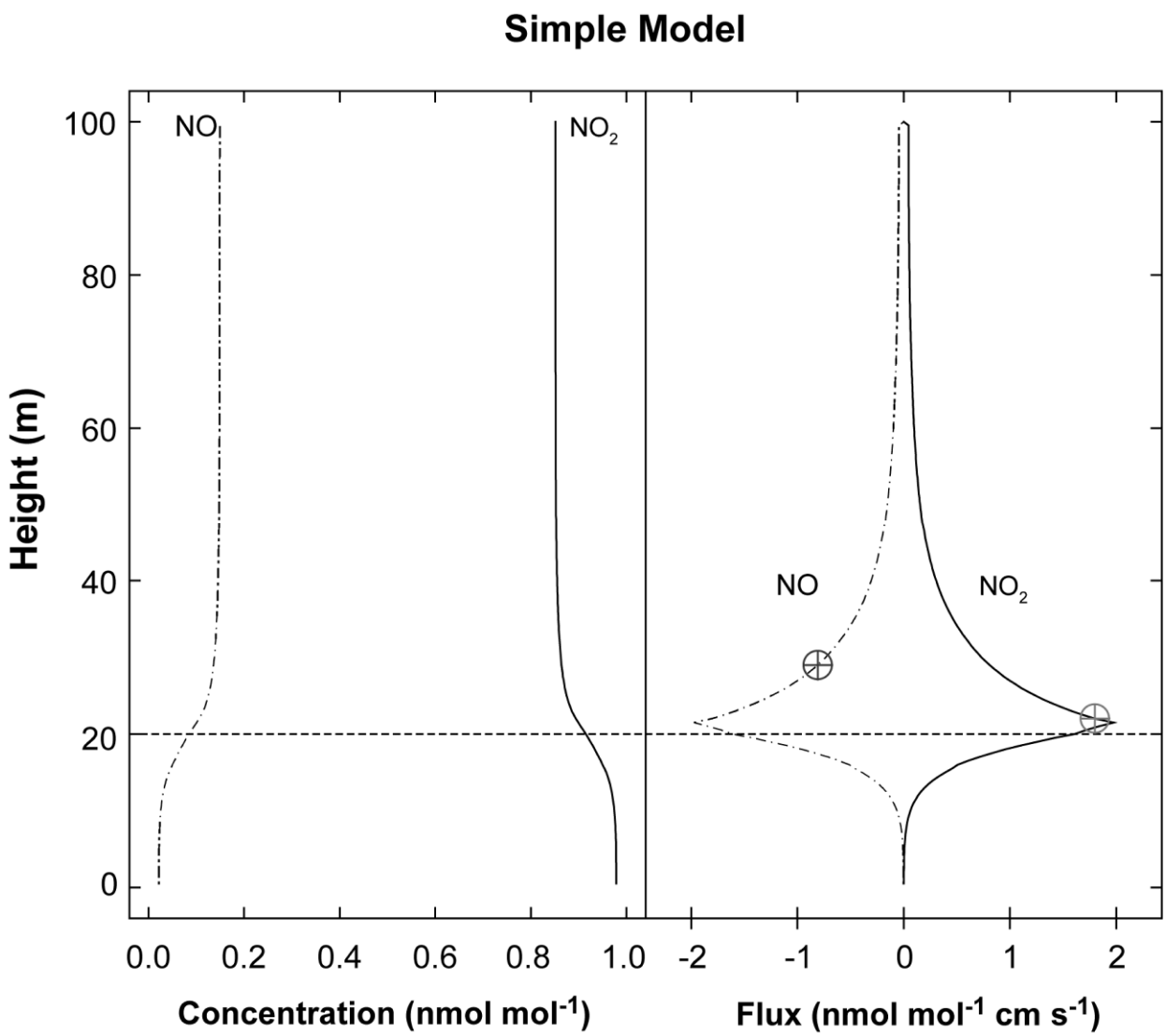
Overall, the results show typical NO_2 concentrations of 1 ppb under clean-air conditions and mean concentrations up to 3 ppb at night and 1 ppb during daytime for polluted conditions. Net positive fluxes (emission) of NO_2 were evident in the daytime and negative fluxes (deposition) were observed at night (Figure AX2.4-1). Nitric oxide fluxes were negative during the daytime and near zero at night.



Source: Horii et al. (2004).

Figure AX2.4-1. Diel cycles of median concentrations (upper panels) and fluxes (lower panels). These are for the Northwest (clean sector, left panels) and Southwest (polluted sector, right panels) wind sectors at Harvard Forest, April-November, 2000, for NO, NO_2, and O_3/10. NO and O_3 were sampled at a height of 29 m, and NO_2 at 22 m. Vertical bars indicate 25th and 27th quartiles for NO and NO_2 measurements. NO_2 concentration and nighttime deposition are enhanced under southwesterly conditions, as are O_3 and the morning NO maximum.

In part the opposite NO and NO_2 fluxes are simply consequences of variable NO/NO_2 distributions responding to vertical gradients in light intensity and O_3 concentration, which resulted in no net flux of NO_X (Gao et al., 1993). In the Harvard Forest situation, the NO and NO_2 measurements were not at the same height above the canopy, and the resulting differences derive at least in part from the gradient in flux magnitude between the two inlets (Figure AX2.4-2).

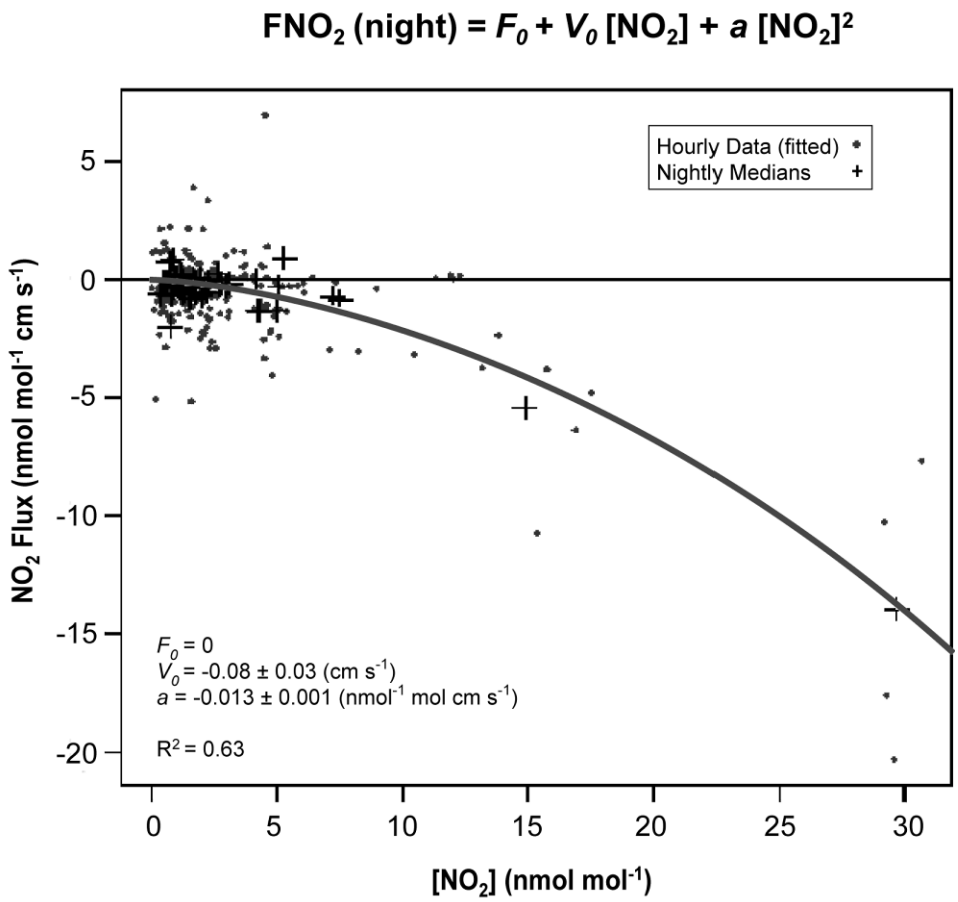


Source: Horii (2002).

Figure AX2.4-2. Simple NO_X photochemical canopy model outputs. Left panel, concentrations of NO (dashed) and NO_2 (solid); right, fluxes of NO (dashed) and NO_2 (solid). Symbols indicate measurement heights for NO (29m) and NO_2 (22m) at Harvard Forest. The model solves the continuity equation for NO concentration at 200 levels, d/dz(-Kc(dNO/dz)) = PNO - LNO, where PNO = [NO]/t1, LNO = [NO]/t2, and zero net deposition or emission of NO_X is allowed. NO_X (NO + NO_2) is normalized to 1ppb. t1 = 70s in this example. Due to the measurement height difference, observed upward NO_2 flux due to photochemical cycling alone should be substantially larger than observed downward NO flux attributable to the same process.

At night, when NO concentrations are near 0 due to titration by ambient O_3 there is not a flux of NO to offset NO_2 fluxes. Nighttime data consistently show NO_2 deposition (Figure AX2.4-3), which increases with increasing NO_2 concentrations. Concentrations above 10 ppb were rare at this site, but the few high NO_2 observations suggest a nonlinear dependence on concentration. The data fit a model with V_d of −0.08 plus an enhancement term that was second order in NO_2 concentration. The second order

term implies that NO_2 deposition rates to vegetation in polluted urban sites would be considerably larger than what was observed at this rural site.

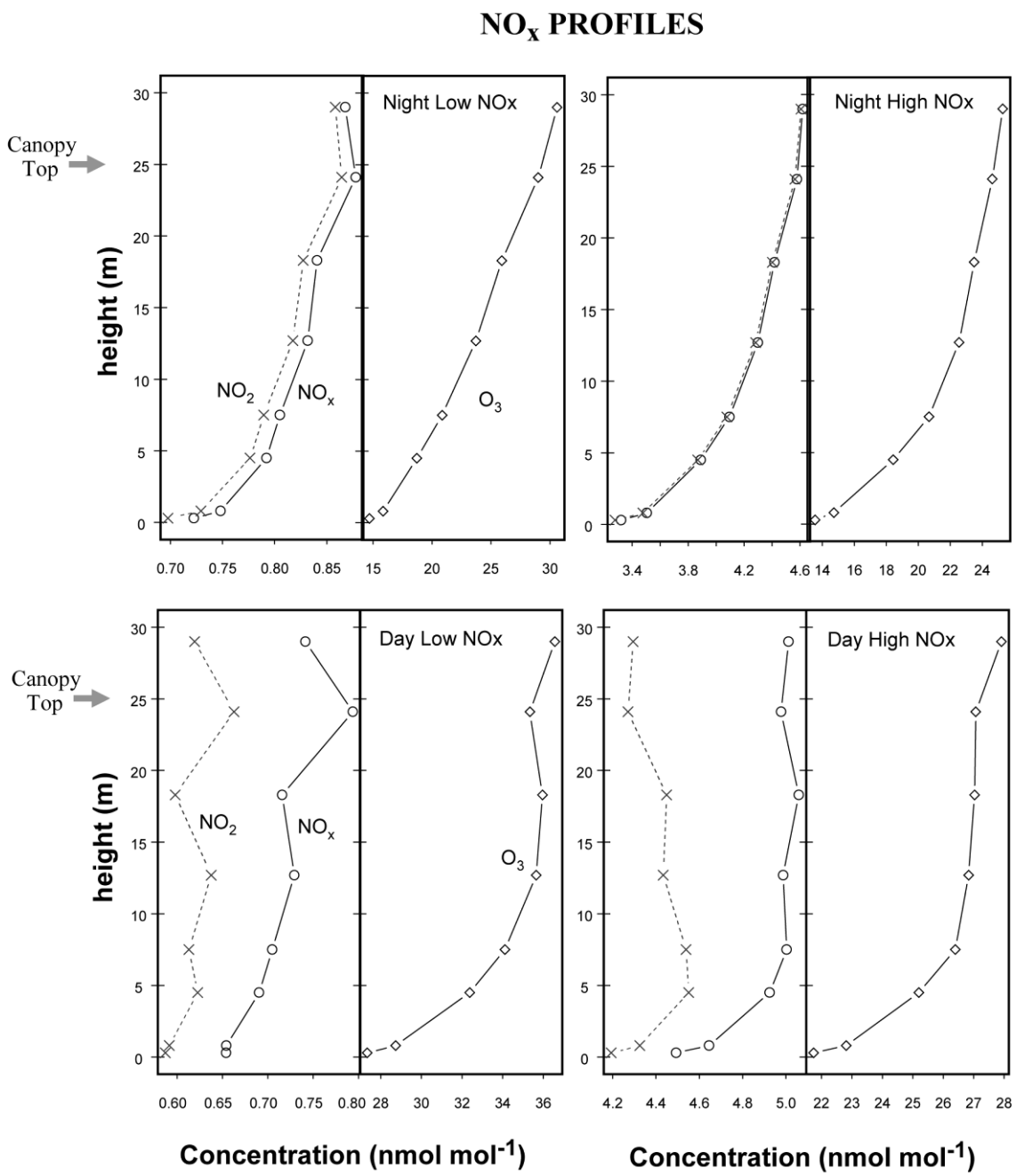


Source: Horii et al. (2004).

Figure AX2.4-3. Hourly (dots) and median nightly (pluses) NO_2 flux vs. concentration. The results of least-squares fit on the hourly data (curve). The flux is expressed in units of concentration times velocity (nmol/mol·cm·s) in order to simplify the interpretation of the coefficients in the least-squares fit. Pressure and temperature corrections have been taken into account in the conversion from density to mixing ratio.

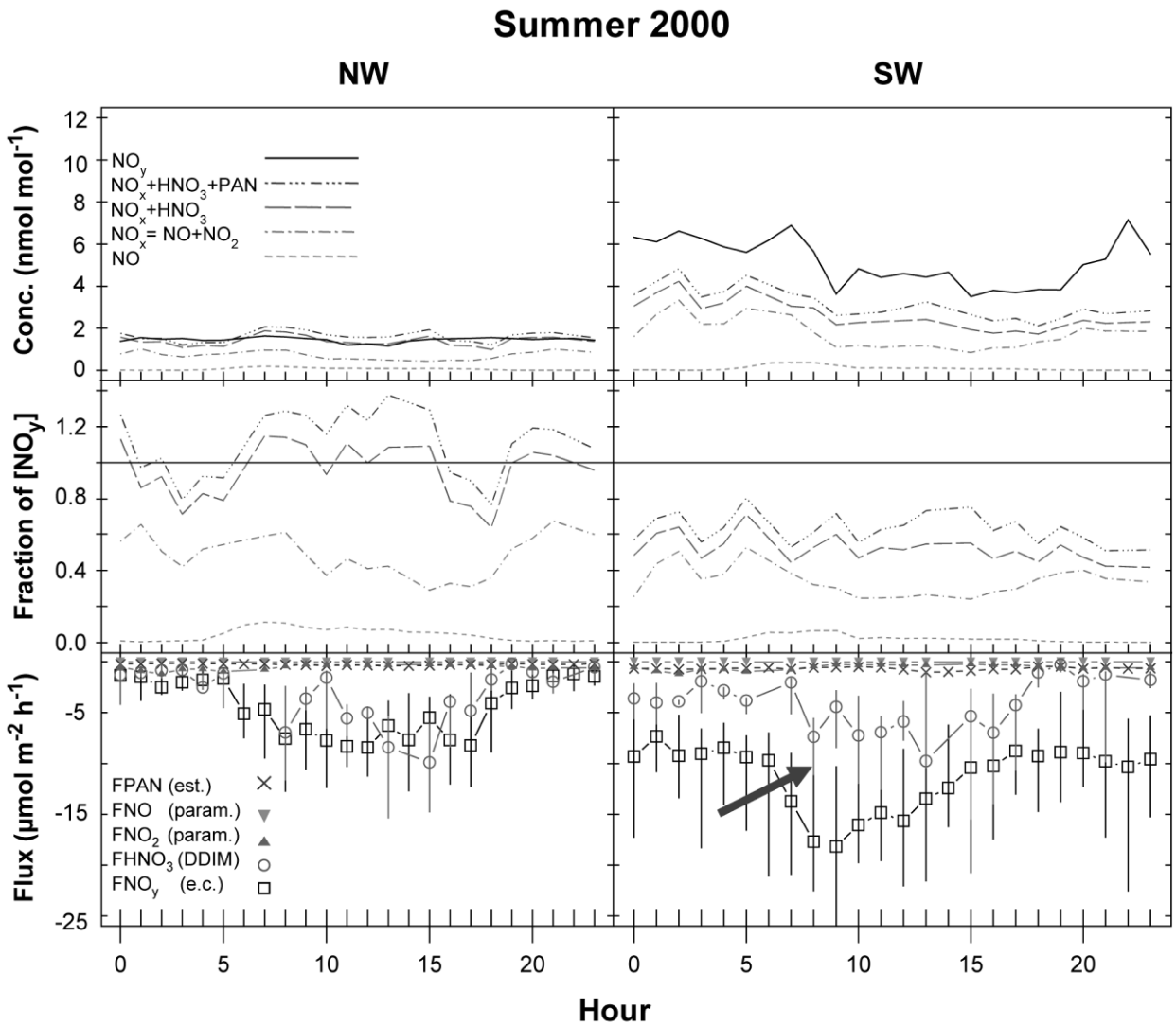
After accounting for the NO-NO_2 null cycle the net NO_X flux could be derived. Overall, there was a net deposition of NO_X during the night and essentially zero flux in the day, with large variability in the magnitude and sign of individual flux observations. For the periods with $[NO_2] > 2$ ppb, deposition was always observed. These canopy-scale field observations are consistent with a finite compensation point for NO_2 in the canopy that offsets foliar uptake or even reverses it when concentrations are especially low. At concentrations above the compensation point, NO_X is absorbed by the canopy. Examination of concentration profiles corroborates the flux measurements (Figure AX2.4-4). During daytime for low-NO_X conditions, there is a local maximum in the concentration profile near the top of the canopy where O_3 has a local minimum, which is consistent with foliar emission or light-dependent production of NO_X in the upper canopy. Depletion is evident for both NO_X and O_3 near the forest floor. Air reaching the ground

has passed through the canopy where uptake is efficient and the vertical exchange rates near the ground are slow. At night, the profiles generally decrease with decreasing height above the ground, showing only uptake. At higher concentrations, the daytime NO_X concentrations are nearly constant through the canopy; no emission is evident from the sunlit leaves.



Source: Horii et al. (2004).

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



Source: Horii et al. (2006).

Figure AX2.4-5. Summer (June-August) 2000 median concentrations (upper panels), fractions of NO_Y (middle panels), and fluxes (lower panels) of NO_Y and component species. These are separated by wind direction (Northwest on the left and Southwest on the right). Vertical lines in the flux panels show 25th and 75th quartiles of $F(NO_Y)$ and $F(HNO_3)$; negative fluxes represent deposition; $F(NO_X)$ is derived from eddy covariance F(NO) and $F(NO_2)$ measurements (corrected for photochemical cycling), $F(HNO_3)$ is inferred, and $F(NO_Y)$ was measured by eddy covariance. The sum of NO_X, HNO_3, and PAN accounts for all of the NO_Y concentration and flux for Northwesterly (unpolluted background) flows, whereas up to 50% of NO_Y and $F(NO_Y)$ under Southwesterly flows are in the form of reactive nitrogen species whose fluxes are not measured or estimated here.

Figure AX2.4-5 compares observed fluxes of all the observed species. The measured NO_X and estimated PAN fluxes are small relative to the observed total NO_Y flux. In clean air, HNO_3 accounts for nearly all the NO_Y flux and the sum of all measured species is about equal to the NO_Y concentration. However, in polluted conditions, unmeasured species are up to 25% of the NO_Y, and HNO_3 fluxes cannot

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

AX2.4.2. Emissions of NO_X

Estimated annual emissions of NO_X for 2002 (U.S. Environmental Protection Agency, 2006) are shown at end of Annex AX2, in Table AX2.4-1. Information relevant for estimating emissions of criteria pollutants is given in U.S. Environmental Protection Agency (1999). Discussions of uncertainties in current emissions inventories and strategies for improving them can be found in NARSTO (2005).

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

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

$$N_2 + O_2 \rightarrow 2NO \tag{AX2.4-5}$$

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

$$C_aH_bO_cN_d + O_2 \rightarrow xCO_2 + yH_2O + zNO \tag{AX2.4-6}$$

In addition to NO formation by the schematic reactions given above, some NO_2 and CO are also formed depending on temperatures, concentrations of OH and HO_2 radicals and O_2 levels. Fuel nitrogen is highly variable in fossil fuels, ranging from 0.5 to 2.0 percent by weight (wt %) in coal to 0.05% in light distillates (e.g., diesel fuel), to 1.5 wt % in heavy fuel oils (UK AQEG, 2004).

AX2.4.2.1. Emissions of NO_2 from Motor Vehicles

NO_2 in exhaust gasoline-powered engines generally comprises <1-3% of total NO_X (Heeb et al., 2008; Hilliard and Wheeler, 1979), according to dynamometer studies. Some European studies have reported NO_2/NO_X ratios of 15% or higher from gasoline vehicles based on integrated measurements from Tedlar bags (Lenner, 1987; Soltic and Weilenmann, 2003). However, subsequent studies suggesting that NO-to-NO_2 conversion can occur within bag sample of a diluted exhaust have led the groups performing these measurement to revise their measurement techniques and avoid the use of Tedlar bag samples (Alvarez et al., 2007; Heeb et al., 2008). As a result, dynamometer-based measurements generally indicate that in the absence of post-tailpipe transformation, NO_2 comprises, at most, a few percent of total NO_X in gasoline exhaust.

Emission control devices for diesel engines can increase the fraction of exhaust NO_X emitted as NO_2. The two major types that can increase NO_2/NO_X ratios include diesel oxidation catalysts (DOCs) and catalyzed diesel particle filters (CDPFs). Both are considered "after treatment" devices, in that they affect exhaust after it leaves an engine. In both DOCs and CDPFs, the effect on NO_2/NO_X ratios depends on the composition of the catalytic washcoats.

DOCs are flow-through devices consisting of porous ceramic with a catalytic washcoat. Catalysis within the DOC reduces exhaust concentrations of organic material, including PM and hydrocarbons. In doing so, DOCs convert NO to NO_2, the excess of which may be emitted through the tailpipe.

Like DOCs, CDPFs also may be a part of the emission control system for diesel vehicles. CDPFs can reduce PM emissions from a diesel vehicle by ≥ 90%. They commonly consist of a DOC and a particle trapping filter or a particle trap with a catalytic wash coat, generally containing noble metals. As exhaust gases pass through a CDPF, soot and organic material in the exhaust becomes trapped in the filter. The DOC or the filter's catalytic washcoat converts exhaust NO to NO_2 to use in oxidizing the particulate matter trapped by the filter. Excess NO_2 is emitted through the tailpipe.

Widespread use of CDPFs in European cities has been identified as a cause for increasing NO_2/NO_X ratios at urban air quality monitors. Carslaw et al. (2007a) report upward trends in roadside concentrations of NO_2 between 2002 and 2006 at Marylebone Road, site on the edge of central London, UK. Using ambient data analysis methods developed in earlier publications (Carslaw et al., 2005a), Carslaw et al. (2007b) estimated the NO_2/NO_X emission ratio from the London vehicle fleet over time. NO_2/NO_X emission ratios increased significantly along Marylebone Road between 2002 and 2006, from approximately 10% by volume to over 20% by volume. Using multivariate regression, Carslaw et al. (2005b) estimated that the largest contributor to the increasing NO_2/NO_X emission ratios was the retrofit of London transit buses with catalyzed diesel particle filters (CDPF).

Kessler et al. (2006) employed the methods developed by Carslaw et al. (2005a) to estimate the NO_2/NO_X ratio from traffic in Baden-Württemberg, Germany between 1995 and 2005. The estimates increase from approximately 5% in 1995 to over 20% in 2005. The investigators attributed the increase to an increase in the use of oxidation catalysts in diesel-fueled passenger cars.

Ayala et al. (2002) compared NO_2/NO_X ratios in a bus before and after installation of a CDPF. NO_2 emissions before retrofit were 0.92-2.14 g/mi across different test cycles, comprising 3-9% of total NO_X. After retrofit, NO_2 emissions were 9.0-24.0 g/mi, comprising 39-49% of total NO_X.

Two U.S. studies where investigators sampled the plumes of heavy-duty diesel vehicles found that, vehicles retrofitted with CDPFs had lower PM emissions and higher NO_2/NO_X ratios compared to diesel vehicles without CDPFs. Shorter et al. (2005) conducted a "chase" experiment of vehicles in New York City, including metropolitan transit buses equipped with CDPFs. Overall, while following CDPF-equipped buses, approximately one-third of exhaust NO_X was NO_2. In contrast, less than 10% of NO_X was NO_2 behind city buses lacking a CDPF. Kittleson et al. (2006) used an on-road laboratory to sample the exhaust plumes of a truck under highway cruise conditions, equipped with one of two different CDPFs. NO_2/NO_X ratios for CDPF-treated exhaust under highway cruise conditions ranged from 59-70%. The comparison of these two studies illustrates the role that temperature can play in increasing CDPF catalytic activity.

The ratio of NO_2 to NO_X in primary emissions ranges from 3 to 5 % from gasoline engines, 5 to 12% from heavy-duty diesel trucks, 5 to 10% from vehicles fueled by compressed natural gas and from 5 to 10% from stationary sources. In addition to NO_X, motor vehicles also emit HONO, with ratios of HONO to NO_X ranging from 0.3% in the Caldecott Tunnel, San Francisco Bay (Kirchstetter and Harley, 1996) to 0.5 to 1.0% in studies in the United Kingdom (UK AQEG, 2004).

The NO_2 to NO_X ratios in emissions from turbine jet engines are as high as 32 to 35 % during taxi and takeoff (1993 AQCD for NO_X). Sawyer et al. (2000) have reviewed the factors associated with NO_X emissions by mobile sources. Marine transport represents a minor source of NO_X, but constitutes a larger source in the EU where it is expected to represent about two-thirds of land-based sources (UK AQEG, 2004).

AX2.4.2.2. NO_X Emissions from Natural Sources

Soil

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

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

Emissions of NO from soils peak in summer when O_3 formation is also at a maximum. An NRC panel report (NRC, 2002) outlined the role of agriculture in emissions of air pollutants including NO and NH_3. That report recommends immediate implementation of best management practices to control these emissions, and further research to quantify the magnitude of emissions and the impact of agriculture on air quality. Civerolo and Dickerson (1998) report that use of the no-till cultivation technique on a fertilized cornfield in Maryland reduced NO emissions by a factor of seven.

NO_X from Biomass Burning

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

Lightning Production of NO

Annual global production of NO by lightning is the most uncertain source of reactive nitrogen. In the last decade, literature values of the global average production rate range from 2 to 20 Tg N per year. However, the most likely range is from 3 to 8 Tg N per year, because the majority of the recent estimates fall in this range. The large uncertainty stems from several factors: (1) a large range of NO production rates per meter of flash length (as much as two orders of magnitude); (2) the open question of whether

cloud-to-ground (CG) flashes and intracloud flashes (IC) produce substantially different amounts of NO; (3) the global flash rate; and (4) the ratio of the number of IC flashes to the number of CG flashes. Estimates of the amount of NO produced per flash have been made based on theoretical considerations (e.g., Price et al., 1997), laboratory experiments (e.g., Wang et al., 1998); field experiments (e.g., Stith et al., 1999; Huntrieser et al., 2002, 2007); and through a combination of cloud-resolving model simulations, observed lightning flash rates, and anvil measurements of NO (e.g., DeCaria et al., 2000, 2005; Ott et al., 2007). The latter method was also used by Pickering et al. (1998), who showed that only ~5 to 20% of the total NO produced by lightning in a given storm exists in the boundary layer at the end of a thunderstorm. Therefore, the direct contribution to boundary layer O_3 production by lightning NO is thought to be small. However, lightning NO production can contribute substantially to O_3 production in the middle and upper troposphere. DeCaria et al. (2005) estimated that up to 10 ppb of O_3 was produced in the upper troposphere in the first 24 h following a Colorado thunderstorm due to the injection of lightning NO. A series of midlatitude and subtropical thunderstorm events have been simulated with the model of DeCaria et al. (2005), and the derived NO production per CG flash averaged 500 moles/flash while average production per IC flash was 425 moles/flash (Ott et al., 2006).

A major uncertainty in mesoscale and global chemical transport models is the parameterization of lightning flash rates. Model variables such as cloud top height, convective precipitation rate, and upward cloud mass flux have been used to estimate flash rates. Allen and Pickering (2002) have evaluated these methods against observed flash rates from satellite, and examined the effects on O_3 production using each method.

AX2.4.2.3. Uses of Satellite Data to Derive Emissions

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

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

Jaeglé et al. (2005) applied additional information on the spatial distribution of emissions and on fire activity to partition NO_X emissions into sources from fossil fuel combustion, soils, and biomass burning. Global a posteriori estimates of soil NO_X emissions are 68% larger than the a priori estimates. Large increases are found for the agricultural region of the western United States during summer, increasing total U.S. soil NO_X emissions by a factor of 2 to 0.9 Tg N/yr. Bertram et al. (2005) found clear signals in the SCIAMACHY observations of short intense NO_X pulses following springtime fertilizer application and subsequent precipitation over agricultural regions of the western United States. For the agricultural region in North-Central Montana, they calculate a yearly SCIAMACHY top-down estimate that is 60% higher than a commonly used model of soil NO_X emissions by Yienger and Levy (1995).

Martin et al. (2006) retrieved tropospheric NO_2 columns for May 2004 to April 2005 from the SCIAMACHY satellite instrument to derive top-down NO_X emissions estimates via inverse modeling with a global chemical transport model (GEOS-Chem). The top-down emissions were combined with a priori information from a bottom-up emission inventory with error weighting to achieve an improved a

posteriori estimate of the global distribution of surface NO_X emissions. Their a posteriori inventory improves the GEOS-Chem simulation of NO_X, PAN, and HNO_3 with respect to airborne in situ measurements over and downwind of New York City. Their a posteriori inventory shows lower NO_X emissions from the Ohio River valley during summer than during winter, reflecting recent controls on NO_X emissions from electric utilities. Their a posteriori inventory is highly consistent ($R^2 = 0.82$, bias = 3%) with the NEI99 inventory for the United States. In contrast, their a posteriori inventory is 68% larger than a recent inventory by Streets et al. (2003) for East Asia for the year 2000.

AX2.4.2.4. Field Studies Evaluating Emissions Inventories

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

Emissions inventories for North America can be evaluated by comparison to measured long-term trends and or ratios of pollutants in ambient air. A decadal field study of ambient CO at a rural site in the eastern United States (Hallock-Waters et al., 1999) indicates a downward trend consistent with the downward trend in estimated emissions over the period 1988 to 1999 (U.S. Environmental Protection Agency, 1997), even when a global downward trend is accounted for. Measurements at two urban areas in the United States confirmed the decrease in CO emissions (Parrish et al., 2002). That study also indicated that the ratio of CO to NO_X emissions decreased by a factor of almost three over 12 years. (Such a downward trend was noted in the 1996 O_3 AQCD). Emissions estimates (U.S. Environmental Protection Agency, 1997) indicate a much smaller decrease in this ratio, suggesting that NO_X emissions from mobile sources may be underestimated and/or increasing. Parrish et al. (2002) conclude that O_3 photochemistry in U.S. urban areas may have become more NO_X-limited over the past decade.

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

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

Parrish et al. (1998) and Parrish and Fehsenfeld (2000) proposed methods to derive emission rates by examining measured ambient ratios among individual VOC, NO_X and NO_Y. There is typically a strong correlation among measured values for these species because emission sources are geographically collocated, even when individual sources are different. Correlations can be used to derive emissions ratios

between species, including adjustments for the impact of photochemical aging. Investigations of this type include correlations between CO and NO_Y (e.g., Parrish et al., 1991), between individual VOC species and NO_Y (Goldan et al., 1995, 1997, 2000) and between various individual VOC (Goldan et al., 1995, 1997; McKeen and Liu, 1993; McKeen et al., 1996). Buhr et al. (1992) derived emission estimates from principal component analysis (PCA) and other statistical methods. Many of these studies are summarized in Trainer et al. (2000), Parrish et al. (1998), and Parrish and Fehsenfeld (2000). Goldstein and Schade (2000) also used species correlations to identify the relative impacts of anthropogenic and biogenic emissions. Chang et al. (1996, 1997) and Mendoza-Dominguez and Russell (2000, 2001) used the more quantitative technique of inverse modeling to derive emission rates, in conjunction with results from chemistry-transport models.

AX2.5. Methods for Calculating NO_X Concentrations 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 meteorological 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 because human activities can affect directly or indirectly emissions from what would have been considered natural sources during the preindustrial era. Moreover, emissions from plants and animals used in agriculture have been referred to as anthropogenic or natural in different applications. Wildfire emissions may be considered to be natural, except that forest management practices may have led to the buildup of fuels on the forest floor, thereby altering the frequency and severity of forest fires. Needed meteorological quantities such as winds and temperatures are taken from operational analyses, reanalyses, or circulation models. In most cases, these are off-line analyses, i.e., they are not modified by radiatively active species such as O_3 and particles generated by the model.

A brief overview of atmospheric chemistry-transport models is given in Section AX2.5.1. A discussion of emissions inventories of precursors used by these models is given in Section AX2.5. Uncertainties in emissions estimates have also been discussed in the AQCD for PM (U.S. Environmental Protection Agency, 2004). Chemistry-transport model evaluation and an evaluation of the reliability of emissions inventories are presented in Section AX2.5.4.

AX2.5.1. Chemistry-Transport Models

Atmospheric CTMs have been developed for application over a wide range of spatial scales ranging from neighborhood to global. Regional scale CTMs are used chiefly for four purposes: (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; (3) to understand relations among the concentration patterns of various pollutants that may exert adverse health effects; (4) for determining control strategies for O_3 precursors. However, this last application has met with varying degrees of success because of the highly nonlinear

relations between O_3 and emissions of its precursors, and uncertainties in emissions, parameterizations of transport, and chemical production and loss terms. Uncertainties in meteorological variables and emissions can be large enough to lead to significant errors in developing control strategies (e.g., Russell and Dennis, 2000; Sillman et al., 1995).

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

There are two major formulations of CTMs in current use. The first approach, grid-based or Eulerian air quality models subdivide the region to be modeled (the modeling domain) into a three-dimensional array of grid cells. Spatial derivatives in the species continuity equations are cast in finite-difference 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. Finite element Eulerian models also exist and have been applied, but less frequently. 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 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 treated in an Eulerian manner (e.g., 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).

AX2.5.1.1. Regional Scale Chemistry Transport Models

Major modeling efforts within the U.S. Environmental Protection Agency center on the Community Multiscale Air Quality modeling system (CMAQ) (Byun and Ching, 1999; Byun and Schere, 2006). A number of other modeling platforms using Lagrangian and Eulerian frameworks have been reviewed in the 96 AQCD for O_3 (U.S. Environmental Protection Agency, 1997), and in Russell and Dennis (2000). The capabilities of a number of CTMs designed to study local- and regional-scale air pollution problems were summarized by Russell and Dennis (2000). Evaluations of the performance of CMAQ are given in Arnold et al. (2003), Eder and Yu (2005), Appel et al. (2005), and Fuentes and Raftery (2005). The domain of CMAQ and other Eulerian CTMs can extend from several hundred km to the entire hemisphere. In addition, both of these classes of models allow 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 including RAMS. Simulations of pollution 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), as well as finer-scale emissions. Finer spatial resolution is necessary to resolve features such as urban heat island circulation; sea, bay, and land breezes; mountain and valley breezes, and the nocturnal low-level jet, all of which can affect pollutant concentrations.

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 (such as for convection) valid on a relatively coarse grid scale 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 generated either by a model using initial fields alone or with four-dimensional data assimilation to improve the model's performance; (i.e., model equations can be updated periodically "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 longer term modeling series of several months or multiple seasons of the year are now common. 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 individual reactive species are too computationally demanding to be incorporated into CTMs for regulatory use. So, for example, one very extensive "master mechanism" (Derwent et al., 2001) includes approximately 10,500 reactions involving 3603 chemical species (Derwent et al., 2001), but "lumped" mechanisms that group compounds of similar chemistry together may be used. The chemical mechanisms used in existing photochemical O_3 models contain significant uncertainties that may limit the accuracy of their predictions; the accuracy of each of these mechanisms is also limited by missing chemistry. Because of different approaches to the lumping of organic compounds into surrogate groups, chemical mechanisms can produce somewhat different results under similar conditions. The CB-IV chemical mechanism (Gery et al., 1989), the RADM II mechanism (Stockwell et al., 1990), the SAPRC (e.g., Wang et al., 2000a,b; Carter, 1990) and the RACM mechanisms can be used in CMAQ. Jimenez et al. (2003) provide brief descriptions of the features of the main mechanisms in use and they compared concentrations of several key species predicted by seven chemical mechanisms in a box model simulation over 24 h. The average deviation from the average of all mechanism predictions for O_3 and NO over the

daylight period was less than 20%, and was 10% for NO_2 for all mechanisms. However, much larger deviations were found for HNO_3, PAN, HO_2, H_2O_2, ethylene (C_2H_4), and isoprene (C_5H_8). 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. 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 CB-IV. They attributed differences in predicted O_3 concentrations to differences in the mechanisms of oxidation of aromatic hydrocarbons.

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

Spatial and temporal characterizations of anthropogenic and biogenic precursor emissions must be specified as inputs to a CTM. Emissions inventories have been compiled on grids of varying resolution for many hydrocarbons, aldehydes, ketones, CO, NH_3, and NO_X. Emissions inventories for many species require the application of algorithms for calculating the dependence of emissions on physical variables such as temperature and to convert the inventories into formatted emission files which can be used 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 can include 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 prediction 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 deposition velocity (V_d), which is represented as

$$v_d = (r_a + r_b + r_c)^{-1} \quad \text{AX2.5-1}$$

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, Wesely and Hicks (2000) pointed out several shortcomings of current knowledge of dry deposition. Among those shortcomings are difficulties in representing dry deposition over varying terrain where horizontal advection plays a

significant role in determining the magnitude of r_a and difficulties in adequately determining a V_d for extremely stable conditions such as those occurring at night (e.g., Mahrt, 1998). Under the best of conditions, when a model is exercised over a relatively small area where dry deposition measurements have been made, uncertainties as large as ±30% (e.g., Massman et al., 1994; Brook et al., 1996; Padro, 1996) persist. Wesely and Hicks (2000) stated 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 U.S.

The initial conditions, i.e., the starting 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. Both initial and boundary conditions can be estimated from models or data or, more generally, model-data hybrids. Because data for vertical profiles of most species of interest are sparse, results of model simulations over larger, usually global, domains are often used. As may be expected, the influence of boundary conditions depends on the lifetime of the species under consideration and the time scales for transport from the boundaries to the interior of the model domain (Liu et al., 2001b).

Each of the model components described above has associated uncertainties 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, 1999), and 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, else 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 within and without of a power plant plume (e.g., Ryerson et al., 1998 and Sillman, 2000), inclusion of a separate, meteorological module for treating large, tight plumes can be useful. 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 explicit 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. These differences in simulations may be significant for calculated sensitivity of O_3 to its precursors (e.g., Sillman et al., 1995).

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

AX2.5.1.2. Intra-urban Scale Dispersion Modeling

The grid spacing in regional chemistry transport models between 1 and 12 km^2, is usually too coarse to resolve spatial variations on the neighborhood scale. The interface between regional scale models and models of personal exposure described in Annex 3, Section AX3.5 is provided by smaller scale dispersion models. Several models could be used to simulate concentration fields near roads, each with its own set of strengths and weaknesses. For example, AERMOD (http://www.epa.gov/scram001/dispersion_prefrec.htm) is a steady-state plume model that was formulated as a replacement to the ISC3 dispersion model. In the stable boundary layer (SBL), it assumes the concentration distribution to be Gaussian in both the vertical and horizontal. In the convective boundary layer, the horizontal distribution is also assumed to be Gaussian, but the vertical distribution is described with a bi-Gaussian probability density function (pdf). AERMOD has provisions to be applied to flat and complex terrain, and multiple source types (including, point, area and volume sources) in both urban and rural areas. It incorporates air dispersion based on planetary boundary layer turbulence structure and scaling concepts, and is meant to treat both surface and elevated sources and simple and complex terrain in rural and urban areas. The dispersion of emissions from line sources like highways is treated as the sum of emissions from a number of point sources placed side by side. However, emissions are usually not in steady state and there are different functional relationships between buoyant plume rise in point and line sources. It should be remembered that NO_2 is largely secondary in nature as it is produced by Reaction AX 2.2-3. However, AERMOD does not have provision for including secondary sources. The more appropriate use of AERMOD would be to simulate the total of NO and NO_2, or NO_X.

There are models that are non-steady state and can incorporate plume rise explicitly from different types of sources. For example, CALPUFF (http://www.src.com/calpuff/calpuff1.htm) is a non-steady-state puff dispersion model that simulates the effects of time- and space-varying meteorological conditions on pollution transport, transformation, and removal and has provisions for calculating dispersion from surface sources. However, it should be noted that neither model was designed to treat the dispersion of emissions from roads or to include secondary sources. In using either model, the user would have to specify dispersion parameters that are specific to traffic. The distinction between a steady–state and time varying model might not be important for long time scales; however for short time scales, the temporal variability in traffic emissions could result in underestimation of peak concentration and exposures.

AX2.5.1.3. 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 now apparent. There are at present on the order of 20 three-dimensional global models 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 200 km^2 or more. 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 Atmospheric Composition Change: the European Network of excellence (ACCENT), 26 atmospheric CTMs were used to estimate the impacts of three emissions scenarios on global atmospheric composition, climate, and air quality in 2030 (Dentener et al., 2006a). All models were required to use anthropogenic emissions developed at IIASA (Dentener et al., 2005) and GFED version 1 biomass burning emissions (Van der Werf et al., 2003) as described in Stevenson et al. (2006). The base simulations from these models were evaluated against a suite of present-day observations. Most relevant to this assessment report are the evaluations with ozone, NO_2, and nitrogen deposition (Stevenson et al., 2006; Van Noije et al., 2006; Dentener et al., 2006a), which are summarized briefly below.

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

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

The mean present-day global ozone budget across the current generation of CTMs differs substantially from that reported in the IPCC Third Assessment Report (TAR), with a 50% increase in the mean chemical production (to 5100 Tg O_3/yr), a 30% increase in the chemical and deposition loss terms (to 4650 and 1000 Tg O_3/yr, respectively) and a 30% decrease in the mean stratospheric input flux (to 550 Tg O_3/yr) (Stevenson et al., 2006). The larger chemical terms as compared to the IPCC TAR are attributed mainly to higher NO_X (as well as an equatorward shift in distribution) and isoprene emissions, although more detailed schemes and/or improved representations of photolysis, convection, and stratospheric-tropospheric exchange may also contribute (Stevenson et al., 2006).

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

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

AX2.5.1.4. Modeling the Effects of Convection

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

Such methods were used by Pickering et al. (1992b) to examine transport of urban plumes by deep convection. Transport of an Oklahoma City plume by the 10-11 June 1985 PRE-STORM squall line was simulated with the 2-D GCE model. This major squall line passed over the Oklahoma City metropolitan area, as well as more rural areas to the north. Chemical observations ahead of the squall line were conducted by the PRE-STORM aircraft. In this event, forward trajectories from the boundary layer at the leading edge of the storm showed that almost 75% of the low level inflow was transported to altitudes exceeding 8 km. Over 35% of the air parcels reached altitudes over 12 km. Tracer transport calculations were performed for CO, NO_X, O_3, and hydrocarbons. Rural boundary layer NO_X was only 0.9 ppb, whereas the urban plume contained about 3 ppb. In the rural case, mixing ratios of 0.6 ppb were transported up to 11 km. Cleaner air descended at the rear of the storm lowering NO_X at the surface from 0.9 to 0.5 ppb. In the urban plume, mixing ratios in the updraft core reached 1 ppb between 14 and 15 km. At the surface, the main downdraft lowered the NO_X mixing ratios from 3 to 0.7 ppb.

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

Wang et al. (1996) simulated the 10-11 June 1985 PRE-STORM squall line with the NCAR/Penn State Mesoscale Model (MM5) (Grell et al., 1994; Dudhia, 1993). Convection was parameterized as a sub-grid-scale process in MM5 using the Kain and Fritsch (1993) scheme. Mass fluxes and detrainment profiles from the convective parameterization were used along with the 3-D wind fields in CO tracer transport calculations for this convective event.

Convective transport in global chemistry and transport models is treated as a sub-grid-scale process that is parameterized typically using cloud mass flux information from a general circulation model or global data assimilation system. While GCMs can provide data only for a “typical” year, data assimilation systems can provide “real” day-by-day meteorological conditions, such that CTM output can be compared

directly with observations of trace gases. The NASA Goddard Earth Observing System Data Assimilation System (GEOS-1 DAS and successor systems; Schubert et al., 1993; Bloom et al., 1996; Bloom et al., 2005) provides archived global data sets for the period 1980 to present, at 2E H 2.5E or better resolution with 20 layers or more in the vertical. Deep convection is parameterized with the Relaxed Arakawa-Schubert scheme (Moorthi and Suarez, 1992) in GEOS-1 and GEOS-3 and with the Zhang and McFarlane (1995) scheme in GEOS-4. Pickering et al. (1995) showed that the cloud mass fluxes from GEOS-1 DAS are reasonable for the 10-11 June 1985 PRE-STORM squall line based on comparisons with the GCE model (cloud-resolving model) simulations of the same storm. In addition, the GEOS-1 DAS cloud mass fluxes compared favorably with the regional estimates of convective transport for the central United States presented by Thompson et al. (1994). However, Allen et al. (1997) have shown that the GEOS-1 DAS overestimates the amount and frequency of convection in the tropics and underestimates the convective activity over midlatitude marine storm tracks.

Global models with parameterized convection and lightning have been run to examine the roles of these processes over North America. Lightning contributed 23% of upper tropospheric NO_Y over the SONEX region according to the UMD-CTM modeling analysis of Allen et al. (2000). During the summer of 2004 the NASA Intercontinental Chemical Transport Experiment - North America (INTEX-NA) was conducted primarily over the eastern two-thirds of the United States, as a part of the International Consortium for Atmospheric Research on Transport and Transformation (ICARTT). Deep convection was prevalent over this region during the experimental period. Cooper et al. (2006) used a particle dispersion model simulation for NO_X to show that 69-84% of the upper tropospheric O_3 enhancement over the region in Summer 2004 was due to lightning NO_X. The remainder of the enhancement was due to convective transport of O_3 from the boundary layer or other sources of NO_X. Hudman et al. (2007) used a GEOS-Chem model simulation to show that lightning was the dominant source of upper tropospheric NO_X over this region during this period. Approximately 15% of North American boundary layer NO_X emissions were shown to have been vented to the free troposphere over this region based on both the observations and the model.

AX2.5.2. CTM Evaluation

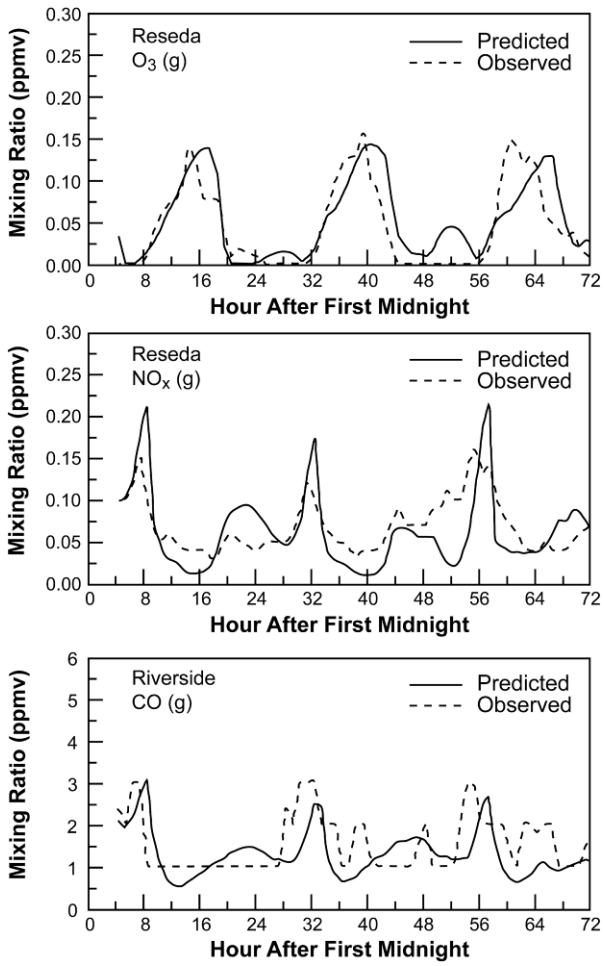
The comparison of model predictions with ambient measurements represents a critical task for establishing the accuracy of photochemical models and evaluating their ability to serve as the basis for making effective control strategy decisions. The evaluation of a model's performance, or its adequacy to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

Global-scale CTMs have generally been evaluated by comparison with measurements for a wide array of species, rather than just for O_3 (e.g., Wang et al., 1998; Emmons et al., 2000; Bey et al., 2001; Hess, 2001; Fiore et al., 2002). These have included evaluation of major primary species (NO_X, CO, and selected VOCs) and an array of secondary species (HNO_3, PAN, H_2O_2) that are often formed concurrently with O_3. Models for urban and regional O_3 have also been evaluated against a broader ensemble of measurements in a few cases, often associated with measurement intensives (e.g., Jacobson et al., 1996; Lu et al., 1997; Sillman et al., 1998). The results of a comparison between observed and computed concentrations from Jacobson et al. (1996) for the Los Angeles Basin are shown in Figures AX2.5-1 and AX2.5-2.

The highest concentrations of primary species usually occur in close proximity to emission sources (typically in urban centers) and at times when dispersion rates are low. The diurnal cycle includes high concentrations at night, with maxima during the morning rush hour, and low concentrations during the afternoon (Figure AX2.5-1). The afternoon minima are driven by the much greater rate of vertical mixing at that time. Primary species also show a seasonal maximum during winter, and are often high during fog

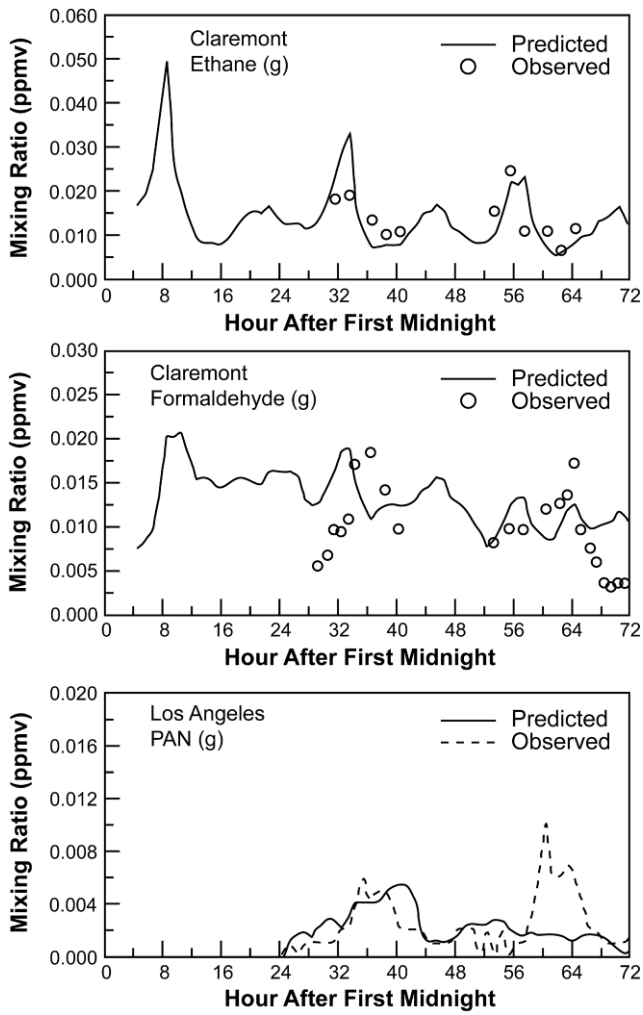
episodes in winter when vertical mixing, is suppressed. By contrast, secondary species such as O_3 are typically highest during the afternoon (the time of greatest photochemical activity), on sunny days and during summer.

During these conditions, concentrations of primary species may be relatively low. Strong correlations between primary and secondary species are generally observed only in downwind rural areas where all anthropogenic species are simultaneously elevated. The difference in the diurnal cycles of primary species (CO, NO_X and ethane) and secondary species (O_3, PAN, and HCHO) is evident in Figure AX2.5-2.



Source: Jacobson et al. (1996)

Figure AX2.5-1. Time series for measured gas-phase species in comparison with results from aphotochemical model. The dashed lines represent measurements, and solid lines represent model predictions (in parts per million, ppmv) for August 26–28, 1988 at sites in southern California. The horizontal axis represents hours past midnight, August 25. Results represent O_3 and NO_X at Reseda, and CO at Riverside.



Source: Jacobson et al. (1996).

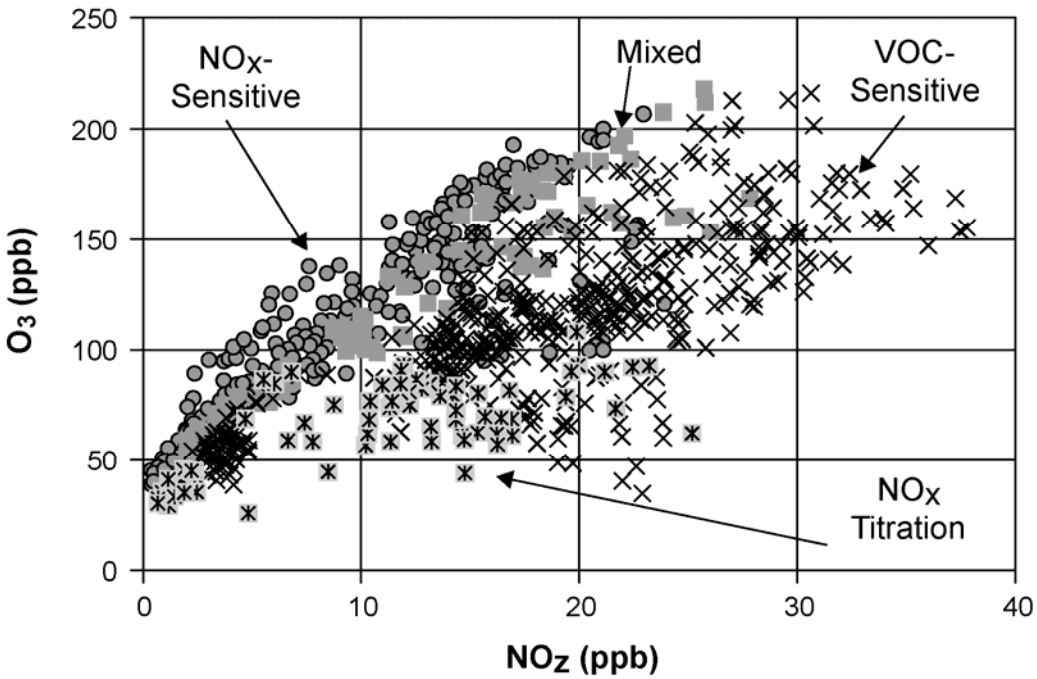
Figure AX2.5-2. Time series for measured gas-phase species in comparison with results from a photochemical model. The circles represent measurements, and solid lines represent model predictions (in parts per million, ppmv) for August 26–28, 1988 at sites in southern California. The horizontal axis represents hours past midnight, August 25. Results represent ethane and formaldehyde at Claremont, and PAN at Los Angeles.

Models for urban and regional chemistry have been evaluated less extensively than global-scale models in part because the urban/regional context presents a number of difficult challenges. Global-scale models typically represent continental-scale events and can be evaluated effectively against a sparse network of measurements. By contrast, urban/regional models are critically dependent on the accuracy of local emission inventories and event-specific meteorology, and must be evaluated separately for each urban area that is represented.

The evaluation of urban/regional models is also limited by the availability of data. Measured NO_X and speciated VOC concentrations are widely available through the regulatory networks of the U.S. EPA. Evaluation of urban/regional models versus measurements has generally relied on results from a limited number of field studies in the United States. Short-term, research-grade measurements for species relevant to O_3 formation, including VOCs, NO_X, PAN, HNO_3, and H_2O_2 are also available at selected

rural and remote sites (e.g., Daum et al., 1990, 1996; Martin et al., 1997; Young et al., 1997; Thompson et al., 2000; Hoell et al., 1997, 1999; Fehsenfeld et al., 1996; Emmons et al., 2000; Hess, 2001; Carroll et al., 2001). The equivalent measurements are available for some polluted rural sites in the eastern United States, but only at a few urban locations (Meagher et al., 1998; Hübler et al., 1998; Kleinman et al., 2000, 2001; Fast et al., 2002; Lu et al., 1997). Extensive measurements have also been made in Vancouver (Steyn et al., 1997) and in several European cities (Staffelbach et al., 1997; Prévôt et al., 1997, Dommen et al., 1999; Geyer et al., 2001; Thielman et al., 2001; Martilli et al., 2002; Vautard et al., 2002).

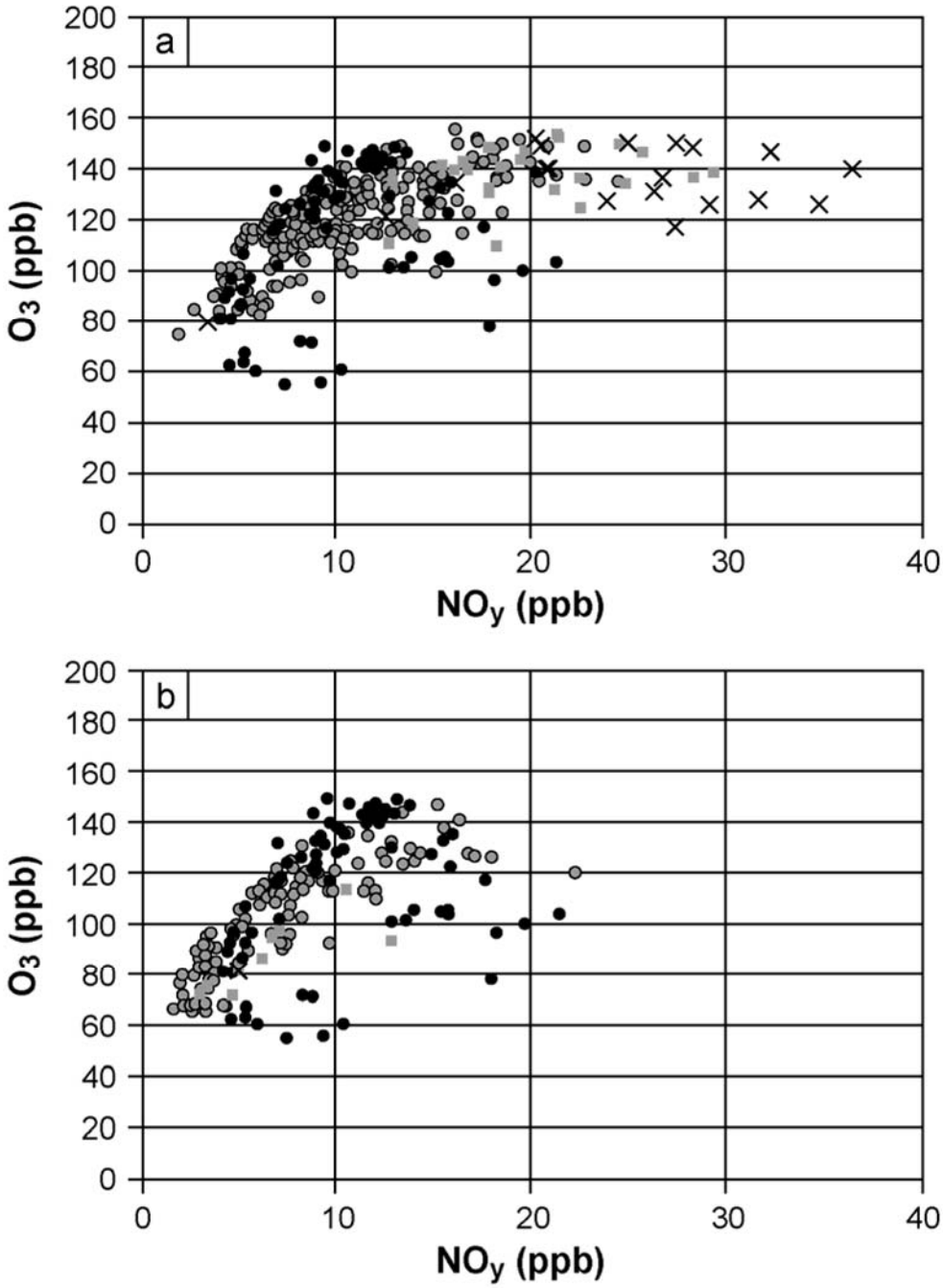
The results of straightforward comparisons between observed and predicted concentrations of O_3 can be misleading because of compensating errors, although this possibility is diminished when a number of species are compared. Ideally, each of the main modules of a CTM system (for example, the meteorological model and the chemistry and radiative transfer routines) should be evaluated separately. However, this is rarely done in practice. To better indicate how well physical and chemical processes are being represented in the model, comparisons of relations between concentrations measured in the field and concentrations predicted by the model can be made. These comparisons could involve ratios and correlations between species. For example, correlation coefficients could be calculated between primary species as a means of evaluating the accuracy of emission inventories or between secondary species as a means of evaluating the treatment of photochemistry in the model. In addition, spatial relations involving individual species (correlations, gradients) can also be used as a means of evaluating the accuracy of transport parameterizations. Sillman and He (2002) examined differences in correlation patterns between O_3 and NO_Z in Los Angeles, CA, Nashville, TN, and various sites in the rural United States. Model calculations (Figure AX2.5-3) show differences in correlation patterns associated with differences in the sensitivity of O_3 to NO_X and VOCs. Primarily NO_X-sensitive (NO_X-limited) areas in models show a strong correlation between O_3 and NO_Z with a relatively steep slope, while primarily VOC-sensitive (NO_X-saturated) areas in models show lower O_3 for a given NO_Z and a lower O_3-NO_Z slope. They found that differences found in measured data ensembles were matched by predictions from chemical transport models. Measurements in rural areas in the eastern United States show differences in the pattern of correlations for O_3 versus NO_Z between summer and autumn (Jacob et al., 1995; Hirsch et al., 1996), corresponding to the transition from NO_X-limited to NO_X-saturated patterns, a feature which is also matched by CTMs.



Source: Sillman and He (2002).

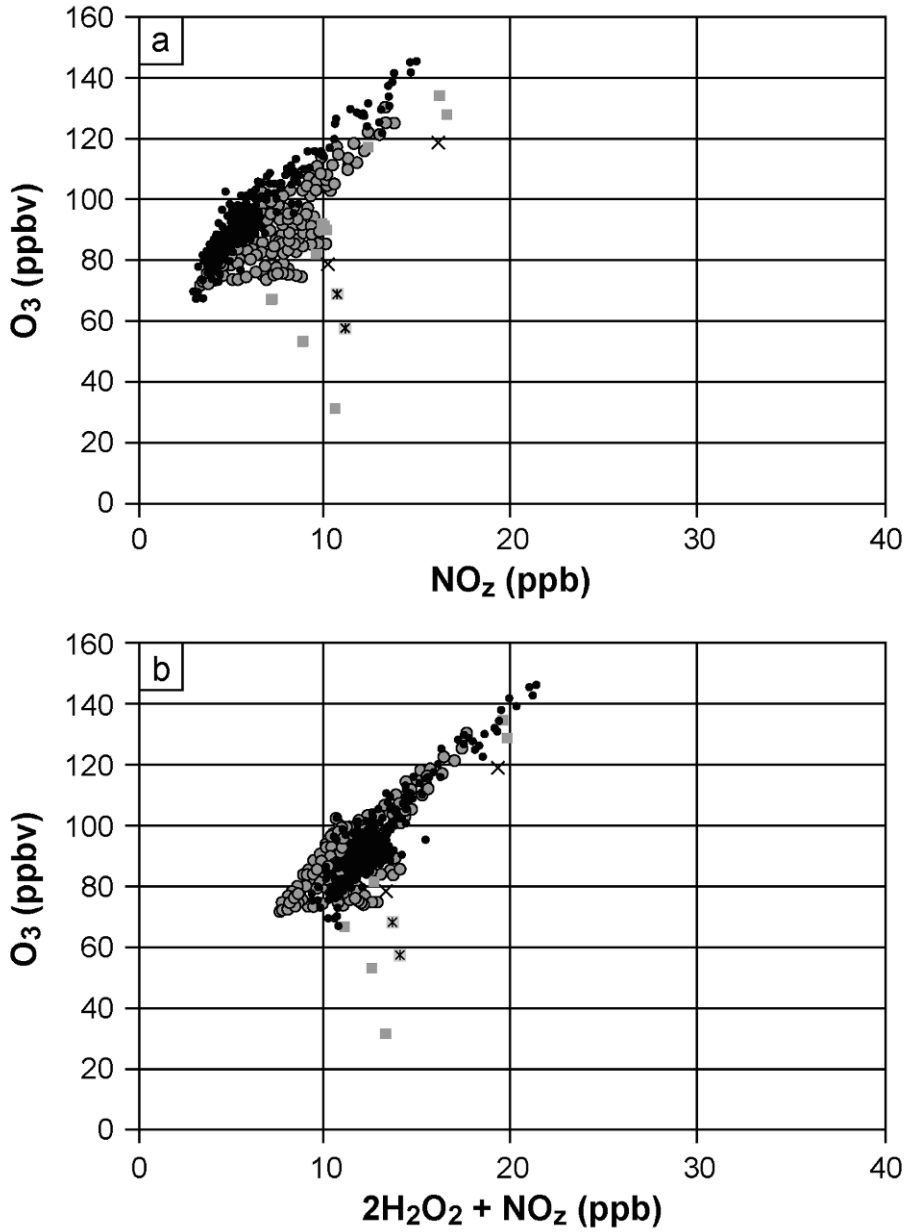
Figure AX2.5-3. Correlations for O_3 versus NO_Z (NO_Y–NO_X) in ppb from chemical transport models for the northeast corridor, Lake Michigan, Nashville, the San Joaquin Valley, and Los Angeles. Each location is classified as NO_X-limited or NO_X-sensitive (circles), NO_X-saturated or VOC-sensitive (crosses), mixed or with near-zero sensitivity (squares), and dominated by NO_X titration (asterisks) based on the model response to reduced NO_X and VOC.

The difference in correlations between secondary species in NO_X-limited to NO_X-saturated environments can also be used to evaluate the accuracy of model predictions in individual applications. Figures AX2.5-4, show results for two different model scenarios for Atlanta. As shown in the figures, the first model scenario predicts an urban plume with high NO_Y and O_3 formation apparently suppressed by high NO_Y. Measurements show much lower NO_Y in the Atlanta plume. This error was especially significant because the model locations sensitive to NO_X. The second model scenario (with primarily NO_X sensitive conditions) shows much better agreement with measured values. Figure AX2.5-5 shows model-measurement comparison for secondary species in Nashville, showing better agreement with measured conditions. Greater confidence in the predictions made by CTMs will be gained by the application of techniques such as these on a more routine basis.



Source: Sillman et al. (1997).

Figure AX.2.5-4. Evaluation of model versus measured O_3 versus NO_Y for two model scenarios for Atlanta. The model values are classified as NO_X-limited (circles), NO_X-saturated (crosses), or mixed or with low sensitivity to NO_X (squares). Diamonds represent aircraft measurements.



Source: Sillman et al. (1998).

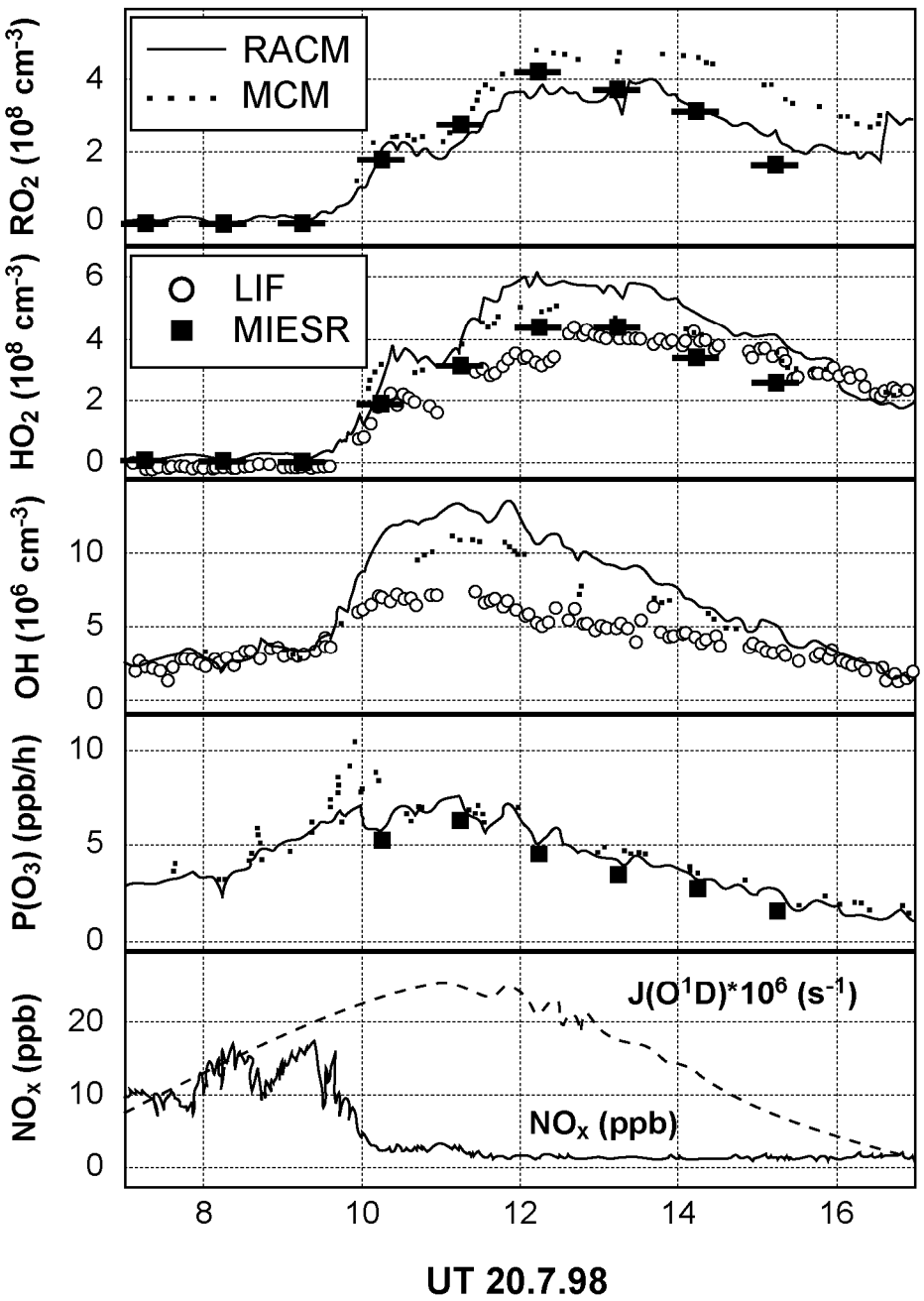
Figure AX2.5-5. Evaluation of model versus: (a) measured O_3 versus NO_Z and (b) O_3 versus the sum $2H_2O_2$ + NO_Z for Nashville, TN. The model values are classified as NO_X-limited (gray circles), NO_X-saturated (X's), mixed or near-zero sensitivity (squares), or dominated by NO_X titration (filled circles). Diamonds represent aircraft measurements.

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

Concentrations of major compounds such as O_3, hydrocarbons, etc., were fixed at observed values. Figure AX2.5-6 compares the concentrations of RO_2, HO_2, and OH radicals predicted by RACM and

MCM with observations made by the laser-induced fluorescence (LIF) technique and by matrix isolation ESR spectroscopy (MIESR). Also shown are the production rates of O_3 calculated using radical concentrations predicted by the mechanisms and those obtained by measurements, and measurements of NO_X concentrations. As can be seen, there is good agreement between measurements of RO_2, HO_2, OH, radicals with values predicted by both mechanisms at high concentrations of NO_X (>10 ppb). However, at lower NO_X concentrations, both mechanisms substantially overestimate OH concentrations and moderately overestimate HO_2 concentrations. Agreement between models and measurements is generally better for organic peroxy radicals, although the MCM appears to overestimate their concentrations somewhat. In general, the mechanisms reproduced the HO_2 to OH and RO_2 to OH ratios better than the individual measurements. The production of O_3 was found to increase linearly with NO (for NO < 0.3 ppb) and to decrease with NO (for NO > 0.5 ppb).

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



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

Figure AX2.5-6. Time series of concentrations of RO_2, HO_2, and OH radicals, local O_3 photochemical production rate and concentrations of NO_X. These are from measurements made during BERLIOZ. Also shown are comparisons with results of photochemical box model calculations using the RACM and MCM chemical mechanisms.

AX2.6. Sampling and Analysis of NO_X

AX2.6.1. Availability and Accuracy of Ambient NO_Y Measurements

Sections AX2.6.1-AX2.6.4 focus on current methods and on promising new technologies, but no attempt is made here to cover the extensive development of these methods or of methods such as wet chemical techniques no longer in widespread use. More detailed discussions of these methods may be found elsewhere (U.S. Environmental Protection Agency, 1993, 1996). McClenny (2000), Parrish and Fehsenfeld (2000), and Clemitshaw (2004) reviewed methods for measuring NO_X and NO_Y compounds. Discussions in Sections 2.6.1-2.6.4 center on chemiluminescence and optical Federal Reference and Equivalent Methods (FRM and FEM, respectively).

The use of methods such as observationally based methods or source apportionment models, either as stand-alone methods or as a basis for evaluating chemical transport models, is often limited by the availability and accuracy of measurements. Measured NO_X and speciated VOC concentrations are widely available in the United States through the Photochemical Assessment Monitoring Stations (PAMS) network. The PAMs network currently includes measured NO and NO_X. However, Cardelino and Chameides (2000) reported that measured NO during the afternoon was frequently at or below the detection limit of the instruments (1 ppb), even in large metropolitan regions (Washington, DC; Houston, TX; New York, NY). NO_2 measurements are made with commercial chemiluminescent detectors with hot molybdenum converters. However, these measurements typically include a wide variety of other reactive N species, such as organic nitrates in addition to NO_X, and cannot be interpreted as a "pure" NO_X measurement (see summary in Parrish and Fehsenfeld, 2000).

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

AX2.6.1.1. Measurement of NO

Gas-phase Chemiluminescence (CL) Methods

Nitric oxide can be measured reliably using the principle of gas-phase chemiluminescence induced by the reaction of NO with O_3 at low pressure. Modern commercial NO_X analyzers have sufficient sensitivity and specificity for adequate measurement in urban and many rural locations (U.S. Environmental Protection Agency, 1993, 1996, 2006). Research grade CL instruments have been compared under realistic field conditions to spectroscopic instruments, and the results indicate that both methods are reliable (at concentrations relevant to smog studies) to better than 15 percent with 95 percent confidence. Response times are on the order of 1 minute. For measurements meaningful for understanding O_3 formation, emissions modeling, and N deposition, special care must be taken to zero and calibrate the instrument frequently. A chemical zero, obtained by reacting the NO up-stream and out of view of the photomultiplier tube, is preferred because it accounts for interferences such as light emitting reactions

with unsaturated hydrocarbons. Standard additions of NO at the inlet will account for NO loss or conversion to NO_2 in the lines. In summary, CL methods, when operated carefully in an appropriate manner, can be suitable for measuring or monitoring NO (e.g., Crosley, 1996).

Spectroscopic Methods for NO_X

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

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

AX2.6.1.2. Measurements of NO_2

Gas-Phase Chemiluminescence Methods

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

Other Methods

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

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

NO_2 can be detected by differential optical absorption spectroscopy (DOAS) in an open, long-path system by measuring narrow band absorption features over a background of broad band extinction (e.g., Stutz et al., 2000; Kim and Kim, 2001). A DOAS system manufactured by OPSIS is designated as a Federal Equivalent Method for measuring NO_2. DOAS systems can also be configured to measure NO, HONO, and NO_3 radicals. Typical detection limits are 0.2 to 0.3 ppb for NO, 0.05 to 0.1 ppb for NO_2, 0.05 to 0.1 ppb for HONO, and 0.001 to 0.002 ppb for NO_3, at path lengths of 0.2, 5, 5, and 10 km, respectively. The obvious advantage compared to fixed point measurements is that concentrations relevant to a much larger area are obtained, especially if multiple targets are used. At the same time, any microenvironmental artifacts are minimized over the long path integration. However, comparisons to other measurements made at point not a real location are difficult. A major limitation in this technique had involved inadequate knowledge of absorption cross sections. Harder et al. (1997) conducted an experiment in rural Colorado involving simultaneous measurements of NO_2 by DOAS and by photolysis followed by chemiluminescence. They found differences of as much as 110% in clean air from the west, but for NO_2 mixing ratios in excess of 300 ppt, the two methods agreed to better than 10%. Stutz et al. (2000) cites two intercomparisons of note. NO was measured by DOAS, by photolysis of NO_2 followed by chemiluminescence, and by LIF during July 1999 as part of the SOS in Nashville, TN. On average, the three methods agreed to within 2%, with some larger differences likely caused by spatial variability over the DOAS path. In another study in Europe, and a multi-reflection set-up over a 15 km path, negated the problem of spatial averaging here agreement with the chemiluminescence detector following photolytic conversion was excellent (slope = 1.006 ± 0.005; intercept = 0.036 ± 0.019; r = 0.99) over a concentration range from about 0.2 to 20 ppb.

NO_2 can also be detected from space with DOAS-like UV spectroscopy techniques (Kim et al., 2006; Ma et al., 2006). These measurements appear to track well with emissions estimates and can be a useful indicator of column content as well as for identifying hot spots in sources. See also Richter et al., 2005. Leigh (2006) report on a DOAS method that uses the sun as a light source and compares well with an in situ chemiluminescence detector in an urban environment.

Chemiluminescence on the surface of liquid luminol has also been used for measurement of NO_2 (Gaffney et al., 1998; Kelly et al., 1990; Marley et al., 2004; Nikitas et al., 1997; Wendel et al., 1983). This technique is sensitive and linear and more specific than hot MoO_X. Luminol does not emit light when exposed to HNO_3 or alkyl nitrates, but does react with PAN. This interference can be removed by chromatographic separation prior to detection and the resulting measurement compares well with more specific techniques for moderate to high (≥1 ppb) mixing ratios of NO_2.

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

Measurements of NO_Y

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

AX2.6.1.3. Monitoring for NO_2 Compliance Versus Monitoring for O_3 Formation

Regulatory measurements of NO_2 have been focused on demonstrating compliance with the NAAQS for NO_2. Today, few locations violate that standard, but NO_2 and related NO_Y compounds remain among the most important atmospheric trace gases to measure and understand. Unfortunately, with an internal MoO_x converter for NO_X to NO conversion, the instruments may not give a faithful indication of total NO_Y either; reactive species such as HNO_3 will adhere to the walls of the inlet system. Most recently, commercial vendors such as Thermo Environmental (Franklin, MA) have offered NO/NO_Y detectors with external MoO_x converters. If such instruments are calibrated through the inlet with a reactive nitrogen species such as propyl nitrate, they give accurate measurements of total NO_Y suitable for evaluation of photochemical models. (Crosley, 1996; Fehsenfeld et al., 1987; Nunnermacker et al., 1998; Rodgers and Davis, 1989). Under conditions of fresh emissions, such as in urban areas during the rush hour, $NO_Y \sim NO_X$ and these monitors can be used for testing emissions inventories (Dickerson, et al., 1995; Parrish, 2006).

AX2.6.2. Summary of Methods for Measuring NO_2

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

AX2.6.3. Measurements of HNO_3

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

$$HNO_{3g} \overset{K_H}{\leftrightarrow} [HNO_{3aq}] \overset{K_a}{\leftrightarrow} [H^+] + [NO_3^-] \qquad \text{(AX2.6-1)}$$

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

Thus, the primary controls on HNO_3 phase partitioning are its thermodynamic properties (K_H, K_a, and associated temperature corrections), aerosol liquid water content (LWC), solution pH, and kinetics. Aerosol LWC and pH are controlled by the relative mix of different acids and bases in the system, hygroscopic properties of condensed compounds, and meteorological conditions such as RH, temperature, and pressure. It is evident from relationship AX2.6-1 that, in the presence of chemically distinct aerosols of varying acidities (e.g., supermicron predominantly sea salt and submicron predominantly S aerosol), HNO_3 will partition preferentially with the less-acidic particles; and this is consistent with observations (e.g., Huebert et al., 1996; Keene and Savoie, 1998; Keene et al., 2002). Kinetics are controlled by atmospheric concentrations of HNO_3 vapor and particulate NO_3^- and the size distribution and corresponding atmospheric lifetimes of particles against deposition. Submicron diameter aerosols typically equilibrate with the gas phase in seconds to minutes while supermicron aerosols require hours to a day or more (e.g., Meng and Seinfeld, 1996; Erickson et al., 1999). Consequently, smaller aerosol size fractions are typically close to thermodynamic equilibrium with respect to HNO_3 whereas larger size fractions (for which atmospheric lifetimes against deposition range from hours to a few days) are often undersaturated (e.g., Erickson et al., 1999; Keene and Savioe, 1998).

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

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

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

Three semi-continuous methods for detecting nitric acid (HNO_3) were tested against the annular denuder filter pack (ADS) integrated collection technique at the Tampa Bay Regional Atmospheric Chemistry Experiment (BRACE) Sydney research station ~20 km downwind of the Tampa, Florida, urban core. The semi-continuous instruments included: two slightly differing implementations of the NO_Y -- NO_{Y*} (total oxides of nitrogen minus that total denuded of HNO_3) denuder difference technique, one from the NOAA Air Resources Lab (ARL), and one from Atmospheric Research and Analysis, Inc. (ARA); the parallel plate wet diffusion scrubber online ion chromatography technique from Texas Tech

University (TTU); and the chemical ionization mass spectrometer from the Georgia Institute of Technology (GIT). Twelve hour ADS samples were collected by the University of South Florida (USF). Results for 10 min samples computed from the various higher sampling frequencies of each semi-continuous instrument showed good agreement (R^2>0.7)for afternoon periods of the highest production and accumulation of HNO_3. Further, agreement was within ± 30% for these instruments even at HNO_3 concentrations 0.30 ppb. The USF ADS results were biased low, however, by 44%, on average, compared to the corporate 12-h aggregated means from the semi-continuous methods, and by 460% for the nighttime samples; ADS results were below the corporate mean maximum HNO_3 concentration by 430% as well. The four instruments using semi-continuous methods, by contrast, were all within 10% of each other's 12-h mean mixing ratios. While only ARA employed a formal minimum detection limit at 0.050 ppb, error analysis with the other techniques established that at the same level of precision, TTU's effective limit was approximately the same as ARA's and that ARL's limit was 0.030 ppb; analysis for GIT showed no apparent effective limit at the levels of HNO_3 encountered in this field study. The importance of sample inlet height for HNO_3 measurements was indirectly shown through comparison to previous field work at this site when sample inlet heights ranged from 1.5–10 m and produced systematic discrepancies in HNO_3 concentrations correlated with height of more than a factor of 2 (Arnold et al., 2007).

AX2.6.4. Techniques for Measuring Other NO_Y Species

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

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

AX2.6.5. Remote Sensing of Tropospheric NO_2 Columns for Surface NO_X Emissions and Surface NO_2 Concentrations

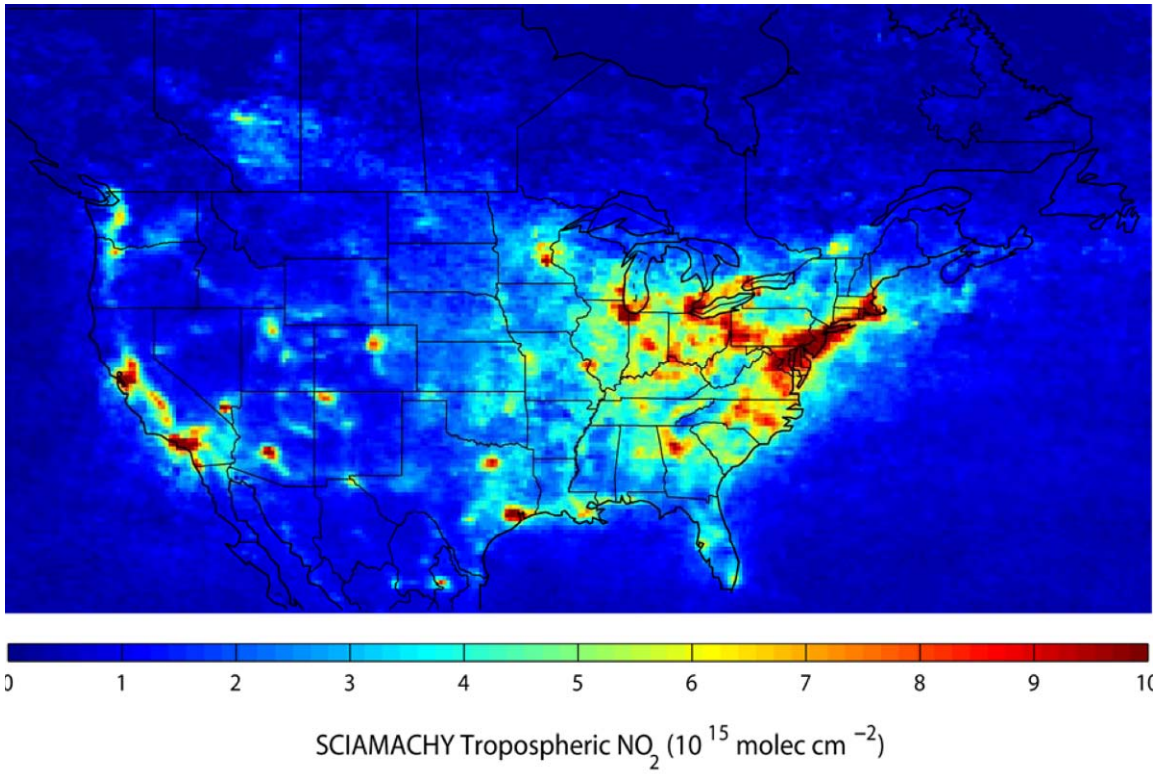
Table AX2.6-1 contains an overview of the three satellite instruments that are used retrieve tropospheric NO_2 columns from measurements of solar backscatter. All three instruments are in polar sun-synchronous orbits with global measurements in the late morning and early afternoon. The spatial resolution of the measurement from SCIAMACHY is 7 times better than that from Ozone Monitoring Instrument (GOME), and that from Ozone Monitoring Instrument (OMI) is 40 times better than that from GOME.

Table AX2.6-1. Satellite Instruments Used to Retrieve Tropospheric NO_2 Columns.

INSTRUMENT	COVERAGE	TYPICAL U.S. MEASUREMENT TIME	TYPICAL RESOLUTION (KM)	RETURN TIME (DAYS)[1]	INSTRUMENT OVERVIEW
GOME	1995-2002	10:30-11:30 AM	320 H 40	3	Burrows et al. (1999)
SCIAMACHY	2002-	10:00-11:00 AM	30 H 60	6	Bovensmann et al. (1999)
OMI	2004-	12:45-1:45 PM	13 H 24	1	Levelt et al. (2006)

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

Figure AX2.6-1 shows tropospheric NO_2 columns retrieved from SCIAMACHY. Pronounced enhancements are evident over major urban and industrial emissions. The high degree of spatial heterogeneity over the southwestern United States provides empirical evidence that most of the tropospheric NO_2 column is concentrated in the lower troposphere. Tropospheric NO_2 columns are more sensitive to NO_X in the lower troposphere than in the upper troposphere (Martin et al., 2002). This sensitivity to NO_X in the lower troposphere is due to the factor of 25 decrease in the NO_2/NO ratio from the surface to the upper troposphere (Bradshaw et al., 1999) that is driven by the temperature dependence of the NO + O_3 reaction. Martin et al. (2004a) integrated in situ airborne measurements of NO_2 and found that during summer the lower mixed layer contains 75% of the tropospheric NO_2 column over Houston and Nashville. However, it should be noted that these measurements are also sensitive to surface albedo and aerosol loading.



Source: Martin et al. (2006).

Figure AX2.6-1. Tropospheric NO_2 columns (molecules NO_2/cm^2) retrieved from the SCIAMACHY satellite instrument for 2004-2005.

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

The paucity of in situ NO_2 measurements motivates the inference of surface NO_2 concentrations from satellite measurements of tropospheric NO_2 columns. This prospect would take advantage of the greater sensitivity of tropospheric NO_2 columns to NO_X in the lower troposphere than in the upper troposphere as discussed earlier. Tropospheric NO_2 columns show a strong correlation with in situ NO_2 measurements in northern Italy (Ordóñez et al., 2006).

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

However, the satellites carrying the spectrometer (GOME/SCIAMACHY/OMI) are in near polar, sun-synchronous orbits. As a result, these measurements are made only once per day, typically between

about 10:00 to 11:00 a.m. or 1 p.m. local time, during a brief overflight. Thus the utility of these measurements is limited as they would likely miss short-term features.

AX2.7. Policy-relevant Background NO_X Concentrations

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

Contributions to PRB concentrations include natural emissions of NO_2 and photochemical reactions involving natural emissions of reduced nitrogen compounds, as well as their long-range transport from outside North America. Natural sources of NO_2 and its precursors include biogenic emissions, wildfires, lightning, and the stratosphere. Natural sources of reduced nitrogen compounds, mainly NH_3, include biogenic emissions and wildfires. Biogenic emissions from agricultural activities are not considered in the formation of PRB concentrations. Discussions of the sources and estimates of emissions are given in Section AX2.4.2.

AX2.7.1. Analysis of PRB Contribution to U.S. NO_X Concentrations and Deposition

The MOZART-2 global model of tropospheric chemistry (Horowitz et al., 2003) was used to diagnose the PRB contribution to nitrogen oxide concentrations, as well as to total (wet plus dry) deposition. The model setup for the present-day simulation has been published in a series of papers from a recent model intercomparison (Dentener et al., 2006a,b; Shindell et al., 2006; Stevenson et al., 2006; Van Noije et al., 2006). MOZART-2 is driven by National Center for Environmental Prediction meteorological fields and IIASA 2000 emissions at a resolution of 1.9° H 1.9° with 28 sigma levels in the vertical, and it includes gas- and aerosol phase chemistry. Results shown in Figures AX2.7-1 to AX2.7-3 are for the meteorological year 2001. Note that color images are available on the web. An additional PRB simulation was conducted in which continental North American anthropogenic emissions were set to zero.

We first examine the role of PRB in contributing to NO_2 concentrations in surface air. Figure AX2.7-1 shows the annual mean NO_2 concentrations in surface air in the base case simulation (top panel) and the PRB simulation (middle panel), along with the percentage contribution of the background to the total base case NO_2 (bottom panel). Maximum concentrations in the base case simulation occur along the Ohio River Valley and in the Los Angeles basin. While present-day concentrations are often above 5 ppb, PRB is less than 300 ppt over most of the continental United States, and less than 100 ppt in the eastern United States. The distribution of PRB (middle panel of Figure AX2.7-1) largely reflects the distribution of soil NO emissions, with some local enhancements due to biomass burning such as is seen in western Montana. In the northeastern United States, where present-day NO_2 concentrations are highest, PRB contributes <1% to the total.

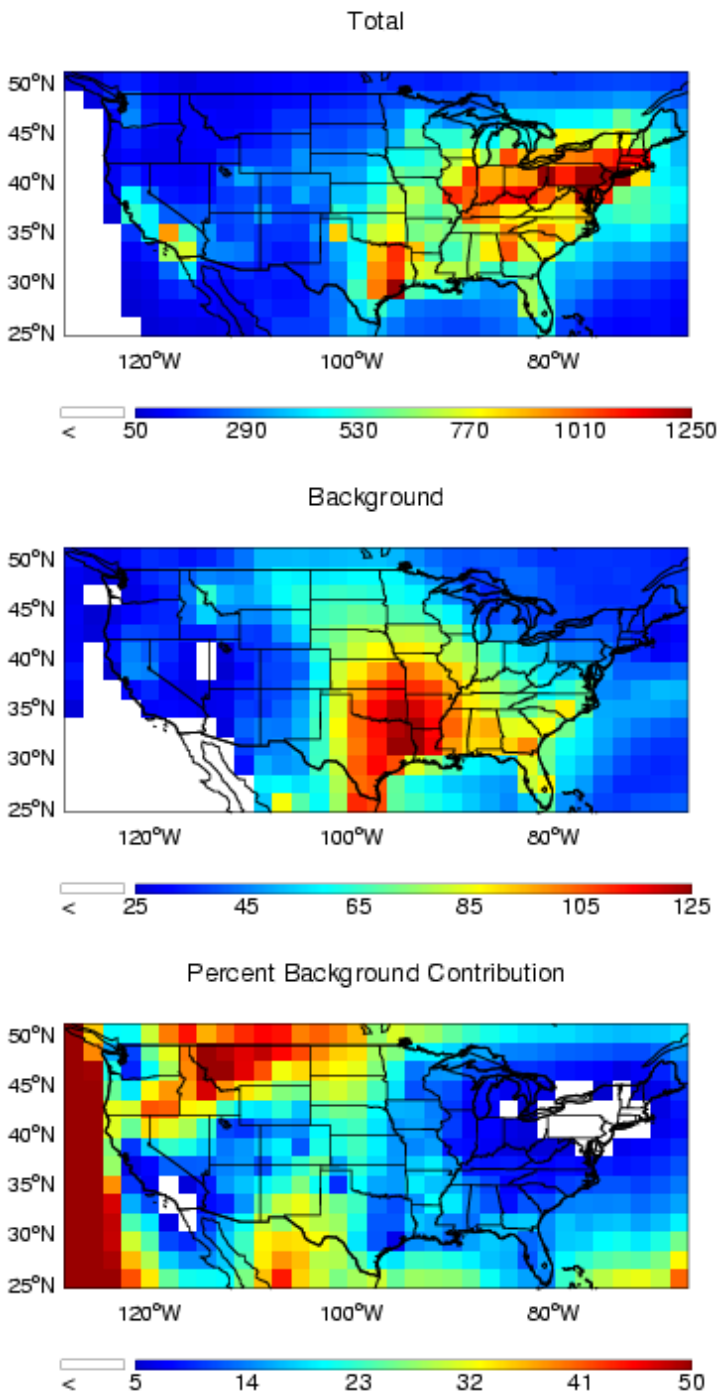


Figure AX2.7-1. Annual mean concentrations of NO_2 (ppb) in surface air over the United States in the present-day (upper panel) and policy relevant background (middle panel) MOZART-2 simulations. The bottom panel shows the percentage contribution of the background to the present-day concentrations. Please see text for details.

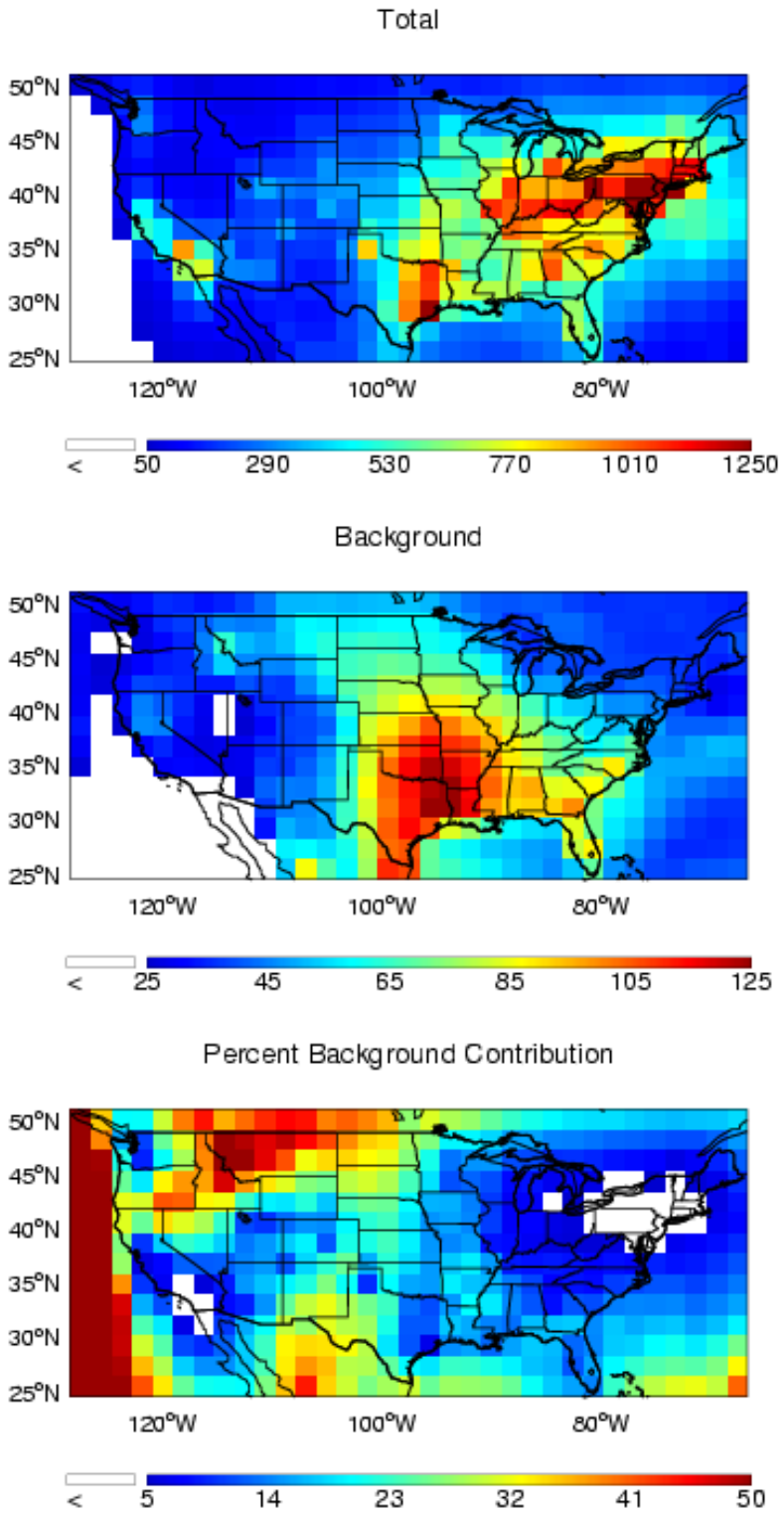


Figure AX2.7-2. Same as for Figure AX2.7-1 but for wet and dry deposition of HNO_3, NH_4NO_3, NO_X, HO_2NO_2, and organic nitrates (mg N m^{-2}/y).

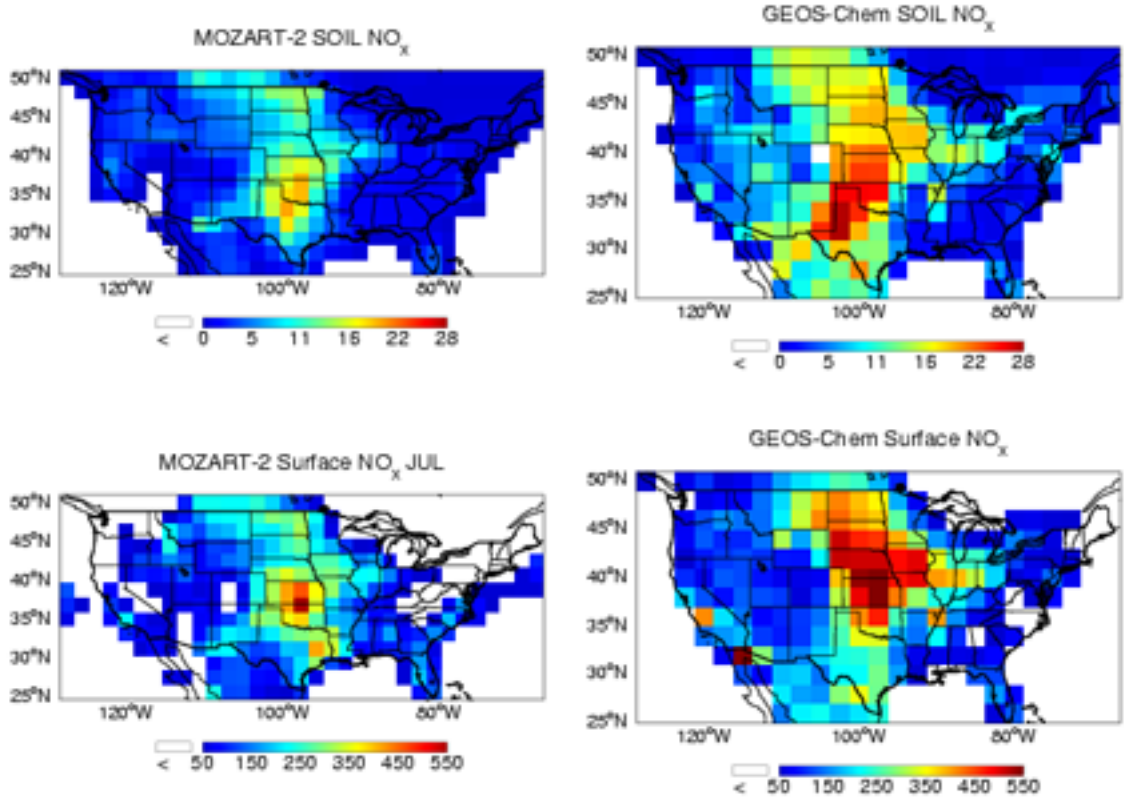


Figure AX2.7-3. July mean soil NO emissions (upper panels; 1 H 10 ^{9} molecules cm^{-2} s^{1}) and surface PRB NO_X concentrations (lower panels; ppt). These are over the United States from MOZART-2 (left) and GEOS-Chem (right) model simulations in which anthropogenic O_3 precursor emissions were set to zero in North America.

The spatial pattern of NO_Y (defined here as HNO_3, NH_4NO_3, NO_X, HO_2NO_2, and organic nitrates) wet and dry deposition is shown in Figure AX2.7-2. Figure AX2.7-2 (upper panel) shows that highest values are found in the eastern United States in and downwind of the Ohio River Valley. The pattern of nitrogen deposition in the PRB simulation (Figure AX2.7-2, middle panel), however, shows maximum deposition centered over Texas and in the Gulf Coast region, reflecting a combination of nitrogen emissions from lightning in the Gulf region, biomass burning in the Southeast, and from microbial activity in soils (maximum in central Texas and Oklahoma). The bottom panel of Figure AX2.7-2 shows that the PRB contribution to nitrogen deposition is less than 20% over the eastern United States, and typically less than 50% in the western United States where NO_Y deposition is low (25-50 mg N/m^2/yr).

Thus far, the discussion has focused on results from the MOZART-2 tropospheric chemistry model. In Figure AX2.7-3, results from MOZART-2 are compared with those from another tropospheric chemistry model, GEOS-Chem (Bey et al., 2001), which was previously used to diagnose PRB O_3 (Fiore et al., 2003; U.S. Environmental Protection Agency, 2006). In both models, the surface PRB NO_X concentrations tend to mirror the distribution of soil NO emissions, which are highest in the Midwest. The higher soil NO emissions in GEOS-Chem (by nearly a factor of 2) as compared to MOZART-2 reflect different assumptions regarding the contribution to soil NO emissions largely through fertilizer, since GEOS-Chem total soil NO emissions are actually higher than MOZART-2 (0.07 versus 0.11 Tg N) over

the United States in July. Even with the larger PRB soil NO emissions, surface NO_X concentrations in GEOS-Chem are typically below 500 ppt.

Table AX2.4-1. Emissions of nitrogen oxides and ammonia in the United States in 2002

2002 EMISSIONS (TG/YR)	NO_X[1]	NH_3
Source Category		
TOTAL ALL SOURCES	23.19	4.08
FUEL COMBUSTION TOTAL	9.11	0.02
FUEL COMB. ELEC. UTIL	5.16	<0.01
Coal	4.50	<0.01
Bituminous	2.90	
Subituminous	1.42	
Anthracite & lignite	0.18	
Other	<0.01	
Oil	0.14	<0.01
Residual	0.13	
Distillate	0.01	
Gas	0.30	<0.01
Natural	0.29	
Process	0.01	
Other	0.05	<0.01
Internal Combustion	0.17	<0.01
FUEL COMBUSTION INDUSTRIAL	3.15	<0.01
Coal	0.49	<0.01
Bituminous	0.25	
Subbituminous	0.07	
Anthracite & Lignite	0.04	
Other	0.13	
Oil	0.19	<0.01
Residual	0.09	
Distillate	0.09	
Other	0.01	
Gas	1.16	<0.01
Natural	0.92	
Process	0.24	
Other	<0.01	
Other	0.16	<0.01

2002 EMISSIONS (TG/YR)	NO_X[1]	NH_3
Wood/bark waste	0.11	
Liquid waste	0.01	
Other	0.04	
Internal Combustion	1.15	<0.01
FUEL COMB. OTHER	0.80	<0.01
Commercial/Institutional Coal	0.04	<0.01
Commercial/Institutional Oil	0.08	<0.01
Commercial/Institutional Gas	0.25	<0.01
Misc. Fuel Comb. (Except Residential)	0.03	<0.01
Residential Wood	0.03	
Residential Other	0.36	
Distillate oil	0.06	
Bituminous/subituminous	0.26	
Other	0.04	
INDUSTRIAL PROCESS TOTAL	1.10	0.21
CHEMICAL & ALLIED PRODUCT MFG	0.12	0.02
Organic Chemical Mfg	0.02	<0.01
Inorganic Chemical Mfg	0.01	<0.01
Sulfur compounds		
Other		
Polymer & Resin Mfg	<0.01	<0.01
Agricultural Chemical Mfg	0.05	0.02
Ammonium nitrate/urea mfg.		<0.01
Other		0.02
Paint, Varnish, Lacquer, Enamel Mfg	0.00	
Pharmaceutical Mfg	0.00	
Other Chemical Mfg	0.03	<0.01
METALS PROCESSING	0.09	<0.01
Non-Ferrous Metals Processing	0.01	<0.01
Copper		
Lead		
Zinc		
Other		
Ferrous Metals Processing	0.07	<0.01
Metals Processing	0.01	<0.01
PETROLEUM & RELATED INDUSTRIES	0.16	<0.01
Oil & Gas Production	0.07	<0.01

2002 EMISSIONS (TG/YR)	NO_X[1]	NH_3
Natural gas		
Other		
Petroleum Refineries & Related Industries	0.05	<0.01
Fluid catalytic cracking units		<0.01
Other		<0.01
Asphalt Manufacturing	0.04	
OTHER INDUSTRIAL PROCESSES	0.54	0.05
Agriculture, Food, & Kindred Products	0.01	<0.01
Textiles, Leather, & Apparel Products	<0.01	<0.01
Wood, Pulp & Paper, & Publishing Products	0.09	<0.01
Rubber & Miscellaneous Plastic Products	<0.01	<0.01
Mineral Products	0.42	<0.01
Cement mfg	0.24	
Glass mfg	0.01	
Other	0.10	
Machinery Products	<0.01	<0.01
Electronic Equipment	<0.01	<0.01
Transportation Equipment	<0.01	
Miscellaneous Industrial Processes	0.01	0.05
SOLVENT UTILIZATION	0.01	<0.01
Degreasing	<0.01	<0.01
Graphic Arts	<0.01	<0.01
Dry Cleaning	<0.01	<0.01
Surface Coating	<0.01	<0.01
Other Industrial	<0.01	<0.01
Nonindustrial	<0.01	
Solvent Utilization NEC	<0.01	
STORAGE & TRANSPORT	<0.01	<0.01
Bulk Terminals & Plants	<0.01	<0.01
Petroleum & Petroleum Product Storage	<0.01	<0.01
Petroleum & Petroleum Product Transport	<0.01	<0.01
Service Stations: Stage II	<0.01	
Organic Chemical Storage	<0.01	<0.01
Organic Chemical Transport	0.01	
Inorganic Chemical Storage	<0.01	<0.01
Inorganic Chemical Transport	<0.01	
Bulk Materials Storage	0.01	<0.01

2002 EMISSIONS (TG/YR)	NO_X[1]	NH_3
WASTE DISPOSAL & RECYCLING	0.17	0.14
Incineration	0.06	<0.01
Industrial		
Other		
Open Burning	0.10	<0.01
Industrial		
Land clearing debris		
Other		
Public Operating Treatment Works	<0.01	0.14
Industrial Waste Water	<0.01	<0.01
Treatment, Storage, and Disposal Facility	<0.01	<0.01
Landfills	<0.01	<0.01
Industrial		
Other		
Other	<0.01	<0.01
TRANSPORTATION TOTAL	12.58	0.32
HIGHWAY VEHICLES	8.09	0.32
Light-Duty Gas Vehicles & Motorcycles	2.38	0.20
light-duty gas vehicles	2.36	
Motorcycles	0.02	
Light-Duty Gas Trucks	1.54	0.10
Light-duty gas trucks [1]	1.07	
Light-duty gas trucks [2]	0.47	
Heavy-Duty Gas Vehicles	0.44	<0.01
Diesels	3.73	<0.01
Heavy-duty diesel vehicles	3.71	
Light-duty diesel trucks	0.01	
Light-duty diesel vehicles	0.01	
OFF-HIGHWAY	4.49	<0.01
Non-Road Gasoline	0.23	<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	

2002 EMISSIONS (TG/YR)	NO_X[1]	NH_3
Airport service	<0.01	
Railway maintenance	<0.01	
Recreational marine vessels	0.05	
Non-Road Diesel	1.76	<0.01
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	
Marine Vessels	1.11	
Diesel	1.11	
Residual oil		
Other		
Railroads	0.98	
Other	0.32	<0.01
Liquefied petroleum gas	0.29	
Compressed natural gas	**0.04**	
MISCELLANEOUS	**0.39**	**3.53**
Agriculture & Forestry	<0.01	3.45
Agricultural crops		<0.01
Agricultural livestock		2.66
Other Combustion		0.08
Health Services		
Cooling Towers		
Fugitive Dust		
Other		
Natural Sources	3.10	0.03

Annex 3. Ambient Concentrations and Exposures

AX3.1. Introduction

Topics discussed in this chapter include the characterization of ambient air quality for nitrogen dioxide (NO_2), the uses of these data in assessing human exposures to NO_2; concentrations and sources of NO_2 in different microenvironments, and personal exposures to NO_2. The NO_2 data contained in this chapter are taken mainly from the U.S. Environmental Protection Agency's Air Quality System (AQS) database (formerly the AIRS database) (U.S. Environmental Protection Agency, 2007).

AX3.1.1. Characterizing Ambient NO_2 Concentrations

The "concentration" of a specific air pollutant is typically defined as the amount (mass) of that material per unit volume of air. However, most of the data presented in this chapter are expressed as "mixing ratios" in terms of a volume-to-volume ratio (e.g., parts per million [ppm] or parts per billion [ppb]. Data expressed this way are often referred to as concentrations, both in the literature and in the text, following common usage. Human exposures are expressed in units of mixing ratio times time.

AX3.1.2. Relationship to the 1993 AQCD for NO_X

The 1993 AQCD for Oxides of Nitrogen emphasized NO_2 indoor sources (gas stoves) and the relationship between personal total exposure and indoor or outdoor NO_2 concentrations (U.S. Environmental Protection Agency, 1993). At that time, only few personal exposure studies had been conducted with an emphasis on residential indoor NO_2 sources and concentrations. Although the concept of microenvironment had been introduced in the document, NO_2 concentrations were seldom reported for microenvironments other than residences. Exposure measurements at that time relied on Palmes tubes and Yanagisawa badges; and exposure-modeling techniques were limited mainly to simple linear regression. In the 1993 AQCD, NO_2 was treated as an independent risk factor, and confounding issues were not mentioned in the human environmental exposure chapters.

The current chapter summarizes and discusses the state-of-the-science and technology regarding NO_2 human exposures since 1993. Since then, numerous human exposure studies have been conducted with new measurement and modeling techniques. Microenvironmental measurements were not limited to residential indoor environments; NO_2 concentrations were also measured in vehicles, schools and offices, and microenvironments close to traffic. More indoor sources have been identified and more NO_2 formation and transformation mechanisms in the indoor environment have been reported.

AX3.2. Ambient Concentrations of NO_X

As discussed in Chapter 2 of the ISA, most measurements of NO_X are made by instruments that convert NO_2 to NO, which is then measured by chemiluminescence. However, the surface converters that reduce NO_2 to NO also reduce other reactive NO_Y species. As indicated in Chapter 2, NO_Y compounds consist of NO_X, gas phase inorganic nitrates, such as chlorine nitrate ($ClNO_3$); organic nitrates, such as

PANs; inorganic acids, given by the formulas HNO_Y (Y = 2 to 4); and particulate nitrate. In urban areas or in rural areas where there are large local sources, NO and NO_2 are expected to be the major forms of NO_Y. Thus, interference from PANs and other NO_Y species near sources are expected to minor; in most rural and remote areas, interference may be substantial as concentrations of other NO_Y species may be much larger than those for NO and NO_2 (National Research Council, 1991).

Because of their short lifetime with respect to oxidation to PANs and HNO_3, NO_X concentrations are highly spatially and temporally variable. Average concentrations range from tens of ppt in remote areas of the globe to tens of ppb in urban cores, i.e., by three orders of magnitude. Median NO, NO_X, and NO_Y concentrations at the surface are typically below 0.01, 0.05, and 0.3 ppb, respectively, in remote areas such as Alaska, northern Canada, and the eastern Pacific; median NO_Y concentrations range from about 0.7 to about 4.3 ppb at regional background sites in the eastern United States (Emmons et al., 1997). Note that the last two values, especially, contain a substantial contribution from pollution. Maximum short-term average (1-h) NO_X concentrations near heavy traffic (e.g., in Los Angeles, CA) approach 1 ppm, but these levels decrease rapidly away from sources. Even at sites where such high hourly values are found, 24-h avg concentrations are much lower. For example, the maximum 24-h average NO_X concentration at any site in Los Angeles in 2004 was 82 ppb.

AX3.2.1. Temporal Variability in Ambient NO_X Concentrations in Urban Areas

AX3.2.1.1. Diurnal Variability in NO_2 Concentrations

As might be expected from a pollutant having a major traffic source, the diurnal cycle of NO_2 in typical urban areas is characterized by traffic emissions, with peaks in emissions occurring during morning and evening rush hour traffic. Motor vehicle emissions consist mainly of NO, with only about 10% of primary emissions in the form of NO_2. The diurnal pattern of NO and NO_2 concentrations is also strongly influenced by the diurnal variation in the mixing layer height. Thus, during the morning rush hour when mixing layer heights are still low, traffic produces a peak in NO and NO_2 concentrations. As the mixing layer height increases during the day, dilution of emissions occurs. During the afternoon rush hour, mixing layer heights are at or are near their daily maximum values resulting in dilution of traffic emissions through a larger volume than in the morning. Starting near sunset, the mixing layer height drops and conversion of NO to NO_2 occurs without photolysis of NO_2 recycling NO.

The composite diurnal variability of NO_2 in selected urban areas with multiple sites (New York, NY; Atlanta, GA; Baton Rouge, LA; Chicago. IL; Houston, TX; Riverside, CA; and Los Angeles, CA) shows that lowest hourly median concentrations are typically found at around midday and that highest hourly median concentrations are found either in the early morning or in mid-evening. Median values range by about a factor of two from about 13 ppb to about 25 ppb (Figures AX3.2-1 to AX3.2-6). However, individual hourly concentrations can be considerably higher than these typical median values, and hourly NO_2 concentrations > 0.10 ppm can be found at any time of day.

AX3.2.1.2. Seasonal Variability in NO_2 Concentrations

AX3.2.1.3. Urban Sites

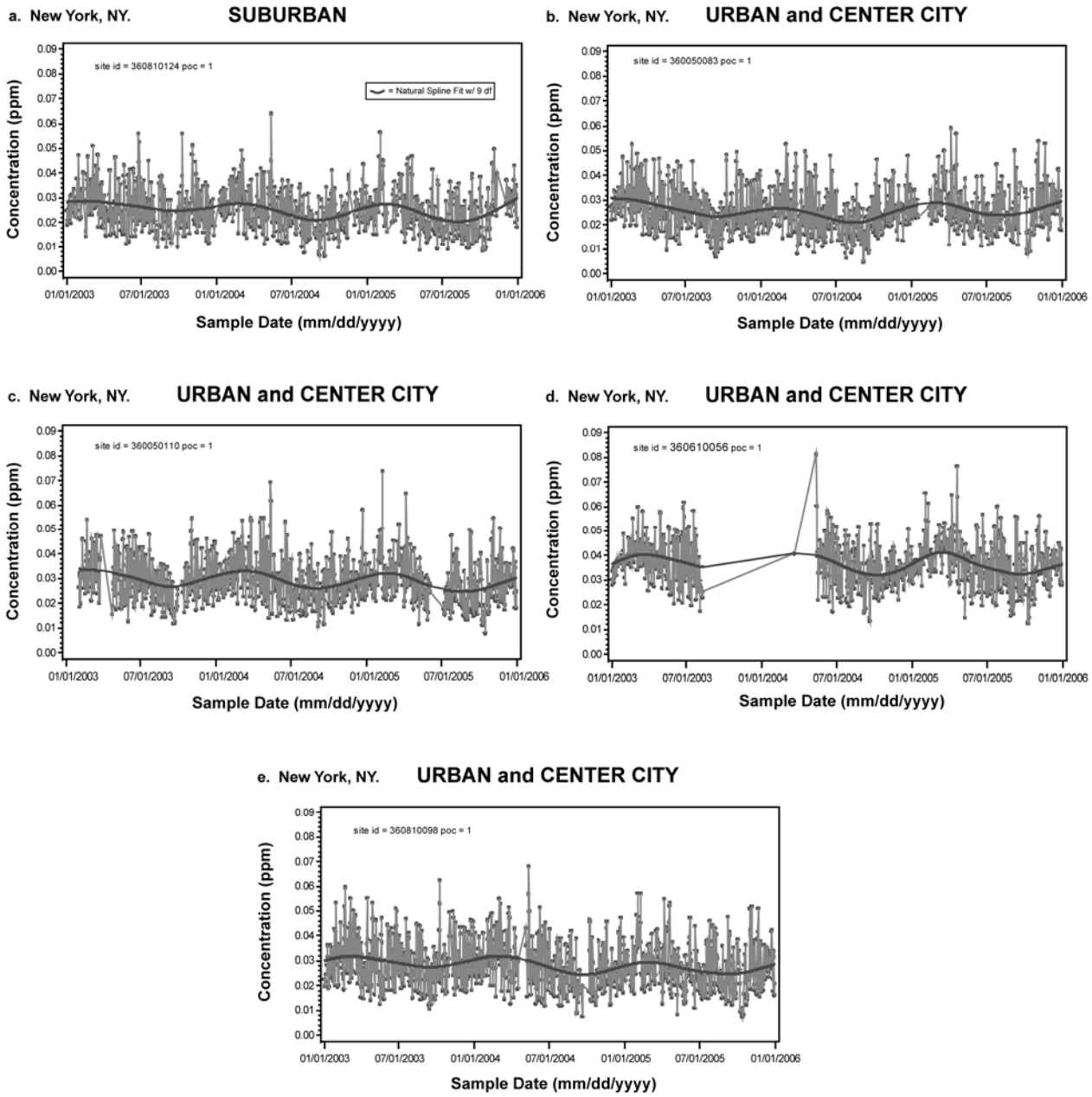
As might be expected from an atmospheric species that behaves essentially like a primary pollutant emitted from surface sources, there is strong seasonal variability in NO_X and NO_2 concentrations. Highest concentrations are found during winter, consistent with lowest mixing layer heights found during the year.

Mean and peak concentrations in winter can be up to a factor of two larger than in the summer at several sites in Los Angeles County.

The month-to-month variability in NO_2 at individual sites in selected urban areas is illustrated in Figures AX3.2-1 to AX3.2-6. Seasonal patterns can be found at some sites but not in others. There appears to be a somewhat regular pattern for the southern cities with winter maxima and summer minima. Monthly maxima tend to be found from late winter to early spring in Chicago and New York with minima occurring from summer through the fall. However, in Los Angeles and Riverside, monthly maxima tend to occur from autumn through early winter with minima occurring from spring through early summer.

AX3.2.1.4. Regional Background Sites

Surface NO_X and NO_Y data obtained in Shenandoah National Park, VA from 1988 to 1989 show wintertime maxima and summertime minima (Doddridge et al., 1991, 1992; Poulida et al., 1991). NO_X and NO_Y data collected in Harvard Forest, MA from 1990 to 1993 show a similar seasonal pattern (Munger et al., 1996). In addition the within-season variability was found to be smaller in the summer than in the winter as shown in Table AX3.2-1.



Source: U.S. EPA AQS, 2007

Figure AX3.2-1. Time series of 24-h avg NO_2 concentrations at individual sites in New York City from 2003 through 2006. A natural spline function (with 9 degrees of freedom) was fit and overlaid to the data (dark solid line).

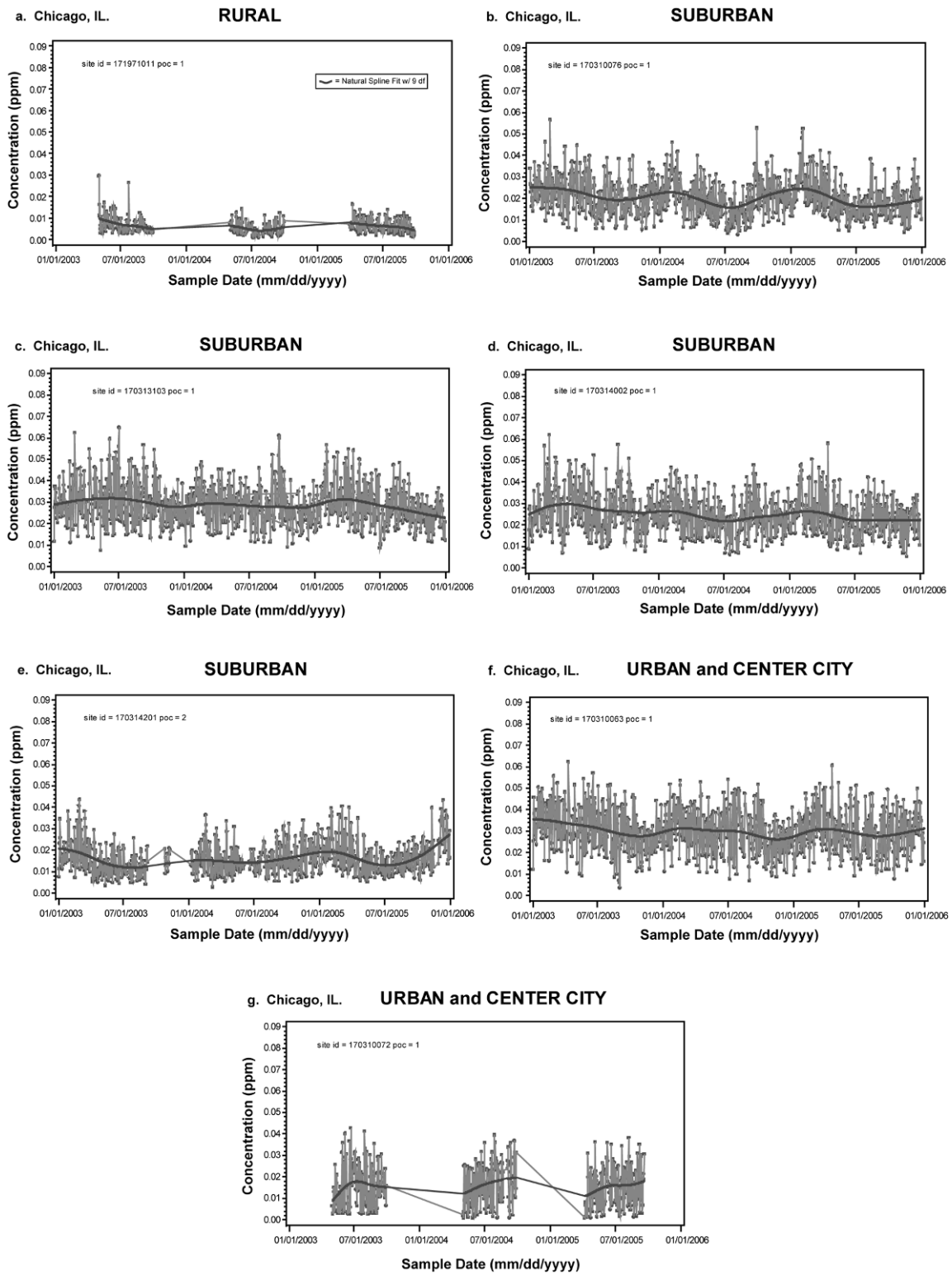
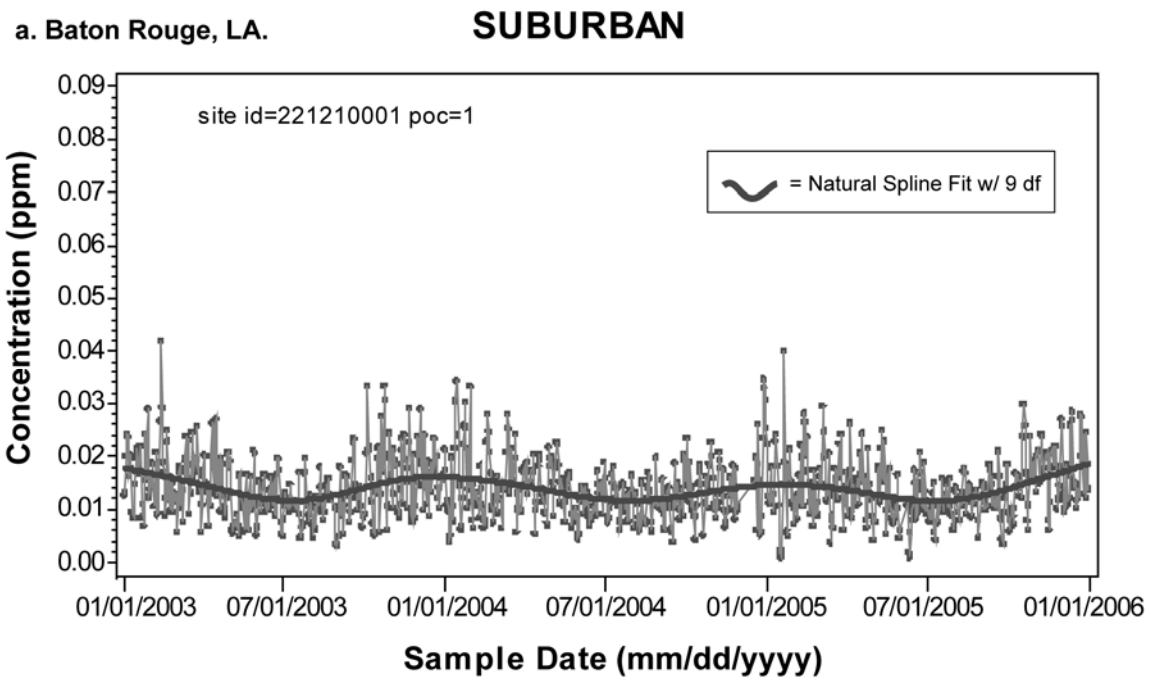


Figure AX3.2-2. Time series of 24-h average NO_2 concentrations at individual sites in Chicago, IL from 2003 through 2005. A natural spline function (with 9 degrees of freedom) was fit and overlaid to the data (dark solid line).



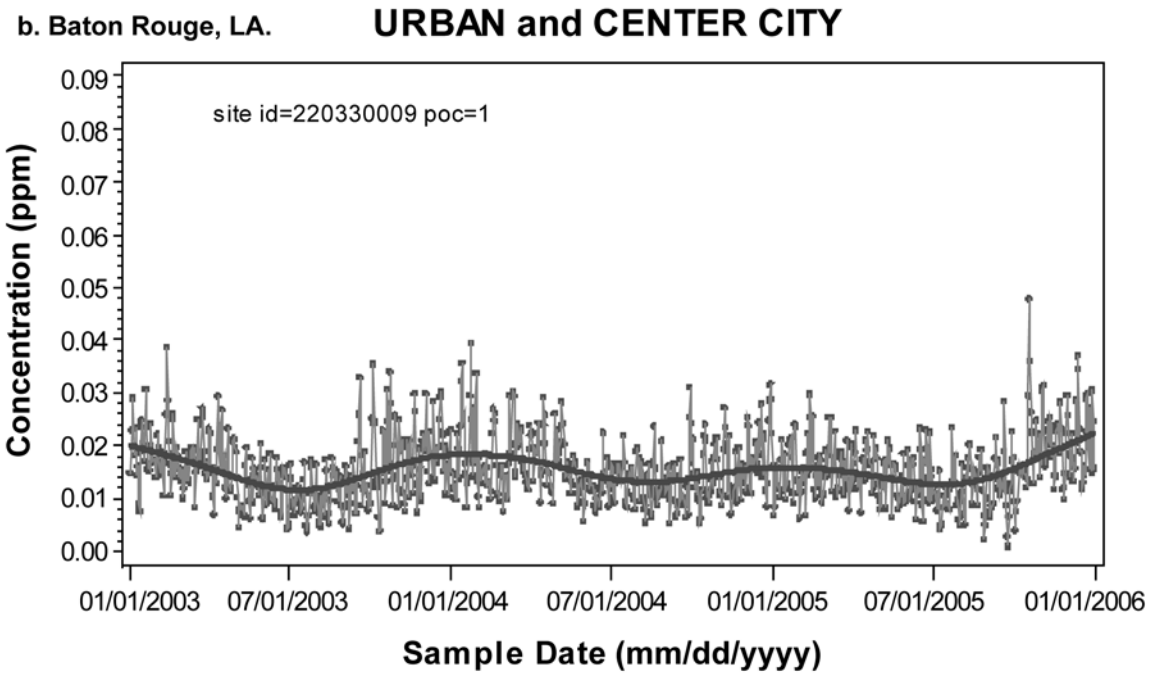


Figure AX3.2-3. Time series of 24-h avg NO_2 concentrations at individual sites in Baton Rouge, LA from 2003 through 2005. A natural spline function (with 9 degrees of freedom) was fit and overlaid to the data (dark solid line).

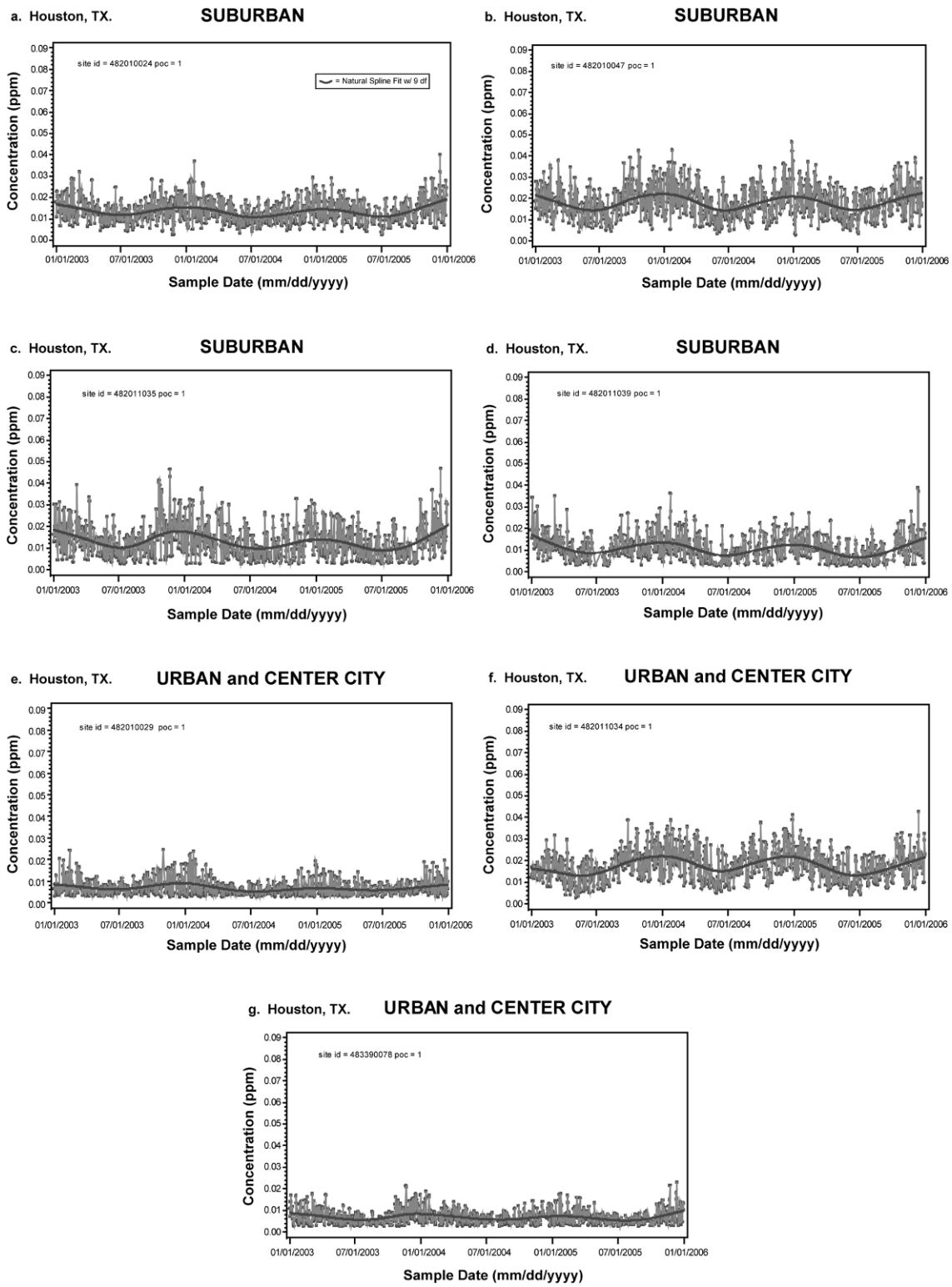


Figure AX3.2-4. Time series of 24-h avg NO_2 concentrations at individual sites in Houston, TX from 2003 through 2005. A natural spline function (with 9 degrees of freedom) was fit and overlaid to the data (dark solid line).

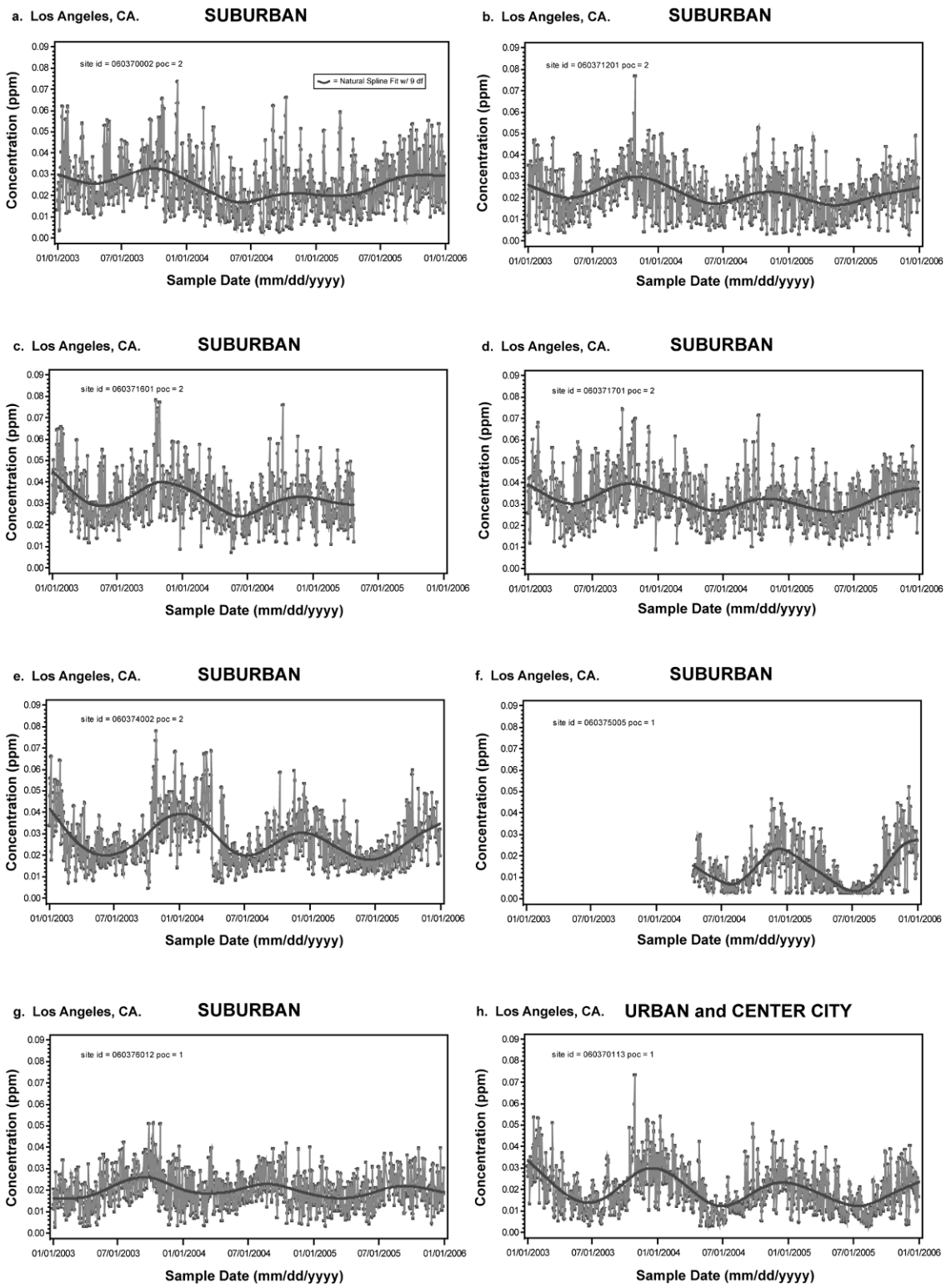


Figure AX3.2-5. Time series of 24-h avg NO_2 concentrations at individual sites in Los Angeles, CA from 2003 through 2005. A natural spline function (with 9 degrees of freedom) was fit and overlaid to the data (dark solid line).

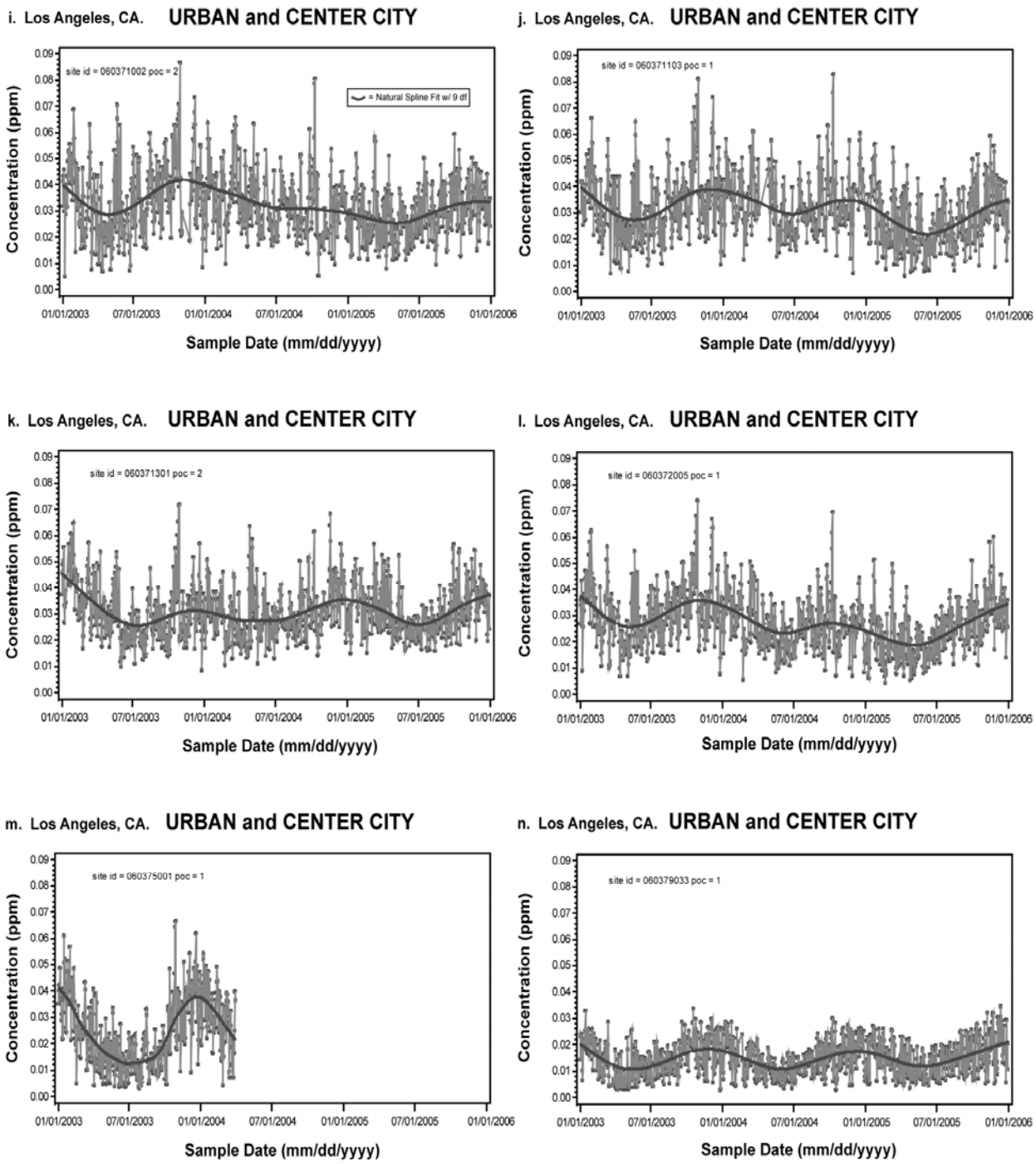


Figure AX3.2-5. (Continued) Time series of 24-h avg NO_2 concentrations at individual sites in Los Angeles, CA from 2003 through 2006. A natural spline function (with 9 degrees of freedom) was fit and overlaid to the data (dark solid line).

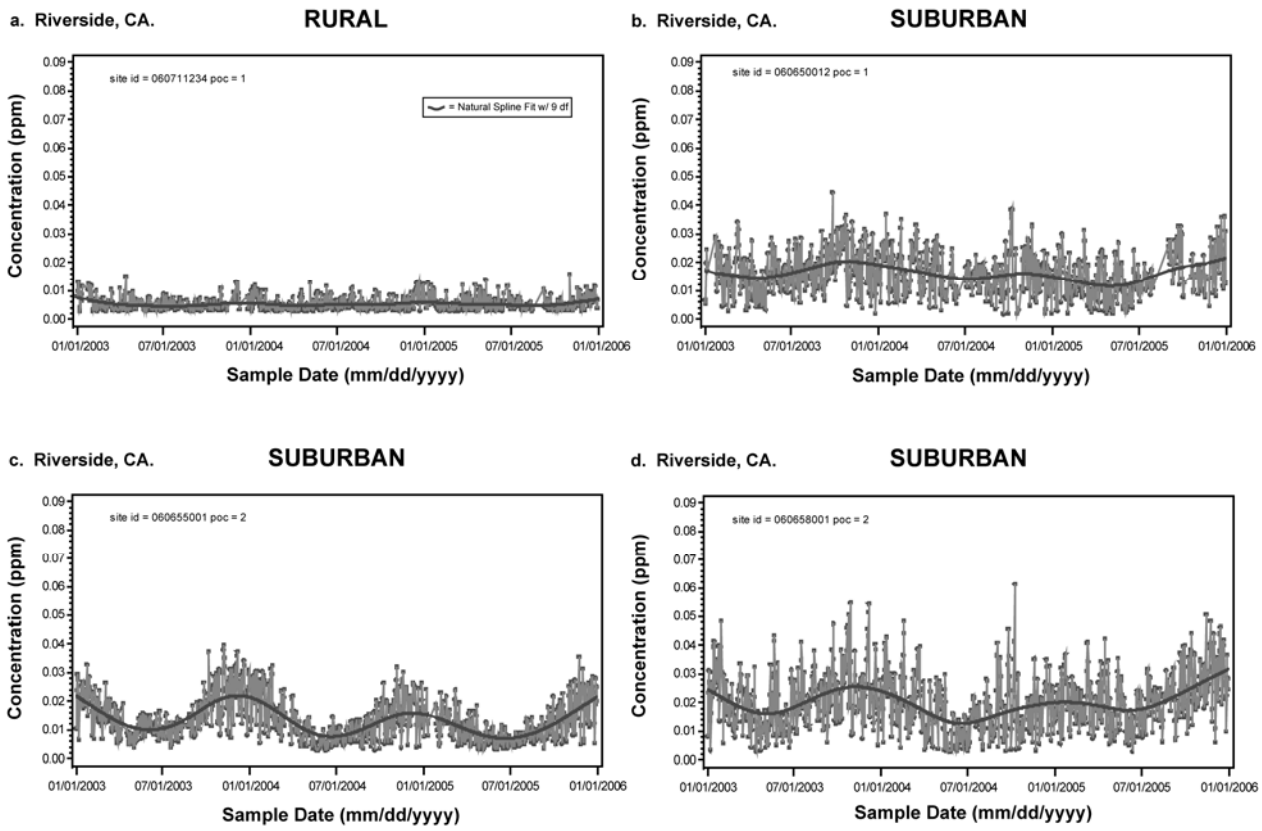


Figure AX3.2-6. Time series of 24-h avg NO_2 concentrations at individual sites in Riverside, CA from 2003 through 2006. A natural spline function (with 9 degrees of freedom) was fit and overlaid to the data (dark solid line).

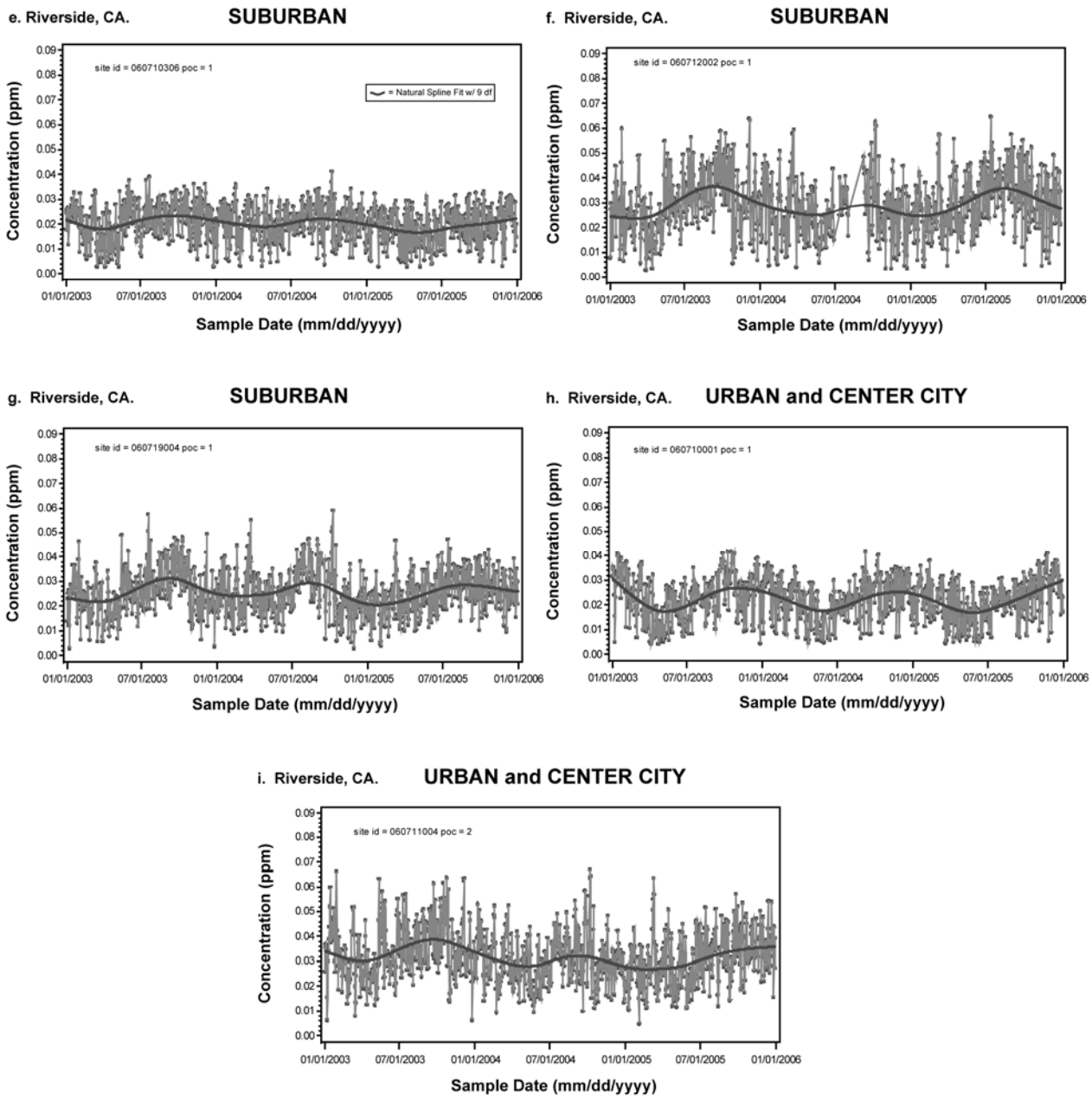


Figure AX3.2-6. (Continued) Time series of 24-h avg NO_2 concentrations at individual sites in Riverside, CA from 2003 through 2006. A natural spline function (with 9 degrees of freedom) was fit and overlaid to the data (dark solid line).

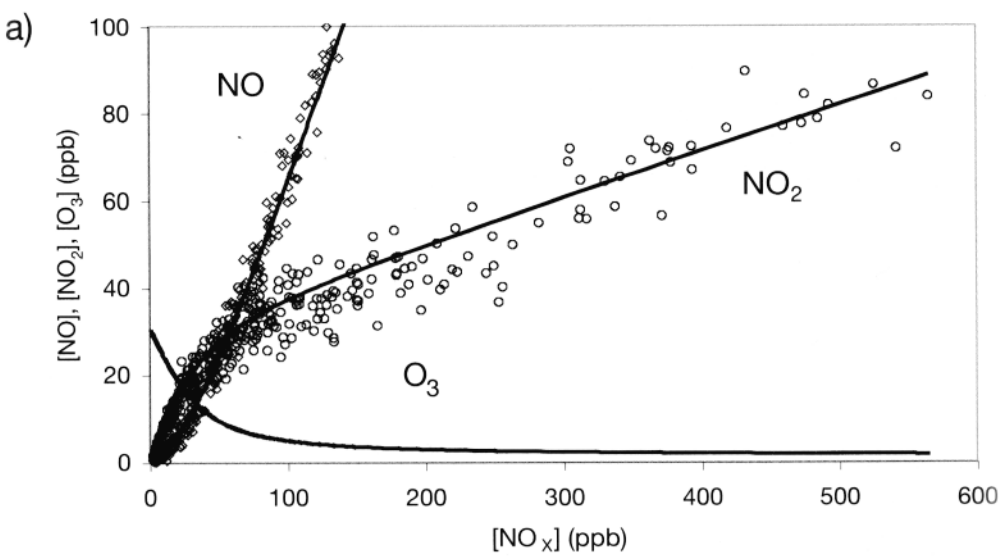
Source: U.S. Environmental Protection Agency (2003)

AX3.2.2. Relationships between NO_2 and Other Pollutants

Relationships between O_3, NO, and NO_2 are shown in Figures AX3.2-7 and AX3.2-8. Figure AX3.2-7 shows daylight average concentrations based on data collected from November 1998 and 1999 at several sites in the United Kingdom representing a wide range of pollution conditions (open symbols). The solid lines represent calculations of photostationary state values subject to the constraint that O_X =

31.1 + 0.104 (NO_X), where $O_X = O_3 + NO_2$. Note that O_X is defined in the UK AQG report as oxidant, as used in this document, and in the latest AQCD for Ozone and other Photochemical Oxidants (U.S. Environmental Protection Agency, 2006a) it is taken to refer to "odd oxygen" as defined in Section 2.2. The reason is that oxidants also include PANs, peroxides, and reactive oxygen species in particles etc., in addition to O_3 and NO_2. The concentrations of NO_2 (an oxidant and a component of odd oxygen) varying linearly with emissions of NO_X, especially after NO has reacted with O_3 to form NO_2 as shown in Figure AX3.2-7. Thus the concentration of O_X (and not O_3, as is often stated) can be taken to be the sum of regional and local contributions.

Figure AX3.2-8 shows that primary emissions from motor vehicles are major sources of oxidant in the form of NO_2, as evidenced by the high values of O_X at elevated NO_X.



Source: Clapp and Jenkin (2001).

Figure AX3.2-7. Relationship between O_3, NO, and NO_2 as a function of NO_X concentration. Open circles represent data collected at a number of sites in the United Kingdom. Lines represent calculated relationships based on photostationary state.

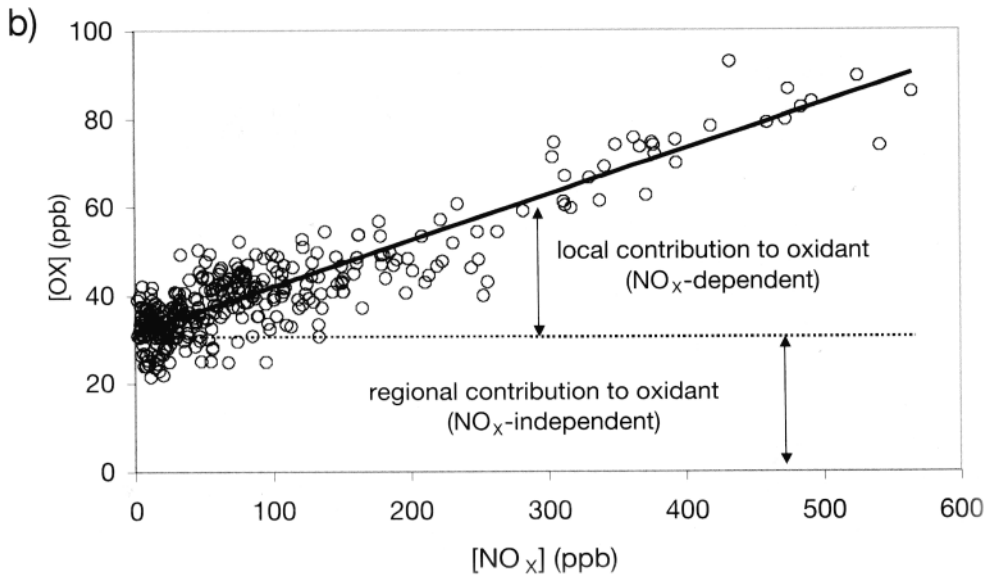


Figure AX3.2-8. Variation of odd oxygen (= O_3 + NO_2) with NO_X. The figure shows the "regional" and the "local" contributions. Note that O_X refers to odd oxygen in the document and the latest O_3 AQCD.

AX3.2.3. Abundance of NO_Y Species

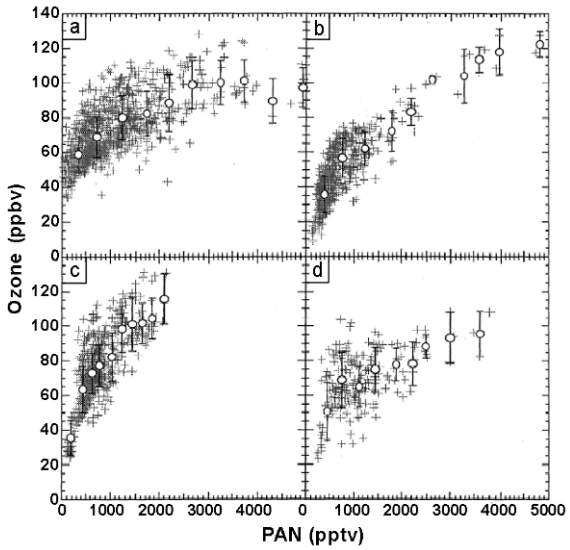
Data for individual NO_Y species are much less abundant than for either oxides of nitrogen or for total NO_Y. Data for several NO_Y species are collected typically only as part of research field studies, e.g., the Southern Oxidant Study (SOS), Texas Air Quality Study (TexAQS I and TexAQS II) in the United States. As a result, this information is simply not available for a large number of areas in the United States.

AX3.2.3.1. PANs

Organic nitrates consist of PAN, a number of higher-order species with photochemistry similar to PAN (e.g., PPN), and species such as alkyl nitrates with somewhat different photochemistry. These species are produced by a photochemical process very similar to that of O_3. Photochemical production is initiated by the reaction of primary and secondary VOCs with OH radicals, the resulting organic radicals subsequently react with NO_2 (producing Source: Clapp and Jenkin (2001). PAN and analogous species) or with NO (producing alkyl nitrates). The same sequence (with organic radicals reacting with NO) leads to the formation of O_3.

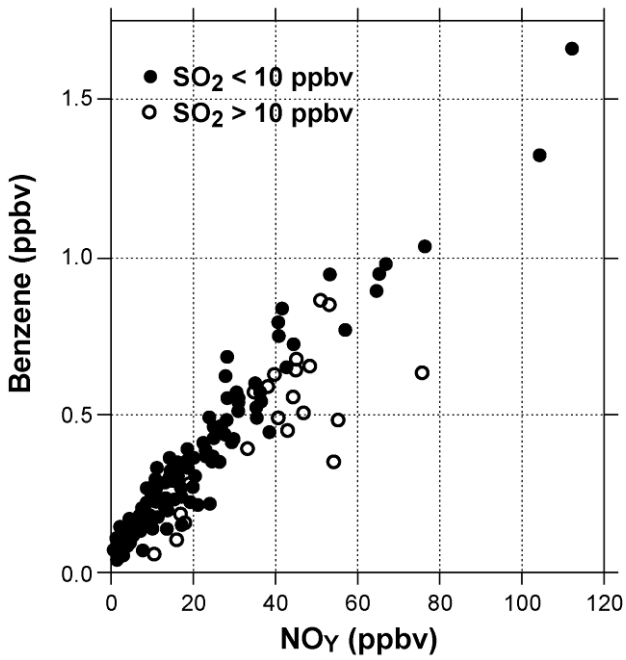
In addition, at warm temperatures, the concentration of PAN forms a photochemical steady state with its radical precursors on a timescale of roughly 30 min. This steady state value increases with the ambient concentration of O_3 (Sillman et al., 1990). O_3 and PAN may show different seasonal cycles, because they are affected differently by temperature. Ambient O_3 increases with temperature, driven in part by the photochemistry of PAN (see description in Chapter 2). The atmospheric lifetime of PAN decreases rapidly with increasing temperature due to thermal decomposition. Based on the above, the

ratio of O_3 to PAN is expected to show seasonal changes, with highest ratios in summer, although there is no evidence from measurements. Measured ambient concentrations (Figure AX3.2-9) show a strong nonlinear association between O_3 and PAN, and between O_3 and other organic nitrates (Pippin et al., 2001; Roberts et al., 1998). Moreover, uncertainty in the relationship between O_3 and PAN grows as the level of PAN increases. Individual primary VOCs are generally highly correlated with each other and with NO_X (Figure AX3.2-10).



Source: Roberts et al. (1998).

Figure AX3.2-9. Measured O_3 (ppb) versus PAN (ppt) in Tennessee, including (a) aircraft measurements, and (b, c, and d) suburban sites near Nashville.



Source: Goldan et al. (1995).

Figure AX3.2-10. Relationship between benzene and NO_Y at a measurement site in Boulder, CO. Instances with SO_2 >10 ppb are identified separately (open circles), because these may reflect different emission sources.

Measurements and models show that PAN in the United States includes major contributions from both anthropogenic and biogenic VOC precursors (Horowitz et al., 1998; Roberts et al., 1998). Measurements in Nashville during the 1999 summertime Southern Oxidants Study (SOS) showed PPN and MPAN amounting to 14% and 25% of PANs, respectively (Roberts et al., 2002). Measurements during the TexAQS 2000 study in Houston indicated PAN concentrations of up to 6.5 ppb (Roberts et al., 2003). PAN measurements in southern California during the SCOS97-NARSTO study indicated peak concentrations of 5-10 ppb, which can be contrasted to values of 60-70 ppb measured back in 1960 (Grosjean, 2003). Vertical profiles measured from aircraft over the United States and off the Pacific coasts typically show PAN concentrations above the boundary layer of only a few hundred ppt, although there are significant enhancements associated with long-range transport of pollution plumes from Asia (Kotchenruther et al., 2001; Roberts et al., 2004).

Observed ratios of PAN to NO_2 as a function of NO_X at a site at Silwood Park, Ascot, Berkshire, UK are shown in Figure AX3.2-11 United Kingdom Air Quality Expert Group (U.K. AQEG, 2004). As can be seen there is a very strong inverse relation between the ratio and the NO_X concentration, indicating photochemical oxidation of NO_X has occurred in aged air masses and that PAN can make a significant contribution to measurements of NO_2 especially at low levels of NO_2 (cf. ISA, Section 2-3). It should be noted that these ratios will likely differ from those found in the United States because of differences in the composition of precursor emissions, the higher solar zenith angles found in the UK compared to the United States., and different climactic conditions.

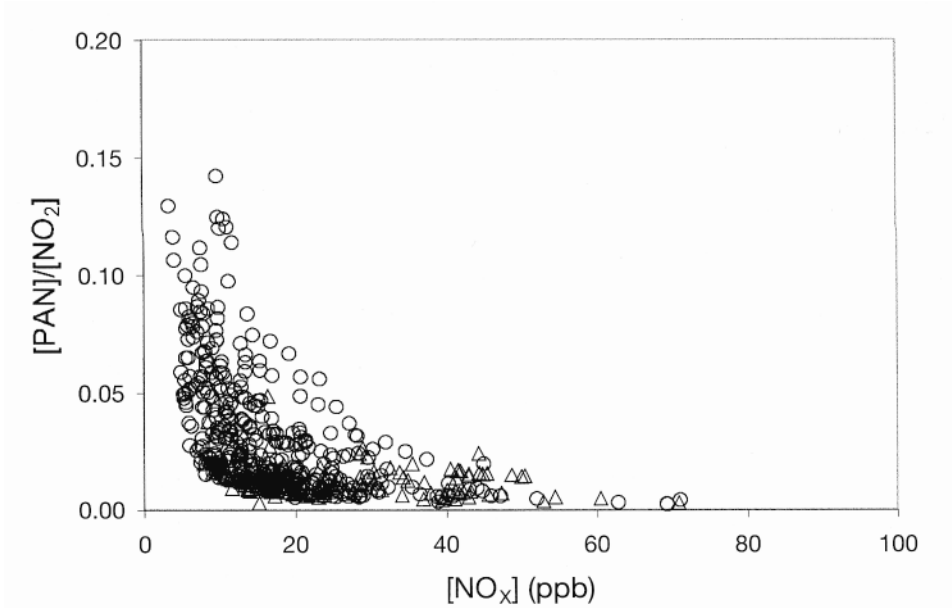
Nevertheless, these results indicate the potential importance of interference from NO_Y compounds in measurements of NO_2.

AX3.2.3.2. HONO

The ratio of HONO to NO_2 as a function of NO_X measured at a curbside site in a street canyon in London, UK is shown in Figure AX3.2-12 (U.K. AQEG, 2004). The ratio is highly variable, ranging from about 0.01 to 0.1, with a mean ~0.05. As NO_2 constitutes several percent of motor vehicle emissions of NO_X, the above implies that emissions of HONO represent a few tenths of a percent of mobile NO_X emissions. A similar range of ratios have been observed at other urban sites in the United Kingdom (Lammel and Cape, 1996). The ratios of HONO to NO_2 shown in Figure AX3.2-12 indicate that HONO can make a measurable contribution to measurements of NO_2 (cf. ISA, Section 2-3). However, similar arguments about extrapolating the use of UK data to the United States can be made for HONO as for PAN.

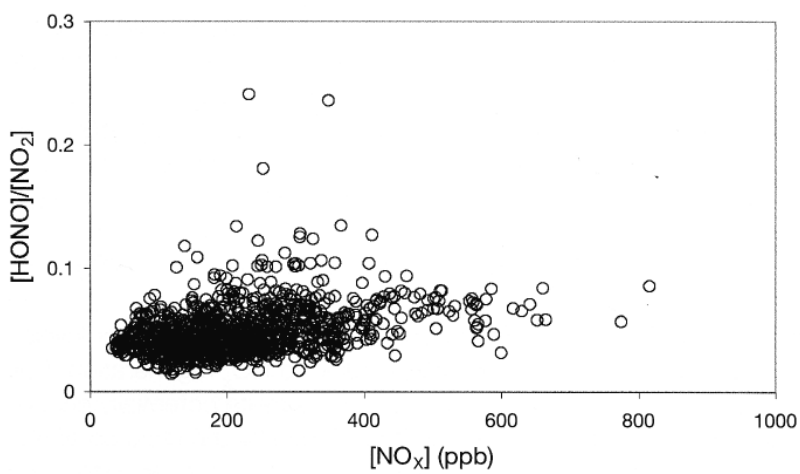
AX3.2.3.3. HNO_3 and NO_3

Elevated O_3 is generally accompanied by elevated HNO_3, although the correlation is not as strong as between O_3 and organic nitrates. O_3 is often associated with HNO_3 because they have the same precursor NO_X. However, HNO_3 can be produced in significant quantities in winter, even when O_3 is low. The ratio between O_3 and HNO_3 also shows great variation in air pollution events, with NO_X-saturated environments having much lower ratios of O_3 to HNO_3 (Ryerson et al., 2001). Aerosol nitrate is formed primarily by the combination of nitrate (supplied by HNO_3) with ammonia, and may be limited by the availability of either nitrate or ammonia. Nitrate is expected to correlate loosely with O_3 (see above), whereas ammonia is not expected to correlate with O_3. Concentrations of particulate nitrate measured as part of the Environmental Protection Agency's speciation network at several locations are shown in Figure AX3.2-13. Concentrations shown are annual averages for 2003. Also shown are the estimated contributions from regional and local sources. A concentration of 1 $\mu g/m^3$ corresponds to ~0.40 ppb equivalent gas phase concentration for NO_3^-.



Source: UK AQEG (2004).

Figure AX3.2-11. Ratios of PAN to NO_2 observed at Silwood Park, Ascot, Berkshire, U.K. from July 24 to August 12 1999. Each data point represents a measurement averaged over 30 minutes.



Source: UK AQEG (2004).

Figure AX3.2-12. Ratios of HONO to NO_2 observed in a street canyon (Marylebone Road) in London, U.K. from 11 a.m. to midnight during October 1999. Data points reflect 15-min avg concentrations of HONO and NO_2.

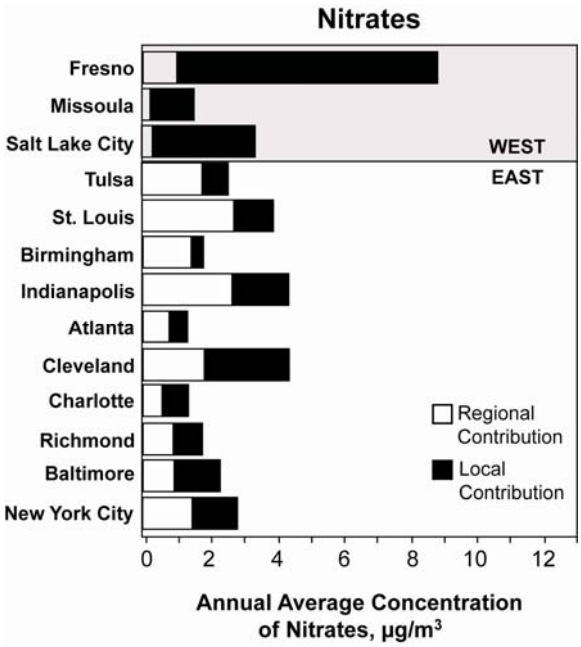
Thus, annual average particulate nitrate can account for several ppb of NO_Y, with the higher values in the West. There is a strong seasonal variation, which is especially pronounced in western areas where

there is extensive wood burning in the winter resulting in a larger fractional contribution of local sources. Areas in the East where there are topographic barriers might be expected to show higher fractional contributions from local sources than other eastern areas that are influenced by regionally dispersed sources.

However, depending on the acidity of the particles, which in turn depends strongly on their sulfate and ammonium contents, higher nitrate concentrations could be found in coarse mode particles $PM_{10-2.5}$ than in $PM_{2.5}$ samples. The average nitrate content of $PM_{2.5}$ and PM_{10} is typically about a percent in the eastern United States; and 15.7% and 4.5% in the western United States (U.S. Environmental Protection Agency, 1996). These values suggest that most of the nitrate was in the $PM_{2.5}$ size fraction in the studies conducted in the western United States, but nitrate in the studies in the eastern United States was mainly in the $PM_{10-2.5}$ size fraction.

AX3.2.3.4. Nitro-PAHs

Nitro-PAHs are widespread and found even in high altitude, relatively unpolluted environments (Schauer et al., 2004) but there are differences in composition and concentration profiles both within and between sites (rural vs. urban) as well as between and within urban areas (Albinet et al., 2006; Söderström et al., 2005; Naumova et al., 2002, 2003), with some differences in relative abundances of nitro- and oxo-PAHs also reported. Source attribution has remained largely qualitative with respect to concentrations or mutagenicity (Eide et al., 2002). The spatial and temporal concentration pattern for the NPAHs may differ from that of the parent compounds (PAHs) because concentrations of the latter are dominated by direct emission from local combustion sources. These emissions results in higher concentrations during atmospheric conditions more typical of wintertime when mixing heights tend to be low. The concentrations of secondary Nitro-PAHs are elevated under conditions that favor hydroxyl and nitrate radical formation, i.e., during conditions more typical of summertime, and are enhanced downwind of areas of high emission density of parent PAHs and show diurnal variation (Fraser et al., 1998; Reisen and Arey, 2005; Kameda et al., 2004). Nitro-napthalene concentrations in Los Angeles, CA varied between about 0.15 to almost 0.30 ng/m^3 compared to 760 to 1500 ng/m^3 for napthalene. Corresponding values for Riverside, CA were 0.012 to more than 0.30 ng/m^3 for nitro-napthalene and 100 to 500 ng/m^3 for napthalene. Nitro-pyrene concentrations in LA varied between approximately 0.020 to 0.060 ng/m^3 compared to 3.3 to 6.9 ng/m^3 pyrene, whereas corresponding values for Riverside were 0.012 to 0.025 ng/m^3 and 0.9 to 2.7 ng/m^3.



Source: U.S. Environmental Protection Agency (2004).

Figure AX3.2-13. Concentrations of particulate nitrate measures as part of the EPA's speciation network. 1 µg/m^3 ~0.45 ppb equivalent gas phase concentration for NO_3-. (Note: Regional concentrations are derived from the rural IMPROVE monitoring network, http://vista.cira.colostate.edu/improve.

AX3.3. Measuring Personal and Indoor NO_2 Concentrations

AX3.3.1. Issues in Measuring Personal/Indoor NO_2

Nitrogen dioxide has been sampled in ambient and indoor air using active pumped systems both for continuous monitoring and collection onto adsorbents, and by diffusive samplers of various designs, including badges and tubes. Nitrogen dioxide concentrations in personal air have been typically measured using diffusive samplers because they are: (1) small in size and light-weight, (2) unobtrusive and thus more readily used by study participants, (3) comparatively easier to use and handle in field studies because they do not require power (e.g., battery or extra electrical sources), (4) cost-effective, and (5) usable not only for residential indoor and outdoor air sampling but also personal monitoring. However, diffusive samplers usually have lower equivalent sampling rates than active methods and so require relatively long sampling times (24-h or longer). Consequently, diffusive samplers including those used for NO_2 monitoring provide integrated but not short-term concentration measurements.

Both active and passive sampling methods can collect other gas-phase nitrogen oxide species. However, semivolatile nitrogen oxide compounds require separation of the gas- and particle-bound phases. This selective separation of gases from gas-particle matrices is commonly done by means of diffusion denuders (Vogel, 2005), an approach also useful for measuring other gas phase airborne contaminants such as SO_2 (Rosman et al., 2001). Application of denuder sampling to personal exposure or indoor air monitoring has been relatively limited.

Active air sampling with a pump can collect larger volumes of air and thus detect the lower concentrations found in community environments within relatively short time periods. Automated active

sampling methods have been the preferred method used to monitor NO_2 continuously at ambient sites for environmental regulation compliance purposes. However, practical considerations impede the use of these continuous monitors in residential air and exposure monitoring studies. Small, low flow active samplers using battery-operated pumps have been used instead, however, there are only a few such studies.

The first passive sampling devices for NO_2 were intended for occupational exposure monitoring, but were later adapted for environmental monitoring purposes. Since this sampler, the Palmes tubes (Palmes et al., 1976), was first developed, other tube, badge-type (Yanagisawa and Nishimura, 1982) and radial (Cocheo et al., 1996) diffusive samplers have been employed as monitors in exposure studies worldwide. The theories behind and applications of Palmes tubes and Yanagisawa badges have been described in the last AQCD for Oxides of Nitrogen (U.S. Environmental Protection Agency, 1993). There are currently several commercially available samplers (e.g., Ogawa, 1998; Radiello, 2006) which are modifications of the original Palmes tube design. Most modifications are directed at reducing effects related to meteorological conditions (e.g., insufficient or too high a wind speed, humidity, temperature), increasing the sampling uptake rate, and improving analytical sensitivity.

AX3.3.1.1. Active (Pumped) Sampling

Nitrogen dioxide measurement by active pumping systems as part of continuous monitors has been widely employed for ambient air monitoring as these instruments require relatively little maintenance; however they have been used less frequently for indoor sampling. Devices needing a pump to draw air can measure average concentrations of pollutants over short time periods, but are not generally suitable for measuring personal exposures because they are heavy and large. Some exposure studies employed this approach for active sampling with stationary chemiluminescent analyzers or portable monitors to measure nitrogen dioxide levels in residential indoor air (Mourgeon et al., 1997; Levesque et al., 2000; Chau et al., 2002). Recently, Staimer and his colleagues (2005) evaluated a miniaturized active sampler, suitable for personal exposure monitoring, to estimate the daily exposure of pediatric asthmatics to nitrogen dioxide, and reported that this small active sampling system is useful for this purpose in exposure studies where daily measurements are desired.

AX3.3.1.2. Passive (Diffusive) Sampling

Passive samplers are based on the well known diffusion principle described by Fick's law (Krupa and Legge, 2000). A convenient formulation of this law that can be easily related to sampler design considerations is:

$$J = D(A/L)(C_{air}\text{-}C_{sor}) \qquad \text{(AX3.3-1)}$$

where:

J = flux (mg/s)

D = diffusion coefficient in air (cm^2/s)

A = diffusion cross-sectional area of the sampler (cm^2)

L = diffusion path length from the inlet to sorbent (cm),

C_{air} = concentration of analyte in air (mg/cm^3)

C_{sor} = concentration of analyte at the sorbent (mg/cm^3)

The term D(A/L) can be related to the uptake or sampling rate (cm^3/s) which is conceptually analogous to the sampling rate in an active monitor. Once the amount of analyte in the passive sampler sorbent is determined, the concentration in air (C_{air}) can be calculated as:

$$Concentration(mg/cm^3) = M(mg)/D(A/L)(cm^3/s)/t(sec) \qquad \text{(AX3.3-2)}$$

where:

M = mass of analyte collected in the sorbent
t = sampling time

Fick's law strictly applies only under ideal, steady state conditions assuming that the sorbent is a perfect sink. However, there can be deviations between the theoretical sampling rate for a given analyte and the actual rate depending on sampling conditions. It is also clear that sampling rate can be optimized by modifying the geometry of the diffusive sampler, either by reducing L, increasing A or a suitable combination. However, the impact of deviations from ideality on actual sampling rate due to geometry also poses a limit to the extent of possible modifications. Thus, passive samplers, either diffusive or permeation, are prepared as tubes or badges. These two main designs are the basis for all further modifications which, as indicated above, have been made in order to improve efficiency, reduce sensitivity to wind turbulence of the samplers, and to simplify analyte desorption. Tube-type samplers are characterized by a long, axial diffusion length, and a low cross-sectional area; this results in relatively low sampling rates (Namieśnik et al., 2005). Badge-type samplers have a shorter diffusion path length and a greater cross-sectional area which results in uptake rates that are typically higher than diffusion tubes (Namieśnik et al., 2005) but the sampling rate may be more variable because it is more affected by turbulence. Physical characteristics of these two fundamental passive sampler types, tube-type and badge-type, are summarized and provided in Table AX3.3-1. Performance characteristics are presented in Table AX3.3-2.

The sorbent can be either physically sorptive or chemisorptive; passive samplers for NO_2 are chemisorptive, that is, a reagent coated on a support (e.g., metal mesh, filter) reacts with the NO_2. The sorbent is extracted and analyzed for one or more reactive derivatives; the mass of NO_2 collected is derived from the concentration of the derivative(s) based on the stoichiometry of the reaction. Thus, an additional approach to reducing detection limits associated with passive samplers is to modify the chemisorptive reaction and the extraction and analysis methods to increase analytical sensitivity. However, although chemisorption is less prone to the back diffusion phenomenon of sorptive-only methods, analyte losses could occur due to interferences from other pollutants that also react with the sorbent or the derivatives. The most commonly used NO_2 passive samplers rely on the classical reaction with triethanolamine (TEA). TEA requires hydration for quantitative NO_2 sampling (i.e., 1:1 conversion to nitrite) and the reaction products have been subject to a number of investigations and several have been reported, including TEA-nitrate and nitrite, triethanolammonium nitrate, nitrosodiethanolamine, and triethanolamine N-oxide (Glasius et al., 1999). Known interferences include HONO, PAN, and nitric acid (Gair et al., 1991.).

The tube-type passive samplers (Palmes tubes) require week-long sampling periods and have been extensively used for residential indoor/outdoor measurements, mostly for exploring the relationship between indoor and outdoor levels (Cyrys et al., 2000; Raw et al., 2004; Simoni et al., 2004; Janssen et al., 2001). Passive diffusion tubes have also been widely used for measurements of NO_2 in ambient air (Gonzales et al., 2005; Gauderman et al., 2005; Da Silva et al., 2006; Lewné et al., 2004; Stevenson et al., 2001; Glasius et al., 1999). Personal exposure studies have also been conducted using the Palmes tubes (Mukala et al., 1996; Kousa et al., 2001). Some of these studies evaluated passive sampler performance by collocating them with chemiluminescence analyzers during at least some portion of the field studies (Gair et al., 1991; Gair and Penkett, 1995; Plaisance et al., 2004; Kirby et al., 2001). The majority of these studies indicate that these samplers have very good precision (generally within 5%) but tend to

overestimate NO_2 by 10 to 30%. However, there has not been a methodical evaluation of variables contributing to variance for the range of samplers available when used in field conditions. Thus, it is not clear if the bias is due to deviations from ideal sampling conditions that can affect actual sampling rates, contributions from co-reacting contaminants or, most probably, a combination of these variables.

A badge-type sampler was introduced by Yanagisawa and Nishimura (1982) to overcome the long sampling time required by Palmes tubes. Since then, these sensitive NO_2 short path length samplers (Toyo Roshi Ltd) have been optimized and evaluated for indoor air and for personal monitoring (Lee et al., 1993a,b). They have been used extensively for personal exposure studies (Ramirez-Aguilar et al., 2002; Yanagisawa et al., 1986; Berglund et al., 1994, Lee et al., 2004) and indoor air measurements (Kodama et al., 2002; Bae et al., 2004; Algar et al., 2004; Shima and Adachi, 2000; Smedje, et al., 1997) and to a more limited amount for ambient monitoring (Tashiro and Taniyama, 2002; Levy et al., 2006; Norris and Larson, 1999). Due to the greater uptake rate resulting from the larger cross sectional area of the badges and shorter diffusion length compared to the tube-type samplers, sampling times can be decreased from one-week to one-day for typical environmental air concentrations. This makes diffusive filter-badges more suitable for shorter-term sampling while long-term ambient monitoring can still be conducted using the Palmes-tubes.

AX3.3.1.3. Tube Type Samplers

Gradko Sampler (http://www.gradko.co.uk)

The Gradko sampler is based on the Palmes tube design (Gerboles et al., 2006a). It collects O_3 or NO_2 by molecular diffusion along an inert tube by chemisorption. A stable complex is formed with triethanolamine coated on a stainless steel screen in the tube. The complex is spectroscopically analyzed by adding an azo dye (Chao and Law, 2000). The sampler has a detection limit of 0.5 ppb for NO/NO_2 and the precision of ± 6% above 5 ppb levels when used for two weeks (Table AX3.3-2). This sampler has been used to measure personal exposures, concentrations of residential air indoors such as in the kitchen and bedroom, and concentrations of outdoor air (Chao and Law, 2000; Gallelli et al., 2002; Lai et al., 2004). It has been used to measure ambient NO_2 levels in Southern California as a marker of traffic-related pollution in San Diego County (Ross et al., 2006).

Passam Sampler (http://www.passam.ch)

This sampler is also based on the design of the Palmes tube (Palmes et al., 1976). It collects NO_2 by molecular diffusion along an inert polypropylene tube to an absorbent, triethanolamine. The collected NO_2 is determined spectrophotometrically by the well-established Saltzmann method. When used outdoors the samplers are placed in a special shelter to protect them from rain and minimize wind turbulence effects. The Passam sampler is sold in two different models, one for long-term and one for short-term sampling.

Analyst™ Sampler (http://www.monitoreurope.com)

The Analyst™ sampler is also a modification of the open-Palmes-tube design and was developed by the Italian National Research Council (CNR – Instituto Inquinamento Atmosferico) in 2000 (Bertoni et al., 2001). The Analyst™ consists of a glass vessel, which contains a reactant supported on a stainless steel grid. It is suitable for long-term monitoring (typically one month) of oxides of nitrogen, sulfur dioxide, and volatile organic compounds in ambient air. The target compound is analyzed by gas chromatography with minimum detection limit of 0.1 mg/m^3 (~52 ppb) for a twelve-week sample duration, and has relatively high precision. The Analyst™ method development (De Santis et al., 1997, 2002) and actual field application (De Santis et al., 2004) have been described. The primary use for Analyst™ is as a reliable tool for long-term determination of concentration in indoor as well as outdoor environments (Bertoni et al., 2001) and as a screening tool for ambient monitoring to identify pollution "hot spots" (De Santis et al., 2004).

AX3.3.1.4. Badge-Types Samplers

Ogawa Passive Sampler (http://www.ogawausa.com)

This sampler is a double face badge that can monitor NO, NO_X, and NO_2. The design can be used also for the determination of SO_2, O_3, and NH_3 levels in air. The manufacturer-reported detection limits for nitrogen oxides are 2.3 ppb and 0.32 ppb for 24-h and 168-h sampling, respectively. Reported actual sampling rates for NO_2 are two to three times higher than the manufacturer's values. The normal operation ranges are 0 to 25 ppm for 24-h exposure and 0 to 3.6 ppm for 168-h exposure. The manufacturer recommends a sampling height of 2.5 meters and storage time of up to 1 year when kept frozen. Ogawa passive samplers have been extensively used for human exposure studies to measure personal air concentrations and (or) indoor/outdoor levels for residents in a number of locations, including adults of Richmond, Virginia (Zipprich et al., 2002), children of Santiago, Chile (Rojas-Bracho et al., 2002), office workers of Paris, France (Mosqueron et al., 2002), and cardiac compromised individuals of Toronto, Canada (Kim et al., 2006). The samplers have been used also in air monitoring networks to assess traffic-related pollutant exposure (Singer et al., 2004), as well as to evaluate spatial variability of nitrogen dioxide ambient concentrations in Montreal, Canada (Gilbert et al., 2005).

IVL Sampler (http//www.ivl.se/en/business/monitoring/diffusive_samplers.asp)

The IVL method development has been described in detail by Ferm and Svanberg (1998). It was developed by Swedish Environmental Research Institute in the mid of 1980s (Sjödin et al., 1996), is designed to minimize turbulent wind effects outdoors as well as "starvation effects" indoors (i.e., very low face velocities), interferences from within sampling tube chemistry, temperature and humidity effects, and artifacts and losses during post-sampling storage. Manufacturer-reported detection limits for this sampler with sampling times of ~1 month are 0.1 $\mu g/m^3$ (0.05 ppb) for NO_2, and 0.5 $\mu g/m^3$ (0.42 ppb) for NO, respectively. Due to its long sampling time, this sampler has been extensively used for NO_2 background monitoring in ambient air in rural or urban areas (Fagundez et al., 2001; Sjödin et al., 1996; Pleijel et al., 2004).

Willems Badge Sampler

The Willems badge, a short-term diffusion sampler, was developed at the University of Wageningen, Netherlands, originally for airborne ammonia measurements and later for measuring NO_2 (Hagenbjörk-Gustafsson et al., 1996). It consists of a cylinder of polystyrene with a Whatman GF-A glass fiber filter impregnated with triethanolamine at its based held in place by a 6 mm distance ring. A Teflon filter is placed on the 6 mm polystyrene ring, which is secured with a polystyrene ring of 3 mm (Hagenbjörk-Gustafsson et al., 1996). The badge is closed by a polyethylene cap to limit influences by air turbulence. The diffusion length in the badge is 6 mm. This sampler was evaluated for ambient air measurements in laboratory and field tests (Hagenbjörk-Gustafsson et al., 1999). It has a manufacturer's reported detection limit of 2 $\mu g/m^3$ (~1 ppb) for 48-h sampling duration. When used for personal sampling in an occupational setting with a minimum wind velocity of 0.3 m/s, detection limits of 18 (~9.4 ppb) and 2 $\mu g/m^3$ (~1 ppb) for 1-h and 8-h sampling, respectively, have been reported (Hagenbjörk-Gustafsson et al., 2002, Glas et al., 2004).

AX3.3.1.5. Radial Sampler Types

Radiello® -the radial diffusive sampler (http://www.radiello.com)

Radiello® samplers use radial diffusion over a microporous cylinder into an absorbing inner cylinder, instead of axial diffusion, which increases the uptake rate by a factor of about 100 (Hertel et al., 2001). Nitrogen dioxide is chemiadsorbed onto triethanolamine as nitrite, which is quantified by visible spectrometry. Sample collection of up to 15 days is feasible but relative humidity higher than 70% can cause interferences when used for extended periods of more than 7 days. The manufacturer-reported typical sampling rate for nitrogen dioxide sampling is 75 ± 3.72 ml/min at temperatures between –10 and 40 °C. The rate can vary with humidity in the range of 15 to 90% and wind speed between 0.1 and 10 m/s

(Radiello® Manual, 2006). A Danish study (Sørensen et al., 2005) recruited 30 subjects during each of four seasons in Copenhagen, and measured the subjects' personal exposures, home indoor/front door air concentrations during 2-day periods with this sampler.

EMD (Ecole des Mines de Douai) Sampler

A new high-uptake rate diffusive sampler has been recently developed by the Ecole des Mines de Douai (EMD) laboratory (Piechocki-Minguy et al., 2003) and evaluated in the laboratory and field for measurement of NO_2 levels in ambient air. It is composed of a porous cartridge impregnated with triethanolamine and fitted in a cylindrical protective box equipped with caps at its extremities (Piechocki-Minguy et al., 2006). The large sampling area (cartridge surface) and the two circular openings provide a high uptake rate (exceeding 50 cm^3/min). The sampling rate was reported to be on average 0.89 cm^3/s for indoor sampling and 1.00 cm^3/s for outdoor sampling. Detection limits were determined to be 11 $\mu g/m^3$ (~5.8 ppb) for 1-h measurement. The sampling rate was not significantly influenced by wind at speeds higher than 0.3 m/s (Piechocki-Minguy et al., 2003). This sampler has been used in France to assess personal exposures in a series of microenvironments (home, other indoor places, transport and outdoor) for two 24-h time periods (weekday and weekend) (Piechocki-Minguy et al., 2006).

AX3.4. NO_X in Indoor Air

AX3.4.1. Indoor Sources and Concentrations of NO_X

Penetration of outdoor NO_2 and combustion in various forms are the major sources of NO_2 to indoor environments. These environments include homes, schools, restaurants, theaters etc. As might be expected, indoor concentrations of NO_2 in the absence of combustion sources are determined by the infiltration of outdoor NO_2 (Spengler et al., 1994; Weschler et al., 1994; Levy et al., 1998a), with a much smaller contribution from chemical reactions in indoor air. Indoor sources of nitrogen oxides have been characterized in several reviews, namely the last AQCD for Oxides of Nitrogen (U.S. Environmental Protection Agency, 1993); the Review of the Health Risks Associated with Nitrogen Dioxide and Sulfur Dioxide in Indoor Air for Health Canada (Brauer et al., 2002); and the Staff Recommendations for revision of the NO_2 Standard in California (CARB, 2007). Mechanisms by which nitrogen oxides are produced in the combustion zones of indoor sources were reviewed in the last AQCD for Oxides of Nitrogen (U.S. Environmental Protection Agency, 1993) and will not be repeated here. Sources of ambient NO_2 are reviewed in Chapter 2 of this document. It should also be noted that indoor sources can affect ambient NO_2 levels, particularly in areas in which atmospheric mixing is limited.

Ideally, exposure to NO_2 should be cumulated over all indoor environments in which an individual spends time. These indoor environments may include homes, schools, offices, restaurants, theaters, ice skating rinks, stores, etc. However, in a study by Leaderer et al. that used two-week integrated measures, concentrations of NO_2 inside the home accounted for 80% of the variance in total personal exposure, indicating that home concentrations are a reasonable proxy for personal exposure (Leaderer et al., 1986).

AX3.4.1.1. Gas Cooking Appliances

A large number of studies, as described in the reviews cited above, have all noted the importance of gas cooking appliances as sources of NO_2 emissions. Depending on geographical location, season, other sources, length of monitoring period, and household characteristics, homes with gas cooking appliances have approximately 50% to over 400% higher NO_2 concentrations than homes with electric cooking appliances (Gilbert et al., 2006; Lee et al., 2000, 2002; García-Algar et al., 2004; Raw et al., 2004; Leaderer et al., 1986; García-Algar, 2003). Gas cooking appliances remain significantly associated with

indoor NO_2 concentrations after adjusting for several potential confounders including season, type of community, socioeconomic status, use of extractor fans, household smoking, and type of heating (García-Algar et al., 2004; Garrett et al., 1999).

Gas appliances with pilot lights emit more NO_2 than gas appliances with electronic ignition. Spengler et al. (1994) found that NO_2 concentrations in bedrooms of homes with a gas range without a pilot light averaged 4 ppb higher than in homes with an electric range, but were 15 ppb higher in homes with gas ranges with pilot lights. Lee et al. (1998) found somewhat larger differences in NO_2 concentrations in homes in the Boston area, with minor seasonal variation. Homes with gas stoves without pilot lights averaged between 11 ppb (summer) and 18 ppb (fall) higher than homes with electric stoves, while those with pilot lights averaged between 19 ppb (summer) and 27 ppb (fall) higher than electric stove homes.

Use of extractor fans reduces NO_2 concentrations in homes with gas cooking appliances (Gallelli et al., 2002; García-Algar et al., 2003), although absolute NO_2 levels tend to remain higher than in homes with electric stoves. In a multivariate analysis, García-Algar et al. (2004) found that having a gas cooker remained significantly increased NO_2 concentrations even after adjusting for extractor fan use. Raw et al. (2004) found only a small effect of extraction fan use on NO_2 levels in the bedroom in gas cooker homes. Among homes with gas cooking, geometric mean bedroom NO_2 levels were 1.7 ppb lower in homes with an extractor fan than in homes without one. As expected, among homes with no fossil fuel cooking, there were no differences in mean bedroom levels of NO_2 in homes with and without extractor fans.

AX3.4.1.2. Other Combustion Sources

Secondary heating appliances are additional sources of NO_2 in indoor environments, particularly if they are unvented or inadequately vented. As heating costs increase, the use of these secondary heating appliances tends to increase. From 1988 to 1994, an estimated 13.7 million homes used unvented heating appliances, with disproportionately higher usage rates among southern, rural, low-income, and African-American homes (Slack and Heumann, 1997). Of the 83.1 million households using gas stoves or ovens for cooking, 7.7 million (9.3%) also used the stove for heating (Slack and Heumann, 1997).

Gas heaters, particularly when unvented or inadequately vented, produce high levels of NO_2. Kodama et al. (2002) examined the associations between secondary heating sources and NO_2 concentrations measured over a 48-h exposure period in the living rooms of homes in Tokyo, Japan. They found much higher NO_2 concentrations during February 1998 and January 1999 in homes with kerosene heaters in both southern (152.6 ppb and 139.7 ppb for 1998 and 1999, respectively) and northern (102.4 and 93.1 ppb for 1998 and 1999, respectively) areas of Tokyo compared to homes with electric heaters (30.8 and 31.1 for the southern and 37.2 and 31.6 for northern areas, 1998 and 1999, respectively).

In a study by Garrett et al. (1999) of 78 homes in Latrobe Valley, Australia, the two highest indoor NO_2 levels recorded in the study were 129 ppb for the only home with an unvented gas heater and 69 ppb for a home with a vented gas heater. Levels of NO_2 in the kitchens and living rooms of homes with a vented gas heater (mean = 6.9 ppb in living room, 7.3 ppb in kitchen, n = 15) were comparable to homes with gas stoves (mean = 6.7 ppb in living room, 8.0 ppb in kitchen, n = 15) (Table AX3.4-1). These concentrations include results from all seasons combined, so the levels are somewhat lower than those found by Triche et al. (2005) for winter monitoring periods only.

Triche et al. (2005) also found high levels of NO_2 in homes with gas space heaters, although information on whether the appliance was vented or unvented was not available. Data from this study were analyzed in more detail and are shown in Table AX3.4-2. The median NO_2 concentration in the 6 homes with gas space heater use during monitoring periods with no gas stove use was 15.3 ppb; a similar incremental increase in total NO_2 levels was noted for homes with gas space heater use during periods when gas stoves were also used (Median = 36.6 ppb) compared to homes where gas stoves were used but no secondary heating sources were present (Median = 22.7 ppb) (Table AX3.4-2).

Shima and Adachi (1998) examined associations between household characteristics, outdoor NO_2, and indoor NO_2 in 950 homes during the heating season (640 with unvented and 310 vented heaters) and 905 homes during the non-heating season in urban, suburban, and rural areas of Japan. While no information is provided on gas stove use, the authors note that nearly all homes in Japan have gas stoves, though relatively few have pilot lights. During the heating season, geometric mean NO_2 levels in homes with unvented heaters (66.4 ppb) are about three times higher than in homes with vented heaters (20.6 ppb). In the non-heating season, the mean levels were lower at only 13.8 ppb, suggesting a contribution from vented heaters as well.

In multivariate analyses, Gilbert et al. (2006) found that gas and mixed/other heating systems were significantly associated with NO_2 levels, adjusting for presence of gas stoves and air exchange rates in 96 homes in Quebec City, Canada during the winter/early spring period. Many homes with gas space heaters also have gas stoves, and the contribution from multiple sources is much higher than from any single source alone (Garrett et al., 1999). In the Garrett et al. (1999) study, homes were classified into five categories: no indoor source (n = 15), gas stove only (n = 15), gas heater only (n = 14), smoker in the household only (n = 7), and multiple sources (n = 29). Homes with multiple sources had much higher NO_2 concentrations homes with either a gas stove only or gas heater only Table 3.4-1.

Kerosene heaters are also important contributors to indoor NO_2 levels. Leaderer et al. (1986) enrolled a cohort of kerosene heater users identified from local kerosene dealers and a cohort of controls systematically chosen from the same neighborhoods with each matched pair treated as a sampling unit (i.e., sampled at the same randomly assigned time period). A total of 302 homes were monitored for at least one two-week period. While outdoor concentrations never exceeded 100 $\mu g/m^3$ (53 ppb), approximately 5% of homes with either no gas but 1 kerosene heater or gas but no kerosene heater had levels exceeding 53 ppb. Between 17%-33% of homes with both gas and kerosene heater(s) exceeded this limit, while nearly one quarter of homes with no gas, but two or more kerosene heaters had these levels.

Data from Triche et al. (2005) (Table AX3.4-2) also indicated increased levels of NO_2 for kerosene heater homes during monitoring periods with no gas stove use (Median = 18.9 ppb) compared to homes with no sources (Median = 6.3 ppb), which is similar to levels found in homes using gas space heaters (Median = 15.3 ppb). However, these NO_2 concentrations are of the same magnitude as those in homes with gas stove use (Median = 17.2 ppb).

Data are available for unvented gas hot water heaters from a number of studies conducted in the Netherlands. Results summarized by Brauer et al. (2002) indicate that concentrations of NO_2 in homes with unvented gas hot water heaters were 10 to 21 ppb higher than in homes with vented heaters, which in turn, had NO_2 concentrations 7.5 to 38 ppb higher than homes without gas hot water heaters.

The contribution from combustion of biomass fuels has not been studied as extensively as that from gas. A main conclusion from the previous AQCD was that properly vented wood stoves and fireplaces would make only minor contributions to indoor NO_2 levels. Several studies conclude that use of wood burning appliances does not increase indoor NO_2 concentrations. Levesque et al. (2001) examined the effects of wood-burning appliances on indoor NO_2 concentrations in 49 homes in Quebec City, Canada. The homes, which had no other combustion source, were sampled for 24 h while the wood-burning appliance was being used. No significant differences in mean NO_2 levels were found in homes with (6.6 + 3.6 ppb) and without (8.8 + 1.9 ppb) a wood-burning appliance. Data from Triche et al. (2005) confirm these findings (Table AX3.4-2). Homes with wood burning sources had comparable NO_2 concentrations to homes without other secondary heating sources, with (Median = 5.9 ppb) and without (Median = 16.7 ppb) gas stove use.

Data are available for unvented gas hot water heaters from a number of studies conducted in the Netherlands. Results summarized by Brauer et al. (2002) indicate that concentrations of NO_2 in homes with unvented gas hot water heaters were 10 to 21 ppb higher than in homes with vented heaters, which in turn, had NO_2 concentrations 7.5 to 38 ppb higher than homes without gas hot water heaters.

As can be seen from the tables, shorter-term average concentrations tend to be much higher than longer term averages. However, as Triche et al. (2005) point out, the 90th percentile concentrations can be

substantially greater than the medians, even for two week long samples. This finding illustrates the high variability found among homes.

In 10% of homes with fireplaces studied by Triche et al. (2005), NO_2 concentrations were greater than or equal to 80 ppb, or about twice the level found in homes with no indoor combustion source (see Table AX3.4-2). In a study of students living in Copenhagen, Sørensen et al. (2005) found that personal exposures to NO_2 were significantly associated with time exposed to burning candles in addition to other sources. However, they did not provide data for concentrations in spaces in which candles were burned. Results of studies relating NO_2 concentrations and exposures to environmental tobacco smoke (ETS) have been mixed. Several studies found positive associations between NO_2 levels and ETS (e.g., Linaker et al., 1996); Farrow et al., 1997; Alm et al., 1998; Levy et al., 1998a; Monn et al., 1998; Cyrys et al., 2000; Lee et al., 2000; García-Algar et al., 2004) whereas others have not (e.g., Hackney et al., 1992; Kawamoto et al., 1993). In a study of 57 homes in Brisbane, Australia (Lee et al., 2000), levels of NO_2 were higher in homes with smokers present (14.9 ± 7.7 ppb) than without smokers (9.9 ± 5.0 ppb). However, these concentrations did not account for presence of a gas range (n = 18 of 57 homes had a gas range). Garrett et al. (1999) found that smoking in the home increased levels of NO_2 in the winter, but not in the summer when windows tended to be opened. In a study of students living in Copenhagen, Sørensen et al. (2005) did not find a significant association between ETS and personal exposures to NO_2. However, they found that burning candles was a significant prediction of bedroom levels of NO_2.

AX3.4.1.3. Other Indoor Environments

Indoor ice skating rinks have been cited as environments containing high levels of NO_2 when fuel powered ice resurfacing machines are used especially without ventilation. As part of a three year study, Levy et al. (1998b) measured NO_2 concentrations at 2 locations at the outside of the ice surface in 19 skating rinks in the Boston area over 3 winters. Although different passive samplers were used in the first year (Palmes tubes, 7 day sampling time) and in years 2 and 3 (Yanagisawa badges, 1 day working hours) of the study, consistently high mean NO_2 concentrations were associated with the use of propane fueled resurfacers (248 ppb in the first year and 206 ppb in the following years) and gasoline fueled resurfacers (54 ppb in the first year and 132 ppb in the following years) than with electric resurfacers (30 ppb in the first year and 37 ppb in the following years). During all three years of the study peak NO_2 concentrations were several times higher in the rinks with propane and gasoline fueled resurfacers than the values given above. A number of earlier studies have also indicated NO_2 concentrations of this order and even higher (Paulozzi et al., 1993; Berglund et al., 1994; Lee et al., 1994; Brauer et al., 1997). In these studies peak averages were in the range of a few ppm.

AX3.4.2. Reactions of NO_2 in Indoor Air

Chemistry in indoor settings can be both a source and a sink for NO_2 (Weschler and Shields, 1997). NO_2 is produced by reactions of NO with ozone or peroxy radicals, while NO_2 is removed by gas phase reactions with ozone and assorted free radicals and by surface promoted hydrolysis and reduction reactions. The concentration of indoor NO_2 also affects the decomposition of peroxyacyl nitrates. Each of these processes is discussed in the following paragraphs. They are important not only because they influence the indoor NO_2 concentrations to which humans are exposed, but also because certain products of indoor chemistry may confound attempts to examine associations between NO_2 and health.

Indoor NO can be oxidized to NO_2 by reaction with ozone or peroxy radicals; the latter are generated by indoor air chemistry involving O_3 and unsaturated hydrocarbons such as terpenes found in air fresheners and other household products (Sarwar et al., 2002a,b; Nazaroff and Weschler, 2004; Carslaw, 2007). The rate coefficient for the reaction

$$O_3 + NO \rightarrow NO_2 + O_2 \qquad \text{(AX3.4-1)}$$

at room temperature (298 K) is 1.9×10^{-14} cm^3/molec-sec or 4.67 H 10^{-4} ppb^{-1} s^{-1} (Jet Propulsion Laboratory, 2006). At an indoor O_3 concentration of 10 ppb and an indoor NO concentration that is significantly less than that of O_3, the half-life of NO is 2.5 min. This reaction is sufficiently fast to compete with even relatively fast air exchange rates. Hence, the amount of NO_2 produced from NO tends to be limited by the amount of O_3 available. The indoor concentrations of NO and O_3 are negatively correlated; significant concentrations of NO can only accumulate when small amounts of O_3 are present and vice versa (Weschler et al., 1994).

The rapid reaction between NO and O_3 also means that humans, themselves, can be indirect sources of NO_2 in the rooms they occupy. Exhaled human breath contains NO that is generated endogenously (Gustafsson et al., 1991). For a typical adult male, the average nasal NO output is 325 nL min^{-1} or 23.9 μg h^{-1} (Imada et al., 1996). If ozone is present in the indoor air, some or all of these exhaled NO molecules will be oxidized to NO_2. To put this source in perspective, consider the example of an adult male in a 30 m^3 room ventilated at 1 air change per hour (h^{-1}) with outdoor air. The steady-state concentration of NO in the room as a consequence of NO in exhaled breath is 0.80 μg/m^3 or 0.65 ppb if none of the NO were to be oxidized. However, assuming a meaningful concentration of ozone in the ventilation air (>5 ppb), most of this NO is oxidized to NO_2 before it is exhausted from the room. In this scenario, the single human occupant is indirectly a source for 0.65 ppb of NO_2 in the surrounding air. At higher occupant densities, lower air exchange rates and elevated concentrations of O_3 in the ventilation air, human exhaled breath could contribute as much as 5 ppb to the total concentration of indoor NO_2.

The reaction of NO_2 with ozone produces nitrate radicals (NO_3):

$$O_3 + NO_2 \rightarrow NO_3 + O_2 \qquad \text{(AX3.4-2)}$$

The second order rate-constant for this reaction at room temperature (298 K) is 3.2×10^{-17} cm^3/molec-sec or 7.9 x 10^{-7} ppb^{-1} s^{-1} (Jet Propulsion Labatory, 2006). For indoor concentrations of 20 ppb and 30 ppb for O_3 and NO_2, respectively, the production rate of NO_3 radicals is 1.7 ppb h^{-1}. This reaction is strongly temperature dependent, an important consideration given the variability of indoor temperatures with time of day and season. The nitrate radical is photolytically unstable (Finlayson-Pitts and Pitts, 2000). As a consequence, it rapidly decomposes outdoors during daylight hours. Indoors, absent direct sunlight, nitrate radical concentrations may approach those measured during nighttime hours outdoors. To date there have been no indoor measurements of the concentration of nitrate radicals in indoor settings. Modeling studies by Nazaroff and Cass (1986), Weschler et al. (1992), Sarwar et al. (2002b), and Carslaw (2007) estimate indoor nitrate radical concentrations in the range of 0.01 to 5 ppt, depending on the indoor levels of O_3 and NO_2.

The nitrate radical and NO_2 are in equilibrium with dinitrogen pentoxide (N_2O_5):

$$NO_3 + NO_2 \leftrightarrow N_2O_5 \qquad \text{(AX3.4-3)}$$

Dinitrogen pentoxide reacts with water to form nitric acid. The gas phase reaction with water is too slow (Sverdrup et al., 1987) to compete with air exchange rates in most indoor environments. Due to mass transport limits on the rate at which N_2O_5 is transported to indoor surfaces, reactions of N_2O_5 with

water sorbed to indoor surfaces are much slower than gas phase reactions between nitrate radicals and commonly occurring indoor alkenes.

Once formed, NO_3 radicals can oxidize organic compounds by either adding to an unsaturated carbon bond or abstracting a hydrogen atom (Wayne et al., 1991). In certain indoor settings, the nitrate radical may be a more important indoor oxidant than either ozone or the hydroxyl radical. Table 8 in Nazaroff and Weschler (2004) illustrates this point. Assuming indoor concentrations of 20 ppb, 5×10^{-6} ppb, and 0.001 ppb for O_3, OH, and NO_3, respectively, the pseudo first-order rate constants for reactions of most terpenoids are larger for reactions with NO_3 than for reactions with either O_3 or OH. For example, for the stated conditions, the half-lives of d-limonene and α-pinene are roughly three times shorter as a consequence of reaction with NO_3 versus reaction with O_3. The products of reactions between NO_3 and various organic compounds include nitric acid, aldehydes, ketones, organic acids and organic nitrates; these have been summarized by Wayne et al. (1991). Nitrate radicals and the products of nitrate radical chemistry may be meaningful confounders in NO_2 exposure studies.

Reactions between NO_2 and various free radicals can be an indoor source of organo-nitrates, analogous to the chain-terminating reactions observed in photochemical smog (Weschler and Shields, 1997). Additionally, based on laboratory measurements and measurements in outdoor air (Finlayson-Pitts and Pitts, 2000), one would anticipate that NO_2, in the presence of trace amounts of HNO_3, can react with PAHs sorbed on indoor surfaces to produce mono- and dinitro-PAHs.

As noted in the ISA, Section 2.2, HONO occurs in the atmosphere mainly via multiphase processes involving NO_2. HONO is observed to form on surfaces containing partially oxidized aromatic structures (Stemmler et al., 2006) and on soot (Ammann et al., 1998). Indoors, surface-to-volume ratios are much larger than outdoors, and the surface mediated hydrolysis of NO_2 is a major indoor source of HONO (Brauer et al., 1990; Febo and Perrino, 1991; Spicer et al., 1993; Brauer et al., 1993; Spengler et al., 1993; Wainman et al., 2001; Lee et al., 2002). Spicer et al. (1993) made measurements in a test house that demonstrated HONO formation as a consequence of NO_2 surface reactions and postulated the following mechanism to explain their observations.

$$2NO_2 + H_2O/surface \rightarrow HONO(aq) + H^+ + NO_3^- \quad \text{(AX3.4-4)}$$

$$HONO(aq) \leftrightarrow HONO(g) \quad \text{(AX3.4-5)}$$

In a series of chamber studies, Brauer et al. (1993) reported HONO formation as a consequence of NO_2 surface reactions and further reported that HONO production increased with increasing relative humidity. Wainman et al. (2001) confirmed Brauer's findings regarding the influence of relative humidity. They also found that NO_2 removal and concomitant HONO production was greater on synthetic carpet surfaces compared to Teflon surfaces, and that the affinity of a surface for water influences HONO's desorption from that surface. Lee et al. (2002) measured HONO and NO_2 concentrations in 119 Southern California homes. Average indoor HONO levels were about 6 times larger than outdoors (4.6 ppb versus 0.8 ppb). Indoor HONO concentrations averaged 17% of indoor NO_2 concentrations, and the two were strongly correlated. Indoor HONO levels were higher in homes with humidifiers compared to homes without humidifiers (5.9 ppb versus 2.6 ppb). This last observation is consistent with the studies of Brauer et al. (1993) and Wainman et al. (2001) indicating that the production rate of HONO from NO_2/surface reactions is larger at higher relative humidities. Based on detailed laboratory studies, the hydrolysis mechanism, Equations AX3.4-4 and AX3.4-5, have been refined. Finlayson-Pitts et al. (2003) hypothesize that the symmetric form of the NO_2 dimer is sorbed on surfaces, isomerizes to the asymmetric dimer which auto ionizes to $NO^+NO_3^-$; the latter then reacts with water to form HONO and surface adsorbed HNO_3. FTIR-based analyses indicate that the surface adsorbed HNO_3 exists as both undissociated nitric acid-water complexes, $(HNO_3)_X(H_2O)_Y$, and nitrate ion-water complexes,

$(NO_3^-)_X(H_2O)_Y$ (Dubowski et al., 2004, Ramazan et al., 2006). Such adsorbed species may serve as oxidizing agents for organic compounds sorbed to these same surfaces (Ramazan et al., 2006).

HONO and much smaller amounts of HNO_3 are also emitted directly by combustion by gas appliances and can infiltrate from outdoors. Spicer et al. (1993) compared the measured increase in HONO in a test house resulting from direct emissions of HONO from a gas range and from production by surface reactions of NO_2. They found that emissions from the gas range could account for about 84% of the measured increase in HONO and surface reactions for 11% in an experiment that lasted several hours. An equilibrium between adsorption of HONO from the gas range (or other indoor combustion sources) and HONO produced by surface reactions (see Equation AX3.4-5) also determines the relative importance of these processes in producing HONO in indoor air. In a study of Southern CA homes (Lee et al., 2002), indoor levels of NO_2 and HONO were positively associated with the presence of gas ranges.

It is known that the photolysis of HONO (g) in the atmosphere (outdoors) is a major source of the hydroxyl radical (OH). Given high indoor HONO concentrations and the presence of lighting (sun light penetrating windows, incandescent lights, fluorescent lights), the photolysis of indoor HONO may be a meaningful source of indoor hydroxyl radical, under favorable reaction conditions. Given the large suite of man-made chemicals present indoors at elevated concentrations, indoor free radicals (e.g., OH and NO_3) can initiate and drive a complex series of indoor chemical reactions.

NO_2 can also be reduced on certain surfaces, forming NO. Spicer et al. (1989) found that as much as 15% of the NO_2 removed on the surfaces of masonite, ceiling tile, plywood, plasterboard, bricks, polyester carpet, wool carpet, acrylic carpet and oak paneling was re-emitted as NO. Weschler and Shields (1996) found that the amount of NO_2 removed by charcoal building filters were almost equally matched by the amount of NO subsequently emitted by these same filters.

Spicer et al. (1993) determined the 1st order rate constants for removal of several NO_Y components by reaction with indoor surfaces. They found lifetimes (e-folding times) of about half an hour for HNO_3, an hour for NO_2, and hours for NO and HONO. Thus the latter two components, if generated indoors are more likely to be lost to the indoor environment through exchange with outside air than by removal on indoor surfaces. However, HONO is in equilibrium with the nitrite ion (NO_2^-) in aqueous surface films

$$HONO(aq) \leftrightarrow H^+ + NO_2^- \qquad \text{(AX3.4-6)}$$

Ozone oxidation of nitrite ions in such films is a potential sink for indoor HONO (Lee et al., 2002). Jakobi and Fabian (1997) measured indoor and outdoor concentrations of ozone and peroxyacetyl nitrate (PAN) in several offices, private residences, a classroom, a gymnasium and a car. They found that indoor levels of PAN were 70% to 90% outdoor levels, and that PAN's indoor half-life ranged from 0.5 to 1 h. The primary indoor removal process is thermal decomposition.

$$CH_3C(O)OONO_2 \leftrightarrow CH_3C(O)OO + NO_2 \qquad \text{(AX3.4-7)}$$

As is indicated by Equation AX3.4-7, PAN is in equilibrium with the peroxylacetyl radical and NO_2. Hence, the indoor concentration of NO_2 affects the thermal decomposition of PAN and, analogously, other peroxyacyl nitrates. Peroxylalkyl radicals rapidly oxidize NO to NO_2, so the indoor concentration of NO also influences the thermal decomposition of PAN type species (Finlayson-Pitts and Pitts, 2000).

Reactions between hydroxyl radicals and aldehydes in the presence of NO_2 can lead to the formation of peroxyacyl nitrates. Weschler and Shields (1997) have speculated that such chemistry may sometimes occur indoors. For example, the requisite conditions for the formation of the highly irritating compound peroxybenzoyl nitrate may occur when ozone, certain terpenes, styrene and NO_2 are present simultaneously at low air exchange rates. This relatively common indoor mixture of pollutants produces hydroxyl radicals and benzaldehyde, which can subsequently react as noted above. In her detailed model

of indoor chemistry, Carslaw (2007) explores the indoor formation of PAN-type species (see Figure 2 in the cited reference).

Recent work indicates that indoor NO_2 also can affect the formation of secondary organic aerosols (SOA) resulting from the reaction of O_3 with terpenes such as d-limonene and α-pinene (Nøjgaard et al., 2006). At concentrations of 50 ppb for O_3 and the terpenes, NO_2 decreased the formation of SOA compared to the levels formed in the absence of NO_2. The effect was more pronounced for SOA derived from α-pinene than d-limonene, and at lower NO_2 concentrations, appears to be explained by the O_3 loss resulting from its reaction with NO_2. The resultant nitrate radicals apparently are not as efficient at producing SOA as the lost O_3.

Nitro-PAHs have been found in indoor environments (Mumford et al., 1991; Wilson et al., 1991). The major indoor sources of nitro-PAHs include cooking, wood burning, and the use of kerosene heater (World Health Organization (WHO), 2003). It is also likely that nitro-PAHs outdoors can infiltrate indoors. One of the potential sources of nitro-PAHs indoors, which has not been characterized, is reactions via indoor chemistry. The reactions of PAHs with OH and NO_3 may occur in indoor environments. Although no direct measurements of OH or NO_3 in indoor environments, OH and NO_3 can be formed via indoor chemistry and may present at significant levels indoors (Nazaroff and Cass 1986, Sarwar et al., 2002a; Carslaw, 2007). Concentrations of $\sim 10^{-6}$ ppb for OH and 0.01-5 ppt of NO_3 have been predicted through indoor chemical reactions (Nazaroff and Cass 1986, Sarwar et al., 2002a, Carslaw, 2007), depending on the indoor levels of O_3, alkenes, and NO_2. Observation of secondary organic aerosols (SOA) formation in a simulated indoor environment also suggested that $\sim 10^{-5}$ ppb steady-state OH radicals were generated from the reactions of O_3 with terpenes (Fan et al., 2003). PAHs are common indoor air pollutants (Chuang et al., 1991; Naumova et al., 2002), and the concentrations of some PAHs indoors are often higher than outdoors (Naumova et al., 2002). Therefore, the reactions of OH and NO_3 with PAHs may occur at rates comparable to air exchange rates to form nitro-PAHs indoors. In addition, the reactions of NO_3 with PAHs may be more significant indoors than outdoors because indoor NO_3 is more stable due to the low uv in indoor environments. Given the high surface areas available indoors, the formation of nitro-PAHs via surface reactions of PAHs with nitrating species may be more important compared to heterogeneous reactions outdoors.

In summary, indoor chemistry can meaningfully alter the indoor concentration of NO_2. Indoor exposure to NO_2 may be accompanied by indoor exposures to nitrate radicals, organic nitrates, and nitro-PAHs.

AX3.5. Personal Exposure

AX3.5.1. Personal Exposure in the Residential Indoor Environment

People spend most of their daily time in a residential indoor environment (Klepeis et al., 2001). NO_2 found in an indoor environment originates both indoor and outdoors; and therefore, people in an indoor environment are exposed to both indoor and outdoor generated NO_2. In a residential indoor environment, personal exposure concentration equals the residential indoor concentration (if there is no personal cloud) which can be broken down into two parts: indoor generation and ambient contribution.

The relationship between personal NO_2 exposure and ambient NO_2 can be modified by the indoor environment in the following ways: (1) during the infiltration processes, ambient NO_2 can be lost through penetration and decay (chemical and physical processes) in the indoor environment, and therefore, the concentration of indoor NO_2 of ambient origin is not the ambient NO_2 concentration but the product of the ambient NO_2 concentration and the infiltration factor (F_{inf}, or α if people spend 100% of their time indoors); (2) in an indoor environment, people are exposed to not only ambient generated NO_2 but also indoor generated NO_2, and therefore, the relative contribution of ambient and nonambient NO_2 to

personal exposure depends not only on the ambient NO_2 concentration but also on the infiltration factor (attenuation factor) and the indoor source contribution; (3) the strength of the association between personal exposure to NO_2 of ambient origin and ambient NO_2 concentration is determined by the temporal and spatial variation in the infiltration factor; and (4) the strength of the association between personal total exposure and ambient NO_2 is determined by the variation in the indoor source contribution and the variation in the infiltration factor. Below, factors affecting infiltration factor and the indoor source contribution will be evaluated, and the key issues, such as those mentioned above, related to ambient contribution to personal NO_2 exposure will be addressed.

Due to the lack of specific P, k, and a for study homes or a study population, instead of using P, k, and a, alternative approaches to obtain the infiltration factor are the ratio of indoor/outdoor NO_2 and the regression based RCS model. The basic rationale of the RCS model has been introduced in the previous section. Without indoor sources, the ratio between indoor NO_2 and outdoor NO_2 should be always less than or equal to 1. If the indoor to outdoor ratio is larger than 1 (after adjusting for measurement error), we can surely say that indoor sources exist. However, if an indoor/outdoor ratio is less than one, we cannot exclude the effect of indoor sources; otherwise, the infiltration factor would be overestimated. In order to use an indoor/outdoor ratio as the infiltration factor, study designs and questionnaires must be carefully read, and only the ratio for homes without identified indoor sources can be used as an indicator of infiltration factor. The population averaged infiltration factor is the slope of the regression line of indoor concentration vs. outdoor concentration. The reliability of the regression slope is dependent upon the sample size and how to deal with the outlier effects. Indoor/outdoor ratios and the regression slopes are summarized in Table AX3.5-1a. Most of the infiltration factors range from 0.4 to 0.7. Similarly, α ranges from 0.3 to 0.61 (Table AX3.5-1b). Theoretically, infiltration factor is a function of air exchange rate, which has been indicated by season in some studies. However, most studies do not report the infiltration factor by season, and therefore, a seasonal trend of infiltration factor could not be observed in Table AX3.5-1a.

As mentioned before, personal NO_2 exposure is not only affected by air infiltrating from outdoors but also by indoor sources. The NO_2 residential indoor sources reported are gas cooking, gas heating, kerosene heating, smoking and burning candles (Schwab et al., 1994; Spengler et al., 1994; Nakai et al., 1995; Lee et al., 1996; Linaker et al., 1996; Cotterill and Kingham, 1997; Farrow et al., 1997; Kawamoto et al., 1997; Lee, 1997; Raaschou-Nielsen et al., 1997; Alm et al., 1998; Levy et al., 1998a; Monn et al., 1998; Garrett et al., 1999; Chao, 2001; Dennekamp et al., 2001; Dutton et al., 2001; Emenius et al., 2003; Kodama et al., 2002; Lee et al., 2002; Mosqueron et al., 2002; García-Algar et al., 2003; García-Algar et al., 2004; Lai et al., 2004; Lee et al., 2004; Yang et al., 2004; Zota et al., 2005; Sørensen et al., 2005; Lai et al., 2006). Spengler et al. (1994) reported that personal exposures in homes with gas range with pilot light were 15 ppb higher than those in homes with electric range, and it was 5 ppb higher in homes with gas range without pilot light than homes with electric ranges. Schwab et al. (1994) reported that homes with gas stove with pilot light had higher indoor NO_2 concentrations (peak concentrations ranging from 30 to 35 ppb), followed by homes with gas stove without a pilot light (peak concentrations ranging from 15 to 20 ppb) and then homes with electric stoves (peak concentrations ranging from 5 to 10 ppb). In an international study, Levy et al., (1998a) reported that the use of a gas stove in the home was the dominant activity influencing NO_2 concentrations with a 67% increase in mean personal NO_2 exposure and an increase in indoor-outdoor ratios from 0.7 to 1.2. Smoking was found to be another significant factor elevating personal and indoor NO_2 exposure. Monn et al. (1998) reported that during 1-week integrated measurement, smoking contributed 1 ppb more NO_2 exposure. Alm et al. (1998) reported that one-week integrated personal NO_2 exposure for smokers and nonsmokers were 12.9 ppb and 10.7 ppb, respectively. Zota et al. (2005) observed that smoking was not a significant indoor source. However, the authors pointed out that the effect of smoking might have been overwhelmed by the presence of the gas stove. Sørensen et al. (2005) found that burning candles were significantly associated with the elevation of indoor NO_2 ($p = 0.02$). NO_2 concentration in an indoor environment affected by the indoor sources is not homogeneously distributed: NO_2 concentration is usually the highest in the kitchen, lowest in the bedroom and the concentration in a living room is in between as shown in Table AX3.5-2. The

concentration differences between a bedroom and a kitchen ranged from 1 ppb to 28 ppb, and largest difference occurred in homes with gas stoves.

The concentration differences in indoor microenvironments reflect the differences in personal exposure in those microenvironments, which is related to personal activities and behaviors. People who spend more time in a kitchen are expected to have higher NO_2 exposures. Also, in most exposure studies, integrated indoor and personal exposures were measured from 2 days to 2 weeks with passive samplers. Therefore, the peak exposure concentration could be even higher.

Indoor source contributions to indoor and personal exposure are determined by indoor source strength (S), house volume (V), air exchange rate (a) and the NO_2 decay rate (k) in an indoor environment, through the equation $C_{nona} = S/[V(a + k)]$. Indoor source strength has been summarized in a previous section (Indoor sources and concentrations of nitrogen oxides). With a mass balance approach, Yang et al. (2004) reported that the source strength for electric range was 3.5 ppb/h, 11.5 ppb/h for gas range in Brisbane, and 23.4 ppb/h for gas range in Seoul. The age of house and the house type are associated with ventilation, indoor sources, and house volume. As mentioned before, Lee et al. (1996) reported that the building type was significantly associated with volume of dwelling unit, and air exchange rate. Garrett et al. (1999) reported that older houses were associated with higher nitrogen dioxide levels, possibly as a result of older and less efficient appliances in older homes or due to smaller rooms.

In theory, personal exposure of ambient origin should be at least as much as the indoor NO_2 of ambient origin in that people spend time in either an indoor or an outdoor environment. However, it was shown in the previous part (Table AX3.5-3a and Table AX3.5-3b) that the ambient contribution to population exposure ranged from 20% to 50% based on four studies (Rojas-Bracho et al., 2002; Monn et al., 1998; Levy et al., 1998a; Spengler et al., 1994); and results here show that the ambient contribution to indoor NO_2 is around 70% with a wide range from 40 to 90% based on another four studies (Mosqueron et al., 2002; Yang et al., 2004; Kulkarni et al., 2002; Monn et al., 1998). It is not clear at present why the indoor NO_2 of ambient origin is larger than the personal NO_2 exposure of ambient origin.

The strength of the indoor, outdoor and personal NO_2 associations (r_p: Pearson correlation coefficient; r_s: Spearman correlation coefficient; and R^2: coefficient of determination) are summarized in Table AX3.5-4. The strength of the associations are determined by the variation in F_{inf} (P, k, and a) and indoor source contributions from home to home and from day to day. In general, the correlation between indoor and outdoor NO_2 ranges from poor to good (r_p: 0.06 to 0.86). When we break down the correlation coefficient by season and indoor sources, it is obvious that the association between indoor and outdoor NO_2 is stronger during spring and summer but weaker during wintertime, and the association is stronger for homes without indoor sources but weaker for homes with strong indoor sources. Mukala et al. (2000) reported an r_p of 0.86 for the indoor and outdoor NO_2 association during the spring and it reduced to 0.54 during the winter. Spengler et al. (1994) reported that the associations were 0.66 and 0.75 (r_p) for homes with and without air conditioning system, respectively. Emenius et al. (2003) reported that the association between indoor and outdoor NO_2 was 0.69 (r_p) for homes without smoker and without gas stove using, but the association was not significant for homes with gas stove or smokers. Yang et al. (2004) reported that the indoor and outdoor NO_2 association was 0.70 (R^2) for homes with electric ranges, and was 0.57 (R^2) for homes with gas ranges. In other words, personal exposure to ambient NO_2 in a residential indoor environment will be modified the least when the air exchange rate is high and the indoor source contribution is not significant. Considering the large spatial variation in ambient NO_2 concentrations and the relative sparseness of ambient NO_2 monitors, the associations between indoor and outdoor concentrations are usually stronger than the associations between indoor and ambient concentrations. As shown in Table AX3.5-4, a stronger personal vs. residential indoor relationship than the personal vs. outdoor relationship has been reported by most studies (Lai et al., 2004; Monn et al., 1998, Levy et al., 1998a; Spengler et al., 1994; Kousa et al., 2001; Linaker et al., 1996), which is a reminder that personal exposure to ambient NO_2 mostly happens in the residential indoor environment. It should be pointed out that the association between indoor, outdoor and personal NO_2 and the relative contributions of indoor and outdoor NO_2 to indoor and personal exposures were calculated based on time integrated indoor, outdoor and personal NO_2 measurement with passive samplers and an average measurement time of a

couple of days to two weeks. In most studies, an equilibrium condition was assumed and the effects of dynamics on the indoor, outdoor, and personal association were not evaluated, which could result in missing the peak exposure and obscuring the real short-term outdoor contribution to indoor and personal exposure. For example, the NO_2 concentrations at locations close to busy streets in urban environments may vary drastically with time. If the measurement is carried out during a non-steady-state period, the indoor/outdoor concentration ratio may indicate either a too low relative importance of indoor sources (if the outdoor concentration is in an increasing phase) or a too high relative importance of indoor resources (if the outdoor concentration is in a decreasing phase). The lower the air exchange rate, the greater the error due to the effects of transients (Ekberg, 1996).

AX3.5.1.1. School and Office

Workplaces (schools and offices) are the places where people spend most of their time after homes in an urban area. The location, indoor sources as well as the ventilation pattern of schools and offices could be different from people's homes. Therefore, personal exposure patterns in schools and offices could be different from exposure patterns at home. However, NO_2 concentrations in schools and offices have only been measured in only a few exposure studies.

Most studies reported the personal exposure levels were lower than or equal to office NO_2 levels. Lai et al. (2004) reported that a cohort in Oxford spent 17.5% of their daily time in offices, and mean personal total NO_2 exposure was 15 ppb and 16.8 ppb for mean office concentrations. Mosqueron et al. (2002) reported Paris office worker exposure levels and no significant difference was found between personal total exposure (22.8 ppb) and NO_2 concentrations in office (23.5 ppb). Personal exposures in schools were studied in Helsinki, Southampton and Southern California. Alm et al. (1998) and Mukala et al. (2000) reported the personal exposure levels in Helsinki for pre-school children. They reported that median personal exposures were lower than the median NO_2 concentrations measured inside the day care center (13.1 ppb for personal exposure versus 18.8 ppb for inside day-care center for downtown winter; 14.7 ppb versus 24.1 ppb for downtown spring; 8.9 ppb versus 15.2 ppb for suburban winter; and 8.9 ppb versus 13.1 ppb for suburban spring). Linaker et al. (1996) found that the geometric mean of school children exposures (18.8 ppb) was higher than geometric means of the NO_2 concentrations in classrooms (8.4 to 14.1 ppb) in a study of children's exposures to NO_2 in Southampton, UK. A similar exposure pattern was found by Linn et al. (1996) during the Southern California school children exposure study. During the study, personal exposure (22 ppb) was higher than the NO_2 concentration inside school (16 ppb). NO_2 concentration in school/office is determined by ambient NO_2 level, local traffic sources, floor height and building ventilation pattern. Partti-Pellinen et al. (2000) studied the effect of ventilation and air filtration systems on indoor air quality in a children's day-car center in Finland. Without filtration, NO_X and PM generated by nearby motor traffic penetrated readily indoors. With chemical filtration, 50 to 70% of nitrogen oxides could be removed. The authors suggested that the possible adverse health effects of nitrogen oxides and particles indoors could be countered by efficient filtration. Mosqueron et al. (2002) reported 24% of variations in in-office NO_2 concentrations could be explained by outdoor NO_2 levels (18%), and floor height (6%) and an inverse relation was observed between in-office concentration and floor height. Alm et al. (1998) attributed the high NO_2 concentration in the day-care center to its close to major roads. Obviously, the relative scale of personal exposure and school concentration also depends on personal activities outside schools and workplaces.

Significant associations between personal exposure and workplace concentrations were reported by most studies. Mosqueron et al. (2002) reported office NO_2 was a significant predictor of personal exposure and 15% of the personal exposure was explained by time weighted office NO_2 concentrations. Alm et al. (1998) reported population NO_2 exposures were highly correlated with the NO_2 levels inside the day-care centers ($R^2 = 0.88$). However, Lai et al. (2004) reported a nonsignificant Pearson correlation coefficient (0.15) between personal exposure and workplace indoor concentration and the authors suggested that the strong residential indoor sources and long time indoors obscured the personal versus

office relationship. Personal total exposure is a function of NO_2 concentrations in different indoor and outdoor microenvironments and how long a person stays in that microenvironment. The large variation of NO_2 exposure in some microenvironments could obscure the association between personal exposure and NO_2 concentrations in other microenvironments.

AX3.5.1.2. Exposure Reconstruction

Personal exposure has been evaluated in each major microenvironment, where either the NO_2 concentration is high or people spend most of their daily time. Personal exposure could be reasonably reconstructed if we know the NO_2 concentration in each microenvironment and the duration of personal exposure in each microenvironment. Levy et al., (1998a) reconstructed personal exposures measured in an international study with a time-weighted average exposure model. The personal exposure was reconstructed based on the measured NO_2 concentrations in residential indoor, residential outdoor, and workplace microenvironments, and the time people spent in those environments. The mean measured personal NO_2 exposure was 28.8 ppb and a mean of estimated NO_2 exposure was 27.2 ppb. The Spearman correlation coefficient between personal measured exposure and reconstructed exposure was 0.81. The same approach was applied by Kousa et al. (2001) to reconstruct the personal exposures in the EXPOLIS study. A correlation coefficient of 0.86 was observed for the association between measured NO_2 exposure and reconstructed NO_2 exposure (data were log-transformed), and the slope and the intercept were 0.90 and 0.22 respectively for the reconstructed exposure vs. measured exposure. In the two studies mentioned above, NO_2 exposure during commuting was not measured. Probably that is part of the reason why reconstructed NO_2 exposure was lower than the measured NO_2 exposure.

AX3.5.2. Factors Affecting Exposure

Physically, personal exposure levels are determined by the time people spend in each microenvironment and the NO_2 concentrations in each microenvironment, which is determined by source emission strength, air exchange rate, penetration coefficient, the NO_2 decay rate and the volume of the microenvironment. Any factors that can influence the above physical parameters can modify the level of personal exposure. The indoor, outdoor and personal NO_2 levels on each stratum of those factors will be summarized.

Those factors can be classified in to the following categories: (1) factors associated with environmental conditions, such as weather and season; (2) factors associated with dwelling conditions, such as the location of the house and ventilation system; (3) factors associated with indoor sources, such as the type of range and the fuel type; (4) factors associated with personal activities, such as the time spent on cooking or commuting; (5) socioeconomic status, such as the level of education and the income level; and (6) demographic factors, such as age and gender.

Most studies addressed the influences of dwelling condition and indoor sources on indoor and personal exposures. A few studies explored the impacts of environmental factors and personal activities on personal exposures. Indoor and personal exposures have rarely been stratified by socioeconomic and demographic factors. Indoor, outdoor, and personal exposure levels are presented in Table AX3.5-5, stratified by environmental factors, dwelling conditions, indoor sources, and personal activities factors. The effects of socioeconomic and demographic factors on the indoor, outdoor, and personal levels are summarized in Table AX3.5-6.

Season is an environmental factor affecting both indoor and outdoor levels, and thus personal NO_2 levels. During the wintertime, the mixing height is usually lower than during the summer, and therefore concentrations of many primary pollutants are higher than in the summer. Wintertime is also a heating season, which usually leads to higher indoor source emissions and lower air exchange rates. Therefore, a higher indoor NO_2 concentration can be expected during the winter. For most cases, the differences of indoor or personal NO_2 exposure between the heating and non-heating season are within several ppb, but

sometimes the difference could be close to 20 ppb (Zota et al., 2005). Other environmental factors include day of the week (weekday versus weekend), and the wind direction.

The dwelling conditions are also associated with indoor, outdoor, and personal NO_2 levels. A house located in an urban center or close to a major road is expected to have higher outdoor and indoor NO_2 levels, and the differences in NO_2 exposures are often within 20 ppb based on passive sampler monitoring. The age of the house, house type, and window type can affect the ventilation of dwelling units, and sometimes the type of heating and cooking appliances in a house. Range and fuel type are the indoor source factors discussed the most in the literature. It is common to see differences larger than 10 ppb in indoor and personal NO_2 exposures between a gas range home (especially gas range with pilot light) and an electric range home. Sometimes the differences could be as high as 40 ppb. For peak short-term exposures, the difference could reach 100 ppb.

The level of personal exposure is dependent upon the time a person spends in each microenvironment. Kawamoto et al. (1997), Levy et al. (1998a), and Chao and Law (2000) clearly showed that personal NO_2 exposure increases with time spent cooking or commuting.

There are inconsistencies in the literature. For example, smoking is found to be a significant factor in some studies but not in others, and the same can be said for proximity to a major road. For another example, a higher indoor NO_2 level could be found in a rural home rather than in an urban home, although most studies found the opposite. Part of the reason is that exposure indicators function together, as a multidimensional parameter space, on indoor and personal exposures. They are not independent of each other. Unfortunately, studies have rarely been conducted to understand the associations between these exposure indicators and to use the study findings to explain indoor and personal NO_2 exposures.

More effort put on exposure indicator studies should help in finding better surrogate measurements for personal exposures. Although misclassifying exposures in epidemiological studies is almost inevitable, and it is unlikely that the personal exposures of all subjects will be measured, a better knowledge of the effects of exposure indicators on personal exposure will help reduce exposure errors in exposure and epidemiological studies and help interpret those study results.

AX3.5.3. Associations between HONO and NO_2

Spicer et al. (1993) and Wainman et al. (2000) suggested the presence of a strong indoor source of HONO from heterogeneous reactions involving NO_2 and water films on indoor surfaces. Hence, combustion appliances are sources for exposures to both NO_2 exposure and HNO_2. Epidemiological studies of NO_2 health effects should consequently consider the potential confounding effects of NO_2 and vice versa.

Jarvis et al. (2005) reported the indoor nitrous acid and lung function in adults as part of European Community Respiratory Health Survey (ECRHS). Indoor HONO and indoor and outdoor NO_2 were measured. Indoor NO_2 were correlated with HONO ($r_p = 0.77$) but no significant association of indoor NO_2 with symptoms or lung function was observed.

Lee et al. (2002) studied the nitrous acid, nitrogen dioxide, and ozone concentrations in residential environments. The authors found that indoor NO_2 was significantly correlated with HONO ($r_p = 0.511$).

As shown above, very few studies showed the relationship between personal NO_2 exposure and other pollutant exposures. In general, personal NO_2 was moderately correlated with $PM_{2.5}$ and CO. Due to the lack of personal HONO exposure data, indoor HONO was used as an indicator for personal exposure, and current studies showed that indoor HONO was correlated with indoor NO_2 with high correlation coefficients, which suggested that the collect ion of HONO exposure data would help interpret adverse health outcome in the NO_2 health risk assessment.

AX3.6. Modeling Human Exposures to NO_2

AX3.6.1. Exposure Models

Predictive (or prognostic) exposure modeling studies[1], specifically focusing on NO_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, NO_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 NO_2 can be classified and differentiated based upon a variety of attributes. For example, exposure models can be classified as:

- models of potential (typically maximum) outdoor exposure versus models of actual exposures (the latter including locally modified microenvironmental exposures, both outdoor and indoor),
- Population Based Exposure Models (PBEM) versus Individual Based Exposure Models (IBEM),
- deterministic versus probabilistic (or statistical) exposure models,
- observation-driven versus mechanistic air quality models.

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

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

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

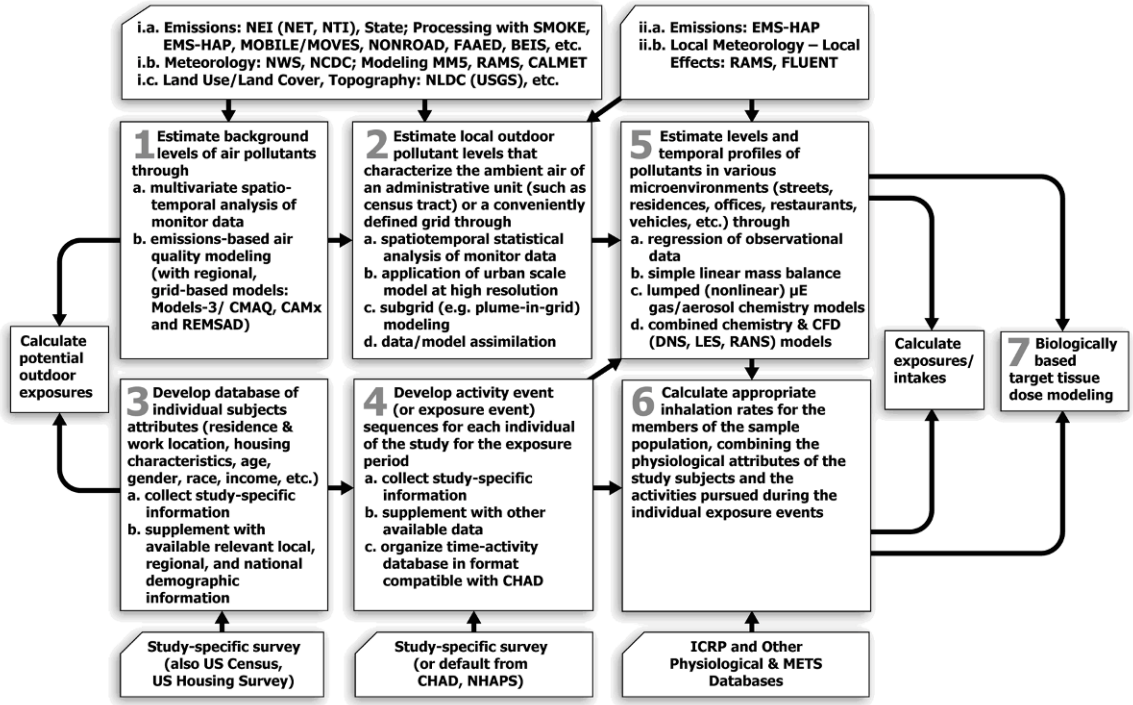
Third, the process of modeling human exposures to photochemical pollutants (traditionally focused on ozone) is very often identified explicitly with population-based modeling, while models describing the specific mechanisms affecting the exposure of an actual individual (at specific locations) to an 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

[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.

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 NO_2 (and related pollutants) will in general require seven steps (or components, as some of them do not have to be performed in sequence) that are listed below. This list represents a composite based on approaches and frameworks described in the literature over the last twenty-five years (Ott, 1982; Ott, 1985; Lioy, 1990; U.S. Environmental Protection Agency, 1992; Georgopoulos and Lioy, 1994; U.S. Environmental Protection Agency, 1997; Buck et al., 2003; Price et al., 2003; Georgopoulos et al., 2005; WHO, 2005; U.S. Environmental Protection Agency, 2006a; Georgopoulos and Lioy, 2006) as well on the structure of various inhalation exposure models (NEM/pNEM, HAPEM, SHEDS, REHEX, EDMAS, MENTOR, ORAMUS, APEX, AIRPEX, AIRQUIS, etc., to be discussed in the following section) that have been used in the past or in current studies to specifically assess inhalation exposures. Figure AX3.6-1, adapted from Georgopoulos et al. (2005), schematically depicts the sequence of steps involved that are summarized here (and further discussed in the following sub-sections).



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

Figure AX3.6-1. 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.

6. Estimation of the background d or ambient levels of both NO_2 and related photochemical 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.

7. Estimation of local outdoor pollutant levels of both NO_2 and related photochemical 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.

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

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

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

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

a. study-specific information, if available

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

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

10. Estimation of levels and temporal profiles of both NO_2 and related photochemical pollutants in various outdoor and indoor microenvironments such as street canyons, roadway intersections, parks, residences, offices, restaurants, vehicles, etc. This is done through either:

a. linear regression of available observational data sets,

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

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

d. detailed combined chemistry and Computational Fluid Dynamics modeling.

11. 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.

12. Calculation of target tissue dose through biologically based modeling estimation (specifically, respiratory dosimetry modeling in the case of NO_2 and related reactive photochemical pollutants) if sufficient information is available.

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

In fact, only relatively recently comprehensive, predictive, inhalation exposure modeling studies for ozone, PM, and various air toxics, have attempted to address/incorporate all the components of the general framework described here. In practice, the majority of past exposure modeling studies have either incorporated only subsets of these components or treated some of them in a simplified manner, often focusing on the importance of specific factors affecting exposure. Of course, depending on the objective

of a particular modeling study, implementation of only a limited number of steps may be necessary. For example, in a regulatory setting, when comparing the relative effectiveness of emission control strategies, the focus can be on expected changes in ambient levels (corresponding to those observed at NAAQS monitors) in relation to the density of nearby populations. The outdoor levels of pollutants, in conjunction with basic demographic information, can thus be used to calculate upper bounds of population exposures associated with ambient air (as opposed to total exposures that would include contributions from indoor sources) useful in comparing alternative control strategies. Though the metrics derived would not be quantitative indicators of actual human exposures, they can serve as surrogates of population exposures associated with outdoor air, and thus aid in regulatory decision making concerning pollutant standards and in studying the efficacy of emission control strategies. This approach has been used in studies performing comparative evaluations of regional and local emissions reduction strategies in the eastern United States (e.g., Purushothaman and Georgopoulos, 1997; Georgopoulos et al., 1997a; Foley et al., 2003).

AX3.6.1.1. Population Exposure Models

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

The NEM/pNEM, SHEDS, APEX, and MENTOR-1A (MENTOR for One-Atmosphere studies) families of models provide exposure estimates defined by concentration and breathing rate for each individual exposure event, and then average these estimates over periods typically ranging from one 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 NO_2, and could provide useful information for enhancing related health assessments. More specifically, regarding the consideration of population demographics and activity patterns:

1. pNEM divides the population of interest into representative cohorts based on the combinations of demographic characteristics (age, gender, and employment), home/work district, residential cooking fuel and replicate number, and then assigns activity diary record from CHAD (Consolidated Human Activities Database) to each cohort according to demographic characteristic, season, day-type (weekday/weekend) and temperature.
2. HAPEM6 divides the population of interest into demographic groups based on age, gender and race, and then for each demographic group/day-type (weekday/weekend) combination,

select multiple activity patterns randomly (with replacement) from CHAD and combine them to find the averaged annual time allocations for group members in each census tract for different day types.

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

The essential attributes of the pNEM, HAPEM, APEX, SHEDS, and MENTOR-1A models are summarized in Table AX3.6-1.

The conceptual approach originated by the SHEDS models was modified and expanded for use in the development of MENTOR-1A (Modeling Environment for Total Risk – One Atmosphere). Flexibility was incorporated into this modeling system, such as the option of including detailed indoor chemistry of the O_3-NO_X system and other relevant microenvironmental processes, and providing interactive linking with CHAD for consistent definition of population characteristics and activity events (Georgopoulos et al., 2005).

NEM/pNEM implementations have been extensively applied to ozone studies in the 1980s and 1990s. The historical evolution of the pNEM family of models of OAQPS started with the introduction of the first NEM model in the 1980's (Biller et al., 1981). The first such implementations of pNEM/O_3 in the 1980's 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-1990's, Environmental Protection Agency applied updated versions of pNEM/O_3 to three different population groups in selected cities: (1) the general population of urban residents, (2) outdoor workers, and (3) children who tend to spend more time outdoors than the average child. This version of pNEM/O_3 used a revised probabilistic mass balance model to determine ozone concentrations over one-h periods in indoor and in-vehicle microenvironments (Johnson, 2001).

In recent years, pNEM has been replaced by (or "evolved to") the Air Pollution Exposure Model (APEX). APEX differs from earlier pNEM models in that the probabilistic features of the model are incorporated into a Monte Carlo framework (Langstaff, 2007; U.S. Environmental Protection Agency, 2006b,c). Like SHEDS and MENTOR-1A, instead of dividing the population-of-interest into a set of cohorts, APEX generates individuals as if they were being randomly sampled from the population. APEX provides each generated individual with a demographic profile that specifies values for all parameters required by the model. The values are selected from distributions and databases that are specific to the age, gender, and other specifications stated in the demographic profile. Environmental Protection Agency has applied APEX to the study of exposures to ozone and other criteria pollutants; APEX can be modified and used for the estimation of NO_2 exposures, if required.

Reconfiguration of APEX for use with NO_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 probablistic capabilities of APEX, distributions of model input parameters should be used wherever possible.

AX3.6.1.2. Ambient Concentrations of NO_2 and Related Air Pollutants

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

Spatio-temporal distributions of pollutant concentrations, such as ozone, PM, and various air toxics have alternatively been obtained using methods of the Spatio-Temporal Random Field (STRF) theory (Christakos and Vyas, 1998a,b). The STRF approach interpolates monitor data in both space and time simultaneously. This method can thus analyze information on temporal trends, which cannot be incorporated directly in purely spatial interpolation methods such as standard kriging. Furthermore, the STRF method can optimize the use of data that 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).

Subgrid spatial variability is a major issue with respect to characterizing local concentrations of NO_2. Indeed, the fast rates of the reactions involving the O_3-NO_X system result in significant concentration gradients in the vicinity of sources of NO_X. These gradients are not resolved directly by currently operational grid photochemical air quality simulation models (PAQSMs) such as CMAQ and CAMx. However, both these models include a plume-in-grid. (PinG) option (AER, 2004; Emery and Yarwood, 2005; Gillani and Godowitch, 1999; U.S. Environmental Protection Agency, 2006d) that can be used for large point NO_X sources (such as smokestacks). Nevertheless, PinG formulations typically will resolve gradients in upper atmospheric layers and thus are not necessarily relevant to human exposure calculations, which are affected by gradients caused by a multiplicity of smaller ground level or near ground level combustion sources such as motor vehicles.

Currently PAQSMs are typically applied with horizontal resolutions of 36 km, 12 km, and 4 km and a surface layer thickness that is typically of the order of 30 m. Though computationally it is possible to increase the resolution of these simulations, there are critical limits that reflect assumptions inherent in the governing equations for both (a) the fluid mechanical processes embodied in the meteorological models (e.g., typically MM5 and RAMS) that provide the inputs for the PAQSMs, and (b) the dispersion processes which become more complex at fine scales (see, e.g., Georgopoulos and Seinfeld, 1989) and

thus cannot be described by simple formulations (such as constant dispersion coefficients) when the horizontal resolutions is 2 km or finer.

Application of PAQSMs to urban domains is further complicated by urban topography, the urban heat island, etc. It is beyond the scope, however, of the present discussion, to overview the various issues relevant to urban fluid dynamics and related transport/fate processes of contaminants. However, the issue of modeling subgrid atmospheric dispersion phenomena within complex urban areas in a consistent manner is a very active research area. Reviews of relevant issues and of available approaches for modeling urban fluid mechanics and dispersion can be found in, e.g., Fernando et al. (2001) and Britter and Hanna (2003).

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

AX3.6.1.3. Characterization of Microenvironmental Concentrations

Concentrations in microenvironments that can represent either outdoor or indoor settings when individuals come in contact with the contaminant of concern (e.g., NO_2) can be characterized. This process can involve modeling of various local sources and sinks, and interrelationships between ambient and microenvironmental concentration levels. Three general approaches have been used in the past to model microenvironmental concentrations:

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

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

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

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

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

Examples of the above are discussed next, specifically for outdoor and for indoor microenvironments.

AX3.6.1.4. Characterization of Outdoor Microenvironments Concentrations

Empirical regression analyses have been used in some studies to relate specific outdoor locations - that can be interpreted as generalized types of exposure microenvironments - to spatial variability of NO_2 concentrations. For example, Gilbert et al. (2005) in May 2003 measured NO_2 for 14 consecutive days at 67 sites across Montreal, Canada. Concentrations ranged from 4.9 to 21.2 ppb (median 11.8 ppb), and they used linear regression analysis to assess the association between logarithmic values of NO_2 concentrations and land-use variables via a geographic information system. In univariate analyses, NO_2 was negatively associated with the area of open space and positively associated with traffic count on nearest highway, the length of highways within any radius from 100 to 750 m, the length of major roads within 750 m, and population density within 2000 m. Industrial land-use and the length of minor roads showed no association with NO_2. In multiple regression analyses, distance from the nearest highway, traffic count on the nearest highway, length of highways and major roads within 100 m, and population density showed significant associations with NO_2. The authors of that study point out the value of using land-use regression modeling to assign exposures in large-scale epidemiologic studies. Similar analyses have been performed in a predictive setting by Sahsuvaroglu et al. (2006) for Hamilton, Ontario, Canada.

The category of parameterized mass balance models for outdoor microenvironments includes various local roadway, intersection, and street canyon models. For example, Fraigneau et al. (1995) developed a simple model to account for fast nitrogen oxide – ozone reaction/dispersion in the vicinity of a motorway. Venegas and Mazzeo (2004) applied a combination of simple point and area source analytical plume models to characterize NO_2 concentration patterns in Buenos Aires, Argentina, which they used for a simplified (potential) population exposure study. ROADWAY-2 (Rao, 2002), is another near-highway pollutant dispersion model that incorporates vehicle wake parameterizations derived from canopy flow theory and wind tunnel measurements. The atmospheric velocity and turbulence fields are adjusted to account for velocity-deficit and turbulence production in vehicle wakes and a turbulent kinetic energy closure model of the atmospheric boundary layer is used to derive the mean velocity, temperature, and turbulence profiles from input meteorological data.

In parameterized street canyon models, typically, concentrations of exhaust gases are calculated using a combination of a plume model for the direct contribution and a box model for the recirculating part of the pollutants in the street. Parameterization of flow and dispersion conditions in these models is usually deduced from analysis of experimental data and model tests that considered different street configurations and various meteorological conditions. An example of a current model that belongs in the parameterized mass balance category is the Danish Operational Street Pollution Model (OSPM) (Berkowicz, 2002), which updates earlier formulations of street canyon models such as STREET of Johnson et al. (1973) and CPBM (Canyon Plume-Box Model) of Yamartino and Weigand (1986). A variation of this simple approach is the model of Proyou et al. (1998), which uses a three-layer photochemical box model to represent a street canyon.

A variety of CFD based street canyon models have been developed in recent years (see, e.g., the series of International Conferences on Harmonization - http://www.harmo.org), employing various

alternatives for closure of the turbulent transport equations. A review and intercomparison of five of these models (CHENSI, CHENSI-2, MIMO, MISKAM, TASCflow) vis-a-vis field data from a street canyon in Hannover, Germany can be found in the articles by Sahm et al. (2002) and by Ketzel et al. (2002).

These complex localized models could be useful for improving population exposure model estimates by calculating pollutant concentrations at the microenvironmental level. Lack of input parameter data and parameter variation across the modeling domain (spatial and temporal) contributes to uncertainty in microenvironmental concentrations calculated by exposure models. In such cases, parameterized mass balance models could provide outdoor concentration values for estimating exposure. If infiltration factors are known, these concentrations could also be used to estimate indoor exposures.

AX3.6.1.5. Characterization of Indoor Microenvironments

Numerous indoor air quality modeling studies have been reported in the literature; however, depending on the modeling scenario, only few of them address (and typically only a limited subset of) physical and chemical processes that affect photochemical oxidants indoors (Nazaroff and Cass, 1986; Hayes, 1989, 1991; Freijer and Bloemen, 2000).

It is beyond the scope of the present discussion to review in detail the current status of indoor air modeling. Existing indoor air concentration models indeed are available as a wide range of (a) empirical regression relationships, (b) parameterized mass balance models (that can be either single-zone—that is, single well-mixed room—or multi-zone models), and (c) CFD formulations. Recent overviews of this area can be found in Milner et al. (2005), who focus, in particular, on the issue of entrainment from outdoor sources, and in Teshome and Haghighat, (2004), who focus on different formulations of zonal models and on how they compare with more complex CFD models.

Few indoor air models have considered detailed nonlinear chemistry, which, however, can have a significant effect on the indoor air quality, especially in the presence of strong indoor sources (e.g., gas stores and kerosene heaters, in the case of NO_2). Indeed, the need for more comprehensive models that can take into account the complex, multiphase processes that affect indoor concentrations of interacting gas phase pollutants and particulate matter has been recognized and a number of formulations have appeared in recent years. For example, the Exposure and Dose Modeling and Analysis System (EDMAS) (Georgopoulos et al., 1997c) included an indoor model with detailed gas-phase atmospheric chemistry to estimate indoor concentrations resulting from penetration and reaction of ambient pollutants. This indoor model was dynamically coupled with (a) the outdoor photochemical air quality models UAM-IV and UAM-V, which provided the gas-phase composition of influent air; and (b) with a physiologically based uptake and dosimetry model. Subsequent work (Isukapalli et al., 1999) expanded the approach of the EDMAS model to incorporate alternative representations of gas-phase chemistry as well as multiphase photochemistry and gas/aerosol interactions. The microenvironmental model corresponding to this more general formulation is mathematically represented by the following equation, when an assumption of uniform mixing is used for each component (e.g., individual room) of the indoor environment. Sarwar et al. (2001) presented a more comprehensive modeling study of the gas phase aspects of ozone indoor chemistry focusing on the impact of different factors (such as outdoor ozone, indoor emissions, ventilation rates, etc.) on the levels of indoor hydroxyl radicals (OH), which in turn are expected to control the rate of formation of secondary toxicants indoors.

$$V_i \frac{dC_i^{(m)}}{dt} = \sum_{i=1}^{N} Q_{ji} C_j^{(m)} - \sum_{j=1}^{N} Q_{ji} C_j^{(m)} + S_i^{(m)} + \sum_{j=1}^{N} K_{ji}^{(m)} a_{ji} (C_{ji}^{*(m)} - C_i^{(m)}) + R_i^{(m)} \quad \text{(AX3.6-1)}$$

where,

V_i = volume of compartment (m^3)

C_i = concentration of species in compartment (mol/m^3)

K_{ij} = mass transfer coefficient from compartment (m/h)

a_{ij} = interfacial air exchange area between compartments (m^2)

C_{ij} = concentration in compartment *i* in equilibrium with concentration in j (mol/m^3)

Q_{ij} = volumetric flow rate from compartment *i* to j (m^3/h)

R_i = rate of formation of species in compartment *i* (gmol/h)

and,

$$S_i \begin{cases} S_{i,\ emis} - S_{i,\ depos} - S_{i,condens} & ;for\ gases \\ S_{i,\ emis} - S_{i,\ depos} + S_{i,resusp} + S_{i,condens} + S_{i,nucl} + S_{i,coag;\ for\ PM} \end{cases} \quad \text{(AX3.6 -2)}$$

More recent work (Sørensen and Weschler, 2002) has coupled CFD calculations with gas-phase atmospheric chemistry mechanisms to account for the impact of nonideal flow mixing (and associated concentration gradients) within a room on the indoor spatial distribution of ozone and other secondary pollutants. This work has identified potential limitations associated with the assumption of uniform mixing in indoor microenvironments when calculating personal exposures.

A recent indoor air model that specifically focuses on NO_2 (along with CO, PM_{10}, and $PM_{2.5}$ is INDAIR (Dimitroulopoulou et al., 2006). The INDAIR model considers three interconnected residential microenvironments: kitchen, lounge, and bedroom. Removal processes are lumped together and quantified via an apparent deposition velocity. Specifically, a loss rate of 0.99 ± 0.19/h (Yamanaka, 1984), is used in this model corresponding to a mean deposition velocity of 1.2 H 10^{-4} m/s. The sources of NO_2 considered in INDAIR are from gas stove cooking and from cigarette smoking, but only the former contributes significantly to indoor NO_2 levels, based on available model parameterizations.

Estimation of NO_2 emission rates from gas cooking utilized the following empirical information: (a) NO_X emission rate equal to 0.125 g kWh^{-1} (Wooders, 1994); (b) an assumption that NO_2 represents 25% of the total NO_X emissions and (c) gas consumption per household in cooking equal to 5–7 kWh/day, assuming 1 h cooking per day. By multiplying the estimates in (a), (b), and (c) together, NO_2 gas cooking emission rates were calculated to be in the range 0.16 to 0.22 g/h, with a uniform distribution.

In a range of simulations performed with INDAIR for houses in the UK, it was found that the predicted maximum 1-h mean concentrations in the kitchen were increased, compared to no-source simulations, by a factor of 10 for NO_2 (30 for PM_{10} and 15 for $PM_{2.5}$) and were higher in winter than in summer. Cooking activity in the kitchen resulted in significantly elevated 24-h mean concentrations of NO_2, PM_{10}, and $PM_{2.5}$ in the lounge, as well as the kitchen, while there was a relatively small effect in the bedroom, which was not connected directly to the kitchen in the model structure (i.e., the direct internal air exchange rate was zero).

A very wide range of predictions was derived from the INDAIR simulations. The 95th percentile concentrations were typically 50% higher than mean concentrations during periods of average concentration, and up to 100% higher than mean concentrations during concentration peaks, which were associated with cooking emissions. There was approximately a factor of 2 variation in concentrations, and all modeled concentrations were below those outdoors. The effect of cooking was to shift the distribution to the right, but the degree of variation was not greatly increased. This may reflect the fact that for the fixed emission scenarios that were used, the additional variation in emission rates was small compared to that of other factors such as deposition rate and air exchange rate. In this scenario, modeled concentrations in the lounge all remained below those outdoors, but a proportion of kitchens (16%) had modeled values above the outdoor concentration. For the gas-cooking scenario, indoor/outdoor ratios for NO_2 ranged from 0.5 to 0.8 for the bedroom, 0.7 to 1.6 for the lounge and 0.9 to 3.6 for the kitchen. According to Dimitrolopoulou et al. (2006), these results were broadly consistent with indoor/outdoor

ratios reported for the UK. Modeled peak concentrations associated with gas cooking, of about 300 ppb in the kitchen and 100 ppb in the lounge, were also consistent with results from UK studies.

AX3.6.1.6. Characterization of Activity Events

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

AX3.6.1.7. Characterization of Inhalation Intake and Uptake

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

McCurdy (1997a,b, 2000) has recommended that the ventilation rate should be estimated as a function of energy expenditure rate. The energy expended by an individual during a particular activity can be expressed as EE = (MET)(RMR) in which EE is the average energy expenditure rate (kcal/min) 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). 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.

Finally, in order to relate intake to dose delivered to the lungs, it is important to take into account the processes affecting uptake following inhalation intake of NO_2, in a biologically based dosimetry

modeling framework. As a reactive gas, NO_2 participates in transformation reactions in the lung epithelial lining fluid, and products of these reactions are thought to be responsible for toxic effects (Postlethwait et., 1991), although kinetic modeling of these reactions has not been performed. Dosimetry models indicate that deposition varies spatially within the lung and that this spatial variation is dependent on ventilation rate (Miller et al., 1982; Overton and Graham, 1995). Controlled exposure studies found that fractional uptake of NO_2 increases with exercises and ventilation rate (e.g., Bauer et al., 1986), making activities with high MET values important for quantifying total NO_2 exposure. Further discussion of NO_2 dosimetry modeling is provided in Section 4.2.

AX3.6.1.8. Issues to be Addressed in Future Exposure Modeling Efforts

An issue that should be mentioned in closing is that of evaluating comprehensive prognostic exposure modeling studies, for either individuals or populations, with field data. Although databases that would be adequate for performing a comprehensive evaluation are not expected to be available any time soon, there have been a number of studies, reviewed in earlier sections of this Chapter, that can be used to start building the necessary information base. Some of these studies report field observations of personal, indoor, and outdoor ozone 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 NO_2 studies that include the following, should be taken into account and be addressed by future research efforts:

- Ambient photochemical modeling systems are not optimized for estimating NO_2 at a local scale.
- Subgrid scale modeling (LES, RANS, DNS) is needed to properly characterize effects of nonhomogeneous mixing (i.e., of spatial subgrid variability) on fast nonlinear chemical transformations; the outcomes of this characterization then should be incorporated in simpler models, appropriate for use in conjunction with exposure modeling systems.
- Microenvironmental modeling efforts need to balance mechanistic detail and usability by developing:
    - — A simplified but adequate indoor chemistry mechanism for NO_2 and related oxidants,
    - — Databases of realistic distributions of indoor NO_2 source magnitudes and activities,
    - — Flexible, multi-zonal models of indoor residential and occupational microenvironments.

Existing prognostic modeling systems for inhalation exposure can in principle be directly applied to, or adapted for, NO_2 studies; APEX, SHEDS, and MENTOR-1A are candidates. However, such applications would be constrained by data limitations such as ambient characterization at the local scale and by lack of quantitative information for indoor sources and sinks.

Table AX3.2-1. NO_X and NO_Y concentrations at regional background sites in the Eastern United States. Concentrations are given in ppb.

	SHENANDOAH NP, VA	HARVARD FOREST, MA
NO		
Winter	0.39-2.2 [1]	—
Summer	0.12-0.28	—
NO_X	—	—
Winter	—	1-15
Summer	—	0.4-1.2
NO_Y	—	—
Winter	2.7-8.6	4.4 [2]
Summer	2.3-5.7	2.7 [2]

1 Ranges represent 1σ limits. 2 Values represent medians.

Table AX3.3-1. Passive samplers used in NO_2 measurements.

PASSIVE SAMPLER		DIMENSION (DIFFUSION LENGTH × CROSS-SECTIONAL AREA)	ABSORBENT	ANALYTICAL METHOD	SAMPLING RATE		REFERENCE
					MANUFACTURER	EXPERIMENT	
Palmes tube		7.1cm × 0.71cm2	Triethanolamine	Spectrophotometry	N.A.	0.92 cm^3/min	Palmes et al. (1976)
Gradko sampler		7.1cm × 0.93cm2	Triethanolamine	Spectrophotometry	1.2 cm^3/min	1.212 cm^3/min	Plaisance et al.(2004) Gradko (2007)
Passam sampler	Short	0.74cm × 0.75cm2	Triethanolamine	Spectrophotometry	15.5 cm^3/min	N.A.	Passam (2007)
	Long				0.854 cm^3/min	0.833 cm^3/min	
Analyst™		2.54cm × 3.27cm2	Active charcoal	Gas chromatography	N.A.	12.3 cm^3/min	De Santis et al. (2002)
Yanagisawa badge		1.0cm × 20cm2	Triethanolamine	Spectrophotometry	N.A.	N.R.	Yanagisawa and Nishimura (1982)
Ogawa sampler		0.6cm × 0.79cm2	Triethanolamine	Spectrophotometry	N.A.	16.2 cm^3/min	Ogawa & Company (1998a) Gerboles et al. (2006a)
IVL sampler		1.0cm × 3.14cm2	Potassium iodide & sodium arsenite	Spectrophotometry	N.A.	29 cm^3/min	Ferm and Svanberg (1998)
Willems badge		0.6cm × 5.31cm2	Triethanolamine-acetone	Spectrophotometry	N.A.	46 cm^3/min	Hagenbjörk-Gustafsson et al. (2002)
Radiello®		1.8cm × 2.0cm2	Triethanolamine	Spectrophotometry	75 cm^3/min	N.R.	Radiello® (2006)
EMD sampler		N.A.	Triethanolamine	Ion chromatography	N.A.	53.4 cm^3/min	Piechocki-Minguy et al. (2006)

*N.A.: not available;

Table AX3.3-2. The performance of sampler/sampling method for NO_2 measurements in the air.

TYPE	SAMPLER		OPTIMAL DURATION OF SAMPLING	CONCENTRATION RANGE	DETECTION LIMIT	COMMENT
Active sampling	Impinger method		2-24 h	10 – 400 ppb	0.2 ppb	
	Chemiluminescence		Continuous	0.5 – 1000 ppb	0.05 ppb	SD < 5%
	Personal monitor		Real-time	0.1 – 50 ppm	0.1 ppm	Accuracy ± 5%
Passive sampling	Palmes tube		1-4 wks	10 - 100 ppb	10 ppb	
	Gradko sampler		2-4 wks	1.0 – 10,000 ppb	0.5 ppb	Precision ± 5% above 5 ppb
	Passam sampler	Short	8-48 h	5 – 240 μg/m^3	2-5 μg/m^3	Uncertainty ~ 27% at 80 μg/m^3
		Long	1-4 wks	1 – 200 μg/m^3	0.64 μg/m^3	Uncertainty ~ 25% at 20-40 μg/m^3
	Analyst™		1-3 mos	24 – 1,237 μg/m^3	100 μg/m^3	Accuracy ± 5%; Precision within 3%
	Yanagisawa badge		1-14 days	NR	3.0 ppb	
	Ogawa sampler		24-168 h	0 – 3,600 ppb	2.3 ppb	
	IVL sampler		1 mo +	0.1 – 400 μg/m^3	0.1 μg/m^3	SD ~ 4%
	Willems badge		2-8 h & 1-7 days	2.0 – 150 μg/m^3	2 μg/m^3	Uncertainty ~ 24%; RSD 22%
	Radiello®		1-24 h & 1-7 days	1.0 – 496 ppb	1.0 ppb	Uncertainty ~ 12%
	EMD sampler		1-24 h	NR	11 μg/m^3	Uncertainty ~ 28%

Table AX3.4-1. NO_2 concentrations (ppb) in homes in Latrobe Valley, Victoria, Australia.

	LIVING ROOM			KITCHEN		
	Mean ppb	Min ppb	Max ppb	Mean ppb	Min ppb	Max ppb
No source	3.77	< 0.37	9.27	3.82	< 0.37	8.17
Gas stove only	6.70	1.57	18.32	8.01	2.62	24.14
Gas heater only	6.86	2.20	18.06	7.33	2.88	26.23
Smoking only	6.02	0.94	14.61	6.60	1.83	16.44
Multiple sources	14.50	2.25	114.66	10.73	2.62	128.80

Source: Garrett et al. (1999).

Table AX3.4-2. NO_2 concentrations (ppb) in homes in Connecticut.

	NO GAS STOVE USED IN MONITORING PERIOD						YES GAS STOVE USED IN MONITORING PERIOD					
Secondary Heating Source	N	10th	25th	Median	75th	90th	N	10th	25th	Median	75th	90th
None	1018	1.7	3.5	6.3	12.3	28.2	564	8.4	14.5	22.7	33.8	48.1
Gas space heater	6	0.1	9.2	15.3	68	69.6	6	19.5	34.6	36.6	54.8	147.2
Wood burning source	200	1.8	3.6	5.9	12.2	28.2	78	6	9.5	16.7	31.4	58.6
Kerosene heater	159	3.3	7.1	18.9	42.7	88.3	14	0	9.6	17.2	33.6	46.1
GSH + Wood	3	12.6	12.6	80.6	81.9	81.9	5	36.2	44.8	57.1	114.2	156.6
GSH + KH	0	--	--	--	--	--	1	n/a	n/a	147.7	n/a	n/a
Wood + KH	73	1.9	8.2	16.4	35.2	66.8	5	8.9	12.7	17.3	23.5	72.9
GSH + Wood + KH	0	--	--	--	--	--	1	n/a	n/a	107.8	n/a	n/a

Source: Triche et al. (2005).

Table AX3.4-3. NO_2 concentrations near indoor sources – short-term averages.

AVERAGE CONCENTRATION (ppb)	PEAK CONCENTRATION (ppb)	COMMENT	REFERENCE
191 kitchen 195 living room 184 bedroom	375 kitchen 401 living room 421 bedroom	Cooked full meal with use of gas stove and range for 2 h, 20 min; avg conc. is time-weighted over 7 h.	Fortmann et al. (2001)
400 kitchen, living room, bedroom	673 bedroom	Automatic oven cleaning of gas stove. Avgs are over the entire cycle.	Fortmann et al. (2001)
90 (low setting) 350 (med setting) 360 (high setting)	NR	Natural gas unvented fireplace,[1] 2-h-time-weighted avg in main living area of house (177 m^3).	Dutton et al. (2001)
NR	1000	Room concentration with kerosene heater operating for 46 min.	Girman et al. (1982)
NR	1500	Room concentration with gas heater operating for 10 min.	Girman et al. (1982)
180 to 650	NR	Calculated steady-state concentration from specific unvented gas space heaters operating in a 1400 ft^2 house, 1.0 ach.	Girman et al. (1982)

1 Unvented fireplaces are not permitted in many areas such as California.

Table 3.5-1a. Indoor/outdoor ratio and the indoor vs. outdoor regression slope.

STUDY	DESCRIPTION	SEASON	REGRESSION FORMAT OR RATIO	INDOOR CHARACTERISTICS	FINF	COMMENTS
Baxter et al. (2007a)	Location: Boston, MA Subjects: 43 homes (a lower social-economic status population) Time period: May-October (non-heating season), and Dec-Mar (heating season), 2003-2005 Method: indoor and outdoor 3- to 4-day samples of NO_2 were collected simultaneously at each home in both seasons; when possible, 2 consecutive measurements were collected.	Overall study seasons	Residential indoor vs. ambient and indoor source and proximity to traffic	Gas stove usage	0.66–0.79	The overall R^2 was 0.20–0.25.
Baxter et al. (2007b)	Location: Boston, MA Subjects: 43 homes (a lower social-economic status population) Time period: May-Oct (non-heating season), and Dec-Mar (heating season), 2003-2005 Method: indoor and outdoor 3- to 4-day samples of NO_2 were collected simultaneously at each home in both seasons; when possible, 2 consecutive measurements were collected.	Overall study seasons	Residential indoor vs. residential outdoor	Overall homes	0.48	Home with an indoor/outdoor sulfur ratio larger than 0.76 (the median) was defined as a high ventilation home; Home with an indoor/outdoor sulfur ratio less than 0.76 (the median) was defined as a low ventilation home.
				Homes with high ventilation rate	0.56	
				Homes with low ventilation rate	0.47	
			Residential indoor vs. residential outdoor and indoor sources	Overall homes	0.53	The overall R^2 was 0.16.
Mosqueron et al. (2002)	Location: Paris, France Subjects: 62 office workers Time period: Dec 1999 to Sept 2000 Method: 48-h residential indoor, workplace, outdoor, and personal exposure were measured.	Overall study seasons	Residential indoor vs. ambient and using gas cooking	Cooking	0.26 (n = 62)	The overall R^2 was 0.14, and ambient NOR^2R and indoor cooking account accounted for 0.07 each.
			Office indoor vs. ambient and floor height	None	0.56 (n = 62)	The overall R^2 was 0.24, partial R^2 for ambient and floor height were 0.18 and 0.06, respectively.
Lee et al. (1999)	Location: Hong Kong, China Subjects: 14 public places with mechanical ventilation systems, Time period: Oct 1996 to Mar 1997 Method: Teflon bags were used to collect indoor and outdoor NO and NOR2R ring peak hours.	Overall study seasons	Indoor vs. outdoor	—	0.59 (n = 14)	R^2 was 0.59. The slopes for NO and NO_X were 1.11 and 1.04 respectively.
Monn et al. (1997)	Location: Switzerland Subjects: 17 homes across Switzerland Time period: winter 1994 to summer 1995 Method: 48- to 72-h indoor, outdoor, and personal NOR2R were measured.	Overall study seasons	Indoor/outdoor ratio	Without gas cooking	0.4, -0.7 (n = 26)	—

STUDY	DESCRIPTION	SEASON	REGRESSION FORMAT OR RATIO	INDOOR CHARACTERISTICS	FINF	COMMENTS
Lee et al. (1995)	Location: Boston area, MA Subjects: 517 residential homes Time period: Nov 1984 to Oct 1986 Method: 2-wk averaged indoor (kitchen, living room, and bedroom) and outdoor NO_2 were measured.	Summer	Indoor/outdoor ratio	Electric stove homes	0.77 (bedroom) (Sample size was not reported)	Homes with gas stove and gas stove with pilot light have an I/O ratio > 1, but the values were not reported.
Garrett et al. (1999)	Location: Latrobe Valley, Victoria, Australia Subjects: 80 homes Time period: Mar-Apr 1994, and Jan-Feb 1995 Method: 4-day averaged indoor (bedroom, living room, and kitchen) and outdoor NO_2 was monitored.	Overall study seasons	Indoor/outdoor ratio	No major indoor sources (major sources were gas stove, vented gas heater, and smoking)	0.8 (n = 15)	The ratio increased to 1.3, to 1.8, and to 2.2 for homes with one, two and three major indoor sources.
Monn et al. (1998)	Location: Geneva, Basle, Lugano, Aarau, Wald, Payerne, Montana, and Davos (SAPALDIA study, Switzerland) Subjects: 140 subjects Time period: Dec 1993 to Dec 1994 Method: each home was monitored for 3 periods of 1 mo; in the 1st wk of each period, personal, indoor and outdoor levels were measured; for the next 3 wks, only outdoor levels were measured (1-wk averaged measurement).	Overall study seasons	Residential indoor vs. residential outdoor	All homes	0.47 (n = 1544)	R^2 was 0.37.
				Homes without smokers and gas-cooking	0.40 (n = 968)	R^2 was 0.33.
Spengler et al. (1994)	Location: Los Angeles Basin, CA Subjects: probability-based sample, 70 subjects Time period: May 1987 to May 1988 Method: 48-h averaged, in the micro-environmental component, each participant was monitored during each of 8 sampling cycles throughout the yr.	Overall study seasons	Residential indoor vs. residential outdoor	Gas range with pilot light	0.49 (n = 314)	R^2 was 0.44.
				Gas range without pilot light	0.4 (n = 148)	R^2 was 0.39.
				Electric stove	0.4 (n = 170)	R^2 was 0.41.

Table 3.5-1b. Summary of regression models of personal exposure to ambient/outdoor NO_2

STUDY	LOCATION	SEASON	MODEL TYPE	SLOPE (SE)	INTERCEPT / ppb	R^2
Rojas-Bracho et al. (2002)	Location: Santiago, Chile Subjects: 20 children Time period: winters of 1998 and 1999 Method: five, 24-h avg samples on consecutive days for each child.	Winter	Personal vs. outdoor (n = 87)	0.33 (0.05)	7.2	0.27
Alm et al. (1998)	Location: Helsinki, Finland Subjects: 246 children aged 3-6 yrs Time period: winter and spring of 1991 Method: 1-wk averaged sample for each person, 6 consecutive wks in the winter and 7 consecutive wks in the spring.	Winter + Spring	Population vs. outdoor (n = 23)	0.4	4.7	0.86
Monn et al. (1998)	Location: Geneva, Basle, Lugano, Aarau, Wald, Payerne, Montana, and Davos (SAPALDIA study, Switzerland) Subjects: 140 subjects Time period: Dec 1993 to Dec 1994 Method: each home was monitored for 3 periods of 1 mo; in the 1st wk of each period, personal, indoor rand outdoor levels were measured, and in the next 3 consecutive wks, only outdoor levels were measured (1-wk averaged measurement).	All	Personal (all subjects) vs. outdoor (n = 1,494)	0.45	7.2	0.33
			Personal (no smokers and gas cooking) vs. outdoor (n = 943)	0.38	7.2	0.27
Levy et al. (1998b)	Location: 18 cities across 15 countries Subjects: 568 adults Time period: Feb or Mar 1996 Method: One, 48-h avg measurement for each person, all people were measured on the same day.	Winter	Personal vs. outdoor (n = 546)	0.49	14.5	—
Spengler et al. (1994)	Location: Los Angeles Basin Subjects: probability-based sample, 70 subjects Time period: May 1987 to May 1988 Method: in the microenvironmental component of the study, each participant was monitored for 48 h during each of 8 sampling cycles throughout the yr.	All	Personal vs. outdoor	0.56	15.8	0.51
Sørensen et al. (2005)	Location: Copenhagen, Denmark Subjects: 30 subjects (20-33 yrs old) in each measurement campaign Time period: fall 1999, and winter, spring and summer of 2000 Method: four measurement campaigns in 1 yr; each campaign lasted 5 wks with 6 subjects each wk; one 48-h avg NOR2R measurement for each subject.	All	Personal vs. outdoor (n = 73)	0.60 (0.07)	—	—
		(>8 ºC)	Personal vs. outdoor (n = 35)	0.68 (0.09)	—	—
		(<8 ºC)	Personal vs. outdoor (n = 38)	0.32 (0.13)	—	—
Piechocki-	Location: Pooled, Lille (northern France)	All	Personal vs.	0.13	6.0	0.09

STUDY	LOCATION	SEASON	MODEL TYPE	SLOPE (SE)	INTERCEPT / ppb	R^2
Minguy et al. (2006)	Subjects: 13 participants in the first campaign, and 31 participants in the second campaign Time period: winter 2001 (first campaign), and summer 2002 (second campaign) Method: two 24-h sampling periods (one during the workdays and the other during the weekends) for each subject in each campaign; during each sampling period, each subject received four samplers to measure personal exposure in four different microenvironments (home, other indoor environment, transport, and outdoors).	Summer (homes with no major indoor NOR2R sources)	central (Assuming people stayed indoors all the time)	0.86	!9.7	0.61
Sørensen et al. (2005)	Location: Copenhagen Subjects: 30 subjects (20-33 yrs old) in each measurement campaign Time period: fall 1999, and winter, spring and summer of 2000 Method: four measurement campaigns in 1 yr; each campaign lasted 5 wks with 6 subjects each wk; one 48-h avg NOR2R measurement for each subject.	All	Personal vs. central (n = 66)	0.56 (0.09)	—	—
Alm et al. (1998)	Location: Helsinki, Finland Subjects: 246 children aged 3-6 yrs Time period: winter and spring of 1991 Method: 1-wk averaged sample for each person, 6 consecutive wks in the winter and 7 consecutive wks in the spring.	Winter + Spring	Population vs. central (n = 24)	0.3	5.0	0.37
Sarnat et al. (2001)	Location: Baltimore, MD Subjects: 56 seniors, Schoolchildren, and people with COPD Time period: summer of 1998 and winter of 1999 Method: 14 of 56 subjects participated in both sampling seasons; all subjects were monitored for 12 consecutive days (24-h avg sample) in each of the one or two seasons, with the exception of children who were measured for 8 consecutive days during the summer.	Summer	Personal vs. central (n = 225 for 24 subjects)	0.04*	9.5	—
		Winter	Personal vs. central (n = 487 for 45 subjects)	!0.05*	18.2	—
Sarnat et al. (2005)	Location: Boston, MA Subjects: 43 seniors and schoolchildren Time period: summer of 1999 and winter of 2000 Method: Similar study design as Sarnat et al., 2001.	Summer	Personal vs. central (n = 341)	0.19	—	—
		Winter	Personal vs. central (n = 298)	!0.03*	—	—
Sarnat et al. (2006)	Location: Steubenville Subjects: 15 senior subjects Time period: summer and fall of 2000 Method: two consecutive 24-h samples were collected for each subject for each wk, 23 wks total.	Summer	Personal vs. central (n = 122)	0.25 (0.06)	—	0.14

Table AX3.5-2. NO_2 concentrations (ppb) in different rooms.

STUDY	CONDITIONS	OUTDOOR	KITCHEN	LIVING ROOM	BEDROOM	COMMENTS
Topp et al. (2004)	First visit	12.4	—	7.8	7.2	Indoor and outdoor NO_2 concentrations for 777 residential homes in five study areas were measured: Erfurt, Hamburg, Zerbst, Bitterfeld and Hettstedt during two visits (from June 1995 to May 1997, and from April 1996 to Sept 1998). In the study, one-week averaged NO_2 were measured by Palmes tube.
	Second visit	12.5	—	8.0	7.6	
Garrett et al. (1999)	No identified indoor sources	4.7	3.8	3.8	3.0	Garrett (1999) investigated the levels and sources of NO_2 in Australian homes. During the study, four-day averaged NO_2 was monitored using Yanagisawa passive samplers in 80 homes in the Latrobe Valley, Victoria in March-April 1994, and Jan-Feb 1995.
	Gas stove homes	4.7	8.0	6.7	6.3	
	Gas heater homes	4.7	7.3	6.9	5.0	
	Smoking homes	4.7	6.6	6.0	5.7	
	Homes with multiple sources	4.7	10.7	14.5	11.2	
Cotterill and Kingham (1997)	Gas Stove homes	20.9	35.6	17.3	11.5	Three consecutive two-week averaged outdoor, kitchen, living room, and bedroom NO_2 were measured using Palmes tubes in 40 houses in Huddersfield, UK in late 1994. Half the houses were located close to a busy main road and half on residential roads set back and parallel to the main road. The sample was split so that half had gas cookers and half had electric cookers. These subsets were split again so that half had double glazing and half had single glazed windows.
	Electric cooker homes	20.9	9.9	8.9	7.3	
	Gas cooker home with single glazing window	20.9	31.4	16.8	11.0	
	Gas cooker home with double glazing window	20.9	39.8	18.3	12.0	
Zota et al. (2005)	Overall	19	43	36	—	The indoor and outdoor NO_2 concentrations for low-income, urban neighborhoods were measured, where asthma prevalence is high. NO_2 was measured in 77 homes within three Boston public housing developments, using Palmes tubes (two-wk integrated sample) placed in the kitchen, living room, and outdoors. Air exchange rate for each home was also measured.
	Heating season	21	50	43	—	
	Non-heating season	17	33	26	—	
Gallelli et al. (2002)	Overall study	—	24.6	—	13.0	During the study, one-wk integrated indoor (kitchen and bedroom) and personal NO_2 were measured in Genoa, Italy, for 89 subjects with Palmes samplers. Study volunteers included students, workers, and housewives living in three areas of Genoa differing by street traffic and industrial plant location.
	With vent	—	18.1	—	—	
	Without vent	—	30.9	—	—	
Linaker et al. (1996)	Overall study	—	27.2	20.9	—	During the study, one-wk integrated personal, indoor (kitchen, living room), classroom, and playground NO_2 were measured using Palmes tubes for school children in Southampton.
Kodama et al. (2002)	Feb 1998	40, 31.3	81.8	73.5	55.2	The first number in outdoor column was the ambient concentration in the South Area; and the second number is the ambient concentration in the North Area. During the study, personal, indoor (kitchen, living room, bedroom and study room), and outdoor NO_2 were measured for 150 junior high school students with Yanagisawa badges in Tokyo. The investigation was conducted five times seasonally, 3 days each, from February 1998 to January 1999.
	June 1998	38, 28	33.2	28.8	24	
	July 1998	29, 26.7	24.8	21.9	17.4	
	Oct 1998	40, 35	23.5	24.7	18.2	
	Jan 1999	49, 50	70.9	65.8	50.7	
Chao and Law (2000)	Overall study	37.6	31.9	28.2	26.4	Personal and indoor exposures were monitored with passive sampler in Hong Kong for 60 subjects. Twelve of the subjects were selected to conduct more detailed study to examine the behavioral and microenvironmental effects on personal exposure to NO_2.

Table AX3.5-3a. Average ambient and nonambient contributions to population exposure

STUDY	MODEL TYPE	SLOPE (SE)	INTERCEPT / ppb	MEAN OF PERSONAL TOTAL EXPOSURE / ppb	MEAN AMBIENT CONTRIBUTION / ppb	PERCENT AMBIENT CONTRIBUTION %	PERCENT NONAMBIENT CONTRIBUTION %
Rojas-Bracho et al. (2002)	Personal vs. outdoor	0.33 (0.05)	7.2	36.4	7.2	19.8	80.2
Alm et al. (1998)	Personal vs. central	0.3	5.0	—	5.0	—	—
	Personal vs. outdoor	0.4	4.7	—	4.7	—	—
Monn et al. (1998)	Personal (all subjects) vs. outdoor	0.45	7.2	14.1	7.2	51.1	48.9
	Personal (no smokers and gas cooking) vs. outdoor	0.38	7.2	—	7.2	—	—
Levy et al. (1998a)	Personal vs. outdoor	0.49	14.5	28.8	14.5	50.3	49.7
Spengler et al. (1994)	Personal vs. outdoor	0.56	15.8	37.6	15.8	42.0	58.0

Table AX3.5-3b. Indoor and outdoor contributions to indoor concentrations.

STUDY	CONDITION	SLOPE	INTERCEPT	MEAN INDOOR CONCEN-TRATION	MEAN OUTDOOR CONCEN-TRATION	PERCENT OUTDOOR CONTRIBU-TION	PERCENT INDOOR CONTRIBU-TION	INDOOR SOURCE STRENGTH	COMMENTS
Mosqueron et al. (2002)	Overall study	0.258	—	18.4	31.5	44.2	55.8	—	—
Yang et al. (2004)	Brisbane, electric range	0.65	0.8	10.3	—	92.4	7.6	3.5 ppb/h	—
	Brisbane, gas range	0.56	3.0	18.3	—	83.5	16.5	11.5 ppb/ h	—
	Seoul, gas range	0.58	4.8	33.4	40.4	85.7	14.3	23.4 ppb/ h	—
Monn et al. (1998)	Overall study	0.47	3.2	11.0	16.2	70.5	29.5	—	—
	Homes without smokers and gas cooking	0.40	3.2	6.8	16.2	53.1	46.9	—	Mean indoor was estimated based on the text description.

STUDY	CONDITION	SLOPE	INTERCEPT	MEAN INDOOR CONCEN-TRATION	MEAN OUTDOOR CONCEN-TRATION	PERCENT OUTDOOR CONTRIBU-TION	PERCENT INDOOR CONTRIBU-TION	INDOOR SOURCE STRENGTH	COMMENTS
Spengler et al. (1994)	Gas range with pilot light	0.49	—	30	37	60.4	39.6	—	Mean indoor and mean outdoor are estimated from Figure 2 in Spengler et al. (1994).
	Gas range without pilot light	0.4	—	22	33	60.0	40.0	—	Mean indoor and mean outdoor are estimated from Figure 2 in Spengler et al. (1994).
	Electric stove	0.4	—	17	33	77.6	22.4	—	Mean indoor and mean outdoor are estimated from Figure 2 in Spengler et al. (1994).
	Overall	0.49	8.64	27.2	38.3	68.2	31.8	—	—

Table AX3.5-4. The association between indoor, outdoor, and personal NO_2.

STUDY	SUMMARY	CONDITION	INDOOR VS. OUTDOOR	PERSONAL VS. INDOOR	PERSONAL VS. OUTDOOR	COMMENTS
Mosqueron et al. (2002)	Simultaneous personal, indoor, and in-office 48-h averaged NO_2 concentrations were measured with Ogawa badges for 62 people, and ambient concentrations were provided by local air monitoring network.	Overall study	0.07 (partial R^2)	—	—	Gas cooking interpreted another 7% of indoor NO_2 variation
Emenius et al. (2003)	Palmes tubes were used to measure indoor (in the main living room) and outdoor (outside the window of this room) NO_2 concentrations during a four-wk period (mean 28 days, range 26-31) in the first winter season following recruitment in the case-control study.	Without smoker and gas stove was not used	0.69 (r_p)	—	—	$p < 0.001$
		With gas stove and with smoker	0.13 (r_p)	—	—	$p = 0.43$
		With gas stove but without smoker	0.06 (r_p)	—	—	$p = 0.75$
Lee et al. (1999)	Indoor and outdoor air quality of 14 public places with mechanical ventilation systems in Hong Kong were measured from Oct 1996 to March 1997. Traffic peak h NO, NO_2 was sampled using Teflon bags and then shipped back to the laboratory for further analysis.	Overall study	0.59 (R^2)	—	—	0.92 for NO and 0.92 for NO_X.

STUDY	SUMMARY	CONDITION	INDOOR VS. OUTDOOR	PERSONAL VS. INDOOR	PERSONAL VS. OUTDOOR	COMMENTS
García-Algar et al. (2003)	Yanagisawa passive filter badges were used to measure indoor NO_2 concentrations for 7~15 days for 340 homes in Barcelona, Spain during 1996~1999. Outdoor NO_2 concentrations were obtained from the fixed monitoring stations by the method of CL.	Overall study	0.15 (r_p)	—	—	p = 0.007
Lai et al. (2006)	The study was conducted between 1996 and 2000 in six EU cities: Athens, Basel, Helsinki, Milan, Oxford, and Prague. 48-h averaged indoor and outdoor NO_2 were collected each home using diffusion tubes for 302 homes.	Overall study	0.13 (partial R^2)	—	—	The overall R^2 for the multiple linear regression was 0.67
Lee et al. (2002)	Six-day integrated indoor and outdoor concentrations of NO_2 were measured in two communities in Southern California using Yanagisawa badges for 119 homes in April and May 1996.	Overall study	0.60 (r_p)	—	—	—
Mukala et al. (2000)	The one-week averaged indoor (day-care center), outdoor (outside day care center) and personal NO_2 for 162 children aged 3-6 years old nitrogen dioxide exposure were measured by Palmes tube in Helsinki, in 1991.	Spring	0.86 (r_p)	—	—	—
		Winter	0.54 (r_p)	—	—	—
		Spring (ambient vs. indoor)	0.45 (r_p)	—	—	—
		Winter (ambient vs. indoor)	0.36 (r_p)	—	—	—
Garrett et al. (1999)	Four-day averaged NO_2 was monitored using Yanagisawa passive samplers in 80 homes in the Latrobe Valley, Victoria, Australia in March-April 1994, and Jan-Feb 1995.	Overall study	0.28 (R^2)	—	—	Log10 transformed data
Cotterill and Kingham (1997)	Three consecutive two-week averaged outdoor, kitchen, living room, and bedroom NO_2 were measured using Palme's tubes in 40 houses in Huddersfield, UK in late 1994. Half the houses were located close to a busy main road and half on residential roads set back and parallel to the main road. The sample was split so that half had gas cookers and half had electric cookers. These subsets were split again so that half had double glazing and half had single glazed windows.	Overall study	0.59 (r_p)	—	—	—
Yang et al. (2004)	Daily indoor and outdoor NO_2 concentrations were measured for 30 consecutive days in 28 house in Brisbane (between April and May in 1999), and for 21 consecutive days in 37 houses in Seoul (between June and Aug in 2000) using Yanagisawa badges.	Brisbane, electric range house	0.70 ($R^{2)}$	—	—	—
		Brisbane, gas range house	0.57 (R^2)	—	—	—
		Seoul, gas range house	0.52 (R^2)	—	—	—
Lai et al. (2004)	During the study, 48-averaged personal, residential indoor, residential outdoor, and workplace indoor pollutants were measured for 50 adults between 1998 and 2000 in Oxford, once per person. NO_2 were measured using passive sampling badges.	Overall study	0.29 (r_p) (not significant)	0.47 (r_p) ($p < 0.01$)	-0.41 (r_p) ($p < 0.05$)	Data were log-transformed
Monn et al. (1998)	During the study, one-wk integrated indoor, outdoor and personal samples were collected for a subpopulation (n = 140) of SAPALDIA study using Pamles tube between Dec 1993 and Dec 1994 at eight study centers in Switzerland.	Overall study	0.37 (R^2)	0.51 (R^2)	0.33 (R^2)	—
		Homes without smoker and without gas-cooking	0.34 (R^2)	0.47 (R^2)	0.27 (R^2)	—

STUDY	SUMMARY	CONDITION	INDOOR VS. OUTDOOR	PERSONAL VS. INDOOR	PERSONAL VS. OUTDOOR	COMMENTS
Levy et al., (1998a)	48-h averaged indoor, outdoor and personal NO_2 were measured in 18 cities in 15 countries around the world with passive filter badges in Feb or March, 1996.	Overall study	—	0.75 (r_s)	0.57 (rs)	—
Spengler et al. (1994)	Probability based population, Los Angeles Basin, 48-h averaged indoor, outdoor and personal NO_2 were measured (microenvironmental component of the study), from May 1987 to May 1988	Overall study	0.4 (R^2)	0.6 (R^2)	0.51 (R^2)	—
		Electric range	0.41 (R^2)	—	0.52 (R^2)	—
		Gas range without pilot light	0.39 (R^2)	—		—
		Gas range with pilot light	0.44 (R^2)	—	0.44 (R^2)	—
		With air conditioning	0.66 (rp)	—	—	—
		Without air conditioning	0.75 (rp)	—	—	—
		High ambient concentration	—	—	0.47 (R^2)	—
		Low ambient concentration	—	—	0.33 (R^2)	—
Kousa et al. (2001)	The indoor, outdoor, and personal NO_2 relationship in three EXPOLIS centers (Basel, Helsinki, and Prague) were reported. During the study, 48-averaged indoor, outdoor, and personal NO_2 were measured with Palmes tubes during 1996-1997.	Overall study	0.44 (R^2)	0.53 (R^2)	0.37 (R^2)	Data were log-transformed
		Helsinki	—	0.45 (R^2)	0.40 (R^2)	Data were log-transformed
Linaker et al. (1996)	During the study, one-wk integrated personal, indoor (kitchen, living room), classroom and playground NO_2 were measured using Palmes tubes for 46 school children aged 9-11 in Southampton, UK.	Overall study	—	0.53-0.76 (rp)	0.61-0.65 (rp)	Data were log-transformed
Alm et al. (1998)	During the study, weekly personal, indoor (day care center), outdoor (day care center), and ambient site NO_2 exposures of 246 children aged 3-6 yrs were measured with Palmes tubes during 13 wks in winter and spring in 1991 in Helsinki.	Overall study	—	0.88 (R^2)	0.86 (R^2)	0.37 (R^2) for personal vs. ambient
		Winter	—	—	0.04 (partial R2)	p = 0.01; log transformed data
		Spring	—	—	0.50 (partial R2)	p = 0.0001; log transformed data
		Winter downtown	0.44 (rp)	0.32 (rp)	0.46 (rp)	Personal vs. indoor was not significant (day-care center, not residential indoor).
		Spring downtown	0.84 (rp)	0.75 (rp)	0.80 (rp)	
		Winter suburban	0.22 (rp)	0.04 (rp)	0.49 (rp)	Personal vs. indoor, and indoor vs. outdoor were not significant
		Spring suburban	0.46 (rp)	0.75 (rp)	0.82 (rp)	—
		Downtown electric stove	—	0.67 (rp)	0.55 (rp)	—

STUDY	SUMMARY	CONDITION	INDOOR VS. OUTDOOR	PERSONAL VS. INDOOR	PERSONAL VS. OUTDOOR	COMMENTS
		Downtown gas stove	—	0.50 (rp)	0.59 (rp)	—
		Downtown non-smoking	—	0.67 (rp)	0.73 (rp)	—
		Downtown smoking	—	0.47 (rp)	0.51 (rp)	—
		Suburban electric stove	—	0.55 (rp)	0.63 (rp)	—
		Suburban gas stove	—			—
		Suburban non-smoking	—	0.50 (rp)	0.59 (rp)	—
		Suburban smoking	—	0.48 (rp)	0.46 (rp)	—
Kodama et al. (2002)	During the study, personal, indoor (kitchen, living room, bedroom, and study room), and outdoor NO_2 were measured for 150 junior high school students with Yanagisawa badges in Tokyo. The investigation was conducted five times seasonally, 3 days each, from Feb 1998 to Jan 1999.	Summer	—	0.31 (rp)	0.24 (rp)	—
		Winter	—	0.57 (rp)	0.08 (rp)	—

Table AX3.5-5. Indoor, outdoor, and personal NO_2 levels stratified by exposure factors (concentrations are in ppb and slopes are dimensionless)

REFERENCE	FACTOR NAME	FACTOR LEVEL	AMBIENT NO_2 LEVEL	AMBIENT SLOPE	INDOOR NO_2 LEVEL	INDOOR SLOPE	PERSONAL NO_2 LEVEL	PERSONAL SLOPE	COMMENTS
Environmental conditions									
Singer et al. (2004)	Wind Direction	Upwind of freeway	20.5	—	—	—	—	—	—
		Downwind and close to freeway	26.5	—	—	—	—	—	—
		Downward and far from freeway	21	—	—	—	—	—	—
Zota et al. (2005)	Season	Heating	21	—	43	—	—	—	—
		Non-Heating	17	—	26	—	—	—	—
Sørensen et al. (2005)	Season	< 8C	14.6	—	8.9	—	11.4	—	—
		> 8C	7.8	—	6.6	—	9.2	—	—
Alm et al. (1998)	Season	Winter downtown smoker	—	—	—	—	13.5	—	—

REFERENCE	FACTOR NAME	FACTOR LEVEL	AMBIENT NO_2 LEVEL	AMBIENT SLOPE	INDOOR NO_2 LEVEL	INDOOR SLOPE	PERSONAL NO_2 LEVEL	PERSONAL SLOPE	COMMENTS
		Spring downtown smoker	—	—	—	—	15.4	—	—
		Winter downtown nonsmoker	—	—	—	—	13.0	—	—
		Spring downtown nonsmoker	—	—	—	—	14.1	—	—
		Winter suburban smoker	—	—	—	—	11.2	—	—
		Spring suburban smoker	—	—	—	—	10.7	—	—
		Winter suburban nonsmoker	—	—	—	—	9.2	—	—
		Spring suburban nonsmoker	—	—	—	—	8.7	—	—
Zota et al. (2005)	Heating season	—	—	3.87	—	17.3	—	—	—
Vukovich (2000)	Day	Weekday		—	—	—	—	—	39% more than weekend
Lee (1997)	Day	Weekday	—	—	—	—	—	—	The effect of weekday/week-end is clear but the paper didn't give a value to cite
		Weekend	—	—	—	—	—	—	—
Dwelling conditions									
Levy et al. (1998a)	Window open	With	—	—	—	—	30	—	—
		Without	—	—	—	—	26.7	—	—
Cotterill and Kingham (1997)	Window	Single Glazing	—	—	9.4	—	—	—	—
		Double Glazing	—	—	9.4	—	—	—	—
		Single Glazing	—	—	11.0	—	—	—	Gas cooker homes
		Double Glazing	—	—	12.0	—	—	—	Gas cooker homes
Partti-Pellinen et al. (2000)	Type of Filtration	Mechanical filter	12.3	—	9.6	—	—	—	—
		Mechanical intake and mechanical filter	11.5	—	12.5	—	—	—	—

REFERENCE	FACTOR NAME	FACTOR LEVEL	AMBIENT NO_2 LEVEL	AMBIENT SLOPE	INDOOR NO_2 LEVEL	INDOOR SLOPE	PERSONAL NO_2 LEVEL	PERSONAL SLOPE	COMMENTS
		Mechanical intake and mechanical and chemical filter	12.4	—	6.5	—	—	—	—
Yamanaka (1984)	Surface type	—	—	—	—	—	—		Affect decay rate
Zota et al. (2005)	Occupancy	—	—	—	—	3.2	—	—	—
Levy et al. (1998a)	Occupancy	1	—	—	—	—	25.9	—	—
		2	—	—	—	—	30.8	—	—
Emenius et al. (2003)	Location	Urban	16.5	—	9.6	—	—	—	—
		Semi-urban	11.3	—	6.4	—	—	—	—
		Suburban	7.2	—	4.2	—	—	—	—
Cotterill and Kingham (1997)	Location	On Main Road	—	—	7.9	—	—	—	Electric cooker homes
		50-85m from Main Road	—	—	6.8	—	—	—	Electric cooker homes
Zota et al. (2005)	Location	—	—	-0.0093	—	—	—	—	—
Lee et al. (2004)	Location	Industrial	—	—	—	—	34.9	—	—
		Residential	—	—	—	—	27.8	—	—
Liard et al. (1999)	Location	Main Road	—	—	—	—	28.1	—	—
		Side Road	—	—	—	—	24.3	—	—
Nakai et al. (1995)	Location	< 20 m	42.4	—	43.8	—	43.1	—	Recalculated based published data
		20-150 m	34.9	—	38.4	—	35.9	—	Recalculated based published data
		> 150 m	20.3	—	36.4	—	30.1	—	Recalculated based published data
Alm et al. (1998)	Location	Downtown smoker	—	—	—	—	14.6	—	—
		Suburban smoker	—	—	—	—	10.9	—	—
		Downtown nonsmoker	—	—	—	—	13.6	—	—
		Suburban nonsmoker	—	—	—	—	9.0	—	—
Lee et al. (1996)	House structure	Single DU	17	—	17	—	—	—	Winter
		Small multi-DU	23	—	28.9	—	—	—	Winter
		Large multi-DU	23.6	—	26.8	—	—	—	Winter

REFERENCE	FACTOR NAME	FACTOR LEVEL	AMBIENT NO_2 LEVEL	AMBIENT SLOPE	INDOOR NO_2 LEVEL	INDOOR SLOPE	PERSONAL NO_2 LEVEL	PERSONAL SLOPE	COMMENTS
		Single DU	18.4	—	17.8	—	—	—	Fall
		Small multi-DU	25.1	—	30.2	—	—	—	Fall
		Large multi-DU	25.1	—	25.4	—	—	—	Fall
		Single DU	15.9	—	17.3	—	—	—	Summer
		Small multi-DU	23.7	—	27.8	—	—	—	Summer
		Large multi-DU	24.5	—	29.1	—	—	—	Summer
Gallelli et al. (2002)	Heating system	Individual	—	—	13.7	—	—	—	Bedroom data
		Central	—	—	12.5	—	—	—	Bedroom data
	Frames	Metal	—	—	12.6	—	—	—	Bedroom data
		Wood	—	—	15.0	—	—	—	Bedroom data
Zota et al. (2005)	Floor level	—	—	2	—	—	—	—	—
Mosqueron et al. (2002)	Floor level	—	—	—	—	−1.78	—	—	—
Liard et al. (1999)	Extractor fan over cooker	Without	—	—	—	—	27.5	—	—
		With	—	—	—	—	24.8	—	—
Gallelli et al. (2002)	Chimney	With vent	—	—	18.1	—	—	—	Kitchen data
		Without vent	—	—	30.9	—	—	—	Kitchen data
Yang et al. (2004)	Attached garage	With	—	—	17.3	—	—	—	—
		Without	—	—	11.4	—	—	—	—
Garrett et al. (1999)	Age of house	—	—	—	—	0.5	—	—	—
Indoor sources									
Zota et al. (2005)	Supplemental Heating with stove	—	—	—	—	7.84	—	—	—
Lai et al. (2004)	Smoking	Smoking	—	—	10.9	—	10.8	—	—
		Nonsmoking	—	—	11.5	—	14.1	—	—
Levy et al. (1998a)	Smokers present	With	—	—	—	—	34.8	—	—
		Without	—	—	—	—	26.8	—	—
Belanger et al. (2006)	Ranges	Electric	—	—	8.6	—	—	—	—
		Gas	—	—	25.9	—	—	—	—
Cotterill and Kingham (1997)	Ranges	Gas	—	—	35.6	—	—	—	Kitchen
		Electric	—	—	9.9	—	—	—	Kitchen
		Gas	—	—	11.5	—	—	—	Bedroom
		Electric	—	—	7.3	—	—	—	Bedroom
Yang et al.	Ranges	Gas	—	—	18.3	—	—	—	—

REFERENCE	FACTOR NAME	FACTOR LEVEL	AMBIENT NO_2 LEVEL	AMBIENT SLOPE	INDOOR NO_2 LEVEL	INDOOR SLOPE	PERSONAL NO_2 LEVEL	PERSONAL SLOPE	COMMENTS
(2004)		Not Gas	—	—	10.3	—	—	—	—
Schwab et al. (1994)	Ranges	Gas with pilot light	—	—	20.3	—	—	—	Summer 1998 data
		Gas without pilot light	—	—	11.7	—	—	—	Summer 1998 data
		Electric	—	—	8	—	—	—	Summer 1998 data
Monn et al. (1998)	Ranges	Gas Geneva	—	—	20.9	—	23.6	—	—
		Electric Geneva	—	—	16.8	—	19.9	—	—
		Gas Basle	—	—	15.2	—	18.3	—	—
		Electric Basle	—	—	12.6	—	16.2	—	—
		Gas Lugano	—	—	18.8	—	20.9	—	—
		Electric Lugano	—	—	15.7	—	18.3	—	—
Spengler et al. (1994)	Ranges		—	—	—	—	—	—	Gas with pilot was 15 ppb higher than electric; gas without pilot was 4 ppb higher than electric
Alm et al. (1998)	Ranges	Electric smoker	—	—	—	—	13.0	—	—
Raaschou-Nielsen et al. (1997)	Near fire		—	—	—	—	—	0.052	—
Kawamoto et al. (1997)	Heating time	Oil fan heater	—	—	—	—	—	2.59	—
		Kerosene heater	—	—	—	—	—	1.17	—
		Clean heater	—	—	—	—	—	—	—
Lee et al. (2004)	Heating fuel	Coal briquette	—	—	—	—	22.2	—	—
		Petroleum	—	—	—	—	33.1	—	—
Liard et al. (1999)	Heating appliance	Gas	—	—	—	—	27.9	—	—
		Other	—	—	—	—	25.2	—	—
Kodama et al. (2002)	Heater	Kerosene heater	—	—	152.6	—	—	—	Sourth area, Feb 1998
		Gas stove	—	—	77.5	—	—	—	Sourth area, Feb 1998
		Electric heater	—	—	30.8	—	—	—	Sourth area, Feb 1998
Yang et al. (2004)	Gas water heater	With	—	—	18.1	—	—	—	—
		Without	—	—	11.9	—	—	—	—
Levy et al. (1998a)	Gas water heater	With	—	—	—	—	30.5	—	—
		Without	—	—	—	—	28.2	—	—
		With	—	—	—	—	36.4	—	—

REFERENCE	FACTOR NAME	FACTOR LEVEL	AMBIENT NO_2 LEVEL	AMBIENT SLOPE	INDOOR NO_2 LEVEL	INDOOR SLOPE	PERSONAL NO_2 LEVEL	PERSONAL SLOPE	COMMENTS
		Without	—	—	—	—	28.5	—	—
	Gas range	With	—	—	—	—	34.8	—	—
		Without	—	—	—	—	20.5	—	—
Monn et al. (1997)	Gas cooking	With	—	—	—	—	—	—	I/O > 1.2
		Without	—	—	—	—	—	—	I/O ~ 0.4 – 0.7
Mosqueron et al. (2002)	Gas cooking		—	—	—	0.068	—	—	—
Raaschou-Nielsen et al. (1997)	Gas appliances at home		—	—	—	—	—	0.202	—
Garrett et al. (1999)	Gas and smoking	None	—	—	3.0	—	—	—	I/O ratio increase from 0.8 to 1.3 to 1.8 to 2.2 in houses with no, one, two, or three major indoors sources
		Gas stove	—	—	6.3	—	—	—	—
		Gas heater	—	—	5.0	—	—	—	—
		Smoking	—	—	5.7	—	—	—	—
		Multiple	—	—	11.2	—	—	—	—
Dutton et al. (2001)	Fireplace setting	Low	—	—	90	—	—	—	—
		Middle	—	—	350	—	—	—	—
		High	—	—	360	—	—	—	—
Sørensen et al. (2005)	Exposure to burning candle	—	—	—	—	—	—	0.031	—
Liard et al. (1999)	Exposure to ETS	With	—	—	—	—	25.1	—	—
		Without	—	—	—	—	26.3	—	—
Raaschou-Nielsen et al. (1997)	Exposure to ETS		—	—	—	—	—	0.056	—
Lee et al. (2004)	Cooking fuel	Petroleum	—	—	—	—	26.1	—	—
		Gas	—	—	—	—	33.1	—	—
		Coal briquette	—	—	—	—	20.6	—	—
Liard et al. (1999)	Cooking appliance	Gas	—	—	—	—	25.8	—	—
		Electric	—	—	—	—	25.5	—	—
Dennekamp et al. (2001)	Cooking	1 ring	—	—	437	—	—	—	The max 5 min concentrations
		2 rings	—	—	310	—	—	—	The max 5 min concentrations
		3 rings	—	—	584	—	—	—	The max 5 min concentrations

REFERENCE	FACTOR NAME	FACTOR LEVEL	AMBIENT NO_2 LEVEL	AMBIENT SLOPE	INDOOR NO_2 LEVEL	INDOOR SLOPE	PERSONAL NO_2 LEVEL	PERSONAL SLOPE	COMMENTS
		4 rings	—	—	996	—	—	—	The max 5 min concentrations
		Boil water	—	—	184	—	—	—	The max 5 min concentrations
		Stir fry	—	—	92	—	—	—	The max 5 min concentrations
		Fry bacon	—	—	104	—	—	—	The max 5 min concentrations
		Bake cake	—	—	230	—	—	—	The max 5 min concentrations
		Roast meat	—	—	296	—	—	—	The max 5 min concentrations
		Bake potatoes	—	—	373	—	—	—	The max 5 min concentrations
Personal activities									
Levy et al. (1998a)	Commute	Commuting less than 1 h	—	—	—	—	29.9	—	—
		Without commuting	—	—	—	—	27.9	—	—
Chao and Law (2000)	Commute	< 1 h	—	—	—	—	21.7	—	—
		1-2 h	—	—	—	—	24.7	—	—
		2-3 h	—	—	—	—	24.6	—	—
		3-4 h	—	—	—	—	20.1	—	—
		4-6 h	—	—	—	—	27.9	—	—
	Cooking to stay home h ratio	—	—	—	—	—	—	55.4	—
Kawamoto et al. (1997)	Cooking time	—	—	—	—	—	—	1.61	—

Table AX3.5-6. Personal NO_2 levels stratified by demographic and socioeconomic factors (concentrations are in ppb and slopes are dimensionless).

REFERENCES	FACTOR TYPE	FACTOR NAME	FACTOR LEVELS	PERSONAL NO_2 LEVEL	PERSONAL SLOPE
Rotko et al. (2001)	Demography	Age	25-34	13.1	
Rotko et al. (2001)	Demography	Age	35-55	13.1	
Raaschou-Nielsen (1997)	Demography	Age			0.056
Lee et al., (2004)	Demography	Gender	Female	33	
Lee et al., (2004)	Demography	Gender	Male	29	
Rotko et al. (2001)	Demography	Gender	Female	12.9	

REFERENCES	FACTOR TYPE	FACTOR NAME	FACTOR LEVELS	PERSONAL NO_2 LEVEL	PERSONAL SLOPE
Rotko et al. (2001)	Demography	Gender	Male	13.4	
Raaschou-Nielsen (1997)	Demography	Gender			0.267
Rotko et al. (2001)	Socioeconomic	Education years	<14 years	13.8	
Rotko et al. (2001)	Socioeconomic	Education years	≥14 years	12.8	
Rotko et al. (2001)	Socioeconomic	Employment	Employed	13.3	
Rotko et al. (2001)	Socioeconomic	Employment	Not employed	11.5	
Rotko et al. (2001)	Socioeconomic	Occupational status	Non white collar	13.4	
Rotko et al. (2001)	Socioeconomic	Occupational status	White collar	13.0	
Algar et al. (2004)	Socioeconomic	Employment	Managerial, technical and professional (Barcelona)	12.2	
Algar et al. (2004)	Socioeconomic	Employment	Skilled (manual and non-manual) (Barcelona)	12.3	
Algar et al. (2004)	Socioeconomic	Employment	Unskilled and partly skilled (Barcelona)	12.1	

Table AX3.6-1. 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)
Microenviron-mental (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

	PNEM	HAPEM	APEX	SHEDS	MENTOR-1A
Exposure Routes	Inhalation	Inhalation	Inhalation	Inhalation	Multiple (optional)
Potential Dose Calculation	Yes	No	Yes	Yes	Yes
Physiologically Based Dose	No	No	No	Yes	Yes
Variability/ Uncertainty	Yes	No	Yes	Yes	Yes (Various “Tools”)

Annex 4. Toxicological Effects of NO_X

AX4.1. Pulmonary Effects of NO_X

AX4.1.1. Effects of NO_2 on Oxidant and Antioxidant Metabolism

NO_2 is an oxidant; lipid peroxidation is believed to be a major molecular event responsible for its toxicity. As a result, there has been considerable attention paid to the effect of NO_2 on the antioxidant defense system in the epithelial lining fluid and in pulmonary cells. Repeated exposure to NO_2 at concentrations ranging from 0.04 to 33 ppm has been shown to alter low molecular weight antioxidants such as glutathione, vitamin E, and vitamin C, as well as some enzymes involved in cell oxidant homeostasis.

A number of studies have investigated the hypothesis, originally proposed by Menzel (1970), that antioxidants might protect the lung from NO_2 damage by inhibiting lipid peroxidation (see Table AX4.1). Changes in the activity of enzymes in the lungs of NO_2-exposed animals that regulate levels of glutathione (GSH) have been reported in response to relatively low exposure concentrations. Sagai et al. (1984) studied the effects of prolonged (9 and 18 months) exposure to 0.04, 0.4, and 4.0 ppm NO_2 on rats. After exposure duration, non-protein sulfhydryl levels were increased at 0.4 ppm or greater, and exposure to 4.0 ppm decreased the activity of GSH peroxidase but increased glucose-6-phosphate dehydrogenase activity. Glutathione peroxidase activity was also decreased in rats exposed to 0.4 ppm NO_2 for 18 months. Three GSH S-transferases were also studied, two of which (aryl *S*-transferase and aralkyl *S*-transferase) exhibited decreased activities after 18 months of exposure to 0.4 ppm or greater NO_2. No effects were observed on the activities of 6-phosphogluconate dehydrogenase, superoxide dismutase, or disulfide reductase. Effects followed a concentration- and exposure-duration response function. The decreases in glutathione-related enzyme activities were inversely related to the apparent formation of lipid peroxides (see lipid peroxidation subsection). Shorter exposures (4 months) to NO_2 between 0.4 and 4.0 ppm also caused concentration- and duration-dependent effects on antioxidant enzyme activities (Ichinose and Sagai, 1982). For example, glucose-6-phosphate dehydrogenase increased, reaching a peak at 1 month, and then decreased towards the control value. Shorter (2-week) exposure to 0.4 ppm NO_2 caused no such effects in rats or guinea pigs (Ichinose and Sagai, 1989).

The activities of GSH reductase and glucose-6-phosphate dehydrogenase were significantly increased during exposure to 6.2 ppm NO_2 for 4 days; GSH peroxidase activity was not affected (Chow et al., 1974). The possible role of edema and cellular inflammation in these findings was not examined. Since NO_2 had no significant effect on lung GSH peroxidase activity in this study, but did significantly increase the activities of GSH reductase and glucose-6-phosphate dehydrogenase, the authors concluded that NO_2 attacks mainly GSH and NADPH.

Newer studies also identified effects on GSH. Changes in GSH status in the blood and lung (bronchoalveolar lavage (BAL) fluid) occurred in rats exposed to 5 ppm and 10 ppm NO_2 continuously for 24 h, but not for 7 days (Pagani et al., 1994). Total glutathione – total of reduced (GSH) and oxidized (GSSG) form – was significantly increased in blood but not in BAL fluid; however, GSSG was elevated in BAL fluid only. A decreased GSH/GSSG ratio was observed in the blood and BAL fluid, but not in lung type II cells, of rats continuously exposed to 10 ppm NO_2 for 3 or 20 days (Hochscheid et al., 2005). Interestingly, lipid peroxidation was decreased in type II cells at 3 days, but was similar to controls at 20 days. Gene expression, as measured by mRNA levels of the enzymes involved in the biosynthesis of glutathione – gamma-glutamylcysteine synthetase (γGCS) and glutathione synthetase (GS), decreased at both time points, but gamma-glutamyltranspeptidase (γGT) mRNA expression increased. No GSH

peroxidase activity (important for hydroperoxide reduction of complex lipids) was detected at 3 days, and was barely detected at 20 days.

Malnutrition of animals can drastically affect their response to toxicants, including NO_2. Experimental interest in this area has mainly focused on dietary lipids, vitamin E and other lipid-soluble antioxidants, and vitamin C and other water-soluble antioxidants. Ayaz and Csallany (1978) exposed vitamin E-deficient and vitamin E-supplemented (30 or 300 mg/kg of diet) weanling mice continuously for 17 months to 0.5 or 1.0 ppm NO_2 and assayed blood, lung, and liver tissues for GSH peroxidase activity. Exposure to 1.0 ppm NO_2 alone or combined with vitamin E deficiency decreased the enzyme activity in the blood and lungs. Neither vitamin E deficiency nor NO_2 exposure affected liver GSH peroxidase activity. However, in vitamin E-supplemented mice, GSH peroxidase activity increased at 0.5 ppm and 1.0 ppm NO_2.

AX4.1.2. Lipid Metabolism and Content of the Lung

Lipid peroxidation is an important mechanism of cell damage arising from changes in cell membrane structure and function. The ability of NO_2 exposure to induce lipid peroxidation in the respiratory tract has been demonstrated; as measured by increased ethane exhalation in the breath, as thiobarbituric acid (TBA) reactive substances in tissues, and as the content of conjugated dienes in tissue homogenates.

A number of studies investigated the effects of NO_2 exposure on lipid metabolism and lipid content of the lung. Lipid peroxidation induced by NO_2 exposure has been detected at exposure concentrations as low as 0.04 ppm. Increased ethane exhalation was observed in rats exposed to 0.04 or 0.12 ppm after 9 and 18 months of exposure (Sagai et al., 1984). Exposure to 0.4 ppm NO_2 for 9 months or longer and to 4.0 ppm for 6 months resulted in increased TBA reactants (Ichinose et al., 1983). NO_2 exposure for shorter durations also increased lipid peroxidation in rats. For example, NO_2 exposure of 1.2 ppm or greater for 1 week (Ichinose and Sagai, 1982; Ichinose et al., 1983) increased ethane exhalation in rats, while exposure of pregnant rats to 0.53 or 5.3 ppm NO_2 for 5 h/day for 21 days resulted in increased lung lipid peroxidation products (Balabaeva and Tabakova, 1985). These results indicate at least some degree of duration-dependence in the formation of lipid peroxidation, with lower effect thresholds identified with longer durations of exposure.

Lipid peroxidation results in altered phospholipid composition, which in turn may adversely affect membrane fluidity and thus, membrane function. Significant depression of lipid content and total content of saturated fatty acids such as phosphatidyl-ethanolamine, lecithin (phosphatidylcholine), phosphatidylinositol, and phosphatidylserine were measured in rats exposed to 2.9 ppm NO_2 for 24 h/day, 5 days/week for 9 months (Arner and Rhoades, 1973). Exposure of rabbits to 1.0 ppm NO_2 for 2 weeks also caused depression of lecithin synthesis after one week of exposure (Seto et al., 1975), while exposure of rats to 5.5 ppm NO_2 for 3 h/day for 7 or 14 days elicited only few changes in lipid metabolism (Yokoyama et al., 1980). In beagle dogs, the amount of unsaturated fatty acids in the phospholipids from the lungs was increased after exposure to concentrations ranging from 5 to 16 ppm, but not to 3 ppm (Dowell et al., 1971). Exposure of either mice or guinea pigs to 0.4 ppm for a week resulted in a decreased concentration of phosphatidylethanolamine and a relative increase in the phosphatidylcholine concentration (Sagai et al., 1987). Concentration- and exposure duration-dependent increases were reported in phospholipid components in BAL fluid, when rats were exposed to 10 ppm NO_2 continuously for 1 day or 3 days (Müller et. al., 1994).

Functional studies conducted on surfactant phospholipid extracts indicated that NO_2 exposures of 5 ppm or greater, directly impaired surface tension, although the structure of the surfactant protein A (SP-A) was not altered by NO_2 exposure. Changes in the phospholipid composition of membranes may result in disruption of the cell membrane barrier. Müller et al. (2003) found that uptake of liposomes by type II lung cells occurred more easily from animals exposed to 10 ppm NO_2 for 3 to 28 days, possibly as a result of increased demand of phosphatidylcholine during lung injury.

Lipid peroxidation can also activate phospholipases. Activation of phospholipase A1 in cultured endothelial cells occurred at 5 ppm after 40 h of exposure and was speculated to depend on a specific NO_2-induced increase in phosphatidyl serine in the plasma membranes (Sekharam et al., 1991).

One function of phospholipases is the release of arachidonic acid (AA), which serves as a mediator of inflammatory response. NO_2 exposure affects the release and metabolism of arachidonic acid both in vivo and in vitro. The products of arachidonic acid metabolism, such as prostaglandins, prostacyclin, thromboxanes, and leukotrienes play an important role (such as recruitment of neutrophils to sights of local irritation) in modulating inflammatory response. Schlesinger et al. (1990) reported elevated concentrations of thromboxane B2 (TxB_2) following NO_2 exposures of 1.0 ppm for 2 h, depressed concentrations at 3.0 ppm, and significant depression 24-h postexposure at 10 ppm NO_2. The same investigators also reported depressed level of 6-keto-prostaglandin F1α at 1.0 ppm NO_2, but exposure to NO_2 did not affect prostaglandins E2 and F2 and leukotriene B4 (LTB_4) levels.

Changes in activation of arachidonate metabolism were also reported in rat alveolar macrophages (AMs) when these animals were exposed to 0.5 ppm NO_2 for 0.5, 1, 5, and 10 days (Robison et al., 1993). Unstimulated AM synthesis of LTB_4 was depressed after 0.5 days and again after 5 days of exposure to NO_2. Alveolar macrophage production of TxB_2, LTB_4, and 5-hydroxyeicosatetraenoic acid (5-HETE) in response to stimulation with the calcium ionophore, A23187, was depressed after 0.5 days of exposure and recovered to air-control values with longer exposure periods. 5-HETE levels were increased after 10 days of exposure. However, AM production of LTB_4 in response to zymosan-activated rat serum was depressed only after 5 days of exposure.

The effects of NO_2 on structural proteins of the lungs have been of concern because elastic recoil is lost after exposure. Collagen synthesis rates were increased in rats exposed to NO_2 concentrations as low as 5.0 ppm NO_2. It has been assumed that increased collagen synthesis reflect increases in total lung collagen which, if sufficient, could result in pulmonary fibrosis after longer periods of exposure. Such correlation has yet to be confirmed by in vivo studies involving NO_2 exposure.

Alterations in xenobiotic metabolism pathways following NO_2 exposure are also summarized in Table AX4.2, in addition to changes in phase I enzymes (such as cytochrome P450s) and phase II enzymes (GST as described earlier). While these changes are not necessarily toxic manifestations of NO_2 per se, such changes may impact the metabolism and toxicity of other chemicals. Glycolytic pathways may also be affected. For example, glycolytic metabolism was increased by NO_2 exposure, possibly due to a concurrent increase in type II cells (Mochitate et al., 1985).

AX4.1.3. Lung Host Defense, Lung Permeability and Inflammation, Immune Responses, and Infectious Agents

Impaired lung host-defenses, increased risk of susceptibility to both viral and bacterial agents, as well as increased lung permeability and inflammation, provide some important evidence for mechanisms of action potentially underlying the health effects observed in epidemiology studies. These effects are discussed in Chapter 3 but study details are provided in Tables AX 4.3, 4.4, 4.5, and 4.6.

AX4.1.4. Emphysema Following NO_2 Exposure

Emphysema as a result of chronic exposure to NO_2 has been reported in animal studies. The definition of emphysema has changed over time; thus, it is important to compare the findings of studies using the current definition of emphysema. U.S. Environmental Protection Agency (1993) evaluated animal studies reporting emphysema caused by or in response to chronic exposure to NO_2 based upon the most recent definition of emphysema from the report of the National Heart, Lung and Blood Institute (NHLBI), Division of Lung Diseases Workshop (Snider et al., 1985), and U.S. Environmental Protection Agency (1993). Because the focus of this document is an extrapolation from NO_2 exposure to potential

hazard for humans, only those studies reporting emphysema of the type seen in human lungs were included AQCD (1993).

Humanlike emphysema linked to > 5 ppm NO_2 exposure was reported by Haydon et al. (1967) in rabbits and rats (Freeman et al., 1972; Barth et al., 1995). See Annex Table AX4.7 for more recent studies linking NO_2 exposure and lung structure changes.

AX4.1.5. Lung Function

Lung function is discussed extensively in Section 3.1.5 of the ISA. The limited animal toxicology data is presented in Table AX4.8.

AX4.1.6. Nitrates (NO_3^-)

Busch et al. (1986) exposed rats and guinea pigs with either normal lungs or elastase-induced emphysema to ammonium nitrate aerosols at 1 mg/m^3 for 6 h/day, 5 days/week for 4 weeks. Using light and electron microscopy, the investigators concluded that there were no significant effects of exposure on lung structure.

AX4.2. Dosimetry of Inhaled NO_X

This section provides an overview of NO_2 dosimetry and updates information provided in the 1993 AQCD for NO_X. Dosimetry of NO_2 refers to the measurement or estimation of the amount of NO_2 or its reaction products reaching and persisting at specific sites in the respiratory tract following an exposure. NO_2, classified as a reactive gas, interacts with surfactants, antioxidants, and other compounds in the epithelial lining fluid (ELF). The compounds thought responsible for adverse pulmonary effects of inhaled NO_2 are the reaction products themselves or the metabolites of these products in the ELF. At the time of the 1993 NO_X AQCD, it was thought that inhaled NO_2 probably reacted with the water molecules in the ELF to form nitrous acid (HNO_2) and nitric acid (HNO_3). However, some limited data suggested that the absorption of NO_2 was linked to reactive substrates in the ELF and subsequent nitrite production. Since then, the reactive absorption of NO_2 has been examined in a number of studies (see Section 4.2.2). These studies have characterized the absorption kinetics and reactive substrates for NO_2 delivered to various sites in the respiratory tract. Researchers have attempted to obtain a greater understanding of how these complex interactions affect NO_2 absorption and NO_2-induced injury.

With respect to quantifying absolute NO_2 absorption, the following were reported in the 1993 NO_X AQCD. The principles of O_3 uptake were generally assumed applicable for NO_2 modeling studies. The results indicated that NO_2 is absorbed throughout the lower respiratory tract, but the major delivery site is the centriacinar region, i.e., the junction between the conducting and respiratory airways in humans and animals. Experimental studies have found that the total respiratory tract uptake in humans ranges from 72 to 92% depending on the study and the breathing conditions. The percent total uptake increases with increasing exercise level. In laboratory animals, upper respiratory tract uptakes ranged from as low as 25% to as high as 94% depending on the study, species, air flow rate, and mode of breathing (nasal or oral). Upper respiratory tract uptake of NO_2 was found to decrease with increasing ventilation. Uptake during nasal breathing was determined to be significantly greater than during oral breathing.

AX4.2.1. Mechanisms of NO_2 Absorption

The ELF is the initial barrier against NO_2 delivery to the underlying epithelial cells. Postlethwait and Bidani (1990) suggested that acute NO_2 uptake in the lower respiratory tract was rate limited by chemical reactions of NO_2 with ELF constituents rather than by gas solubility in the ELF. Subsequently, Postlethwait et al. (1991) reported that inhaled NO_2 (10 ppm) did not penetrate the ELF to reach underlying sites and suggested that cytotoxicity may be due to NO_2 reactants formed in the ELF. Since then, the reactive absorption of NO_2 has been examined in a number studies that have sought to identify reactive substrates for NO_2 and quantify the absorption kinetics of NO_2 in the respiratory tract.

Postlethwait and Bidani (1994) concluded that the reaction between NO_2 and water does not significantly contribute to the absorption of inhaled NO_2. Uptake is a first-order process for NO_2 concentrations less than 10 ppm, is aqueous substrate-dependent, and is saturable. The absorption of inhaled NO_2 is thought to be coupled with free radical-mediated hydrogen abstraction to form HNO_2 and an organic radical (Postlethwait and Bidani, 1989, 1994). At physiologic pH, the HNO_2 subsequently dissociates to H^+ and nitrite (NO_2^-). The concentration of the resulting nitrite is thought insufficient to be toxic, so effects are thought to be due to the organic radical and/or the proton load. Nitrite may enter the underlying epithelial cells and blood. In the presence of red blood cells, nitrite is oxidized to nitrate (NO_3^-) (Postlethwait and Mustafa, 1981). Beyond cell susceptibility and the concentration of NO_2 in the lumen, site-specific injury was proposed to depend on rate of 'toxic' reaction product formation and the quenching of these products within the ELF. Related to the balance between reaction product formation and removal, it was further suggested that cellular responses may be nonlinear with greater responses being possible at low levels of NO_2 uptake versus higher levels of uptake. Since the ELF may vary throughout the respiratory tract, the uptake of inhaled NO_2 and reaction with constituents of the pulmonary ELF may be related to the heterogeneous distribution of epithelial injury observed from NO_2 exposure.

Postlethwait et al. (1995) sought to determine the absorption substrates for NO_2 in the ELF lavaged from male Sprague-Dawley rats. Since the bronchoalveolar lavage fluid (BALF) collected from the rats may be diluted up to 100-fold relative to the native ELF, the effect of concentrating the BAL fluid on NO_2 absorption was investigated. A linear association was found between the first-order rate constant for NO_2 absorption and the concentration of the BALF. This suggested that concentration of the reactive substrates in the ELF determines the rate of NO_2 absorption. The absorption due to specific ELF constituents was also examined in chemically pure solutions. Albumin, cysteine, reduced GSH, ascorbic acid, and uric acid were hydrophilic moieties found to be active substrates for NO_2 absorption. Unsaturated fatty acids (such as oleic, linoleic, and linolenic) were also identified as active absorption substrates and thought to account for up to 20% of NO_2 absorption. Vitamins A and E exhibited the greatest reactivity of the substrates that were examined. However, the low concentrations of uric acid and vitamins A and E were thought to preclude them from being appreciable substrates in vivo. The authors concluded that ascorbate and GSH were the primary NO_2 absorption substrates in rat ELF. Postlethwait et al. (1995) also found that the pulmonary surfactant, dipalmitoyl phosphatidylcholine, was not an effective substrate for NO_2 absorption. Later, Connor et al. (2001) suggested that dipalmitoyl phosphatidylcholine may actually inhibit NO_2 absorption.

In Vitro

In a subsequent study, Velsor and Postlethwait (1997) investigated the mechanisms of acute epithelial injury from NO_2 exposure. The impetus for this work was to evaluate the supposition that NO_2 reaction products rather than NO_2 itself caused epithelial injury. Red blood cell membranes were immobilized to the bottom of Petri dishes, covered with a variety of well characterized aqueous layers, and exposed to gaseous NO_2 (10 ppm for 20 min). The study focused on the potential roles of GSH and ascorbic acid reaction products in mediating cellular injury. Based on negligible membrane oxidation when covered with only an aqueous phosphate buffer, the diffusive/reactive resistance of a thin aqueous

layer clearly prevented direct interaction between NO_2 and the underlying membrane. The presence of unsaturated fatty acids was not observed to affect NO_2 absorption, but a sufficiently thin liquid layer was required for membrane oxidation to occur. Interestingly, membrane oxidation was not a simple monotonic function of GSH and ascorbic acid levels. The maximal levels of membrane oxidation were observed at low antioxidant levels versus null or high antioxidant levels. Glutathione and ascorbic acid related membrane oxidation were superoxide and hydrogen peroxide dependent, respectively. The authors suggested that at the higher antioxidant concentrations, there was increased absorption of NO_2, but little secondary oxidation of the membrane because the reactive species (e.g., superoxide and hydrogen peroxide) generated during absorption were quenched. At the low antioxidant concentrations, there was a lower rate of NO_2 absorption, but oxidants were not quenched and so were available to interact with the cell membrane.

Humans (In Vivo)

Kelly et al. (1996a) examined the effect of a 4-h NO_2 (2 ppm) exposure on antioxidant levels in bronchial lavage fluid (BLF) and BALF of 44 healthy nonsmoking adults (19-45 year, median 24 years). Subjects were randomly assigned to three groups and lavaged at either 1.5-h (n = 15), 6-h (n = 15), or 24-h (n = 14) after the NO_2 exposure. The baseline concentrations of uric acid and ascorbic acid were strongly correlated between the BLF and BALF within individuals ($r = 0.88$, $p < 0.001$; $r = 0.78$, $p = 0.001$; respectively), whereas the concentrations of GSH in the BLF and BALF were not correlated. Uric acid levels in both lavage fractions were significantly reduced at 1.5-h ($p < 0.04$), significantly increased at 6-h ($p < 0.05$), and back to baseline at 24-h postexposure. A statistically significant loss of ascorbic acid was also found in both lavage fractions at 1.5-h ($p < 0.05$). At 6 and 24-h postexposure, the ascorbic acid levels had returned to baseline. In contrast, GSH levels were significantly increased at both 1.5-h ($p < 0.01$) and 6-h ($p < 0.03$) in BLF. At 24 h postexposure, the GSH levels in BLF returned to baseline. Although GSH in BLF increased at 1.5 and 6 h postexposure, oxidized GSH levels remained similar to baseline in both BLF and BALF. No changes in BALF levels of GSH were observed at any time point.

Humans (Ex Vivo)

The depletion of uric acid and ascorbic acid, but not GSH has also been observed with ex vivo exposure of human BALF to NO_2. Kelly et al. (1996b) collected BALF from male lung cancer patients (n = 16) and exposed the BALF ex vivo at 37°C to NO_2 (0.05 to 2.0 ppm; 4 h) or O_3 (0.05 to 1.0 ppm; 4 h). Kelly and Tetley (1997) also collected BALF from lung cancer patients (n = 12, 54 ± 16 years) and exposed the BALF ex vivo to NO_2 (0.05 to 1.0 ppm; 4 h). Both studies found that NO_2 depletes uric acid and ascorbic acid, but not GSH from BALF. Kelly et al. (1996b) noted a differential consumption of the antioxidants with uric acid loss being greater than that of ascorbic acid which was lost at a much greater rate than GSH. Kelly and Tetley (1997) found that the rates of uric acid and ascorbic acid consumption were correlated with their initial concentrations in the BAL fluid, such that higher initial antioxidant concentrations were associated with a greater rate of antioxidant depletion. Illustrating the complex interaction of antioxidants, these studies also suggest that GSH oxidized by NO_2 may be again reduced by uric acid and/or ascorbic acid.

AX4.2.2. Regional and Total Respiratory Absorption of NO_2

There has been very limited work related to the quantification of NO_2 uptake since the 1993 NO_X AQCD. As a result, there is an abbreviated discussion here of some papers that were previously reviewed.

AX4.2.2.1. Dosimetry Models

There is a paucity of theoretical studies investigating NO_2 dosimetry. Like O_3, NO_2 is highly reactive in ELF and is not very soluble. An O_3 model has been utilized to predict the uptake of NO_2 in the lower respiratory tract of humans, rats, guinea pigs, and rabbits (Miller et al., 1982; Overton, 1984). In this model, there was a strong distinction between uptake and dose. Uptake referred to the amount of NO_2 being removed from gas phase per lung surface area (μg/cm^2), whereas, dose referred to the amount of NO_2 per lung surface area (μg/cm^2) that diffused through the ELF and reached the underlying tissues. These investigators assessed NO_2 uptake and dose on a breath by breath basis. Miller et al. (1988) provided uptake and dose rates (μg/cm^2-min) for O_3 in the same species.

Miller et al. (1982) and subsequently Overton (1984) did not attempt to predict the amount of reactants in the ELF or the transport of reactants to the tissues. Rather, they focused mainly on the sensitivity of NO_2 tissue dose on NO_2 reaction rates in the ELF and the Henry's law constant. Reaction rates of NO_2 in the ELF were varied from zero, 50%, and 100% of the reaction rate for O_3 in ELF. The Henry's law constant was varied from half to double the Henry's law constant for NO_2 in water at 37 °C. Effects of species, lung morphology, and tidal volume (V_T) were also examined. In general, the model predicted that NO_2 is taken up throughout the lower respiratory tract. In humans, NO_2 uptake was fairly constant from the trachea to the terminal bronchioles, beyond which uptake decreased with distal progression. This pattern of NO_2 uptake predicted for humans is very similar to the pattern of O_3 uptake per unit time predicted for humans, rats, rabbits, and guinea pigs by Miller et al. (1988). Thus, it is reasonable to expect that the pattern NO_2 uptake per unit time will also be similar between these species. The NO_2 tissue dose was highly dependent on the Henry's law constant and reaction rate in the ELF. In the conducting airways, the NO_2 tissue dose decreased as the Henry's law constant increased (i.e., decreased gas solubility), whereas the NO_2 tissue dose in the alveolar region increased. The site of maximal NO_2 tissue dose was fairly similar between species, ranging from the first generation of respiratory bronchioles in humans to the alveolar ducts in rats. In guinea pigs and rabbits, the maximal NO_2 tissue dose was predicted to occur in the last generation of respiratory bronchioles. Based on Miller et al. (1988), the dose rate of NO_2 is also expected to be similar between species. The simulations also showed that exercise increases the NO_2 tissue dose in the pulmonary region relative to rest. Miller et al. (1982) also reported that increasing the NO_2 reaction rate decreased NO_2 tissue dose in the conducting airways, but had no effect on the dose delivered to the pulmonary region.

Simultaneously occurring diffusion and chemical reactions in the ELF have been suggested as the limiting factors in O_3 (Santiago et al., 2001) and NO_2 uptake (Postlethwait and Bidani, 1990). Hence, Miller et al. (1982) should have found an increase in the uptake of NO_2 in the conducting airways with increasing the rate of chemical reactions in the ELF. This increase in NO_2 uptake in the conducting airways would then lead to a reduction in the amount of NO_2 reaching and taken up in the pulmonary region. The Miller et al. (1982) model considered reactions of NO_2 with constituents in the ELF as protective in that these reactions reduced the flux of NO_2 to the tissues. Others have postulated that NO_2^- reactants formed in the ELF, rather than NO_2 itself, could actually cause adverse responses (Overton, 1984; Postlethwait and Bidani, 1994; Velsor and Postlethwait, 1997).

Overton and Graham (1995) examined NO_2 uptake in an asymmetric anatomic model of the rat lung. The multiple path model of Overton and Graham (1995) allowed for variable path lengths from the trachea to the terminal bronchioles, whereas Miller et al. (1982) used a single or typical path model of the conducting airways. The terms "dose" and "uptake" were used synonymously to describe the amount of NO_2 gas lost from the gas phase in a particular lung region or generation by Overton and Graham (1995). Reactions of NO_2 in the ELF were not explicitly considered. Their simulations were conducted for rats breathing at 2 mL V_T at a frequency of 150 breaths per minute. The mass transfer coefficients of 0.173, 0.026, and 0.137 cm/sec were assumed for the upper respiratory tract, the tracheobronchial airways, and the pulmonary region, respectively. Uptake was predicted to decrease with distal progression into the lung. In general, the modeled NO_2 dose varied among anatomically equivalent ventilatory units as a

function of path length from the trachea with shorter paths showing greater dose. A sudden increase in NO_2 uptake was predicted in the proximal alveolar region (PAR) which was due to the increase in the assumed mass transfer coefficient relative to the adjacent terminal bronchiole. Overton et al. (1996) showed that increasing the mass transfer coefficient of the tracheobronchial airways decreased the dose to the PAR and vice versa. Additionally, the PAR dose would also be reduced by the more realistic modeling of tracheobronchial airways expansion during inspiration versus the static condition employed by Overton and Graham (1995).

More recently, two studies examined the influence of age on reactive gas dosimetry in humans (Ginsberg et al., 2005; Sarangapani et al., 2003). Both studies specifically considered the dosimetry O_3 during light activity (on average) in their analysis. It is assumed here that their general findings should also be applicable to NO_2. Sarangapani et al. (2003) used a physiologically based pharmacokinetic model and found that regional uptake of O_3 is relatively insensitive to age (range: infants to elderly). Ozone uptake per unit surface area was 2- to 8-fold higher in infants compared to adults. However, this finding (i.e., uptake per unit surface area) is a less informative expression of dose than the rate of uptake per unit surface area. The rate of uptake, obtained by multiplying by the ventilation rate, adjusts for the greater rate of gas intake by adults relative to children. Ginsberg et al. (2005) utilized the U.S. EPA (1994) reference concentration methodology and found no effect of age (infants vs. adults) on the uptake rate of O_3 per unit surface area.

In summary, these modeling studies predict that the net NO_2 dose (NO_2 flux to air-liquid interface) is relatively constant from the trachea to the terminal bronchioles and then rapidly decreases in the pulmonary region. The pattern of net NO_2 dose rate or uptake rate is expected to be similar between species and unaffected by age in humans. The predicted tissue dose and dose rate of NO_2 (NO_2 flux to liquid-tissue interface) is low in the trachea, increases to a maximum in the terminal bronchioles and the first generation of the pulmonary region, and then decreases rapidly with distal progression. The site of maximal NO_2 tissue dose is predicted to be fairly similar between species, ranging from the first generation of respiratory bronchioles in humans to the alveolar ducts in rats. The production of toxic NO_2-reactants in the ELF and the movement of the reactants to the tissues have not been modeled.

AX4.3. Experimental Studies of NO_2 Uptake

AX4.3.1. Upper Respiratory Tract Absorption

The nasal uptake of NO_2 has been experimentally measured in dogs, rabbits, and rats under conditions of unidirectional flow. Yokoyama (1968) reported 42.1 ± 14.9% (Mean ± SD) uptake of NO_2 in the isolated nasal passages of two dogs (3.5 L/min) and three rabbits (0.75 L/min) exposed to 4 and 41 ppm NO_2. Uptake did not appear to depend on the exposure concentration and was relatively constant over a 10 to 15 min period. Cavanagh and Morris (1987) measured uptakes of 28% and 25% uptake of NO_2 (40.4 ppm) in the noses of four naive and four previously exposed rats (0.10 L/min), respectively. Uptake was not affected by a 4-h prior exposure (naive versus previously exposed rats) to 40.4 ppm NO_2 and was constant over the 24-min period during which uptake was determined.

Kleinman and Mautz (1991) measured the penetration of NO_2 through the upper airways during inhalation in six tracheotomized dogs exposed to 1.0 or 5.0 ppm NO_2. Uptake in the nasal passages was significantly greater at 1.0 ppm than at 5.0 ppm, although the magnitude of this difference was not reported. The mean uptake of NO_2 (1.0 ppm) in the nasal passages decreased from 55% to 40% as the ventilation rate increased from about 2 to 8 L/min. During oral breathing, uptake was not dependent on concentration. The mean oral uptake of NO_2 (1.0 and 5.0 ppm) decreased from 65% to 30% as the ventilation rate increased from 2 to 8 L/min.

AX4.3.2. Lower Respiratory Tract Absorption

Postlethwait and Mustafa (1989) investigated the effect of exposure concentration and breathing frequency on the uptake of NO_2 in isolated perfused rat lungs. To evaluate the effect of exposure concentration, the lungs were exposed to NO_2 (4 to 20 ppm) while ventilated at 50 breaths/min with a V_T of 2.0 mL. To examine the effect of breathing frequency, the lungs were exposed to NO_2 (5 ppm) while ventilated at 30-90 breaths/min with a V_T of 1.5 mL. All exposures were for 90 min. The uptake of NO_2 ranged from 59 to 72% with an average of 65% and was not affected by exposure concentration or breathing frequency. A combined regression showed a linear relationship between NO_2 uptake and total inspired dose (25 to 330 µg NO_2). Illustrating variability in NO_2 uptake measurements, Postlethwait and Mustafa (1989) observed 59% NO_2 uptake in lungs ventilated at 30 breaths/min with a V_T of 1.5 mL, whereas, Postlethwait and Mustafa (1981) measured 35% NO_2 uptake for the same breathing condition. In another study, 73% uptake of NO_2 was reported for rat lungs ventilated 50 breaths/min with a V_T of 2.3 mL (Postlethwait et al., 1992). It should be noted that typical breathing frequencies are around 80, 100, and 160 breaths/min for rats during sleep, rest, and light exercise, respectively (Winter-Sorkina and Cassee, 2002). Hence, the breathing frequencies at which NO_2 uptake has been measured are lower than for rats breathing normally.

In addition to measuring upper respiratory tract uptakes, Kleinman and Mautz (1991) also measured NO_2 uptake in the dog lung. In general, there was about 90% NO_2 uptake in the lungs which was independent of ventilation rates from 3 to 16 L/min.

AX4.3.3. Total Respiratory Tract Absorption

Bauer et al. (1986) measured the uptake of NO_2 (0.3 ppm) in 15 adult asthmatics exposed for 30 min (20 min at rest, then 10 min exercising on a bicycle ergometer) via a mouthpiece during rest and exercise. There was a statistically significant increase in uptake from 72% during rest to 87% during exercise. The minute ventilation also increased from 8.1 L/min during rest to 30.4 L/min during exercise. Hence, exercise increased the uptake exposure rate of NO_2 by 5-fold in these subjects. In an earlier study of seven healthy adults in which subjects were exposed to a nitric oxide (NO)/NO_2 mixture containing 0.29 to 7.2 ppm NO_2 for brief (but unspecified) periods, Wagner (1970) reported that NO_2 uptake increased from 80% during normal respiration (V_T, 0.4 L) to 90% during maximal respiration (V_T, 2 to 4 L).

Kleinman and Mautz (1991) also measured the total respiratory tract uptake of NO_2 (5 ppm) in female beagle dogs while standing at rest or exercising on a treadmill. The dogs breathed through a small face mask. Total respiratory tract uptake of NO_2 was 78% during rest and increased to 94% during exercise. In large part, this increase in uptake may be due to the increase in V_T from 0.18 L during rest to 0.27 L during exercise. Coupled with an increase in minute ventilation from 3.8 L/min during rest to 10.5 L/min during exercise, the uptake rate of NO_2 was 3-fold greater for the dogs during exercise than rest.

AX4.4. Metabolism, Distribution and Elimination of NO_2

As stated earlier, NO_2 absorption is coupled with nitrous acid (HNO_2) formation, which subsequently dissociates to H^+ and nitrite (NO_2^-). Nitrite enters the underlying epithelial cells and subsequently the blood. In the presence of red blood cells and possibly involving oxyhemoglobin, nitrite is oxidized to nitrate (NO_3^-) (Postlethwait and Mustafa, 1981). Nitrate may subsequently be excreted in the urine. There has been concern that inhaled NO_2 may lead to N-nitrosamine production, many of which are carcinogenic, since NO_2 can produce nitrite and nitrate (in blood). Nitrate can be converted to nitrite by bacterial reduction in saliva, the gastrointestinal tract, and the urinary bladder. Nitrite has been found

to react with secondary amines to form N-nitrosamines. This remains speculative since nitrosamines are not detected in tissues of animals exposed by inhalation to NO_2 unless precursors to nitrosamines and/or inhibitors of nitrosamine metabolism are co-administered. Rubenchik et al. (1995) could not detect N-nitrosodimethylamine (NDMA) in tissues of mice exposed to 4 to 4.5 ppm NO_2 for 1 h. However, NDMA was found in tissues if mice were simultaneously given oral doses of amidopyrine and 4-methylpyrazole, an inhibitor of NDMA metabolism. Nevertheless, the main source of NO_2 in the body is formed endogenously, and food is also a contributing source of nitrite from the conversion of nitrates. Thus, the relative importance of inhaled NO_2^- to N-nitrosamine formation has yet to be demonstrated.

Metabolism of inhaled NO_2 may also transform other chemicals that may be present in the body, in some cases into mutagens and carcinogens. Van Stee et al. (1983) reported N-nitrosomorpholine (NMOR), production in mice gavaged with 1 g of morpholine/kg body weight per day and then exposed (5-6 h daily for 5 days) to 16.5 to 20.5 ppm NO_2. N-nitrosomorpholine is a nitrosamine that is a potent animal carcinogen. The single site containing the greatest amount of NMOR was the gastrointestinal tract. Later, Van Stee et al. (1995) exposed mice to approximately 20 ppm $^{15}NO_2$ and to 1 g/kg morpholine simultaneously. N-nitrosomorpholine was found in the body of the exposed mice. Ninety-eight point four percent was labeled with ^{15}N that was derived from the inhaled $^{15}NO_2$ and 1.6% was derived presumably from endogenous sources.

Inhaled NO_2 may also be involved in the production of mutagenic (and carcinogenic) nitro derivatives of other co-exposed compounds, such as PAHs, via nitration reactions. Miyanishi et al. (1996) co-exposed rats, mice, guinea pigs and hamsters to 20 ppm NO_2 with various PAHs (pyrene, fluoranthene, fluorene, anthracene, or chrysene). Nitro derivatives of these PAHs were excreted in the urine of these animals, which were found to be highly mutagenic in the Ames/*S. typhimurium* assay. Specifically, the nitrated metabolite of pyrene (1-nitro-6/8-hydroxypyrene and 1-nitro-3hydroxypyrene) was detected in the urine. Further studies indicated that these metabolites are nitrated by an ionic reaction in vivo after the hydroxylation of pyrene in the liver.

AX4.5. Extra-Pulmonary Effects of NO_2 and NO

Exposure to NO_2 produces a wide array of health effects beyond the confines of the lung. Thus, NO_2 and/or some of its reactive products penetrate the lung or nasal epithelial and endothelial layers to enter the blood and produce alteration in blood and various other organs. Effects on the systemic immune system were discussed above and the summary of other systemic effects is quite brief because the literature suggests that effects on the respiratory tract and immune response are of greatest concern. A more detailed discussion of extrapulmonary responses can be found in U.S. Environmental Protection Agency (1993).

AX4.5.1. Body Weight, Hepatic, Renal, and Miscellaneous Effects

Conflicting results have been reported on whether NO_2 affects body weight gain in experimental animals as a general indicator of toxicity (U.S. Environmental Protection Agency, 1993). More recent subchronic studies show no significant effects on body weight in rats, guinea pigs, and rabbits exposed up to 4 ppm NO_2 (Tepper et al., 1993; Douglas et al., 1994; Fujimaki and Nohara, 1994).

Effects on the liver, such as changes in serum chemistry and xenobiotic metabolism, have been reported by various investigators to result from exposure to NO_2 (U.S. Environmental Protection Agency 1993). Drozdz et al. (1976) found decreased total liver protein and sialic acid, but increased protein-bound hexoses in guinea pigs exposed to 1 ppm NO_2, 8 h/day for 180 days. Liver alanine and aspartate aminotransferase activity was increased in the mitochondrial fraction but decreased in the cytoplasmic

fraction of the liver. Electron micrographs of the liver showed intracellular edema and inflammatory and parenchymal degenerative changes.

No new studies on liver effects were located in the literature since the 1993 NO_X AQCD. Several older studies have shown changes in kidney function and xenobiotic metabolism in animals following NO_2, although no histopathological changes were reported.

Increases in urinary protein and specific gravity of the urine were reported by Sherwin and Layfield (1974) in guinea pigs exposed continuously to 0.5 ppm NO_2 for 14 days. Proteinuria (albumin and alpha-, beta-, and gamma-globulins) was found in another group of animals exposed to 0.4 ppm NO_2 for 4 h/day. However, differences in water consumption or in the histology of the kidney were not found. No new studies were located in the literature since the 1993 NO_X AQCD.

Four studies (Table AX4.9) consider hematologic parameters. Several additional studies report on iron, enzymes and nucleic acid (Table AX4.10).

AX4.5.2. Brain Effects

There are several studies suggesting that NO_2 affects the brain. Decreased activity of protein metabolizing enzymes, increased glycolytic enzymes, changes in neurotransmitter levels (5-HT and noradrenaline), and increased lipid peroxidation, accompanied by lipid profile and antioxidant changes, have been reported (Farahani and Hasan, 1990, 1991, 1992; Sherwin et al., 1986; Drozdz et al., 1975). The U.S. Environmental Protection Agency (1993) concluded that "none of these effects have been replicated and all reports lack sufficient methodological rigor; thus, the implications of these findings, albeit important, are not clear and require further investigation".

A developmental neurotoxicity study by Tabacova et al.(1985) suggest that in utero exposure to NO_2 may result in postnatal neurobehavioral development changes as described in the section on reproductive and developmental toxicology.

AX4.5.3. NO

The genotoxicity of NO has been studied both in vitro and in vivo (Arroyo et al., 1992; Nguyen et al., 1992) (see Tables AX4.11-4.13). Overall, the synthesis of these older studies suggests that NO has some genotoxic potential; however, the effect is slight and to a lesser extent when compared to NO_2.

AX4.5.4. Effects of Mixtures Containing NO_2

Humans are generally exposed to NO_2 in a mixture with other air pollutants. A limitation of animal toxicity studies is the extrapolation of concentration-response data from controlled exposures to NO_2 alone, to air pollutant mixtures that are typically found in the environment. It is difficult to predict the effects of NO_2 in a mixture based on the effects of NO_2 alone. In order to understand how NO_2 is affected by mixtures of other air pollutants, studies are typically conducted with mixtures containing NO_2 and one or two other air pollutants, such as O_3 and/or H_2SO_4. The result of exposure to two or more pollutants may be simply the sum of the responses to individual pollutants (additivity), may be greater than the sum of the individual responses, suggesting some type of interaction or augmentation of the response (synergism) or may be less than additive (antagonism).

Animal toxicity studies have shown an array of interactions, including no interaction, additivity or synergism. Because no clear understanding of NO_2 interactions has yet emerged from this database, only a brief overview is provided here. A more substantive review can be found in U.S. Environmental Protection Agency (1993). There were animal studies, which studied the effects of ambient air mixtures containing NO_2 or gasoline or diesel combustion exhausts containing NO_X. Generally these studies provided useful information on the mixtures, but lacked NO_2-only groups, making it impossible to discern

the influence of NO_2. Therefore, this class of research is not described here, but is reviewed elsewhere (U.S. Environmental Protection Agency, 1993).

AX4.5.5. Simple Mixtures Containing NO_2

Most of the interaction studies involved NO_2 and O_3. After subchronic exposure, lung morphology studies did not show any interaction of NO_2 with O_3 (Freeman et al., 1974) or with SO_2 (Azoulay et al., 1980). Some biochemical responses to NO_2 plus O_3 display no positive interaction or synergism. For example, Mustafa et al. (1984) found synergism for some endpoints (e.g., increased activities of O_2 consumption and antioxidant enzymes), but no interaction for others (e.g., DNA or protein content) in rats exposed for 7 days. Ichinose and Sagai (1989) observed a species dependence in regard to the interaction of O_3 (0.4 ppm) and NO_2 (0.4 ppm) after 2 weeks of exposure. Guinea pigs, but not rats, had a synergistic increase in lung lipid peroxides. Rats, but not guinea pigs, had synergistic increases in antioxidant factors (e.g., non-protein thiols, vitamin C, glucose-6-phosphate dehydrogenase, GSH peroxidase). Duration of exposure can have an impact. Schlesinger et al. (1990) observed a synergistic increase in prostaglandin E_2 and $F_{2\alpha}$ in the lung lavage of rabbits exposed acutely for 2 h to 3.0 ppm NO_2 plus 0.3 ppm O_3; the response appeared to have been driven by O_3. However, with 7 or 14 days of repeated 2-h exposures, only prostaglandin E_2 was decreased and appeared to have been driven by NO_2; there was no synergism (Schlesinger et al., 1991).

Using an infectivity model, Ehrlich et al. (1977) found additivity after acute exposure to mixtures of NO_2 and O_3 and synergism after subchronic exposures. Exposure scenarios involving NO_2 and O_3 have also been performed using a continuous baseline exposure to one concentration or mixture, with superimposed short-term peaks to a higher level (Ehrlich et al., 1979; Gardner, 1980, 1982; Graham et al., 1987). Differences in the pattern and concentrations of the exposure are responsible for the increased susceptibility to pulmonary infection, without indicating clearly the mechanism controlling the interaction.

Some aerosols may potentiate response to NO_2 by producing local changes in the lungs that enhance the toxic action of co-inhaled NO_2. The impacts of NO_2 and H_2SO_4 on lung host defenses have been examined by Schlesinger and Gearhart (1987) and Schlesinger (1987). In the former study, rabbits were exposed for 2 h/day for 14 days to either 0.3 ppm or 1.0 ppm NO_2, or 500 $\mu g/m^3$ H_2SO_4 alone, or to mixtures of the low and high NO_2 concentrations with H_2SO_4. Exposure to either concentration of NO_2 accelerated alveolar clearance, whereas H_2SO_4 alone retarded clearance. Exposure to either concentration of NO_2 with H_2SO_4 resulted in retardation of clearance in a similar manner to that seen with H_2SO_4 alone. Using a similar exposure design but different endpoints, exposure of rabbits to 1.0 ppm NO_2 increased the numbers of PMNs in lavage fluid at all time points (not seen with either pollutant alone), and increased phagocytic capacity of AMs after two or six exposures (Schlesinger et al., 1987). Exposure to 0.3 ppm NO_2 with acid, however, resulted in depressed phagocytic capacity and mobility. The NO_2/H_2SO_4 mixture was generally either additive or synergistic, depending on the specific cellular endpoint being examined.

Exposure to high levels of NO_2 (#5.0 ppm) with very high concentrations of H_2SO_4 (1 mg/m^3) caused a synergistic increase in collagen synthesis rate and protein content of the lavage fluid of rats (Last and Warren, 1987; Last, 1989).

AX4.5.6. Complex Mixtures Containing NO_2

Although many studies have examined the response to NO_2 with only one additional pollutant, the atmosphere in most environments is a complex mixture of more than two materials. A number of studies have attempted to examine the effects of multi-component atmospheres containing NO_2, but as mentioned before, in many cases the exact role of NO_2 in the observed responses is not always clear. One study by Stara et al. (1980) deserves mention because pulmonary function changes appeared to progress after exposure ceased.

In the study by Stara et al. (1980), dogs were exposed for 68 months (16 h/day) to raw or photochemically reactive vehicle exhaust which included mixtures of NO_X: one with a high NO_2 level and a low NO level (0.64 ppm, NO_2; 0.25 ppm, NO), and one with a low NO_2 level and a high NO level (0.14 ppm, NO_2; 1.67 ppm, NO). At the end of exposure, the animals were maintained for about 3 years in normal indoor air. Numerous pulmonary functions, hematological and histological endpoints were examined at various times during and after exposure. The lack of an NO_2-only or NO-only group precludes determination of the nature of the interaction. Nevertheless, the main findings are of interest. Pulmonary function changes appeared to progress after exposure ceased. Dogs in the high NO_2 group had morphological changes considered to be analogous to human centrilobular emphysema. Because these morphological measurements were made after a 2.5- to 3-year holding period in clean air, it cannot be determined with certainty whether these disease processes abated or progressed during this time. This study suggests progression of damage after exposure ends.

Table AX4.1. Oxidant and antioxidant homeostasis.

ppm	EXPOSURE	GENDER	AGE	SPECIES (STRAIN)	EFFECTS	REFERENCES
0.04 0.4 4.0	Continuous, 9 and 18 mos	M	8 wks	Rat (Wistar)	NPSHs increased at ≥0.4 ppm after 9 or 18 mos; GSH peroxidase activity increased after a 9-mo exposure to 4.0 ppm; G-6-P dehydrogenase was increased after a 9- and 18-mo exposure to 4.0 ppm; no effects on 6-P-G dehydrogenase , SOD disulfide reductase; some GSH S-transferase had decreased activities after 18-mo exposure to ≥0.4 ppm.	Sagai et al. (1984) Ichinose et al. (1983)
0.4	2 wks	NR	NR	Rat Guinea Pig	No effect on TBA reactants, antioxidants, or antioxidant enzyme activities.	Ichinose and Sagai (1989)
0.4 1.2 4.0	Continuous, 4 mos	M	13 wks	Rat (Wistar)	Duration dependent pattern for increase in activities of antioxidant enzymes; increase, peaking at wk 4 and then decreasing. Concentration-dependent effects.	Ichinose and Sagai (1982)
0.4-0.5	Continuous, 1.5 yrs	F	NR	Mouse (NR)	Growth reduced; Vitamin E (30 or 300 mg/kg diet) improved growth.	Csallany (1975)
0.5 1.0	Continuous, 17 mos	F	4 wks	Mouse (C57B1/6J)	At 1 ppm, GSH-peroxidase activity decreased in vitamin E-deficient mice and increased in Vitamin E-supplemented mice.	Ayaz and Csallany (1978)
1.0	4 h/day, 6 days	NR	NR	Rat (Sprague-Dawley)	Vitamin E-supplement reduced lipid peroxidation.	Thomas et al. (1967)
1.0 2.3 6.2	Continuous, 4 days	M	8 wks	Rat (Sprague-Dawley)	Activities of GSH reductase and G-6-P dehydrogenase increased at 6.2 ppm proportional to duration of exposure; plasma lysozyme and GSH peroxidase not affected at 6.2 ppm; no effects at 1.0 or 2.3 ppm.	Chow et al. (1974)
1.2 1.8	Continuous, 3 days	M	12 wks	Rat (Sprague-Dawley)	Increases in G-6-P dehydrogenase, isocitrate dehydrogenase, disulfide reductase, and NADPH cytochrome c reductase activities at 1.8 ppm only.	Lee et al. (1989, 1990)
2.0 10.0	3 days	M/F	5->60 days	Rat (Wistar) Guinea pig (Dunkin Hartley)	Decreased SOD activity in 21-day-old animals.	Azoulay-Dupuis et al. (1983)
2.0 4.0 10.0	14 days 10 days 7 days	M	12-24 wks	Rat (Wistar)	G-6-P dehydrogenase increased at ≥2 ppm; at 2 ppm, 14 days of exposure needed	Mochitate et al. (1985)

ppm	EXPOSURE	GENDER	AGE	SPECIES (STRAIN)	EFFECTS	REFERENCES
3.0	7 days	M/F	1 day to >8 wks	Rat (Sprague-Dawley)	Increased lipid peroxidation (TBA-reactive substances) with vitamin E deficiency.	Sevanian et al. (1982)
9.5	7 h/day, 5 days/wks, 6 mos	M	In utero and 6 mos	Rat (Fischer 344)	Increase in GSH reductase activity in younger rats and SDH peroxidase activity in older rats.	Mauderly et al. (1987)
3.0 7.0 10 15	4 days 4 days 4 days 1-7 days	M	NR	Rat (Sprague-Dawley)	No effects on parameters tested. Increase in lung weight, G-6-P dehydrogenase, GSH reductase, and GSH peroxidase activities. Increased lung weight, G-6-P dehydrogenase; and GSH reductase activities. Increase in lung weight, DNA content, G-6-P dehydrogenase, 6-P-G dehydrogenase, GSH reductase, disulfide reductase, GSH peroxidase, disulfide reductase, succinate oxidase, and cytochrome oxidase activities; no effect on lung protein	Mustafa et al. (1979)
4.0	3 h	M/F	21-33 yrs	Human	Decreased elastase inhibitory capacity and increased lipid peroxidation products in BAL of subjects not administered supplement of vitamin C and E prior to NO_2 exposure.	Mohsenin (1991)
5.0 10.0	Continuous, 24 h 7 days	M	NR	Rats (CD Cobs)	Changes in the GSH levels in blood and lung occurred in rats exposed for 24 h, but returned to normal after 7 days.	Pagani et al. (1994)
6.0 15 28	4 h/day, 30 days 7 days	F	NR	Mouse (NR)	Increase in GSH reductase and G-6-P dehydrogenase activities. Increase in GSH levels, G-6-P dehydrogenase, and GSH peroxidase activities.	Csallany (1975)
9.5	7 h/day, 5 days/wk, 24 mos	M	18 wks	Rat (Fischer 344)	Increase in GSH reductase activity in BAL.	Mauderly et al., (1990)
10.0	Continuous 3 days, 20 days	NR	NR	Rat (Fischer 344)	Decreased GSH/GSSG ratio in blood and BAL fluid, but not in lung type II cells. Lipid peroxidation was decreased in type II cells at 3 days, but was similar to controls at 20 days. mRNA expression of the enzymes involved in the biosynthesis ((GCS and GS) was decreased at both time points. (GT (redox of GSH) mRNA expression was increased.	Hochscheid et al. (2005)
14.0	NR	NR	NR	Human	Rapid depletion of vitamin C, glutathione and vitamin E	Halliwell et al. (1992)

M = Male
NPSHs = Nonprotein sulfhydryls
G-6-P dehydrogenase = Glucose-6-phosphate dehydrogenase
G6-P-G dehydrogenase = 6-phosphosgluconate dehydrogenase
SOD = superoxide dismutase
F = Female
NR = Not Reported
NADP = Nicotinamide-adenine dinucleotide phosphate (reduced form)
TBA = Thiobarbituric acid
BAL = Bronchoalveolar lavage
GR = Glutathione reductase
GS = Glutathione synthetase
GSH = Reduced glutathione
GSSG = Oxidized glutathione
(-GCS - (-Glutamyl-cystein synthetase
(-GT - (-Glutamyltranspeptidase

Table AX4.2. Lung amino acids, proteins, lipids, and enzymes.

ppm	EXPOSURE	GENDER	AGE	SPECIES (STRAIN)	EFFECTS	REFERENCES
0.4 1.0 3.0 5.0 5.0 0.4	72 h 3 h Continuous, 1 wk	M	NR	Guinea Pig (Hartley)	No effect at 0.4 ppm; increase in BAL protein in vitamin C-depleted, but not normal, animals at 1.0 ppm and above. Increased BAL protein in vitamin C-depleted guinea pigs 15 h postexposure. No effect on BAL protein.	Selgrade et al. (1981)
0.4	Continuous, 1 wk	M	NR	Guinea Pig	Increased protein content of BAL from vitamin-C-deficient guinea-pigs.	Sherwin and Carlson (1973)
0.4 1.2 4.0	1-14 wks	M	22-24 wks	Rat (Wistar)	Complex concentration and duration dependence of effects. Example: at 0.4 ppm, cytochrome P-450 levels decreased at 2 wks, returned to control level by 5 wks. At 1.2 ppm, cytochrome P-450 levels decreased initially, increased at 5 wks, and decreased at 10 wks. Effects on succinate-cytochrome c reductase also.	Takahashi et al. (1986)
0.5 1.0	6 h/day, 5 days/wk, 4 wks	M	NR	Rat (Fischer 344)	0.5 ppm; increase in urinary hydroxylysine output starting during wk 1; BAL hydroxylysine level, angiotensin-converting enzyme level, and BAL protein content unchanged. 1.0 ppm: gradual increase in urinary hydoxylysine output, becoming significant the week after exposure ended; BAL hydroxylysine level lower following exposure and 4 wks postexposure; andiotensin-converting enzyme level increased.	Evans et al. (1989)
1.0 7.5 15 25 30	6 h/day, 2 days	M	NR	Rat (Fischer 344)	Concentration dependent increase in urinary hydroxylysine output and BAL hydroxyxlysine content, but only significant at ≥7.5 ppm and 15 ppm, respectively; angiotensin-converting enzyme levels and BAL protein increased in highest-exposed groups.	Evans et al. (1989)
1.0 5.0	7 h/day, 5 days/wk, up to 15 wks	M/F	14-16 wks	Rat (Fischer 344)	Change in BAL and tissue levels of enzymes early in exposure, resolved by 15 wks.	Gregory et al. (1983)
1.2 1.2 4.0	7 days	M	10 wks	Rat (Wistar)	Decrease in levels of cytochrome P-450 at 1.2 ppm.	Mochitate et al. (1984)
2.0	1, 2, or 3 wks	M	NR	Guinea pig	Increased lactate dehydrogenase (LDH) content of the lower lobes of the lung.	Sherwin and Carlson (1973)
0.8 5 10	1 or 3 days	M	NR	Rat (Sprague-Dawley)	BAL protein content significantly increased in a concentration- and exposure duration-dependent manner, with the change becoming significant at 5 ppm for 3 days and at 10 ppm for ≥1 day of exposure.	Müller et al. (1994)
2.0 4.0 10	14 days 10 days 7 days	M	12-24 wks	Rats (Wistar)	Increase activity of lung glycolytic enzymes.	Mochitate et al. (1985)
3.0	7 days	M/F	8 wks	Rat (Sprague-Dawley)	Various changes in lung homogenate protein and DNA content and enzyme activities, changes more severe in vitamin E-deficient rats.	Elsayed and Mustafa (1982)

ppm	EXPOSURE	GENDER	AGE	SPECIES (STRAIN)	EFFECTS	REFERENCES
3.6 7.2 10.8 14.4	24 h 12 h 8 h 6 h	M	10-12 wks	Rat (Sprague-Dawley)	Increased BAL protein ≥7.2 ppm.	Gelzleichter et al. (1992)
4.0 10	10 days 7 days	M	21-24 wks	Rat (Wistar)	Initial decrease in lung protein content followed by an increase; changes on microsomal enzyme activities.	Mochitate et al. (1984)
4.0 10 25	6 h/day 5 days/wk, 7, 14, and 21 days	M	NR	Rat (Wistar)	Increased gamma-glutamyl transferase on days 14 and 21; no consistent effect on alkaline phosphatase, LDH, or total protein.	Hooftman et al. (1988)
4.5	16 hrs	M/F	NR	Guinea pig (Hartley)	Increased lung wet weight, alterations in lung antioxidant levels in Vitamin C- deficient animals.	Hatch et al. (1986)
4.8	3 h	M	NR	Guinea pig (Hartley)	Increased lung lavage fluid protein content in vitamin C-deficient animals.	Hatch et al. (1986)
4.8	8 h/day, 7 days	M	8 wks	Mouse (Swiss Webster)	No significant changes in lung homogenate parameters.	Mustafa et al. (1984)
5.0	14-72 h	F	NR	Mouse (NR)	Increase in lung protein (14 to 58 h) by radioactive label incorporation.	Csallany (1975)
5.0	2 wks	M	5 wks	Rat (Fischer 344)	Increased amounts of the tryptophan metabolites and xanthurenic and kynurenic acids excreted in urine during wk 2 of exposure, but had returned to normal levels by wk 4.	Suzuki et al. (1988)
5.0	6 h/day, 6 days	NR	NR	Mice	Modest increase in albumin in BAL; no effect on LDH or lysosomal enzyme peroxidase.\	Rose et al. (1989)
5.0-25.0	Continuous, 7 days	M	10-11 wks	Rat (Sprague-Dawley)	Concentration-related increase in collagen synthesis rate; 125% increase in rats exposed to 5.0 ppm.	Last et al. (1983)
5.0 20.0 50.0	3 h	NR	NR	Rabbit (New Zealand)	Benzo [a] pyrene hydroxylase activity of tracheal mucosa not affected.	Palmer et al. (1972)
5.0	Continuous, 1, 3, or 7 days	M	NR	Rat (Sprague-Dawley)	Increased BAL protein at 3 days (day 7 not measured); increased (120% collagen synthesis at 7 days (not measured other days).	Last & Warren (1987)
8.0	Continuous, 14 days	F	NR	Mouse (NR)	Increase in lung protein.	Csallany (1975)
9.5	7 h/day, 5 days/wk, 6 mos	M	In utero and 6 mos	Rat (Fischer 344)	Increase in BAL alkaline phosphatase, acid phosphatase, and LDH in older rats only.	Mauderly et al. (1987)
9.5	7 h/day, 5 days/wk, 24 mos	M	18 wks	Rat (Fischer 344)	Increase in BAL levels of LDH and alkaline phosphatase activities and in collagenous peptides.	Mauderly et al. (1990)
10	24 h or 7 days	M	NR	Rat (CD cobs)	Protein content of BALF increased significantly in rats after only 24 h. BALF elastase activity was not affected. Concentration-dependent increase in α-1 proteinase inhibitor content after 24 h of exposure, but not with longer exposures.	Pagani et al. (1994)
10	Continuous, 14 days	M	8 wks	Rat (Wistar)	Changes in several enzymes in whole lung homogenates.	Sagai et al. (1982)

ppm	EXPOSURE	GENDER	AGE	SPECIES (STRAIN)	EFFECTS	REFERENCES
10 20 30 40	4 h	M	NR	Rat (Long Evans)	Increased activities of various enzymes, sialic acid, and BAL protein; attenuation by high dietary levels of vitamin E.	Guth and Mavis (1985, 1986)
10	24 h/day, 0 (control), 3 days or 20 days	NR	NR	Rat (Fischer 344)	LPO decreased in type II pneumocytes after 3 days compared to controls but remained comparable to controls after 20 days. Authors stated that LPO is a very early reaction during oxidative stress and that the decrease after 3-day exposure suggests an adaptation mechanism. Exposure duration-dependent, statistically significant increase in GPx and GR enzyme activities after 3 and 20 days over control values. Changes in mRNA expression of GSH synthesizing enzymes in type II pneumocytes were also observed.	Hochscheid et al. (2005)
10	24 h/day, for 0, 3, 20, or 28 days	M	NR	Rat (Sprague-Dawley)	Uptake of surfactant-like liposomes by type II pneumocytes in the presence or absence of SP-A was faster and significantly higher in cells from all NO_2 exposed groups than in control cells. No difference in the uptake kinetics between cells from exposed groups of different duration. Increase in liposome uptake suggests NO_2 exposure likely disrupted cell membranes to allow liposomes to enter the cells easily. Lipid uptake associated with duration-dependent increase in internalization of label found in PC fraction. Suggests increased demand of PC in lung injury.	Muller et al. (2003)
0.8 5.0 10	Presumably continuous, 1 day or 3 days	M	NR	Rat (Sprague-Dawley)	Phospholipid component in BAL increased in a concentration- and exposure duration-dependent manner, with significance only at 10 ppm, but not at 5 ppm or below, for ≥1 day of exposure. PC content in BAL of exposed animal did not change significantly compared to controls. At 10 ppm, but not at 5 ppm or below, percentage of saturated PC decreased and that of unsaturated PC increased statistically significant, while significant decreases in palmitic acid (16:0) and increases in arachidonic acid (20:4) contained in PC were observed. Sphingomyelin – as a marker for an influx of serum into the alveolar airspace – was also not changed by NO_2 exposure. Functional studies on surfactant phospholipid extracts indicated increased values for the surface tension at equilibrium, and for the maximal and minimal surface tension of animals exposed to ≥5 ppm, but not to 0.8 ppm. Suggests NO_2 directly impaired surface tension at ≥5 ppm. Structure of the SP-A not altered by NO_2 exposure. Authors suggested exposure to NO_2 impaired surfactant components may be used as markers of altered surfactant metabolism.	Muller et al. (1994)

ppm	EXPOSURE	GENDER	AGE	SPECIES (STRAIN)	EFFECTS	REFERENCES
5 10	24 h or 24 h/day for 7 days	M	NR	Rat (CD Cobs)	Concentration-dependent increase in α-1 PI content. Exposure to 5 and 10 ppm NO_2 significantly increased α-1 PI content only after 24 h and returned to control values after 7 days at each exposure concentration. Since blood GSH content was also increased together with α-1 PI content at 24 h, authors suggested the increase in these parameters can be considered a prompt protective response resulting in no further increase of α-1 PI.	Pagani et al. (1994)

LPO = Lipid peroxidation
PC = Phosphatidylcholine
SP-A = Surfactant protein-AGPx = Glutathione peroxidase
GPx = Glutathione peroxidase
GR = Glutathione reductase
GSH = Glutathione
α-1 PI = α-1 proteinase inhibitor

Table AX4.3. Alveolar macrophages and lung host defense.

ppm	EXPOSURE	GENDER	AGE	SPECIES (STRAIN)	EFFECTS	REFERENCE
0.05 base + 2.0 peaks	3 h base + three 15-min peaks	NR	NR	Human	No effects at 0.05 ppm NO_2 with peaks; trend ($p < 0.07$) towards AMs losing ability to inactivate influenza virus at 0.6 ppm.	Frampton et al. (1989)
0.6	3 h	NR	NR	Human	No effects at 0.05 ppm NO_2 with peaks; trend ($p < 0.07$) towards AMs losing ability to inactivate influenza virus at 0.6 ppm.	Frampton et al. (1989)
0.1 1.0 5.0 20	1 h	NR	NR	Rat (Sprague-Dawley) (in vitro)	At 5.0 ppm: increase in LTB4; concentration-related decrease in SOD production in AMs at ≥1.0 ppm; increase in LDH in AMS at 5.0 and 20 ppm	Robinson et al. (1990)
0.2 0.5 2.0			Gestation 12 wks	Rat (Brown-Norway)	Reactive oxygen species generation from alveolar macrophages was significantly suppressed in NO_2 exposed weanling animals; no changes in reactive oxygen generating capability in the embryonic exposed animals.	Kumae and Arakawa (2006)
0.5 0.1 base + 1.0 peak 2.0 0.5 base + 2.0 peak	Continuous, 24 wks Continuous base + 3-h peak, 5 days/wk, 24 wks Continuous, 33 wks Continuous base + 1-h peak, 5 days/wk, 33 wks	NR	NR	Mouse	No effects on AM morphology at 0.5 ppm continuous or 0.1 ppm base + peak. After 21 wks of exposure to 2.0 ppm continuous or 0.5 ppm base + peak, morphological changes were identified, such a loss of surface processes, appearance of fenestrae, bleb formation, and denuded surface areas.	Aranyi et al. (1976)
0.3 1.0	2 h/day 2, 6, 13 days	M	NR	Rabbit (New Zealand)	Decreased phagocytic ability of AMs at 0.3 ppm after 2 days of exposure; increased at 1.0 ppm after 2 days of exposure; no effect on cell number or viability; random mobility reduced at 0.3 ppm only; no effects after 6 days of exposure.	Schlesinger (1987)
0.3 1.0	2 h/day up to 14 days	M	NR	Rabbit (New Zealand)	Increase in alveolar clearance.	Schlesinger and Gearhart (1987)

ppm	EXPOSURE	GENDER	AGE	SPECIES (STRAIN)	EFFECTS	REFERENCE
0.3 1.0 3.0 10 1.0 10	2 h 2 h/day, 14 days	M	NR	Rabbit (New Zealand)	Concentration-related acceleration in clearance of particles from lung with the greatest increase at two lowest concentrations, effects from repeated exposures similar to those seen after acute exposures to same concentrations.	Vollmuth et al. (1986)
0.5	0.5, 1, 5 and 10 days exposure	NR	NR	Rat (NR)	Superoxide production in alveolar macrophages from BALF, stimulated by phorbol myrisate acetate (PMA), was decreased after 0.5 days of exposure, and continued to be depressed after 1, 5, and 10 days.	Robinson et al. (1993)
0.5 base + 1.5 peak 2.0 base +6.0 peak	Base 22 h/day, 7 days/wk + two 1-h peaks, 5 days/wk, 6 wks	M	1 day and 6 wks	Rat (Fischer 344)	Trend towards increase in number of AMs and cell volume in younger animals; increase in number of AMs and cell volume in older rats.	Crapo et al. (1984) Chang et al. (1986)
0.5 1.3 2.7	Continuous, 28 days	M	6 wks	Rat (Wistar)	Increase in AMs in highest exposed group; no effects noted in 2 lowest exposure groups.	Rombout et al. (1986)
1.0 2.0 4.0	24 h/day, 12 wks			Guinea pig (NR) Rat (NR)	IgE-mediated histamine release from lung mast cells was enhanced in guinea pigs, but not rats exposed to 4.0 ppm. No effect observed at lower concentrations.	Fujimaki and Nohara (1994)
1.0 5.0 15	6 h/day, 2 days	NR	4-6 wks	Mouse (CD1)	Exposure-related decrease in AM phagocytosis from 1.0-5.0 ppm, decrease was not further affected by 15 ppm.	Rose et al. (1989)
1.0 2.0 4.0	24 h/day, 12 wks			Guinea pig (NR) Rat (NR)	IgE-mediated histamine release from lung mast cells was enhanced in guinea pigs, but not rats exposed to 4.0 ppm. No effect observed at lower concentrations.	Fujimaki and Nohara, (1994)
1.0 + 0.9 ppm No 15 24	7 h/day, 5 days/wks for 11 or 22 exposures	NR	NR	Rat (Long Evans)	Stimulated clearance of particles from lung at lowest concentration, but decreased clearance rate at two highest concentrations.	Ferin and Leach (1977)
1.0 5.0 base + 5.0 peaks	7 h/day, 5 days/wks Base 7 h/day, 5 days/wks; two 1.5-h peaks/day; 15 wks	M/F	14-16 wks	Rat (Fischer 344)	Accumulation of AMs. Superimposed peak exposures produced changes that may persist with continued exposures.	Gregory et al. (1983)
1.3-17	NR (“acute”)	F	NR	Rat (Sprague-Dawley)	Decreased production of superoxide anion radical.	Amoruso et al. (1981)
2.0 10	3 days	M/F	5, 10, 21, 45, 55, 60, and >60 days	Guinea pig (Dunkin Hartley) Rat (Wistar)	Newborns were less affected than adults when AMs were tested for SOD levels.	Azoulay-Dupuis et al. (1983)
2.0	8 h/day, 5 days/wk, 6 mo	M/F	3-4 yrs	Baboon	Impaired AM responsiveness to migration inhibitory factor.	Green and Schneider (1978)

ppm	EXPOSURE	GENDER	AGE	SPECIES (STRAIN)	EFFECTS	REFERENCE
2.0	4 h	NR	NR	Human	Decreased phagocytosis and superoxide anion release.	Devlin et al. (1992)
2.7	24 h	M	6 wks	Rat (Wistar)	Increase in number of AMs.	Rombout et al. (1986)
3-6	3 h	NR	NR	Dog (Beagle)	Enhanced swelling of AMs.	Dowell et al. (1971)
3.6 12.1	1 h 2 h	F	NR	Rat (Sprague-Dawley) (in vitro)	Enhanced macrophage agglutination with concanavalin A at both concentrations tested.	Goldstein et al. (1977)
4 10 25	6 h/day, 7, 14, or 21 days	M	NR	Rat (Wistar)	Changes in morphology at all concentrations; increase in number of AMs at ≥10 ppm; phagocytic capacity reduced after 14 and 21 days of exposure to 25 ppm.	Hooftman et al. (1988)
4.0	10 days		19-23 wks		Increase in number of AMs; no increase in PMNs; increased metabolic activity, protein, and DNA synthesis; all responses peaked on day 4 and returned to normal on day 10.	Mochitate et al. (1986)
4.0 8.0	Up to 10 days	NR	NR	Rat (Fischer 344)	Increase in number of AMs at both concentrations, reaching a peak on day 3 and 5; no increase in number of PMNs; decrease in AM viability throughout exposure period. Suppression of phagocytic activity after 7 days of exposure to 4 ppm and after 5 days of exposure to 8 ppm; returned to normal value at 10 days. Decrease in superoxide radical production, but at 4 ppm, the effect became significant on days 3, 5, and 10; at 8 ppm, the effect was significant at all time periods tested.	Suzuki et al. (1986)
5.0	7 days	F	NR	Mouse (CD-1)	No effect on phagocytic activity.	Lefkowitz et al. (1986)
5 15	3 h after infection with parainfluenza 3 virus	NR	NR	Rabbit (New Zealand)	AMs lost resistance to challenge with rabbit pox virus after exposure to 15 ppm.	Acton and Myrvik (1972)
5 10 15	3 h	M Fb	NR	Humans (in vitro exposure)	No change in cell viability, release of neutrophil chemotactic factor, or interleukin-1.	Pinkston et al. (1988)
5-60	3 h	NR	NR	Rabbit (New Zealand)	Inhibition of phagocytic activity.	Gardner et al. (1969) Acton and Myrvik (1972)
7.0	24 h	NR	NR	Rabbit	Increased rosette formation in AMs treated with lipase.	Hadley et al. (1977)
9.5	7 h/day; 5 days/wk; 18-22 mo	M	18 wks	Rat (Fischer 344)	No effect on long-term clearance of radiolabeled tracer particles.	Mauderly et al. (1990)
10	Continuous 7 days	NR	NR	Rat (NR)	High influx of PMNs in the lung (BALF) after 24 h of exposure, reversed for macrophages; no change in the lymphocyte population.	Pagani et al. (1994)
10	35 days	NR	NR	Guinea pig	63% increase in epithelial cells positive for macrophage congregation.	Sherwin et al. (1968)
10	4 h	F	NR	Mouse (Swiss)	Increase in total pulmonary cells in animals infected with some species of bacteria.	Jakab (1988)
10 25	24 h	M	12-13 wks	Rat (Sprague-Dawley)	Decreased phagocytosis at 25 ppm only.	Katz and Laskin (1976)

ppm	EXPOSURE	GENDER	AGE	SPECIES (STRAIN)	EFFECTS	REFERENCE
Clearance						
3 9	6 h/day, 6 days/wk, for 2 wks	F	NR	Guinea Pig	Significant, dose-dependent decrease in ciliary activity, significant at 3 ppm (12%) and 9 ppm (30%), and increase in eosinophil accumulation on epithelium and submucosal layer.	Ohashi et al. (1994)
10 20	14 h/day, for 15 days, 20 or 25 days	M	NR	Mouse (C57BL/5)	20 ppm NO_2 induced an increased mucus production due to goblet cell hyperplasia in the central airways.	Wegman and Herz (2002)
Alveolar Macrophage Endpoints						
0.5	8 h/day, 5 days/wk, for 0.5, 1, 5, or 10 days	M	NR	Rat (Sprague-Dawley)	Acute depression of pulmonary arachidonate metabolism observed. Unstimulated AM synthesis of LTB4 depressed within 1 day and also on day 5 of exposure. Acute depression of AM synthesis of TxB2, LBT4, and 5-HETE on stimulation by the calcium ionophore, A23187, within 1 day of exposure but not with longer exposure, while 5-HETE increased significantly at 10 days of exposure only. Suggests rapid depression of cyclooxygenase and 5-lipoxygenase activities. ZAS-stimulated LTB4 production delayed until 5 days and remained lower at 10 days. AM superoxide production stimulated by PMA was rapidly and continuously depressed throughout the study. BAL fluid levels of LTB4 and TxB2 paralleled ex vivo depression of AM production.	Robinson et al. (1993)
0.2 0.5 2.0	Continuous, presumably 7 days/wk, up to 12 wks	F	Neonates or 5 wks old	Rat (Brown-Norway)	Animals were exposed during embryonic or weanling (5-wks old) period. ROS generation was significantly suppressed at 0.5 and 2.0 ppm NO_2 in animals exposed during the weanling period. Cytokine level measurement in AM culture mediums indicated that inflammatory reactions (significant increases in TFNα and IFNγ) were initiated at 8 wks and terminated at 12 wks in animals exposed during the embryonic period while inflammatory reactions (significantly increased TFNα level) were not initiated at 8 wks but take place at 12 wks in animals exposed as weanlings. Results suggest that NO_2 exposure from the weanling period has stronger effects on AM activity.	Kumae and Arakawa (2006)

Table AX4.4. Lung permeability and inflammation.

ppm	EXPOSURE	GENDER	AGE	SPECIES (STRAIN)	EFFECTS	REFERENCE
0.8 5 10	Presumably continuous, 1 day or 3 days	M	NR	Rat (Sprague-Dawley)	BAL protein content significantly increased in a concentration- and exposure duration-dependent manner, with the change becoming significant at 5 ppm for 3 days and 10 ppm for ≥1 day of exposure.	Muller et al. (1994)
5 10	24 h or 24 h/day for 7 days	M	NR	Rat (CD Cobs)	Exposure induced inflammatory response in the lungs. At 10 ppm, influx of PMN, maximal at 24 h, but no influx observed after 7 days of exposure, a trend that was also observed with protein content in BAL fluid. In contrast, no influx of macrophages was observed, but the influx was maximal after 7 days of exposure. No significant changes in lymphocyte counts at any exposure concentration and protein content in BAL fluid not significantly affected at 5 ppm. Protein content of BAL fluid increased significantly only after 24 h of exposure to 10 ppm NO_2.	Pagani et al. (1994)
5 25	6 h/day for 1, 3, or 5 days	NR	NR	Mouse (C57BL/6)	Exposure to 5 ppm NO_2 did not cause any lung inflammation or injury. Exposure to 25 ppm NO_2 induced acute lung injury (characterized by increases in protein, LDH, macrophages, and neutrophils recovered by BAL) that peaked after 3 days, lesions within terminal bronchioles, and AHR. OVA-sensitized animals exposed to 25 ppm, but not 5 ppm, NO_2 showed augmentation of eosinophilic inflammation and terminal bronchiolar lesions, which extended significantly into the alveoli. No increased expression of mucus cell-associated gene products in non-sensitized or OVA-sensitized animals exposed at any concentration.	Poynter et al. (2006)
5 20	3 h	M	NR	Mouse (BALB/c)	Exposure of OVA-challenged animals to 20 ppm produced BHR and caused significant increase in neutrophils and fibronectin concentration, significant reduction in eosinophil count, and exudation and release of IL-5 in BAL fluid 24 h and/or 72 h after exposure. Exposure to 5 ppm did not modify BHR, but significantly reduced pulmonary eosiniphilic inflammation (reduced esinophilic count and eosinophil peroxidase activity) and the production of IL-5 in the BAL fluid. Exposure to NO_2 did not cause any significant changes in IgE anti-OVA antibody in exposed animals, while IgG1 titers were significantly increased in animals exposed only to 5 ppm NO_2, compared to controls. There was no development of mucosal metaplasia in any NO_2 exposed group compared to controls.	Proust et al. (2002)
5 10 20	24 h/day, for 3 or 25 days	M	NR	Rat (Sprague-Dawley)	Exposure to NO_2 exhibited concentration- and exposure duration-dependent, and tissue localization-specific differences in Clara cell proliferation. Increased proliferation (measured as BrdU-LI) in both bronchial and bronchiolar epithelium of all exposed groups, with significance starting at exposure to 5 ppm for 3 or 25 days. Exposure to 5 and 10 ppm NO_2 for 3 days showed significantly higher proliferative activity in bronchiolar epithelium than in the bronchial epithelium for corresponding exposure groups, while the difference in proliferation between proximal and distal airways diminished after 25 days of exposure. Clara cell proliferation was not accompanied by a change in Clara cell numbers in any of exposure groups, a finding the authors explained by the assumption that the process of proliferation takes place at the same rate as Clara cell differentiates into other cells, a transition that leads to the loss of phenotypic Clara properties in differentiating cells.	Barth and Muller (1999)
1.2	24 h/day, for 3 days	M	NR	Rat (Sprague-Dawley)	No significant differences in cell viability and percentages of pulmonary AMs or PMNs between animals exposed to 1.2 ppm NO_2 and controls.	Bermudez (2001)

ppm	EXPOSURE	GENDER	AGE	SPECIES (STRAIN)	EFFECTS	REFERENCE
10 20	14 h/day, for 15 days, 20 or 25 days	M	NR	Mouse (C57BL/5)	Exposure to 10 ppm for 15 days – the only exposure duration used for this concentration – did not significantly affect influx of inflammatory cells (leukocyte subpopulations and macrophages). 20 ppm NO_2 induced airway and parenchymal inflammation – dominated by a significant influx of macrophages and neutrophils –, peaking at 15 days of exposure and declining at day 25.	Wegman and Herz (2002)
3.6 7.2 10.8 14.4	24 h, 12h, 8h, and 6 h, respectively, for 3 days, giving a C H T of 86.4 ppm-h	M	NR	Rat (Sprague-Dawley)	Significant cell proliferation (increased labeling index) in peripheral airways compared to controls, regardless of concentration or exposure duration. Suggests Haber's law (c H t = k) was not followed over the concentration ranges studied. No proliferative response was observed in alveolar epithelium.	Rajini et al. (1993)
0.5	8 h/day, 5 days/wk, for 0.5, 1, 5, or 10 days	M	NR	Rat (Sprague-Dawley)	No effect on weight gain. No effects on neutrophil, lymphocyte macrophage/monocyte levels or cell population percentages in BAL. Suggests no significant influx of inflammatory cells into lung airways and alveolar spaces.	Robinson et al. (1993)
5 10 20	24 h/day, for 3 or 25 days	M	NR	Rat (Sprague-Dawley)	Compared to controls, proliferative activity significantly increased, but with no concentration-dependence in respiratory bronchiolar epithelium at 5 ppm and above after 3-day exposure, but increase was concentration-dependent, with significance at ≥10 ppm following 25-day exposure. Proliferative activity increased in a concentration-dependent manner in bronchial epithelium, with significance only at 20 ppm after 3 days of exposure and at ≥10 ppm following 25 days of exposure. Concentration-dependent thickening of alveolar septa and bronchiolar walls, significant only at ≥10 ppm after 3- and 25-day exposure, but 5 ppm caused significant thickening only in bronchiolar walls after 25 days, but not after 3 days, of exposure compared to controls. Statistically significant reduction in alveoli surface density at ≥10 ppm after 25 days of exposure and at 20 ppm only after 3 days of exposure, while alveolar circumference increased statistically significantly at ≥10 ppm after 25 days of exposure and at 20 ppm following 3 days of exposure. 5 ppm did not significantly affect these endpoints after 3 or 25 days of exposure compared to controls. Data suggest concentration- and exposure duration-dependent development of emphysema, significant only at ≥10 ppm, but not at 5 ppm, after 3 or 25 days of exposure. Alveolar duct length increased significantly at ≥10 ppm after 25 days and at 20 ppm after 3 days of exposure; no effect at 5 ppm. Radial alveolar count values decreased significantly at 20 ppm after 3 and 25 days and at 10 ppm after 25 days exposure; no effect at 5 ppm. Increase in avg medial thickness at 10 ppm with significance only after 25 days of exposure and at 20 ppm with significance after 3 and 25 days of exposure. In contrast, 5 ppm caused significant increase at both 3 and 25 days of exposure. Authors suggested effect at 5 ppm was due a reduction of pulmonary arterial mass and not as a result of vasodilation induced by nitrogen oxide.	Barth et al. (1994b)

ppm	EXPOSURE	GENDER	AGE	SPECIES (STRAIN)	EFFECTS	REFERENCE
0, 1.0, 2.0, 4.0	24 h/day, for 12 wks	M	10 wks	Rat (Wistar) Guinea Pig (Hartley)	No change in body weight or absolute lung weight in any exposed group compared to controls, but relative lung weight was significantly increased in animals exposed to 4.0 ppm NO_2. Number of lung cells from animals exposed to ≥2.0 ppm significantly reduced (but extent of reduction at 4.0 ppm < 2.0 ppm), whereas number of mast cells not significantly different in exposed animals compared to controls. IgE-mediated histamine release from lung mast cells significantly reduced at 2.0 ppm NO_2 but not at 4.0 ppm or 1.0 ppm, but no difference observed in A23187-stimulated histamine release in lung mast cells in any exposed group compared to controls. Results from histamine release suggest that NO_2 exposure to rat lung mast cells did not induce histamine-releasing activity. No change in body weight or absolute or relative lung weight in any exposed group compared to controls. Number of lung cells or mast cells was not significantly different in exposed animals compared to controls. Increasing trend observed in IgE-mediated histamine release from lung mast cells, the change becoming significant only at 4.0 ppm. No significant change in ionophore A2318-stimulated histamine release in exposed groups compared to controls. Data suggest NO_2 exposure in guinea pigs enhanced histamine-releasing activity in lung mast cells.	Fujimaki and Nohara (1994)
0.2 0.5 2	Continuous, presumably 7 days/wk, up to 12 wks	F	Neonates or 5 wks old	Rat (Brown-Norway)	Rats were exposed from embryonic or weanlings (5 wks old) period up to 12 wks of age. Significantly decreased levels of AM + Mo in weanling animals exposed to 0.5 and 2.0 ppm, and significantly increased levels of neutrophils in animals exposed to 2.0 ppm at 12 wks. Levels of AM + Mo significantly increased in animals exposed to 0.5 ppm during embryonic period while levels of neutrophil population significantly decreased, compared to controls, at 12 wks. [Changes in cell populations in BAL fluid not investigated in animals exposed to 2.0 ppm during the embryonic period due to loss of sample.] Mean level of lymphocytes significantly increased in the embryonic group exposed to 0.2 ppm and in the weanling group exposed to 0.5 and 2.0 ppm, but increase not concentration-dependent in the weanling group. Except for exposure to 0.2 ppm, NO_2 exposure appeared to improve allergic conditions in the BAL fluid of the embryonic group, but caused inflammatory changes in the BAL fluid of the weanling group. Data suggest NO_2 exposure from the weanling period has stronger effects on AM activity.	Kumae and Arakawa (2006)

AHR = Airway hyperresponsiveness
AM = Alveolar macrophage
BAL = Bronchoalveolar lavage
BHR = Bronchopulmonary hyperreactivity
BrdU-LI = Bromodeoxyuridine-laebling index
IgE = Immunoglobulin E
IgG = Immunoglobulin G
IL-5 = Interleukin-5
LDH = Lactate dehydrogenase
Mo = Monocytes
OVA = Ovalbumin
PMN = Polynorphonuclear neutrophil

Table AX4.5. Immune responses.

ppm	EXPOSURE	GENDER	AGE	SPECIES (STRAIN)	EFFECTS	REFERENCES
0.5 0.1 base + 0.25, 0.5, or 1.0 peak	Continuous Continuous base + 3 h/day, 5 days/wk peak for 1, 3, 6, 9, 12 mos	NR	NR	Mouse	Suppression of splenic T and B cell responsiveness to mitogens variable and not related to concentration or duration, except for the 940 µg/m^3 continuous group, which had a linear decrease in PHA-induced mitogenesis with NO_2 duration.	Maigetter et al. (1978)
0.25	7 h/day, 5 days/wk, 7wks	F	6 wks	Mouse (AKR/cum)	Reduced percentage of total T-cell population and trend towards reduced percentage of certain T-cell subpopulations; no reduction of mature T cells or natural killer cells.	Richters and Damji (1988)
0.25	7 h/day, 5 days/ wk, 36 wks	F	5 wks	Mouse (AKR/cum)	Reduced percentage of total T-cell population and percentages of T helper/inducer cells on days 37 and 181.	Richters and Damji (1990)
0.35	7 h/day, 5 days/ wk, 12 wks	M	6 wks	Mouse (C57BL/6J)	Trend towards suppression in total percentage of T-cells. No effects on percentages of other T-cell subpopulations.	Richters and Damji (1988)
0.4 1.6	24 h/day 4 wks	M	7 wks	Mouse (BALB/c)	Decrease in primary PFC response at ≥ 752 µg/m^3. Increase in secondary PFC response at 3010 µg/m^3.	Fujimaki et al. (1982)
0.5 base + 1.5 peak	22 h/day, 7 days/wk base + 6 h/day, 5 days/wk peak for 1, 3, 13, 52, 78 wks	M	10 wks	Rat (Fischer 344)	No effect on splenic or circulatory B or T cell response to mitogens. After 3 weeks of exposure only, decrease in splenic natural killer cell activity. No histological changes in lymphoid tissues.	Selgrade et al. (1991)
0.5 base + 2.0 peak	24 h/day, 5 days/wk base + 1 h/day, 5 days/wk peak for 3 mos	M	6 wks	Mouse (CD-1)	Vaccination with influenza A2/Taiwan virus after exposure. Decrease in serum neutralizing antibody; hemagglutination inhibition antibody titers unchanged. Before virus challenge, NO_2 exposure decreased serum IgA and increased IgG1, IgM, and IgG2; after virus, serum IgA unchanged and IgM increased.	Ehrlich et al. (1975)
0.5	8 h/day, 5 days/wk, for 0.5, 1, 5, or 10 days	M	NR	Rat (Sprague-Dawley)	Levels of TxB2, LTB4, and PGE2 in BAL fluid were depressed within 4 h of exposure. Suggests acute depression of pulmonary arachidonate metabolism observed in BAL fluid. Unstimulated AM synthesis of LTB4 was depressed within 1 day and also on day 5 of exposure. The AM synthesis of TxB2, LTB4, and 5-HETE on stimulation by the calcium ionophore, A23187, was acutely depressed within 1 day of exposure but not with longer exposure, while 5-HETE was significantly increased at 10 days. Suggests rapid depression of cyclooxygenase and 5-lipoxygenase activities. ZAS-stimulated LTB4 production was delayed until 5 days and remained lower at 10 days. BAL fluid levels of LTB4 and TxB2 paralleled ex vivo depression of AM production. AM superoxide production stimulated by PMA was rapidly and continuously depressed throughout the study.	Robinson et al. (1993)

ppm	EXPOSURE	GENDER	AGE	SPECIES (STRAIN)	EFFECTS	REFERENCES
5	3 h	F	7 wks	Rat (Brown-Norway)	Rats were immunized intraperitoneally and challenged intratracheally with house mite dust. Animals were exposed to NO_2 after sensitization or challenge or after sensitization and challenge (double exposure). A single exposure after sensitization or challenge caused a significant decrease in antigen-specific IgG in BAL fluid, single exposure after sensitization caused significant increase in serum IgE, while exposure only after challenge caused significant decrease in antigen-specific IgA levels in BAL fluid. Double NO_2 exposure caused significantly higher levels of antigen-specific serum IgE and local IgA, IgG, and IgE antibody, and significant increase in lymphocyte responsiveness to antigen in the spleen and mediastinal lymph nodes. Double exposure also significantly increased the ratio of inflammatory cells to alveolar macrophages without affecting the total number of lavageable cells. Data suggest a 3-h exposure to 5 ppm NO_2 after intraperitoneal sensitization and pulmonary challenge with house dust mite allergen was necessary to enhance specific immune responses to the allergen and increased the number of inflammatory cells in the lungs. Additionally, data suggest an upregulation of specific immune responses and subsequent immune-mediated pulmonary inflammation.	Gilmour et al. (1996)
5 20	3 h	M	NR	Mouse (BALB/c)	Animals were sensitized and challenged with the antigen OVA to generate airway inflammation before being exposed to NO_2. Exposure of OVA-challenged animals to 20 ppm produced BHR and caused significant increase in neutrophils and fibronectin concentration, significant reduction in eosinophil count, and exudation and release of IL-5 in broncholaveolar fluid 24 h and/or 72 h after exposure. Exposure to 5 ppm did not modify BHR, but significantly reduced pulmonary eosiniphilic inflammation (reduced esinophilic count and eosinophil peroxidase activity) and the production of IL-5 in the BAL fluid. Authors suggested that potentiation of BHR by 20 ppm NO_2 in allergic mice may be accounted for by an increased vascular/epithelial permeability, facilitating the allergen availability and accelerating the inflammatory process. Exposure to NO_2 did not cause any significant changes in IgE anti-OVA antibody in exposed animals, while IgG1 titers were significantly increased in animals exposed only to 5 ppm NO_2, compared to controls. There was no development of mucosal metaplasia in any NO_2 exposed group compared to controls.	Proust et al. (2002)
4	2 h/day	M and F	From birth until 3 mos of age	Rabbit (NZW)	No effect on mortality, health, behavior, body weight, or basal pulmonary function (lung resistance, dynamic compliance, respiration rates, tidal volume, and minute volumes) in animals immunized against house mite dust compared to littermates exposed to air. Immune parameters were not evaluated.	Douglas et al. (1994)
4.76	4 h/day, 5 days/wk, for 6 wks (30 exposures, total)	M	NR	Guinea Pig (Hartley)	Animals were intraperitoneally sensitized twice and then challenged pulmonarily with C. albicans. Animals were exposed, from the first day of sensitization, and throughout the study period. Exposure to NO_2 resulted in significantly increased respiratory rate (tachypnea) (2.3-2.7 times/s) 15 h after antigen challenge compared to controls, but did not significantly affect the expiration/inspiration ratio. Authors indicated that delayed-type dyspneic symptoms in this study were increased by exposure to NO_2.	Kitabatake et al. (1995)

ppm	EXPOSURE	GENDER	AGE	SPECIES (STRAIN)	EFFECTS	REFERENCES
0.06 0.5 1 2 4	24 h/day, for 6 or 12 wks	M	NR	Guinea Pig (Hartley)	Concentration- and exposure duration-dependent increases in airway responsiveness to inhaled histamine aerosol, significant at 1.0 ppm and above in animals exposed for 12 wks and at 2 ppm and above in those exposed for 6 wks. No significant increase in specific airway resistance (sRaw) values at any NO_2 concentration at 6 wks of exposure, but there was a concentration-dependent increase in this parameter at 12 wks of exposure, with significance at 2.0 ppm and above. Authors concluded NO_2 could be a potent risk factor for alteration of pulmonary function and airway responsiveness.	Kobayashi and Miura (1995)
1 2 4	24 h/day, for 12 wks	M M	10 wks 10 wks	Rat (Wistar) Guinea Pig (Hartley)	No change in body weight or absolute lung weight in any exposed group compared to controls, but relative lung weight significantly increased in animals exposed to 4.0 ppm NO_2. Number of lung cells from animals exposed to ≥ 2.0 ppm significantly reduced (but extent of reduction at 4.0 ppm < 2.0 ppm), but number of mast cells not significantly different in exposed animals compared to controls. IgE-mediated histamine release from lung mast cells significantly reduced at 2.0 ppm NO_2 but not at 4.0 ppm or 1.0 ppm, but no difference observed in A23187-stimulated histamine release in lung mast cells in any exposed group compared to controls. Results from histamine release suggest that NO_2 exposure to rat lung mast cells did not induce histamine-releasing activity in rats. No change in body weight or absolute or relative lung weight in any exposed group compared to controls. Number of lung cells or mast cells not significantly different in exposed animals compared to controls. Increasing trend observed in IgE-mediated histamine release from lung mast cells, the change becoming significant only at 4.0 ppm. No significant change in ionophore A2318-stimulated histamine release in exposed groups compared to controls. Data suggest NO_2 exposure in guinea pigs enhanced histamine-releasing activity in lung mast cells. Thus, species differences exist between the rat and guinea pig in response to induction of histamine-releasing activity following NO_2 exposure.	Fujimaki and Nohara (1994)
5 25	6 h/day for 1, 3, or 5 days	NR	NR	Mouse (C57BL/6)	Exposure to 25 ppm, but not 5 ppm, NO_2 induced acute lung injury (characterized by increases in protein, LDH, macrophages, and neutrophils recovered by bronchoalveolar lavage) that peaked after 3 days, lesions within terminal bronchioles, and AHR. OVA-sensitized animals exposed to 25 ppm, but not 5 ppm, NO_2 showed augmentation of eosinophilic inflammation and terminal bronchiolar lesions, which extended significantly into the alveoli. There was no increased expression of mucus cell-associated gene products in non-sensitized or OVA-sensitized animals exposed at any concentration.	Poynter et al. (2006)

5-HETE = 5-Hydroxyeicosatrtraenoate
AM = Alveolar macrophage
AHR = AHR = Airway hyperresponsiveness
BAL = Bronchoalveolar lavage
BHR = Bronchopulmonary hyperreactivity
IFNγ = Interferon γ
IgA = Immunoglobulin A
IgE = Immunoglobulin E
IgG = Immunoglobulin G
IL-5 = Interleukin-5
LDH = Lactate dehydrogenase
LTB4 = Leukotriene B4
OVA = Ovalbumin
PGE2 = Prostaglandin E2
PMA = Phorbol myristate acetate
ROS = Reactive oxygen species
SRawo = Specific airway resistance
TNFα = Tumor necrosis factor α
TxB2 = Thromboxane B2
ZAS = Zymosan-activated rat serum

Table AX4.6. Infectious agents.

ppm	EXPOSURE	GENDER	AGE	SPECIES (STRAIN)	INFECTIVE AGENT	EFFECTS	REFERENCES
0.05 base + 0.1 peak	Continuous, base + twice/day 1-h peaks, 5 days/wk for 15 days	F	NR	Mouse (CD-1)	Streptococcus sp.	No effect.	Gardner (1980, 1982) Graham et al. (1987)
0.5 + peak						Increased mortality	
1.2 base + 2.5 peak						Increased mortality	
0.2 base + 0.8 peak	23 h/day, 7 days/wk base+ twice daily 1-h peaks, 5 days/wk for 1 yr	F	6-8 wks	Mouse (CD-1)	Streptococcus sp.	Peak plus baseline caused significantly greater mortality than baseline.	Miller et al. (1987)
0.3-0.5	Continuous, 3 mos Continuous, 6 mos	F	4 wks	Mouse (ICR:JCL)	A/PR/8 virus	High incidence of adenomatous proliferation peripheral and bronchial epithelial cells; NO_2 alone and virus alone caused less severe alterations. No enhancement of effect of NO_2 and virus.	Motomiya et al. (1973)
0.5	Intermittent, 6 or 18 h/ day, up to 12 mos Continuous, 90 days	F	NR	Mouse (Swiss)	K. pneumoniae	Increased mortality after 6 mos intermittent exposure or after 3, 6, 9, or 12 mos continuous exposure, increased mortality was significant only in continuously exposed mice.	Ehrlich and Henry (1968)
0.5-1.0 10	Continuous, 39 days 2 h/day, 1, 3, and 5 days	F	NR	Mouse (ICR, dd)	A/PR/8 virus	Increased susceptibility to infection.	Ito (1971)
0.5-28	Varied	F	NR	Mouse (CD-1)	Streptococcus sp.	Increase mortality with increased time and concentration; concentrations is more important than time.	Gardner et al. (1977 a,b) Coffin et al. (1977)
0.5	3 h/day, 3 mos	F	6-8 wks	Mouse (CD2 F1, CD-1)	Streptococcus sp.	Increase in mortality with reduction in mean survival time.	Ehrlich et al. (1979)
0.5 1.0 1.5 5.0	24 h/day, 7 days/wk, 3 mos 3 days	F	NR	Mouse (CF-1)	K. pneumoniae	Significant increase in mortality after 3-day exposure to 5.0 ppm; no effect at other concentrations, but control mortality very high.	McGrath and Oyervides (1985)
0.5 1.0 2.0 5.0	4 h	M/F	8-10 wks	Mouse (C57BL/6N)	Mycoplasma pulmonis	Decrease in intrapulmonary killing only at 5.0 ppm.	Davis et al. (1991, 1992)

ppm	EXPOSURE	GENDER	AGE	SPECIES (STRAIN)	INFECTIVE AGENT	EFFECTS	REFERENCES
1.0 2.3 6.6	17 h	M	NR	Mouse (Swiss)	S. aureus after exposure	No difference in number of bacteria deposited, but at the two highest concentrations, there was a decrease in pulmonary bactericidal activity of 6 and 35%, respectively; no effect at 1.0 ppm	Goldstein et al. (1974)
1.0 2.5 5.0 10.0	4 h	F	NR	Mouse (Swiss)	S. aureus	Injection with corticosteroids increased NO_2-induced impairment of bactericidal activity at ≥2.5 ppm.	Jakab (1988)
1.0	48 h	M	NR	Mouse (Swiss Webster)	Streptococcus sp. S. aureus	Increased proliferation of Streptococcus in lung of exposed mice but no effect with S. aureus.	Sherwood et al. (1981)
1.0 3.0	3 h	F	5-6 wks	Mouse (CD-1)	Streptococcus sp.	Exercise on continuously moving wheels during exposure increased mortality at 3.0 ppm.	Illing et al. (1980)
1.0 2.5 5.0	6 h/day, 6 days	NR	4-6 wks	Mouse (CD-1)	Cytomegalovirus	Increase in virus susceptibility at 5.0 ppm only.	Rose et al. (1988, 1989)
1.5- 50	2 h	NR	NR	Mouse (NR) Hamster (NR) Monkey (Squirrel)	K. pneumoniae	Increased mortality in mice, hamsters, and monkeys at ≥3.5, ≥35, and 50 ppm NO_2, respectively	Ehrlich (1980)
1.5	Continuous or intermittent, 7 h/day, 7 days/wk, up to 15 days	F	NR	Mouse (CD-1)	Streptococcus sp.	After 1 wk, mortality with continuous exposure was greater than that for intermittent after 2 wks, no significant difference between continuous and intermittent exposure.	Gardner et al. (1979) Coffin et al. (1977)
3.5						Increased mortality with increased duration of exposure; no significant difference between continuous and intermittent exposure; with data adjusted for total difference in C H T, mortality essentially the same.	
1.5 base + 4.5 peak	Continuous 64 h, then peak for 1, 3.5, or 7 h, then continuous 18 h base	F	NR	Mouse (CD-1)	Streptococcus sp.	Mortality increased with 3.5- and 7-h single peak when bacterial challenge was after an 18 h baseline exposure.	Gardner (1980) Gardner (1982) Graham et al. (1987)
4.5	1, 3.5, or 7 h					Mortality proportional to duration when bacterial challenge was immediate, but not 18 h postexposure.	
1.5	7 h/day, 4, 5, and 7 days	NR	NR	Mouse (NR)	Streptococcus sp.	Elevated temperature (32°C) increased mortality after 7 days.	Gardner (1982)
1.9 3.8 7.0 9.2 14.8	4 h	M	NR	Mouse (NR)	S. aureus	Physical removal of bacteria unchanged by exposure. Bactericidal activity decreased by 7, 14, and 50%, respectively, in three highest NO_2-exposed groups.	Goldstein et al. (1973)
1.5- 5.0	3 h	F	6-10 wks	Mouse (CF-1, CD2F1)	Streptococcus sp.	Increased mortality in mice exposed to ≥2.0 ppm	Ehrlich et al. (1977) Ehrlich (1980)

ppm	EXPOSURE	GENDER	AGE	SPECIES (STRAIN)	INFECTIVE AGENT	EFFECTS	REFERENCES
1.5 2.5 3.5 5.0 10 15	2 h	NR	6-8 wks	Mouse (Swiss Webster)	K. pneumoniae	No effect at 1.5 or 2.5 ppm; increased mortality at 3.5 ppm and above. Increase in mortality when K. pneumoniae challenge 1 and 6 h after 5 or 10 pm NO_2 exposure; when K. pneumoniae challenge 27 h following NO_2 exposure, effect only at 15 ppm.	Purvis and Ehrlich (1963) Ehrlich (1979)
2.0	1.5 h/day, 5 days/wk for 1, 2, and 3 wks	NR	2 wks	Hamster (Golden Syrian) (in vitro)	A/PR/8/34 influenza virus	Peak virus production in tracheal explants occurred earlier.	Schiff (1977)
2.5 4.0 5.0 10 15	4 h	F	NR	Mouse (Swiss)	S. aureus, Proteus mirabilis, Pasteurella pneumotropica	Concentration-related decrease in bactericidal activity at ≥ 4.0 ppm with S. aureus when NO_2 exposure after bacterial challenge; when NO_2 exposure was before challenge, effect at 10 ppm; NO_2 concentrations >5.0 ppm required to affect bactericidal activity for other tested microorganisms.	Jakab (1987, 1988)
5.0 10	Continuous, 2 mos Continuous, 1 mo	M	NR	Monkey (Squirrel)	K. pneumoniae or A/PR/8 influenza virus	Increased viral-induced mortality (1/3). Increase in Klebsiella-induced mortality (2/7); no control deaths. Increased virus-induced mortality (6/6) within 2-3 days after infection; no control deaths. Increase in Klebsiella-induced mortality (1/4), no control deaths.	Henry et al. (1970)
5.0 10	4 h	M/F	6-10 wks	Mouse (C57BL6N, C3H/HeN)	Mycoplasma pulmonis	NO_2 increased incidence and severity of pneumonia lesions and decreased the number of organisms needed to induce pneumonia; no effect on physical clearance; decreased mycoplasmal killing and increased growth; no effect on specific IgM in serum; C57B1/6N mice generally more sensitive than C3H/HeN mice. At 10 ppm, one strain (C57B1/6N) of mice had increased mortality.	Parker et al. (1989)
10 15 35 50	2 h	M/F	NR	Monkey (Squirrel)	K. pneumoniae	Clearance of bacteria from lungs of 10-, 15-, and 35-ppm groups delayed or prevented. All three animals in highest exposed group died.	Henry et al. (1969)
5	NR	NR	NR	Mice (NR)	Parainfluenza (murine sendei virus)	Altered the severity but not the course of the infection	Jakab (1988)

Source: Modified from U.S. Environmental Protection Agency (1993).

Table AX4.7. Lung structure.

ppm	EXPOSURE	GENDER	AGE	SPECIES (STRAIN)	EFFECTS	REFERENCE
3 9	6 h/day, 6 days/wk, for 2 wks	F	NR	Guinea Pig	Morphological changes observed at both concentrations. Ciliated cells displayed pathological changes such as cytoplasmic vacuolation and protrusion at 3 ppm, but eosinophils displayed normal morphology. Minor to major changes in epithelial cells (decreased number of specific granules, cytoplasmic vacuolization, and morpholigcal changes in specific granules) and ciliated cells showed compound cilia, cytoplasmic vacuolization, and sloughing) at 9 ppm.	Ohashi et al. (1994)
5 25	6 h/day for 1, 3, or 5 days	NR	NR	Mouse (C57BL/6)	No lung inflammation or injury observed at 5 ppm at any time, compared to controls. 25 ppm NO_2 induced acute lung injury (characterized by increases in protein, LDH, macrophages, and neutrophils recovered by BAL) at 25 ppm that peaked after 3 days, lesions within terminal bronchioles, and AHR. Another group of mice exposed for 5 days to 25 ppm and allowed to recover in room air for 20 days demonstrated resolution of the pattern of acute lung injury in these animals.	Poynter et al. (2006)
5 10 20	24 h/day, for 3 days	M	NR	Rat (Sprague-Dawley)	Significant alteration in morphology of Clara cells (loss of apical intra-luminal projects and damaged epithelium covered by a layer of CC10-reactive material) at ≥5 ppm.	Barth and Muller (1999)
5 10 20	24 h/day, for 25 days	M	NR	Rat (Sprague-Dawley)	No significant alteration of morphology of Clara cells compared to controls.	Barth and Muller (1999)
5 10 20	24 h/day, for 25 days	M	NR	Rat (Sprague-Dawley)	Exposure to 5 ppm showed no significant qualitative changes of the lung tissue, but animals exhibited slight fibrosis of the centroacinar alveolar septa, respiratory bronchioli, and interstitium, and irregularly shaped alveolar spaces at ≥10 ppm. Morphometric analysis showed significantly diminished alveolar surface density at ≥10 ppm. Suggests development of emphysema at ≥10 ppm. The avg medial thickness of the pulmonary artery was significantly increased at ≥10 ppm, but at 5 ppm, this parameter was significantly decreased, compared to controls. Authors reported negative correlation between avg medial thickness and alveolar surface density.	Barth et al. (1995)
5 10 20	24 h/day, for 3 days	M	NR	Rat (Sprague-Dawley)	Histopathology revealed structural alterations extending from slight interstitial edema after exposure to 5 ppm, to epithelial necrosis and interstitial inflammatory infiltration after exposure to 10 ppm, and an additional intra-alveolar edema after 20 ppm. Light microscopic examination did not confirm the qualitative histological changes, particularly muscularization of intra-acinar vessels. Exposure to ≥10 ppm for 25 days caused emphysema and slight centrilobular interstitial fibrosis. Morphometric analysis showed significantly diminished alveolar surface density at 10 ppm after 25 days of exposure and at 20 ppm after 3 and 25 days of exposure. Avg medial thickness of the pulmonary artery significantly increased at ≥10 ppm, but at 5 ppm, this parameter was significantly decreased both during after 3-day and 25-day exposures, compared to controls. Authors regarded the decrease in the medial thickness at 5 ppm as reflecting a reduction of pulmonary arterial mass and not as a result of vasodilation. Avg medial thickness and alveolar surface density were negatively correlated. Study indicates exposures to as low as 5 ppm is not likely to induce structural changes in the lung of rats. Effect on the morphometry of the alveolar region appeared to be time-dependent, since significant changes were seen at 10 ppm after 25 days, but only at 20 ppm in the 3-day exposure study.	Barth et al. (1995)

ppm	EXPOSURE	GENDER	AGE	SPECIES (STRAIN)	EFFECTS	REFERENCE
10 20	14 h/day, for 15 days, 20 or 25 days	M	NR	Mouse (C57/BL/5)	Initial dose response experiment identified 20 ppm NO_2 as concentration causing lung injury and air inflammation (marked influx of inflammatory cells in the airways, predominated by macrophages and neutrophils and to a lesser extent by lymphocytes) for exposure that lasted 15 days, whereas 10 ppm did not induce significant increase in leukocyte amount in BAL fluid. Actual study using 20 ppm NO_2 observed induction of air space enlargement (evidenced by a significant increase in mass-specific lung volume and volume-weighted alveolar volume). No significant changes in total alveolar surface area.	Wegman and Herz (2002)
0.8 5 10	24 h/day, for 1 or 3 days	M	NR	Rat (Sprague-Dawley)	Significant increase in Type II cell proliferation (evidenced by increases in AgNOR-number and BrdU-LI) after exposure to 5 ppm NO_2 for 3 days and 10 ppm for 1 and 3 days. Significant increase in bronchiolar epithelial proliferation (increases in AgNOR-number and BrdU-LI) at ≥0.8 ppm for 1 and 3 days. In the bronchial epithelium, statistically significant increase in proliferation as increase in AgNOR-number at 10 ppm only after 3 days of exposure and as increase in BrdU-LI after exposure to 5 and 10 ppm for ≥1 day. Results showed highest rate of epithelial proliferation in the bronchiolar epithelium compared to bronchial epithelium and Type II cells. Study indicates cell proliferation changes beginning at concentrations as low 0.8 ppm NO_2 following a single day of exposure.	Barth et al. (1994a)
5 10 20	24 h/day, for 3 or 25 days	M	NR	Rat (Sprague-Dawley)	Compared to controls, proliferative activity (evidenced by increase in AgNOR-number) significantly increased, but with no concentration-dependence in respiratory bronchiolar epithelium at 5 ppm and above after 3-day exposure, but the increase was concentration-dependent, with significance at ≥10 ppm following 25-day exposure. Activity was increased in a concentration-dependent manner in bronchial epithelium with significance only at 20 ppm after 3 days of exposure and at ≥10 ppm following 25 days of exposure. Concentration-dependent thickening of alveolar septa and bronchiolar walls, significant only at ≥10 ppm after 3- and 25-day exposure, but 5 ppm caused significant thickening only in bronchiolar walls after 25 days, but not 3 days, of exposure compared to controls. Statistically significant reduction in alveoli surface density at ≥10 ppm after 25 days of exposure and at 20 ppm only after 3 days of exposure, while alveolar circumference increased statistically significantly at ≥10 ppm after 25 days of exposure and at 20 ppm following 3 days of exposure. 5 ppm did not significantly affect these endpoints after 3 or 25 days of exposure compared to controls. Data suggest concentration- and exposure duration-dependent development of emphysema, significant only at ≥10 ppm, but not at 5 ppm, after 3 or 25 days of exposure. Alveolar duct length increased significantly at ≥10 ppm after 25 days and at 20 ppm after 3 days of exposure; no effect at 5 ppm. Radial alveolar count values decreased significantly at 20 ppm after 3 and 25 days and at 10 ppm after 25 days exposure; no effect at 5 ppm. Increase in avg medial thickness at 10 ppm with significance only after 25 days of exposure and at 20 ppm with significance after 3 and 25 days of exposure. However, 5 ppm caused significant decrease at both 3 and 25 days of exposure. Authors suggested effect at 5 ppm was due to vasodilation induced by nitrogen oxide.	Barth et al. (1994b)

ppm	EXPOSURE	GENDER	AGE	SPECIES (STRAIN)	EFFECTS	REFERENCE
25 50 75 100 150 200 250	5, 15, or 30 min 2, 5, 15, or 30 min 2, 5, or 15 min	M	NR	Rat (Fischer-344)	Animals exposed to ≥200 ppm NO_2 for 30 min died within 24 h after exposure. NO_2 exposure induced proportional increases in LWW, indicative of pulmonary edematous responses, over the same exposure period after the 15-min exposures. Animals exposed to 25 ppm NO_2 did not produce observable lung injury (i.e., occurrence of alveolar fibrin and Type II cell hyperplasia) on exposure for 5 min. Animals exposed to all exposure concentrations for 15 min showed alveolar fibrin, while Type II hyperplasia occurred at 50 ppm and its level of expression correlated with exposure concentration. After 30 min of exposure, the occurrence of fibrin increased as a function of exposure concentration, while over a concentration range of 25-150 ppm NO_2, the Type II cell hyperplastic response increased with increasing exposure concentration. Data suggest exposure concentration was evidently more important than exposure time in terms of causing lung injury when high concentrations of NO_2 are inhaled.	Lehnert et al. (1994)
3.6 7.2 10.8 14.4	24 h, 12 h, 8 h, and 6 h, respectively, for 3 days, giving a C H T of 86.4 ppm h	M	NR	Rat (Sprague-Dawley)	Short-term exposure was not sufficient to produce significant type I alveolar cell necrosis or a significant migration of inflammatory cells across the interstitium and alveolar epithelium.	Rajini et al. (1993)
0.5 base + 1.5 peak	Base presumably continuous, two 1-h peaks/day, for 9 wks	M	7 wks	Rat (Fischer-344)	No significant differences in thickness of the alveolar septal components, between controls and exposed group. Analysis of parenchymal cell populations showed no significant differences in the avg volumes of different cell types or in their surface areas. Total number of fenestrae in the lungs of NO_2-exposed animals occurred at a greater frequency than in controls, but no significant alterations were found in the connective tissue matrix or interstitial cell population, suggesting that connective tissue matrix and interstitial cells of the lung parenchyma did not undergo significant degeneration on exposure to the low level of NO_2 used in this study.	Mercer et al. (1995)

AgNOR = Silver-stainable nucleolar organizer regions
AHR = Airway hyperresponsiveness
BAL = Bronchoalveolar lavage
BrdU-LI = Bromodeoxyuridine-laebling index
LDH = Lactate dehydrogenase
LWW = Lung wet weight

Table AX4.8. Pulmonary function.

ppm	EXPOSURE	GENDER	AGE	SPECIES (STRAIN)	EFFECTS	REFERENCE
0.5 1.5	0.5 ppm background level for 16 h, a 6-h exposure spike, and a 2-h downtime; profile was run each day for 1, 3, 13, 52 or 78 wks	M	67 days	Rat (Fischer-344)	No NO_2 related-effects on body weight or pulmonary function (total lung capacity, vital capacity, residual volume (difference between total lung capacity and vital capacity), respiratory system compliance, single-breath diffusing capacity of carbon monoxide, slope of nitrogen wash-out curve, and end-expiratory volume) observed following 13-, 52-, or 78-wk exposure. NO_2-related effects on small airway function [FVC, peak flow, flow at 50% (FEF 50%), 25% (FEF 25%) and 10% (FEF 10%) of FVC] evaluated at 52- or 78-wk exposure or at 26- and 17-wks postexposure were not significantly different from controls. However, breathing patterns and mechanics (tidal volume, expiratory resistance, inspiratory and expiratory time) were generally greater and FOB was significantly slower in NO_2-exposed animals compared to controls at all of the time points evaluated.	Tepper et al. (1993)
0.5 base + 1.5 peak	Base presumably continuous, two 1-h peaks/day, for 9 wks	M	7 wks	Rat (Fischer-344)	No significant differences in lung volume, total air volume of the lungs, total lung tissue volume, surface area, body weight, or thickness of the alveolar septal components, between controls and exposed group. Analysis of parenchymal cell populations showed no significant differences in the avg volumes of different cell types or in their surface areas. Total number of fenestrae in the lungs of NO_2-exposed animals occurred at a greater frequency than in baseline controls, but no significant alterations were found in the connective tissue matrix or interstitial cell population, suggesting that connective tissue matrix and interstitial cells of the lung parenchyma did not undergo significant degeneration on exposure to the low level of NO_2 used in this study.	Mercer et al. (1995)
10 20	14 h/day, for 15 days, 20 or 25 days	M	NR	Mouse (C57/BL/6)	20 ppm NO_2 induced development of progressive airflow obstruction (evidenced by decreases in midexpiratory airflow, breathing frequency and tidal volume, with statistical significance only at day 25 of exposure).	Wegman and Herz (2002)

FVC = Forced vital capacity
FOB = Frequency of breathing

Table AX4.9. Hematological parameters.

ppm	EXPOSURE	GENDER	AGE	SPECIES (STRAIN)	EFFECTS	REFERENCES
0.05	Continuous 90 days	NR	NR	Rat	No effect on blood hemoglobin or RBCs.	Shalamberidze (1969)
0.36	1 wk	NR	NR	Guinea Pig	Increase of red blood cell D-2,3-diphosphoglycerate	Mersch et al. (1973)
0.5-0.8 +	Continuous 1 to 1.5 mos	M/F	4 wks	Mouse (ICR:JCL)	Addition of 50 ppm CO to NO_2 failed to affect carboxyhemoglobin.	Nakajima and Kusumoto (1970)
0.8	Continuous, 5 days	M	7 wks	Mouse (ICR)	No effect on methemoglobin.	Nakajima and Kusumoto (1968)
1.0	Continuous, 16 mos	M	NR	Monkey (Squirrel)	No effect on hematocrit or hemoglobin with NO_2 and influenza exposure.	Fenters et al. (1973)
1.0 5.0	Continuous, 18 mos	M	NR	Dog (Mongrel)	No changes in hemoglobin or hematocrit.	Wagner et al. (1965)

ppm	EXPOSURE	GENDER	AGE	SPECIES (STRAIN)	EFFECTS	REFERENCES
1-30	18 h	NR	NR	Mouse (NR)	Concentration-related increase in methemoglobin and nitrosylhemoglobin	Case et al. (1979)
1.3-3.0	2 h/day, 15 and 17 wks	NR	NR	Rabbit (NR)	Decreased RBCs.	Mitina (1962)
2.0	Continuous, 14 mos	M/F M	NR	Monkey (Macaca speciosa) Rat (Sprague-Dawley)	With or without NaCl (330 µg/m^3): polycythemia with reduced mean corpuscular volume and normal mean corpuscular hemoglobin.	Furiosi et al. (1973)
2.0	Continuous, up to 6 wks	M	8 wks	Rat (Wistar)	No effect on hemoglobin, hematocrit or RBC count; no methemoglobin was observed.	Azoulay et al. (1978)
4.0	1-10 days	NR	NR	Rat (NR)	Increase in RBC sialic acid.	Kunimoto et al. (1984)
4.0	NR	NR	NR	NR	Decrease in RBCs.	Mochitate and Miura (1984)
5-40	1 h	F	4 mos	Mouse (JCL:ICR)	No increase in methemoglobin. Increased nitrite and especially nitrate.	Oda et al. (1981)
10	2 h/day, 5 days/wk, up to 30 wks	F	6-8 wks	Mouse (BALB/c)	Small decrease in hemoglobin and mean corpuscular hemoglobin concentration.	Holt et al. (1979)

Source: Modified from U.S. Environmental Protection Agency (1993).

Table AX4.10. Iron, enzymes, and nucleic acids.

EFFECT	REFERENCE
Sodium nitroprusside (NO donor) mobilizes iron from ferritin	Reif and Simmons (1990)
Modulation of arachidonic acid metabolism via interference with iron	Kanner et al. (1991, 1992)
Inhibition of aconitase (an enzyme in the Krebs cycle, and also complex 1 and 2 of the respiratory chain)	Hibbs et al. (1988) Persson et al. (1990) Stadler et al. (1991)
Permanent modification of hemoglobin, possibly via deamination	Moriguchi et al. (1992)
Deamination of DNA	Wink et al. (1991)
DNA strand breaks	Nguyen et al. (1992)
Inhibition of DNA polymerase and ribonucleotide reductase	Lepoivre et al. (1991) Kwon et al. (1991)
Antimitogenic; inhibition of T cell proliferation in rat spleen cells	Fu & Blankenhorn (1992)
Inhibition of DNA synthesis, cell proliferation, and mitogenesis in vascular tissue	Nakaki et al. (1990)
Inhibition of mitogenesis and cell proliferation (vascular smooth muscle cells)	Garg and Hassid (1989)
Adenosine diphosphate ribosylation is stimulated by NO-generating agents	Nakaki et al. (1990)

Table AX4.11. Genotoxicity in vitro and in plants.

TEST ORGANISM	ENDPOINT	EXPOSURE	COMMENTS	RESULTS	REFERENCE
Salmonella TA100	Mutations	6-10 ppm, 40 mins		+	Isomura et al. (1984)
Salmonella TA100	Mutations	10-15 ppm, 6 h	Concentrations >10 ppm were bacteriotoxic	+	Victorin and Ståhlberg (1988)
Salmonella TA100 and TA102	Mutations	Bubbling of 10-90 ppm through bact. susp., 30 mins as above		-	Kosaka et al. (1985)
Salmonella TA100	SOS repair	Bubbling of 10-90 ppm through bact. susp., 30 mins	Effect not considered solely attributed to nitrite in suspension. No effect seen with NO gas.	+	Kosaka et al. (1985)
E. coli, WP2	Mutations	Bubbling of 10-90 ppm through bact. susp., 30 mins		+	Kosaka et al. (1986, 1987)
E. coli	SOS repair	Bubbling of 10-90 ppm through bact. susp., 30 mins		+	Kosaka et al. (1986, 1987)
Bacillus subtilis spores	Mutations	500 ppm, 2-3 h		+	Sasaki et al. (1980)
V79 hamster cells	Chromatid-type aberrations, SCE	10-100 ppm, 10 mins	Effect shown not to be solely due to nitric acid or nitrite. No effect if cells not washed with Hank's salt solution prior to exposure	+	Tsuda et al. (1981)
V79 hamster cells	SCE	2-3 ppm, 10 mins		+	Shiraishi and Bandow (1985)
Don hamster cells	Mutations (8-G resistance)	2-3 ppm, 10 mins	Slight response	-	Isomura et al. (1984)
V79 hamster cells	DNA single-strand breaks	10 ppm, 20 mins	Effect not due to formation of nitrite	+	Görsdorf et al. (1990)
Tradescantia	Micronuclei in pollen	5 ppm, 24 h		+	Ma et al. (1982)
Tradescantia	Mutations in stamen hair	50 ppm, 6 h		+	Schairer et al. (1979)

Source: Victorin (1994).

Table AX4.12. Genoticity in vivo.

TEST ORGANISM	ENDPOINT	EXPOSURE	RESULT	REFERENCE
Drosophila	Recessive lethals	500-7000 ppm, 1 h	-	Inoue et al. (1981)
Drosophila	Somatic mutations (wing spot test)	50-280 ppm, 2 days	-	Victorin et al. (1990)
Rats	Mutations in lung cells (oubain res.)	50-560 ppm, >12 days	+	Isomura et al. (1984)
Rats	Chromosome aberrations in lung cells	27 ppm, 3 h	+	Isomura et al. (1984)
Mice	Chromosome aberrations in lymphocytes and spermatocytes	0.1-10 ppm, 6 h	-	Gooch et al. (1977)
Mice	Micronuclei in bone marrow	20 ppm, 23 h	-	Victorin et al. (1990)

Source: Victorin (1994).

Table AX4.13. Genotoxicity.

TEST ORGANISM	ENDPOINT	EXPOSURE	RESULT	REFERENCE
Salmonella TA100	Mutations	25-30 ppm, 40 min	+	Isomura et al. (1984)
Salmonella	SOS repair	Bubbling of 10-90 ppm	-	Kosaka et al. (1985)
Don hamster cells	Mutations (8-AG resistance)	2-3 ppm, 10 min	+	Isomura et al. (1984)
V79 hamster cells	DNA single-strand breaks	500 ppm, 30 min	-	Görsdorf et al. (1990)
TK 6 human cells	Mutations, DNA single-strand breaks	Injection of 0.12-0.38 ml NO gas/ml of culture medium, 1 h	+	Nguyen et al. (1992)
Salmonella TA1535	Mutations	30 min to 5-90 ppm	+	Arroyo et al. (1992)
Rats	Mutations in lung cells (oubain res.)	27 ppm, 3 h	-	Isomura et al. (1984)

Source: Victorin (1994); Arroyo et al. (1992) added.

Annex 5. Clinical Studies: Exposure to NO_X

AX5.1. Introduction

This annex summarizes the effects of NO_X on human volunteers exposed under controlled conditions. The goal is to review the scientific literature on human clinical studies of NO_X exposure published since the 1993 NO_X Air Quality Criteria Document (AQCD) (EPA 1993). The primary focus was on NO_2 because it is the most abundant NO_X species in the atmosphere and there are few human studies of exposure to other NO_X species.

Clinical summary conclusions from the 1993 AQCD are provided below:

- NO_2 causes decrements in lung function, particularly increased airway resistance in healthy subjects at concentrations exceeding 2.0 ppm for 2 h.
- NO_2 exposure results in increased airway responsiveness in healthy, nonsmoking subjects exposed to concentrations exceeding 1.0 ppm for 1 hour or longer.
- NO_2 exposure at levels above 1.5 ppm may alter numbers and types of inflammatory cells in the distal airways or alveoli, but these responses depend upon exposure concentration, duration, and frequency. NO_2 may alter function of cells within the lung and production of mediators that may be important in lung host defenses.
- NO_2 exposure of asthmatics causes, in some subjects, increased airway responsiveness to a variety of provocative mediators, including cholinergic and histaminergic chemicals, SO_2 and cold air. However, the presence of these responses appears to be influenced by the exposure protocol, particularly whether or not the exposure includes exercise.
- Modest decrements in spirometric measures of lung function (3 to 8%) may occur in some asthmatics and COPD patients under certain NO_2 exposure conditions.
- Nitric acid levels in the range of 50 to 200 ppb may cause some pulmonary function responses in adolescent asthmatics, but not in healthy adults. Other commonly occurring NO_X species do not appear to cause any pulmonary function responses at concentrations expected in the ambient environment, even at higher levels than in worst-case scenarios. However, not all NO_X acid species have been studied sufficiently.
- No association between lung function responses and respiratory symptom responses were observed. Furthermore, there is little evidence of a concentration-response relationship for changes in lung function, airway responsiveness, or symptoms at the NO_2 levels that are reviewed here.

In the summary and integration chapter of the 1993 NO_X criteria document, one of the key health effects at near ambient concentrations of NO_2 was increased airway responsiveness or hyperresponsiveness in asthmatic individuals after short-term exposures. The 1993 AQCD notes the absence of a concentration-response relationship for NO_2 exposure and airway responsiveness in asthmatics. For example, most responses to NO_2 that had been observed in asthmatics occurred at concentrations between 0.2 and 0.5 ppm. However, other studies showed an absence of effects on airway responsiveness or hyperresponsiveness at much higher concentrations, up to 4 ppm. Since 1993, additional studies have suggested that exposure to low concentrations of NO_2, either alone or in

combination with other pollutants such as SO_2, may enhance allergen responsiveness in asthmatic subjects.

In the years since the preparation of the 1993 AQCD, many studies from a variety of disciplines have convincingly demonstrated that exposure to particulate air pollution increases the risk for cardiovascular events. In addition, a number of epidemiological studies have shown associations between ambient NO_2 levels and adverse cardiovascular outcomes, at concentrations well below those shown to cause respiratory effects. However, to date there remain very few clinical studies of NO_2 that include endpoints relevant to cardiovascular disease.

AX5.1.1. Considerations in Controlled Human Clinical Studies

Human clinical studies attempt to engineer laboratory atmospheric conditions relevant to ambient pollutant atmospheres, with careful control of concentrations, duration, timing, and other conditions which may impact responses. These studies provide the opportunity to measure symptoms and physiological markers of health effects that result from breathing the atmospheres. The carefully controlled environment allows investigators to identify responses to individual pollutants, to characterize exposure-response relationships, to examine interactions among pollutants, and to study the effects of other variables such as exercise, humidity, or temperature. Susceptible populations can participate, including individuals with acute and chronic respiratory and cardiovascular diseases, with appropriate limitations based on subject comfort and protection from risk. Endpoint assessment traditionally has included symptoms and pulmonary function, but more recently a variety of markers of pulmonary, systemic, and cardiovascular function have been used to assess pollutant effects.

Human clinical studies have limitations. For practical and ethical reasons, studies must be limited to relatively small groups, to short durations of exposure, and to pollutant concentrations that are expected to produce only mild and transient responses. Findings from the short-term exposures in clinical studies may provide limited insight into the health effects of chronic or repeated exposures.

Specific issues of protocol design in human clinical studies have been reviewed (Frampton, Pietropaoli et al. 2006), and will not be considered further here, except in the context of specific studies of NO_2 exposure described in the following pages.

In clinical studies, humans are the species of interest, so findings have particular relevance to risk assessment. However, the utility of clinical studies in risk assessment is tempered by the obvious need to avoid adverse health effects of the study itself. This usually means selecting subjects that are not the most susceptible to the pollutant being studied. Furthermore, clinical studies depend on outcome markers with variable relevance or validation as markers of true health effects. The statement from the American Thoracic Society, “What constitutes an adverse health effect?” (American Thoracic Society 2000) addresses issues relevant to selection and interpretation of outcome markers in clinical studies.

The 1993 NO_X AQCD included a description of key outcome measures that had been in use up to that date. These included primarily respiratory outcomes, including pulmonary function tests such as spirometry, lung volumes, and airway resistance, and tests of pulmonary clearance of inhaled aerosols. A brief description of bronchoalveolar lavage was also included, which had come into use prior to 1993 to assess airway inflammation and changes in the epithelial lining fluid in response to NO_2 exposure.

AX5.2. Effects of NO_2 in Healthy Subjects

Table AX5.2-1 summarizes the key clinical studies of NO_2 exposure in healthy subjects since 1993, with a few key studies included prior to that date.

AX5.3. Effects of NO_X Exposure in Sensitive Subjects

Table AX5.3-1 summarizes studies of potentially sensitive subjects. The potential for NO_2 exposure to enhance responsiveness to allergen challenge in asthmatics deserves special mention. Several recent studies, summarized in Table AX5.3-2, have reported that low-level exposures to NO_2, both at rest and with exercise, enhance the response to specific allergen challenge in mild asthmatics.

These recent studies involving allergen challenge suggest that NO_2 may enhance the sensitivity to allergen-induced decrements in lung function, and increase the allergen-induced airway inflammatory response.

AX5.4. Effects of Mixtures Containing NO_X

Table AX5.4-1 summarizes human clinical studies of NO_2-containing mixtures or sequential exposures that are most relevant to ambient exposure scenarios.

Table AX5.2-1. Clinical studies – healthy subjects.

STUDY	LOCATION	PARTICIPANTS	METHODS	FINDINGS	COMMENTS
Avissar et al. (2000)	Rochester, NY, USA	21 healthy nonsmokers	Measurements of extracellular glutathione peroxidase (eGPx) activity and protein levels in epithelial lining fluid from NO_2 exposure study described in Frampton et al. (2002) (see below).	No effects of NO_2 exposure on eGPx activity and protein concentrations. (O_3 exposure decreased eGPx activity and protein concentrations.)	NO_2 up to 1.5 ppm for 3 h did not deplete this mode of antioxidant defense in the epithelial lining fluid.
Azadniv et al. (1998)	Rochester, NY, USA	2 studies, 12 healthy nonsmokers in each	Air vs. 2 ppm NO_2 for 6 h with intermittent exercise. Phase 1: BAL 18 h after exposure; Phase 2: BAL immediately after exposure.	Increased BAL neutrophils, decreased blood CD8+ and null T lymphocytes 18 h after exposure. No effects on symptoms or lung function.	2 ppm NO_2 for 6 h caused mild inflammation.
Blomberg et al. (1997)	Sweden	30 healthy nonsmokers	Air vs. 2 ppm NO_2 for 4 h, with intermittent exercise.	Increased neutrophils and interleukin-8 in bronchial wash. Increases in specific lymphocyte subsets in BAL fluid. Symptoms/lung function not reported.	2 ppm NO_2 for 4 h caused airway inflammation.
Blomberg et al. (1999)	Sweden	12 healthy nonsmokers	Air vs. 2 ppm NO_2 for 4 h on 4 days, with intermittent exercise.	After 4 days of NO_2, increased neutrophils in bronchial wash but decreased neutrophils in bronchial biopsy. 2% decrease in FEV1 after first exposure to NO_2, attenuated with repeated exposure. Symptoms not reported.	Decreased lung function, not confirmed in other studies at this concentration. Conflicting information on airway inflammation.

STUDY	LOCATION	PARTICIPANTS	METHODS	FINDINGS	COMMENTS
Devlin et al. (1999; Frampton, Boscia et al. 2002)	Chapel Hill, NC, USA	8 healthy nonsmokers	Air and 2.0 ppm NO_2 for 4 h with intermittent exercise.	Increased bronchial lavage neutrophils, IL-6, IL-8, alpha1-antitrypsin, and tissue plasminogen activator. Decreased alveolar macrophage phagocytosis and superoxide production. No effects on pulmonary function. Symptoms not reported.	2 ppm NO_2 for 4 h caused airway inflammation.
Drechsler-Parks (1995)	Santa Barbara, CA, USA	8 older healthy nonsmokers	4 2-h exposures with intermittent exercise: air, 0.60 ppm NO_2, 0.45 ppm O_3, and 0.60 ppm NO_2 + 0.45 ppm O_3.	Significant reduction in cardiac output during exercise, estimated using noninvasive impedance cardiography, with NO_2 + O_3. Symptoms and pulmonary function not reported.	Suggests cardiac effects of NO_2 + O_3. Small number of subjects limits statistical power, has not been replicated.
Frampton et al. (1991)	Rochester, NY, USA	39 healthy nonsmokers	3 protocols, all for 3 h with control air exposure: (1) continuous 0.06 ppm NO_2, (2) baseline 0.05 ppm NO_2 with peaks of 2.0 ppm, and (3) continuous 1.5 ppm NO_2.	No symptoms or direct effects on pulmonary function. Increased airways responsiveness to carbachol after 1.5 ppm NO_2.	Evidence for increased nonspecific airways responsiveness with NO_2 as low as 1.5 ppm for 3 h.
Frampton et al.(2002)	Rochester, NY, USA	21 healthy nonsmokers	Exposure to air, 0.6, 1.5 ppm NO_2 for 3 h with intermittent exercise.	Dose-related decrease in hematocrit, hemoglobin, blood lymphocytes, and T lymphocytes. Mild increase in neutrophils recovered in bronchial portion of BAL fluid. In vitro viral challenge of bronchial epithelial cells showed increased cytotoxicity after NO_2. No effects on symptoms or pulmonary function.	Indicates NO_2 causes airway inflammation. Suggest subtle effects on red blood cells, possibly RBC destruction (hemolysis).
Gong et al. (2005)	Downey, CA, USA	6 healthy nonsmokers and 18 ex-smokers with COPD	2 h exposures with intermittent exercise to: (1) air, (2) 0.4 ppm NO_2, (3) 200 $\mu g/m^3$ concentrated ambient particulate matter (CAPs), (4) NO_2 + CAPs.	Reduced maximum mid-expiratory flow rate and oxygen saturation with CAPs exposures; no effects of NO_2 alone or additive effect with CAPs.	Exposures not fully randomized. Small number of healthy subjects limits interpretation for healthy group.
Helleday et al. (1994)	Sweden	8 healthy smokers, 8 healthy nonsmokers	3.5 ppm NO_2 for 20 min with 15 min exercise. BAL 24 h after exposure compared with non-exposure control BAL.	Different inflammatory cell increases in smokers and nonsmokers. No effects on symptoms. Pulmonary function not reported.	Lack of control air exposure with exercise is problematic.
Helleday et al. (1995)	Sweden	24 healthy nonsmokers, 8 in each of 3 groups	Bronchoscopic assessment of mucociliary activity: (1) 45 min after 1.5 ppm NO_2 for 20 min, (2) 45 min after 3.5 ppm NO_2 for 20 min, and (3) 24 h after 3.5 ppm NO_2 for 4 h.	Complete abolition of mucociliary activity 20 min after NO_2; increased activity 24 h after NO_2. Symptoms/ pulmonary function not reported.	No true air control exposure, order of procedures not randomized, subjects not blinded.
Jörres et al. (1995)	Germany	8 healthy nonsmokers & 12 mild asthmatics	Air or 1 ppm NO_2 exposure for 3 h with intermittent exercise.	In asthmatics, 2.5% decrease FEV1 after NO_2 vs. 1.3% decrease after air, $p = 0.01$. FEV1 decreased 20% in 1 subject after NO_2. No significant lung function effect in healthy subjects. Changes in eicosanoids (more pronounced in asthmatics), but not inflammatory cells, in BAL fluid.	Lung function effects consistent with other studies, suggesting some asthmatics susceptible. Evidence for mild airway inflammation.

STUDY	LOCATION	PARTICIPANTS	METHODS	FINDINGS	COMMENTS
Kim et al. (1991)	Seattle, WA, USA	9 healthy athletes	Air, 0.18, and 0.30 ppm NO_2 for 30 min with exercise.	No effects on pulmonary function. Symptoms not reported.	Small number of subjects limits conclusions.
Morrow et al. (1992)	Rochester, NY, USA	20 COPD subjects (14 current smokers) and 20 elderly healthy (13 never-smokers, 4 former smokers, 3 current smokers)	Air vs. 0.3 ppm NO_2 for 4 h with intermittent exercise.	COPD: small declines in FVC and FEV1 with NO_2. Healthy: No symptoms or pulmonary function effects for group as a whole. Healthy smokers showed a 2.3% decline in FEV1 with NO_2, and differed from nonsmokers.	Mild lung function effects of 0.3 ppm for 4 h in exercising patients with COPD. Small number of healthy smoking subjects limits conclusions regarding this group.
Pathmanathan et al. (2003)	United Kingdom	12 healthy nonsmokers	Air vs. 2 ppm NO_2 for 4 h on 4 days, with intermittent exercise. Bronchoscopy and biopsy 1 h after exposure.	Epithelial expression of IL-5, IL-10, IL-13, and ICAM-1 increased following NO_2 exposure. No data on inflammatory cells in BAL fluid.	Supportive evidence for pro-allergic airway inflammation favoring following NO_2 exposure.
Posin et al. (1978)	Downey, CA, USA	10 healthy nonsmokers	3 daily exposures for 2.5 h. 1st day: air; 2nd and 3rd days: 1 or 2 ppm NO_2. Intermittent exercise. Subsequent control series of 3 daily air exposures.	Reduced hemoglobin and hematocrit, and red blood cell acetyl cholinesterase.	Suggests red blood cell effects of NO_2 (see Frampton et al., 2002). Exposures not randomized.
Rasmussen et al. (1992)	Denmark	14 healthy nonsmokers	Air vs. 2.3 ppm NO_2 for 5 h.	Small increases in FVC and FEV1. Reduced lung permeability and blood glutathione peroxidase after exposure.	Only 1 wk between exposures may have confounded results.
Rigas et al. (1997)	State College, PA, USA	12 healthy nonsmokers	2 h of 0.36 ppm NO_2, 0.75 ppm NO_2, 0.36 ppm SO_2, or 0.36 ppm O_3. Boluses of O_3 every 30 min to measure O_3 absorption.	NO_2 and SO_2 increased O_3 absorption by increasing biochemical substrates.	Suggests breathing mixtures of NO_2 and O_3 would increase O_3 dose to airways.
Sandström et al. (1990)	Sweden	32 healthy nonsmokers, 4 groups of 8 subjects	4 ppm NO_2 for 20 min with 15 min exercise. BAL 4, 8, 24, 72 h after exposure, compared with non-exposure control BAL.	Increase in BAL mast cells and lymphocytes 4-24 h after exposure.	Study weakened by lack of control air exposure.
Sandström et al. (1991)	Sweden	18 healthy nonsmokers	2.25, 4.0, 5.5 ppm NO_2 for 20 min with light exercise. BAL 24 h after exposure, compared with non-exposure control BAL.	Increase in BAL mast cells (all concentrations) and lymphocytes (4.0 and 5.5 ppm).	Study weakened by lack of control air exposure.
Sandström et al. (1992a)	Sweden	10 healthy nonsmoking men	4 daily exposures to 4 ppm NO_2 for 20 min with 15 min exercise. BAL 24 h after exposure, compared with non-exposure control BAL.	Reduction in alveolar macrophages, NK cells, and CD8 lymphocytes in BAL; reduction in total lymphocytes in blood.	Study weakened by lack of control air exposure.
Sandström et al. (1992b)	Sweden	8 healthy nonsmokers	1.5 ppm NO_2 for 20 min with 15 min exercise, every 2nd day H 6. BAL 24 h after exposure compared with non-exposure control BAL.	Reduced CD8+ T lymphocytes and NK cells in BAL fluid.	Study weakened by lack of control air exposure.

STUDY	LOCATION	PARTICIPANTS	METHODS	FINDINGS	COMMENTS
Solomon et al.(2000)	San Francisco, CA, USA	15 healthy nonsmokers	Air or 2.0 ppm NO_2 with intermittent exercise, for 4 h daily H 4. BAL 18 h after exposure.	Increased neutrophils in bronchial lavage decreased CD4+ T lymphocytes in BAL. No changes in blood.	Airway inflammation with 2 ppm NO_2 for 4 daily 4 h exposures.
Vagaggini et al. (1996)	Italy	7 healthy nonsmokers	Air vs. 0.3 ppm NO_2 for 1 h with intermittent exercise.	Mild increase in symptoms. No effects on lung function, nasal lavage, or induced sputum.	Small number of subjects limits statistical power.

Table AX5.3-1. Subjects with respiratory disease.

REFERENCE	LOCATION	PARTICIPANTS	APPROACH & METHODS	FINDINGS	COMMENTS
Gong et al. (2005)	Downey, CA, USA	6 healthy nonsmokers and 18 ex-smokers with COPD	2 h exposures with intermittent exercise to: (1) air, (2) 0.4 ppm NO_2, (3) 200 µg/m^3 concentrated ambient particulate matter (CAPs), (4) NO_2 + CAPs.	Reduced maximum mid-expiratory flow rate and oxygen saturation with CAPs exposures; no effects of NO_2 alone or additive effect with CAPs.	Exposures not fully randomized. Small number of subjects limits interpretation for healthy group.
Hackney et al. (1992)	Downey, CA, USA	26 smokers with symptoms and reduced FEV_1	Personal monitoring and chamber exposure to air and 0.3 ppm NO_2 for 4 h with intermittent exercise.	No significant effects on lung function.	
Jörres and Magnussen (1991)	Germany	11 mild asthmatics	Air vs. 0.25 ppm NO_2 for 30 min with 10 min exercise.	No effects on lung function or airways responsiveness to methacholine.	
Jörres et al. (1995)	Germany	8 healthy nonsmokers & 12 mild asthmatics	Air or 1 ppm NO_2 exposure for 3 h with intermittent exercise.	In asthmatics, 2.5% decrease FEV_1 after NO_2 vs. 1.3% decrease after air, $p = 0.01$. FEV_1 decreased 20% in 1 subject after NO_2. No significant lung function effect in healthy subjects. Changes in eicosanoids (more pronounced in asthmatics), but not inflammatory cells, in BAL fluid.	Lung function effects consistent with other studies, suggesting some asthmatics susceptible. Evidence for mild airway inflammation. Small number of healthy subjects limits statistical power.
Morrow et al. (1992)	Rochester, NY, USA	20 COPD, 20 healthy elderly	Air vs. 0.3 ppm NO_2 for 4 h with intermittent exercise.	Equivocal reduction in FVC with COPD patients, but not healthy subjects.	
Strand et al. (1997)	Sweden	19 mild asthmatics	Air vs. 0.26 ppm NO_2 for 30 min with intermittent exercise.	Increased airway responsiveness to histamine 5 h after exposure. No effects on lung function.	Suggests increased nonspecific airways responsiveness at much lower concentration than healthy subjects. Differs from findings in Jörres and Magnussen (1991).
Vagaggini et al. (1996)	Italy	8 mild asthmatics, 7 COPD	Air vs. 0.3 ppm NO_2 for 1 h with intermittent exercise.	Mild decrease in FEV_1 in COPD subjects in comparison with air exposure, but not with baseline. No effects on nasal lavage or induced sputum.	No convincing effect of NO_2 in this study. Small number of subjects limits statistical power.

Table AX5.3-2. Inhaled allergen.

REFERENCE	LOCATION	PARTICIPANTS	APPROACH & METHODS	FINDINGS	COMMENTS
Barck et al. (2002)	Sweden	13 mild asthmatics, 4 ex-smokers	30 min exposures to air and 0.26 ppm NO_2 (at rest?), allergen challenge 4 h and BAL 19 h after exposure. Randomized, crossover, double blind.	Increased PMN in bronchial wash and BAL fluid, increased eosinophil cationic protein in bronchial wash, and reduced cell viability and BAL volume with NO_2 + allergen. No effects on lung function response to allergen.	Key study suggesting that NO_2 enhances inflammatory response to allergen in mild asthmatics.
Barck et al. (2005)	Sweden	18 mild asthmatics, 4 ex-smokers	Day 1: 15 min exposures, Day 2: 2 15-min exposures to air and 0.26 ppm NO_2 separated by 1 h, at rest. Allergen challenge 4 h after exposure on day 1 and 3 h after exposure on day 2. Sputum induction before exposure on days 1 & 2, and morning of day 3. Randomized, crossover, single blind.	Increased eosinophilic cationic protein in sputum and blood, and increased myeloperoxidase in blood with NO_2 + allergen. No differences in lung function or sputum cells.	Provides supporting evidence that NO_2 enhances the airway inflammatory response to allergen.
Barck et al. (2005)	Sweden	16 mild asthmatics with rhinitis	30 min exposures to air and 0.26 ppm NO_2 at rest, nasal allergen challenge 4 h after exposure. Nasal lavage before and at intervals after exposure and challenge.	No significant differences between air and NO_2 exposure.	0.26 ppm NO_2 did not enhance nasal inflammatory response to allergen challenge.
Devalia et al. (1994)	United Kingdom	8 mild asthmatics	6 h exposures to combination of 0.4 ppm NO_2 and 0.2 ppm SO_2.	Increased allergen responsiveness 10 min after exposure to combination of NO_2 and SO_2, but not to individual gases.	Small number of subjects limits statistical power.
Jenkins et al. (1999)	United Kingdom	11 mild asthmatics	(1) 6-h exposures to air, 0.1 ppm O_3, 0.2 ppm NO_2, and combination followed by allergen challenge; (2) 3-h exposures to air, 0.2 ppm O_3, 0.4 ppm NO_2, and combination; All exposures with intermittent exercise.	All of the second exposure scenarios (O_3, NO_2, and combination), but none of the first exposure scenarios, resulted in reduced concentration of allergen causing a 20% decline in FEV1. Authors conclude that concentration more important than total inhaled pollutant.	Suggests 0.4 ppm for 3 h with intermittent exercise increases allergen responsiveness.
Rusznak et al. (1996)	United Kingdom	13 mild asthmatics	6 h exposures to combination of 0.4 ppm NO_2 and 0.2 ppm SO_2.	Increased allergen responsiveness to combination of NO_2 and SO_2, 10 min, 24, and 48 h after exposure.	Confirms findings of Devalia et al. (1994), that NO_2 + SO_2 for 6 h increases allergen responsiveness.
Strand et al. (Strand, Rak et al. 1997)	Sweden	18 patients with mild asthma, age 18-50 yrs	Exposure to 0.26 ppm NO_2 for 30 min at rest, allergen challenge 4 h after exposure.	Late phase, but not early phase, response to allergen enhanced by NO_2.	Suggests 0.26 ppm NO_2 for 30 min at rest increases late response.
Strand et al. (1998)	Sweden	16 patients with mild to moderate asthma, age 21-52 yrs	4 daily repeated exposures to 0.26 ppm NO_2 for 30 min at rest.	Significant increases in both early and late phase response to allergen after 4th day of exposure.	Suggests repeated 0.26 ppm NO_2 at rest increases allergen response.
Tunnicliffe et al. (1994)	United Kingdom	10 nonsmoking mild asthmatics age 16-60 yrs. 8 subjects completed.	Exposure to air, 0.1 ppm, and 0.4 ppm NO_2 for 1 h at rest, separated by at least 1 wk, followed by allergen challenge.	Post-challenge reduction in FEV1 after 0.4 ppm NO_2 was greater than after air, for both the early ($p < 0.009$) and late ($p < 0.02$) responses. No difference in nonspecific airway responsiveness.	Suggests threshold for allergen responsiveness effect is between 0.1 and 0.4 ppm for 1 h resting exposure.

REFERENCE	LOCATION	PARTICIPANTS	APPROACH & METHODS	FINDINGS	COMMENTS
Wang et al. (1995)	United Kingdom	2 groups of 8 subjects with allergic rhinitis	Exposure to 0.4 ppm NO_2 (at rest?) for 6 h followed by nasal allergen challenge and nasal lavage.	Increase in myeloperoxidase and eosinophil cationic protein in nasal lavage fluid following allergen challenge.	Suggests enhanced nasal inflammatory response to allergen with 0.4 ppm.
Wang et al. (1999)	United Kingdom	16 subjects with allergic rhinitis	Treatment with nasal fluticasone or placebo for 4 wks followed by exposure to 0.4 ppm NO_2 for 6 h, allergen challenge, and nasal lavage.	Fluticasone suppressed the NO_2 and allergen–induced increase in eosinophil cationic protein in nasal lavage fluid.	Confirms earlier findings of this group that 0.4 ppm NO_2 enhances nasal allergen response.

Table AX5.4-1. NO_2 and other pollutants.

STUDY	LOCATION	PARTICIPANTS	METHODS	FINDINGS	COMMENTS
Devalia et al.(1994)	United Kingdom	8 mild asthmatics	6 h exposures to combination of 0.4 ppm NO_2 and 0.2 ppm SO_2.	Increased allergen responsiveness 10 min after exposure to combination of NO_2 and SO_2, but not to individual gases.	Small number of subjects limits statistical power.
Drechsler-Parks (1995)	Santa Barbara, CA, USA	8 older healthy nonsmokers	4 2-h exposures with intermittent exercise: air, 0.60 ppm NO_2, 0.45 ppm O_3, and 0.60 ppm NO_2 + 0.45 ppm O_3.	Significant reduction in cardiac output during exercise, estimated using noninvasive impedance cardiography, with NO_2 + O_3. Symptoms and pulmonary function not reported.	Suggests cardiac effects of NO_2 + O_3. Small number of subjects limits statistical power, has not been replicated.
Gong et al. (2005)	Downey, CA, USA	6 healthy nonsmokers and 18 ex-smokers with COPD	2 h exposures with intermittent exercise to: (1) air, (2) 0.4 ppm NO_2, (3) 200 µg/m^3 concentrated ambient particulate matter (CAPs), (4) NO_2 + CAPs.	Reduced maximum mid-expiratory flow rate and oxygen saturation with CAPs exposures; no effects of NO_2 alone or additive effect with CAPs.	Exposures not fully randomized. Small number of healthy subjects limits interpretation for healthy group.
Hazucha et al. (1994)	Chapel Hill, NC, USA	21 healthy female nonsmokers	2 h exposure to air or 0.6 ppm NO_2 followed 3 h later by exposure to 0.3 ppm O_3, with intermittent exercise.	NO_2 enhanced spirometric responses and airways responsiveness following subsequent O_3 exposure.	0.6 ppm NO_2 enhanced ozone responses.
Jörres and Magnussen (1990)	Germany	14 nonsmoking mild asthmatics	30 min exposures to air, 0.25 ppm NO_2, or 0.5 ppm SO_2 at rest followed 15 min later by 0.75 ppm SO_2 hyperventilation challenge.	NO_2 but not SO_2 increased airways responsiveness to SO_2 challenge.	Findings contrast with Rubenstein et al. (1990).
Koenig et al. (1994)	Seattle, WA, USA	28 asthmatic adolescents; 6 subjects did not complete.	Exposure for 90 min with intermittent exercise to: (1) 0.12 ppm ozone + 0.3 ppm NO_2, (2) 0.12 ppm ozone + 0.3 ppm NO_2 + 68 µg/m^3 H_2SO_4, or (3) 0.12 ppm ozone + 0.3 ppm NO_2 + 0.05 ppm nitric acid.	No effects on pulmonary function.	Absence of lung function effects of 0.3 ppm NO_2 consistent with other studies; no effects of mixtures.
Rubenstein et al. (1990)	San Francisco, CA, USA	9 stable asthmatics	30 min exposures to air or 0.3 ppm NO_2 with 20 min exercise, followed 1 h later by SO_2 inhalation challenge.	No effects on pulmonary function or SO_2 responsiveness.	Findings contrast with Jörres and Magnussen et al. (1990).

STUDY	LOCATION	PARTICIPANTS	METHODS	FINDINGS	COMMENTS
Rudell et al. (1999)	Sweden	10 healthy nonsmokers	Air and diesel exhaust for 1 h, with and without particle trap. NO_2 concentration 1.2-1.3 ppm. BAL 24 h after exposures.	Increased neutrophils in BAL fluid, no significant reduction in effect with particle trap.	Filter only partially trapped particles. Unable to draw conclusions about role of NO_2 in causing effects.
Rusznak et al. (1996)	United Kingdom	13 mild asthmatics	6 h exposures to combination of 0.4 ppm NO_2 and 0.2 ppm SO_2.	Increased allergen responsiveness to combination of NO_2 and SO_2, 10 min, 24, and 48 h after exposure.	Confirms findings of Devalia et al. (1994), that NO_2 + SO_2 for 6 h increases allergen responsiveness.

Annex 6. Epidemiologic Studies Related to Ambient Exposure to NO_X

This annex provides supplemental information on various epidemiologic methods and studies that are referenced in the 2008 NO_X ISA. The first section describes considerations in the interpretation of epidemiologic studies. This is followed by a section on cardiovascular effects that are related to short-term exposure to NO_2. This topic is discussed in the ISA, but more detail is provided in this annex due to inconsistency with supporting studies. The second section of this annex presents tables detailing the epidemiologic studies presented in the ISA. In general, these tables are divided into sections based on the endpoint of concern. Tables AX6.3-1 through AX6.3-5 cover respiratory endpoints, while tables AX6.3-6 to AX6.3-9 address cardiovascular disease. The two tables, AX6.3-10 and AX6.3-11 summarize heart rate variability. Tables AX6.3-12 through AX6.3-14 address birth outcomes: birthweight, pre-term births, and lung growth, respectively, and tables AX6.3-15 through AX6.3-19 look at the long-term effects associated with NO_2 exposure (i.e., lung function, asthma, respiratory symptoms, lung cancer, and mortality). Lastly, table AX6.3-20 summarizes the effects of NO_2 on asthmatics.

AX6.1. Interpretation of Epidemiologic Studies

This section mainly focuses on the topics of exposure assessment and model specification in air pollution epidemiologic studies. The initial discussion addresses potential biases that may result from NO_2 exposure measurement error and from the choice of exposure index and lag period. The remaining discussion highlights model specification issues and potential confounding by temporal factors, meteorological effects, seasonal trends, and copollutants.

AX6.1.1. Exposure Assessment and Measurement Error

In many air pollution epidemiologic studies, especially time-series studies that use administrative data on mortality and hospitalization outcomes, air pollution data from central ambient monitoring sites are used as the estimate of exposure. Personal exposures of individual study subjects, usually, are not directly measured in epidemiologic studies. The relationship between NO_2 concentrations from ambient monitors and personal NO_2 exposures was discussed previously (Annex AX3). Routinely collected ambient monitor data, though readily available and convenient, may not represent true personal exposure, which includes both ambient and nonambient (i.e., indoor) source exposures. Also, personal exposure measurements and ambient measurements are subject to different types of artifacts and measurement error. Therefore, they may not be measuring the same quantities.

As discussed thoroughly in the 2004 PM AQCD (Section 8.4.5), the resulting exposure measurement error and its effect on the estimates of relative risk is an important consideration for interpreting epidemiologic study results. In theory, there are three components to exposure measurement error in time-series studies as described by Zeger et al. (2000): (1) the use of average population rather than individual exposure data; (2) the difference between average personal ambient exposure and ambient concentrations at central monitoring sites; and (3) the difference between true and measured ambient concentrations. The first error component, having aggregate rather than individual exposure data, is a Berksonian measurement error, which in a simple linear model increases the standard error, but does not bias the risk estimate. The second error component, which results from the difference between community average personal ambient exposure and outdoor ambient concentration level, has the greatest potential to

introduce bias. If the error is of a fixed amount (i.e., absolute differences do not change with increasing concentrations), there is no bias. However, if the error is not a fixed difference, this error will likely attenuate the NO_2 risk estimate as personal NO_2 exposures are generally lower than ambient NO_2 concentrations in homes without sources, while they are higher in homes with sources. The third error component, the instrument measurement error in the ambient levels, is referred to as nondifferential measurement error and is unlikely to cause substantial bias, although it can lead to a bias toward the null.

The impact of exposure measurement error on NO_2 effect estimates was demonstrated in a study by Kim et al. (2006), which is a longitudinal study that investigated personal exposures to NO_2, $PM_{2.5}$, and CO for cardiac compromised individuals in Toronto, Canada. The mean (SD) personal exposure for NO_2 was 14 ppb (6). NO_2 personal exposures were less than central-fixed-site ambient measurements. Ambient NO_2 was correlated with the personal exposure to NO_2 (median Spearman's correlation coefficient of 0.57). Personal exposures to $PM_{2.5}$ were correlated with the personal exposure to NO_2 (median Spearman's correlation coefficient of 0.43). This study suggests that central-fixed-site measurements of $PM_{2.5}$ and NO_2 may be treated as surrogates for both exposure to $PM_{2.5}$ and NO_2 in time-series epidemiology studies, and that NO_2 is a potential confounder of $PM_{2.5}$ and vice versa. As described in Chapter 2, Nerriere et al. (2005) provided additional data from European cities, noting that season, city, and land use dependence were important factors affecting the relationship between personal exposure to ambient NO_2 and corresponding ambient monitoring site concentrations, and recommended a site-specific analysis for a specific study. Zidek (1997) noted that a statistical analysis must balance bias and imprecision (error variance). Ignoring measurement error in air pollution epidemiologic studies often results in underestimated risk estimates and standard errors.

In addition, the use of ambient NO_2 concentrations may obscure the presence of thresholds in epidemiologic studies at the population level due to the overestimation of exposure and the resulting underestimation of effects. Using $PM_{2.5}$ as an example, Brauer et al. (2002) examined the relationship between ambient concentrations and mortality risk in a simulated population with specified common individual threshold levels. They found that no population threshold was detectable when a low threshold level was specified. Even at high-specified individual threshold levels, the apparent threshold at the population level was much lower than the specified threshold. Brauer et al. (2002) concluded that surrogate measures of exposure (i.e., those from centrally-located ambient monitors) that were not highly correlated with personal exposures obscured the presence of thresholds in epidemiologic studies at the population level, even if a common threshold exists for individuals within the population.

As discussed in Chapter 2, NO_2 concentrations measured at central ambient monitors may explain, at least partially, the variance of individual personal exposures; however, this relationship is influenced by factors such as air exchange rates in housing and time spent outdoors, which may vary by city. Other studies conducted in various cities observed that the daily averaged personal NO_2 exposures from the population were well correlated with monitored ambient NO_2 concentrations, although substantial variability existed among the personal measurements. Thus, there is supportive evidence that ambient NO_2 concentrations from central monitors may serve as valid surrogate measures for mean personal NO_2 exposures experienced by the population, which is of most relevance to time-series studies (See Chapter 2). Respiratory hospital visit and admission studies are influenced by the visits and admission of asthmatics. In children, for whom asthma is more prevalent, ambient monitors may correlate, to some extent, with personal exposure to NO_2 of ambient origin because children spend more time outdoors in the warm season and have an increased potential for exposure due to traffic. However, of some concern for mortality and hospitalization time-series studies is the extent to which ambient NO_2 concentrations are representative of personal NO_2 exposures in another particularly susceptible group of individuals, the debilitated elderly. To date, the correlation between the two measurements has not been examined in this population. A better understanding of the relationship between ambient concentrations and personal exposures, as well as the factors that affect the relationship will improve the interpretation of the ambient concentration-population health response associations observed.

Existing epidemiologic models may not fully take into consideration all of the biologically relevant exposure history or reflect the complexities of all the underlying biological processes. Using ambient

concentrations to determine exposure may overestimate true personal NO_2 exposures (depending on indoor sources), resulting in biased descriptions of underlying concentration-response relationships (i.e., in attenuated risk estimates). The implication is that the effects being estimated occur at exposures that are uncertain and the potency of NO_2 is different than these effect estimates indicate. As very few studies evaluating NO_2 health effects with personal NO_2 exposure measurements exist in the literature, effect estimates determined from ambient NO_2 concentrations must be evaluated and used with caution to assess the health risks of NO_2.

The ultimate goal of the NO_2 NAAQS is to set a standard for the ambient level, not personal exposure level, of NO_2. Confidence in the use of ambient concentrations in epidemiologic studies is greatly strengthened if they are shown to be associated with personal exposures. However, until more information on personal NO_2 exposure becomes available, the use of routinely monitored ambient NO_2 concentrations as a surrogate for personal exposures is not generally expected to change the principal conclusions from NO_2 epidemiologic studies.

AX6.1.2. NO_2 Exposure Indices Used

The NO_2-related effect estimates for mortality and morbidity health outcomes are usually presented in this document as relative risk, i.e., the risk rate relative to a baseline mortality or morbidity rate. Relative risks are based on an incremental change in exposure. To enhance comparability between studies, presenting these relative risks by a uniform exposure increment is needed. However, determining a standard increment is complicated by the use of different NO_2 exposure indices in the existing health studies. The daily NO_2 exposure indices that most often appear in the literature are the maximum 1-h average within a 24-h period (1-h max) and 24-h avg (24-h avg) concentrations. As levels are lower and less variable for the longer averaging times, relative risk of adverse health outcomes for a specific numeric concentration range are not directly comparable across metrics. Using the nationwide distributional data for NO_2 monitors in U.S. Metropolitan Statistical Areas, increments representative of a low-to-high change in NO_2 concentrations were approximated on the basis of annual mean to 95th percentile differences (Langstaff, 2006):

Daily Exposure Index

Exposure Increment	ppb
1-h avg NO_2	30
24-h avg NO_2	20
2-wk avg NO_2	20

Efforts were made to standardize the NO_2 risk estimates using these increments throughout the ISA, except as noted. The specified incremental change for each daily NO_2 exposure index ensures that risk estimates are comparable across the different metrics. The different increments for each NO_2 exposure index do not represent inconsistencies; rather, they are appropriately scaled to facilitate comparisons between the various studies that used different indices. Note that in the Chapter 6 Annex Tables (see Annex Section AX6.3), effect estimates are not standardized; there, the results are presented in the tables as reported in the published papers.

AX6.1.3. Lag Time: Period between Exposure and Health Effect

Exposure lags may reflect the distribution of effects across time in a population and the potential mechanisms of effects. The choice of lag days for the relationship between exposure and health effects depends on the hypothesis being tested and the mechanism involved in the expression of the outcome.

Effects can occur acutely with exposure on the same or previous day, cumulatively over several days, or after a delayed period of a few days. With knowledge of the mechanism of effect, the choice of lag days can be determined prior to analysis. As one example, one would expect cough to occur acutely after exposure with a lag of 0 or 1 day, given that NO_2 can act as a short-term irritant. However, an NO_2-related inflammatory response may not lead to asthma exacerbation until several days later. An asthmatic may be impacted by NO_2 on the first day of exposure, have further effects triggered on the second day, and then report to the emergency room for an asthmatic attack three days after exposure. Further, within a population of asthmatics, exacerbation of asthma symptoms may be observed over a period of several days, since each asthmatic may have varying individual aspects of the disease and may be affected by the exposure differently depending on his/her sensitivity and disease severity. The results from controlled human studies may be useful in assessing the adequacy of lags for some respiratory health outcomes.

The concepts of lags are well discussed in the O_3 AQCD (2006) and are only briefly reviewed here, as the concept for O_3 pertains to NO_2 as well. Selection of lag periods should depend on the hypothesis of the study and the potential mechanism of the effect. When the mechanism of the health effect is unknown, investigating the association between outcome and exposure using cumulative distributed lag models may be informative. Analyzing a large number of lags and simply choosing the largest and most significant results may bias the air pollution risk estimates towards or away from the null. Most studies have shown that NO_2 has a fairly consistent, immediate effect on health outcomes, including respiratory hospitalizations and mortality. Several studies also observed significant NO_2 effects over longer cumulative lag periods, suggesting that in addition to single-day lags, multiday lags should be investigated to fully capture a delayed NO_2 effect on health outcomes. In this document, discussion largely focuses on effect estimates from 0- and 1-day lags, with some consideration of cumulative, multiday lag effects. It is not straightforward to compare and contrast results from single-day versus multiday lag models, because the parameters estimated from these models are not the same. These complications need to be taken into consideration when interpreting results from various lag models.

AX6.1.4. Model Specification for Temporal Trends and Meteorological Effects

Several challenges are encountered with respect to designing and interpreting time-series studies. The principal challenge facing the analyst in the daily time-series context is avoiding bias due to confounding by short-term temporal factors operating over time scales from days to seasons, thus adjusting for long-term trends in the evaluation of acute or short-term associations. In the current regression models used to estimate short-term effects of air pollution, two major potential confounders generally need to be considered: (1) seasonal trend and other “long-wave” temporal trends; and (2) weather effects. Both of these variables tend to predict a significant fraction of fluctuations in time-series analyses.

Current weather models used in time-series analyses can be classified by their use of: (1) quantile (e.g., quartile, quintile) indicators; (2) parametric functional forms such as V- or U-shape functions; and (3) parametric (e.g., natural splines) or nonparametric (e.g., locally estimated smoothing splines [LOESS]) smoothing functions. More recent studies tend to use smoothing functions. While these methods provide flexible ways to fit health outcomes as a function of temperature and other weather variables, there are two major issues that need further examination to enable more meaningful interpretation of NO_2 morbidity and mortality effects.

The first issue is the interpretation of weather or temperature effects. Most researchers agree that extreme temperatures (i.e., heat waves or cold spells) contribute to morbidity and mortality effects. However, as extreme hot or cold temperatures, by definition, happen rarely, much of the health effects occur in the mild or moderate temperature range. Given the significant correlation between NO_2 and temperature, ascribing the association between temperature and health outcomes solely to temperature effects may underestimate the effect of NO_2. The second issue deals with the fact that weather model

specifications are fitted for year-round data in most studies. Such models will ignore the correlation structure that can change across seasons, resulting in inefficiency and model mis-specification. This is particularly important for NO_2, which appears to change its relationship with temperature as well as with other pollutants across seasons.

This changing relationship between NO_2 and temperature, as well as between NO_2 and other pollutants across seasons, and its potential implications for health effects modeling have not been examined thoroughly in the time-series literature. Even the flexible smoother-based adjustments for seasonal and other time-varying variables cannot fully take into account these complex relationships. One way to alleviate or avoid this complication is to analyze data by season. While this practice reduces sample size, the reduction would not be as serious as for PM (which is collected only every sixth day in most locations) because NO_2 is collected daily. An alternative approach is to include separate NO_2 concentration variables for each season (e.g., by multiplying NO_2 concentrations by a season indicator variable). However, this approach assumes that all effects in the model that are not indicated to be season-specific do not vary seasonally.

In locations where seasonal variability may be a factor, NO_2 effect estimates calculated using year-round data can be misleading, as the changing relationship between NO_2, temperature, and other pollutants across seasons may have a significant influence on the estimates. Analyses have indicated that confounding from seasonal variability may be controlled effectively by stratifying the data by season.

AX6.1.5. Confounding Effects of Copollutants

Extensive discussion of issues related to confounding effects among air pollutants in time-series studies are provided in Section 8.4.3 of the 2004 PM AQCD (U.S. Environmental Protection Agency, 2004). Since the general issues discussed there are applicable to all pollutants, such discussions are not repeated here.

AX6.1.6. Generalized Estimating Equations

Since the publication of the 1993 NO_2 AQCD (U.S. Environmental Protection Agency, 1993), methods to analyze panel and longitudinal studies have improved. The general mixed model method of Stiratelli et al. (1984) was an improvement over the method of Korn and Whittemore (1979) in that all the data could be used, including that from subjects with insufficient data to permit fitting of a separate logistical regression model. Generalized Estimating Equations, Liang and Zeger (1986) is an extension of generalized linear models. The joint distribution of the subject's observations does not have to be specified to derive the estimating equations. This is avoided by assuming a marginal distribution at each time. However, a covariate that is constant for a subject cannot be included in this model. Besides Gaussian outcome variables, the method can also be used for binomial or Poisson variables.

AX6.1.7. Hypothesis Testing and Model Selection

Epidemiologic studies investigated the association between various measures of NO_2 (e.g., multiple lags, different metrics, etc.) and various health outcomes using different model specifications. Statistically testing a null hypothesis (i.e., there is no effect of NO_2) requires one to calculate the value of a test statistic (i.e., the t-value). If the observed test statistic exceeds a critical value (oftentimes the 95th percentile) or is outside a range of values, the null hypothesis is rejected. However, when multiple testing is done using a critical value determined for a single test, the chance that at least one of the hypotheses is significant may be greater than the specified error rate. Procedures are available to ensure that the rejection error rate does not exceed the expected error rate (usually 5%) when conducting multiple

hypothesis testing. However, often the multiple hypotheses being tested are not statistically independent, thus some corrections, such as the Bonferroni adjustment, may be overly conservative.

Multiple hypothesis testing and model selection also contribute to publication bias. Publication bias is the tendency of investigators to submit manuscripts or editors to accept manuscripts for publication based on the strength of the study findings. Although publication bias commonly exists for many topics of research, it may be present to a lesser degree in the air pollution literature. Several air pollutants often are examined in a single study, leading to the publication of significant, as well as nonsignificant, individual pollutant results. For example, many air pollution papers with a focus on PM health effects also published NO_2 results. NO_2 was largely considered a potentially confounding copollutant of PM; thus, NO_2 effect estimates were often presented regardless of the statistical significance of the results. Another aspect of publication bias is only selecting the largest or statistically strongest effect estimate to report and not the array of models evaluated. See a full discussion in the O_3 AQCD (U.S. Environmental Protection Agency, 2006).

The summary of health effects in this ISA was vulnerable to the errors of publication bias and multiple testing. Efforts have been made to reduce the impact of multiple testing errors on the conclusions in this document. To address multiple hypothesis testing, emphasis was placed in this document on a priori hypotheses. As identifying a priori hypotheses is difficult in the majority of the studies, the most common hypotheses were considered. For example, although many studies examined multiple single-day lag models, priority was given to effects observed at 0- or 1-day lags rather than at longer lags. Both single- and multiple-pollutant models that include NO_2 were considered and examined for robustness of results. Analyses of multiple model specifications for adjustment of temporal or meteorological trends were considered sensitivity analyses. Sensitivity analyses were not granted the same inferential weight as the original hypothesis-driven analysis; however, these analyses are discussed in this document as appropriate given their valuable insights that may lead scientific knowledge in new directions.

AX6.1.8. Generalized Additive Models

Generalized Additive Models (GAM) have been widely utilized for epidemiologic analysis of the health effects attributable to air pollution. The impact of the GAM convergence issue was thoroughly discussed in Section 8.4.2 of the 2004 PM AQCD. Reports have indicated that using the default convergence criteria in the Splus software package for the GAM function can lead to biased regression estimates for PM and an underestimation of the standard error of the effect estimate (Dominici et al., 2002; Ramsay et al., 2003). The GAM default convergence criterion in the Splus software package is 10 with a maximum number of 10 iterations. The user can specify convergence criteria, that is orders of magnitude smaller than the default value and can also allow for many more iterations before terminating the program. The use of the default convergence criterion was found to be a problem when the estimated relative risks were small and two or more nonparametric smoothing curves were included in the GAM (Dominici et al., 2002). The magnitude and direction of the bias depend in part on the concurvity of the independent variables in the GAM and the magnitude of the risk estimate. Recent focus has been on the influence of the GAM function on effect estimates for PM.

The GAM convergence problem appears to vary depending on data sets, and likely depends upon the intercorrelation among covariates and the magnitude of the risk estimate; thus, its impact on the results of individual studies cannot be known without a reanalysis. Consistent with the approach used in the 2004 PM AQCD, the results from studies that analyzed data using GAM with the default convergence criterion and at least two nonparametric smoothing terms are generally not considered in this chapter, with some exceptions as noted.

AX6.2. Cardiovascular Effects Related to Short-Term NO_2 Exposure

AX6.2.1. Hospital Admissions and ED Visits: All CVD

Results of studies of short-term NO_2 exposure and hospitalization or Emergency Department visits for cardiovascular disease are summarized in Figure AX6.2-1. Studies of both 1-h max NO_2 level and 24-h avg NO_2 level are included. With the exception of lag 1 results reported by Jalaludin et al. (2006), most point estimates are positive with confidence limits excluding the null value. Jalaludin et al. report a lag 0 cool season relative risk (not pictured) of 1.09 (95%CI: 1.05, 1.13) per 30 ppb increase in 1-h max NO_2 level (Jalaludin et al., 2006). (Note that the IQR reported by Jalaludin et al. is 9.3 ppb so the 30-ppp increase into which the results were standardized may be unlikely in Sydney, where the study was conducted.) Although results for cardiovascular diseases were not tabulated for a reanalysis of GAM impacted study of Los Angeles and Cook County hospital admissions, authors note that they observed an association of NO_2 with CVD hospital admissions in the reanalyses (Moolgavkar, 2003). The association was diminished with the use of increasingly stringent convergence criteria, however (Moolgavkar, 2003).

Ischemic Heart Disease

Studies that further narrowed the cardiac disease grouping to evaluate Ischemic Heart Diseases (IHD) are summarized in Figure AX6.2-2. Several US studies examined the association of ambient NO_2 level with IHD (Ito, 2004; Mann et al. 2002; Metzger et al. 2004; Peel et al. 2007). Ito (2004) reported a null association of 24-h avg NO_2 level with IHD admissions in Ontario where the mean ambient level was 21.3 ppb. Mann et al. (2002) examined the association of 24-h avg NO_2 level with IHD and secondary diagnoses of arrhythmia, IHD and secondary diagnosis of CHF, IHD and no secondary diagnosis, and all IHD regardless of secondary diagnosis in single-pollutant models. The authors noted that the strongest effect observed (IHD with secondary diagnosis of CHF) may have been driven by the MI primary diagnoses. The 24-h avg NO_2 level in the South Coast Air Basin of California, where this study was conducted was approximately 37 ppb. This study was novel in that exposure level was assigned based on the zip code of the health insurance participant and proximity to the monitoring station (Mann et al., 2002). A non-significant increased risk of ED visit for IHD was observed in single-pollutant models, among those with hypertension but not diabetes in a study conducted in Atlanta where the daily 1-h max NO_2 level was approximately 46 ppb (Peel et al., 2007).

Two studies of IHD and hospital admissions conducted in Europe have produced conflicting results (Atkinson et al., 1999a; Poloniecki et al., 1997). Atkinson et al. (1999a) reported a significant increase in IHD admission in a study in London. A study conducted in Helsinki reported an association of NO with both hospitalization and ED visits for IHD while no association with NO_2 was observed (Pönkä and Virtanen, 1996). In addition, Several Australian studies, including two multicity studies, supported an association of hospital admissions and emergency visits for IHD and ambient NO_2 level among older adults in single-pollutant models (Jalaludin et al., 2006; Barnett et al., 2006; Simpson et al., 2005a,b). One study conducted in Hong Kong reports slightly elevated non-significant association of IHD with 24-h avg NO_2 level (Wong et al., 1999). In addition, Lee et al. (2003a) reported an increase in IHD admissions associated with 24-h avg NO_2 level at lag 5.

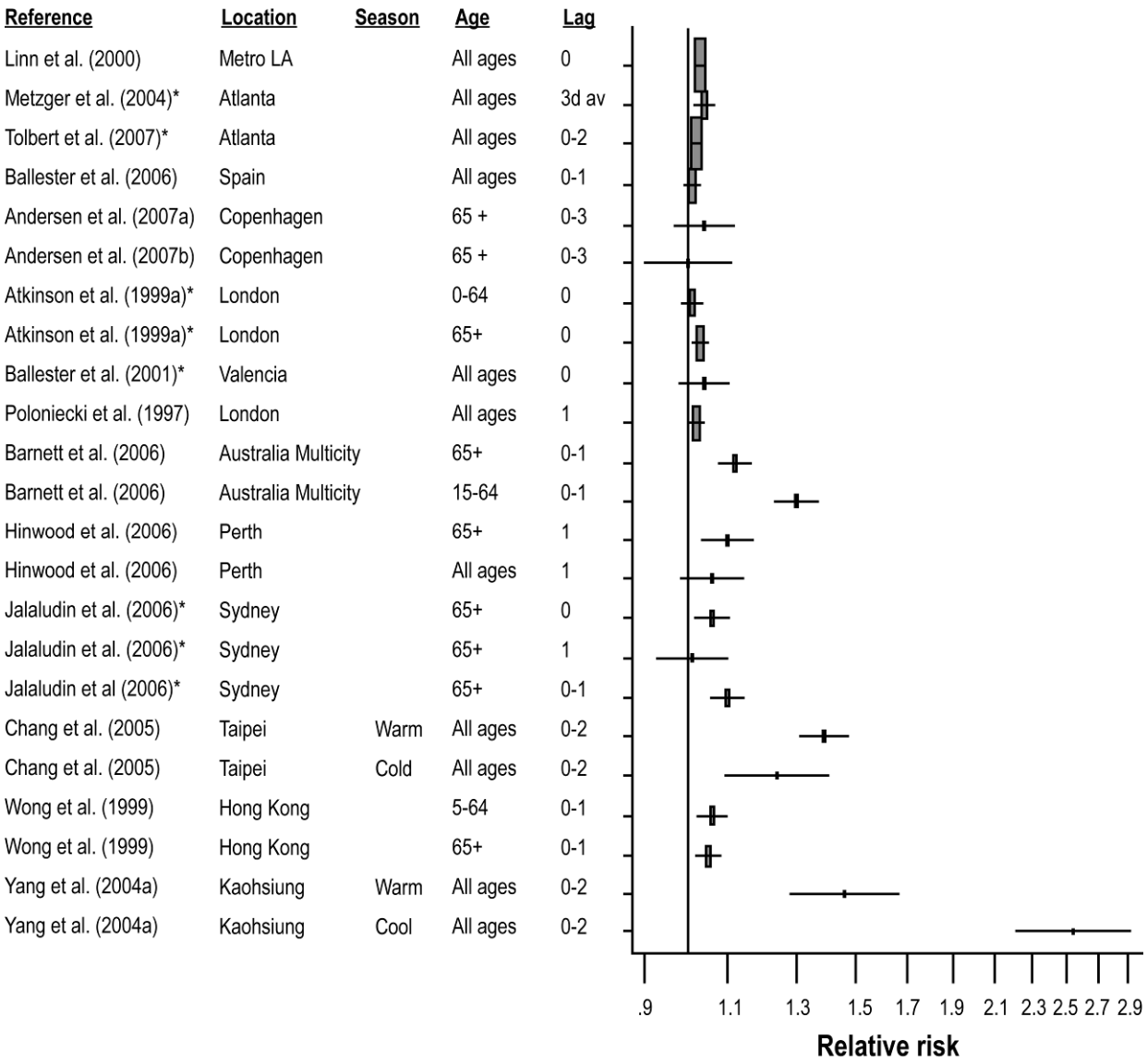


Figure AX6.2-1. Relative risks (95% CI) for associations of 24-h NO_2 (per 20 ppb) and daily 1-h max NO_2* with hospitalizations or emergency department visits for all cardiovascular diseases (CVD). Primary author and year of publication, city, stratification variable(s), and lag are listed. Results for lags 0 or 1 are presented, as available. *NO_2 1 h max; all others 24 h avg.

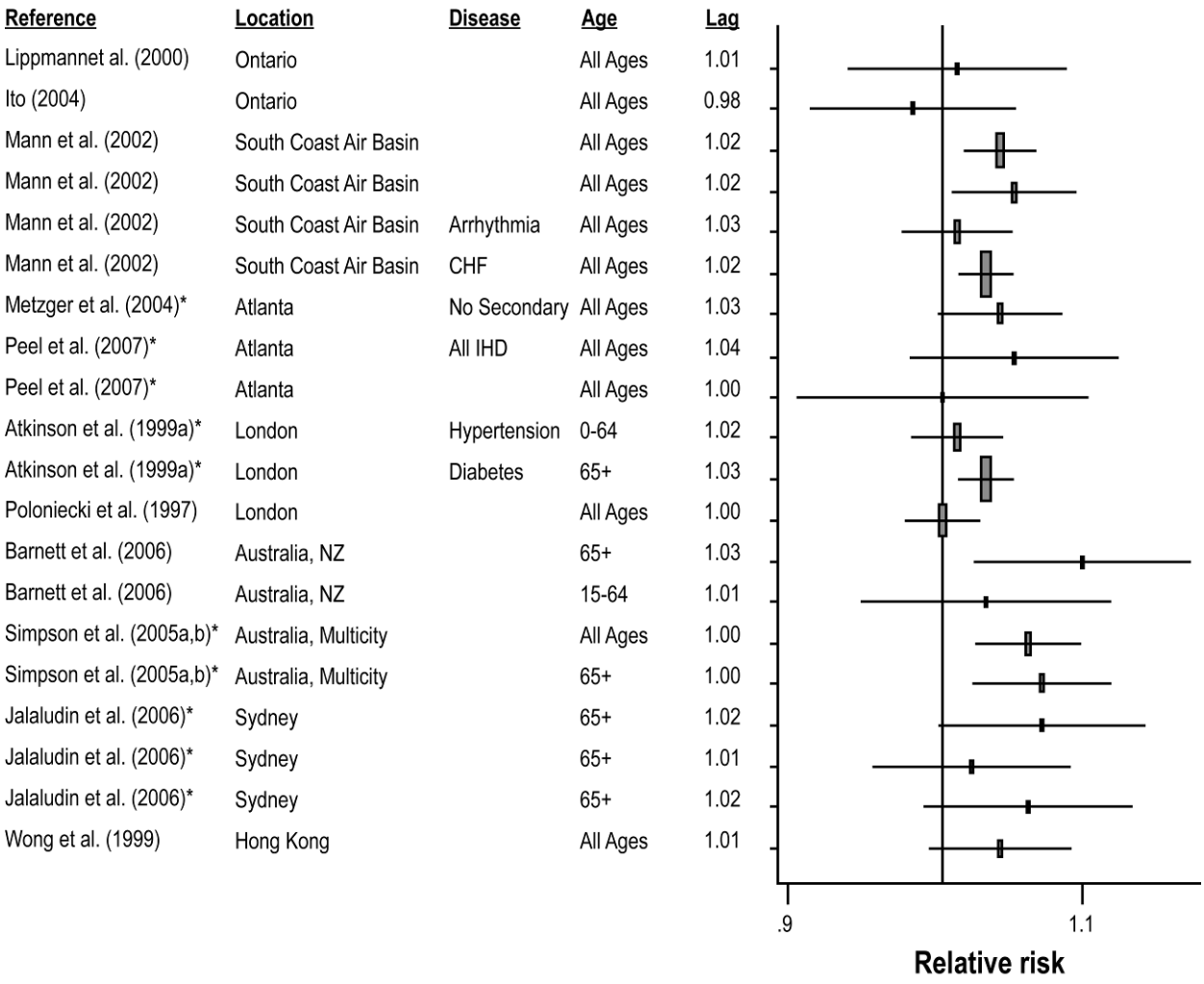


Figure AX6.2-2. Relative risks (95% CI) for associations of 24-h NO_2 (per 20 ppb) and daily 1-h max NO_2* (per 30 ppb) with hospitalizations for Ischemic Heart Disease (IHD). Primary author and year of publication, city, stratification variable(s), and lag are listed. Results for lags 0 or 1 are presented, as available. *NO_2 1 h max; all others 24 h avg.

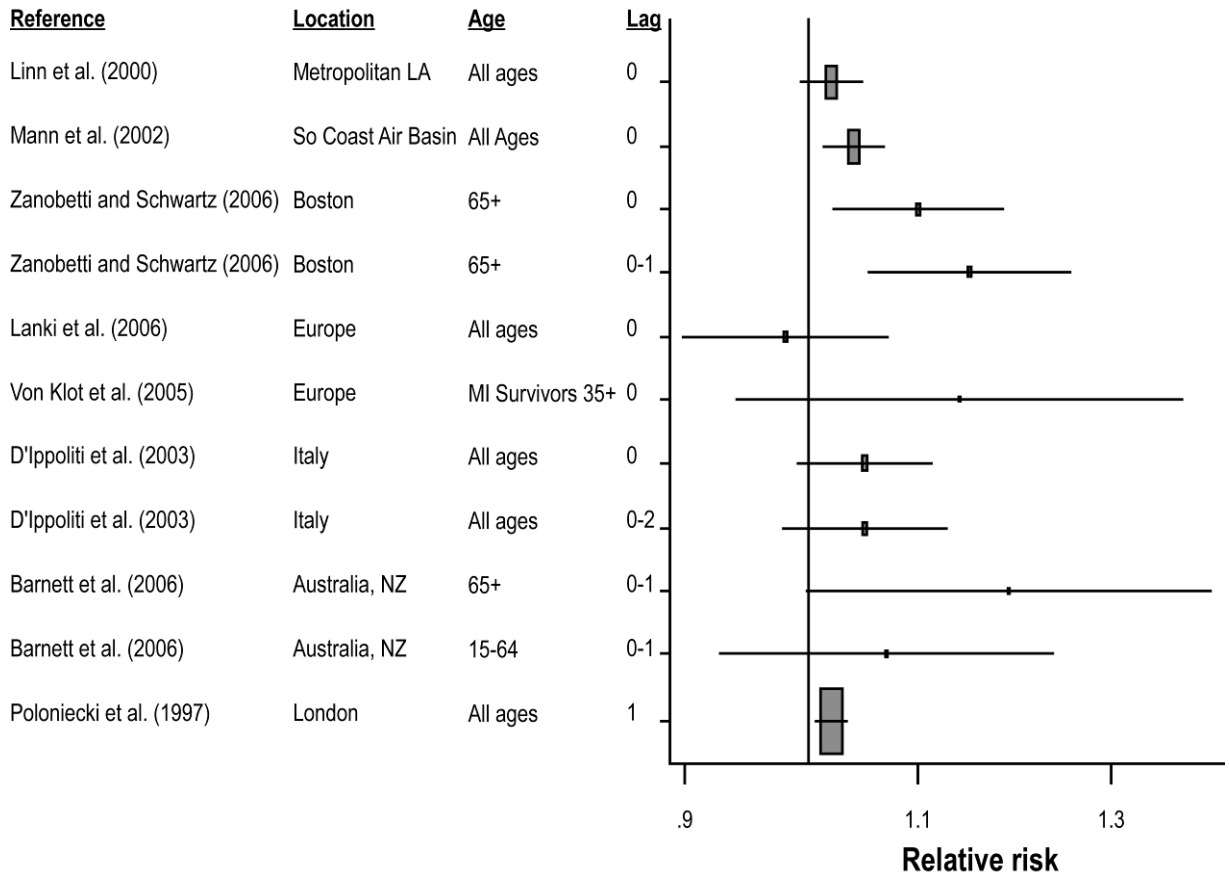


Figure AX6.2-3. Relative risks (95% CI) for associations between 24-h avg NO_2 (per 20 ppb) and hospitalizations for myocardial infarction (MI). Primary author and year of publication, city, stratification variable(s), and lag are listed. Results for lags 0 or 1 are presented as available. *NO_2 1 h max; all others 24 h avg.

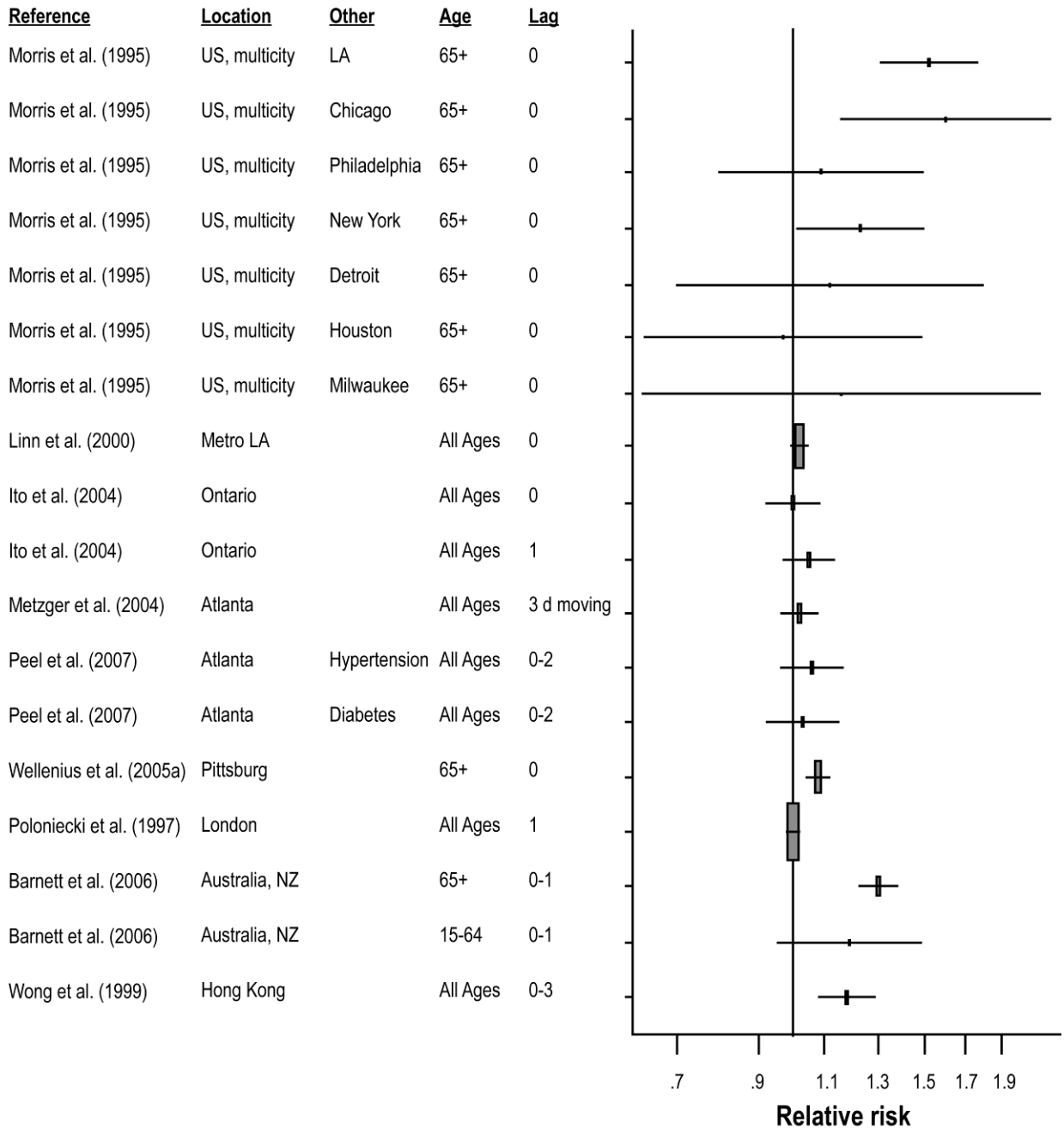


Figure AX6.2-4. Relative risks (95% CI) for associations of 24-h avg NO_2 (per 20 ppb) and 1-h max NO_2* with hospitalizations for congestive heart failure (CHF). Primary author and year of publication, city, stratification variable(s), and lag are listed. Results for lags 0 or 1 are presented as available.

AX6.2.2. Hospital Admissions and ED Visits: Myocardial Infarction (MI)

Studies of hospital admissions for MI are summarized in Figure AX6.2-3. In the United States, positive single-pollutant associations for emergency admissions for MI and increases in ambient NO_2 level were reported in Boston (Zanobetti and Schwartz, 2006) and California (Linn et al., 2000; Mann et al., 2002).

Pooled results from two European multicity studies are inconsistent. Von Klot et al. (2005) reported an increase in MI readmissions at lag 0 while Lanki et al. (2006) reported a null effect at lag 1. The NO_2 levels were similar in the cities studied with Lanki et al. (2006) reporting the 24-h avg level of 23 ppb and Von Klot et al. (2005) reporting a range in 24-h avg across the cities studied of 12-37 ppb. A single-city study in Italy (D'Ippoliti et al., 2003) found positive significant associations between 24-h avg NO_2 level and admission for the first episode of MI. The 24-h avg NO_2 level reported by D'Ippoliti was approximately 45 ppb. A study conducted in London reported a positive association of ED visit for MI with 24-h avg NO_2 where the 24-h avg reported was approximately 35 ppb. Finally, positive associations were reported for MI in a multicity study conducted in Australia and New Zealand among older adults and adults from 15 to 64 years old (Barnett et al., 2006). The 24-h avg NO_2 level ranged from approximately 7-12 ppb in the Australian cities studied (Barnett et al., 2006).

AX6.2.3. Hospital Admissions and ED Visits: Arrhythmia and Congestive Heart Failure (CHF)

Hospital or ED admissions for arrhythmia were inconsistently associated with increases in ambient NO_2 level. Some studies reported positive associations (Rich et al., 2006a; Mann et al., 2002; Barnett et al., 2006) while others reported null associations (Metzger et al., 2004; Lippmann et al., 2000; reanalysis Ito, 2004). Single-pollutant models of hospital admissions and ED visits for CHF have also produced mixed results (Figure AX6.2-4). A seven city study conducted in the U.S. among the elderly found positive associations in Los Angeles (RR: = 1.52 [1.35, 1.71]), Chicago (RR: = 1.60 [1.24, 2.07]) and New York (RR: = 1.23 [1.05, 1.43]) per 30-ppb increase in NO_2 (Morris et al., 1995). Estimates were close to the null value in Philadelphia, Detroit, Houston, and Milwaukee and only the estimate for New York remained significant in multi-pollutant models (Morris et al., 1995). The 1-h max NO_2 level in the cities studied ranged from 40 ppb in Milwaukee to 77 ppb in Los Angeles (Morris et al., 1995). Ito, 2004 reported null associations for CHF and NO_2 in Ontario where the 24-h avg NO_2 level is approximately 21 ppb (Ito, 2004). Elevated but non-significant associations were reported in Atlanta (Metzger et al., 2004; Peel et al., 2007) and elevated significant associations were reported in Pittsburgh (Wellenius et al., 2005a). Null associations were reported in London (Poloniecki et al., 1997) while positive significant associations were reported in a multicity study in Australia and New Zealand (Barnett et al., 2006) and in Hong Kong (Wong et al., 1999).

AX6.2.4. Hospital Admissions and ED Visits: Cerebrovascular Disease

AX6.2.4.1. Vaso-Occlusion in Sickle Cell

A recent study evaluated the association of pain in Sickle Cell patients, which is thought to be caused by vaso-occlusion, with air pollution (Yallop et al., 2007). A time series analysis was performed to link daily hospital admissions for acute pain among sickle cell patients with daily air pollution levels in London using the cross correlation function. No association was reported for NO_2. However, Yallop et al. (2007) observed an association (CCF = -0.063, lag 0) for NO, CO, and O_3.

AX6.2.5. Hospital Admissions and ED Visits: Multipollutant Modeling Results

Multipollutant models may have limited utility to distinguish the independent effects of specific pollutants if model assumptions are not met. However, these models are widely used in air pollution research and results for CVD hospital admissions and ED visits are summarized in Figure AX6.2-5. This figure includes only those studies that present two-pollutant results in tabular form. Studies with qualitative descriptions or figures summarizing two-pollutant results are discussed in the text that follows (Linn et al., 2000; Mann et al., 2002; Metzger et al., 2004; Tolbert et al., 2007; Zanobetti and Schwartz, 2006; Jalaludin et al., 2006; Von Klot et al., 2005; Ballester et al., 2006; Wong et al., 1999). In addition, we included text discussion of studies that simultaneous adjust for several pollutants (Morris et al., 1995; Llorca et al., 2005) and several cerebrovascular disease studies that report multipollutant results (Ballester et al., 2001; Villeneuve et al., 2006; Tsai et al., 2003a; Chan et al., 2006).

A U.S. study showed a diminishment of the relative risk for CHF in two-pollutant models (Wellenius et al., 2005a). Morris et al. (1995) also observed a similar diminishment of the CHF association in multipollutant models containing SO_2, CO, and Ozone (Morris et al., 1995). The association of cardiac disease admissions with NO_2 in several non-U.S. studies was not robust in two-pollutant models (Simpson et al., 2005a,b; Poloniecki et al., 1997; Barnett et al., 2006; Ballester et al., 2006). Llorca et al. (2005) reported a similar lack of robustness in models containing NO_2, TSP, H_2S, NO, and SO_2. Estimates from studies conducted in Taiwan reporting relatively high associations of NO_2 with CVD in single-pollutant models remained robust in two-pollutant models during the cool (Yang et al., 2004a) or warm (Chang et al., 2005) seasons only. In an Australian study of older adults (65+ years), the effect estimate for NO_2 was robust to simultaneous adjustment for O_3 and particles (Morgan et al., 1998a).

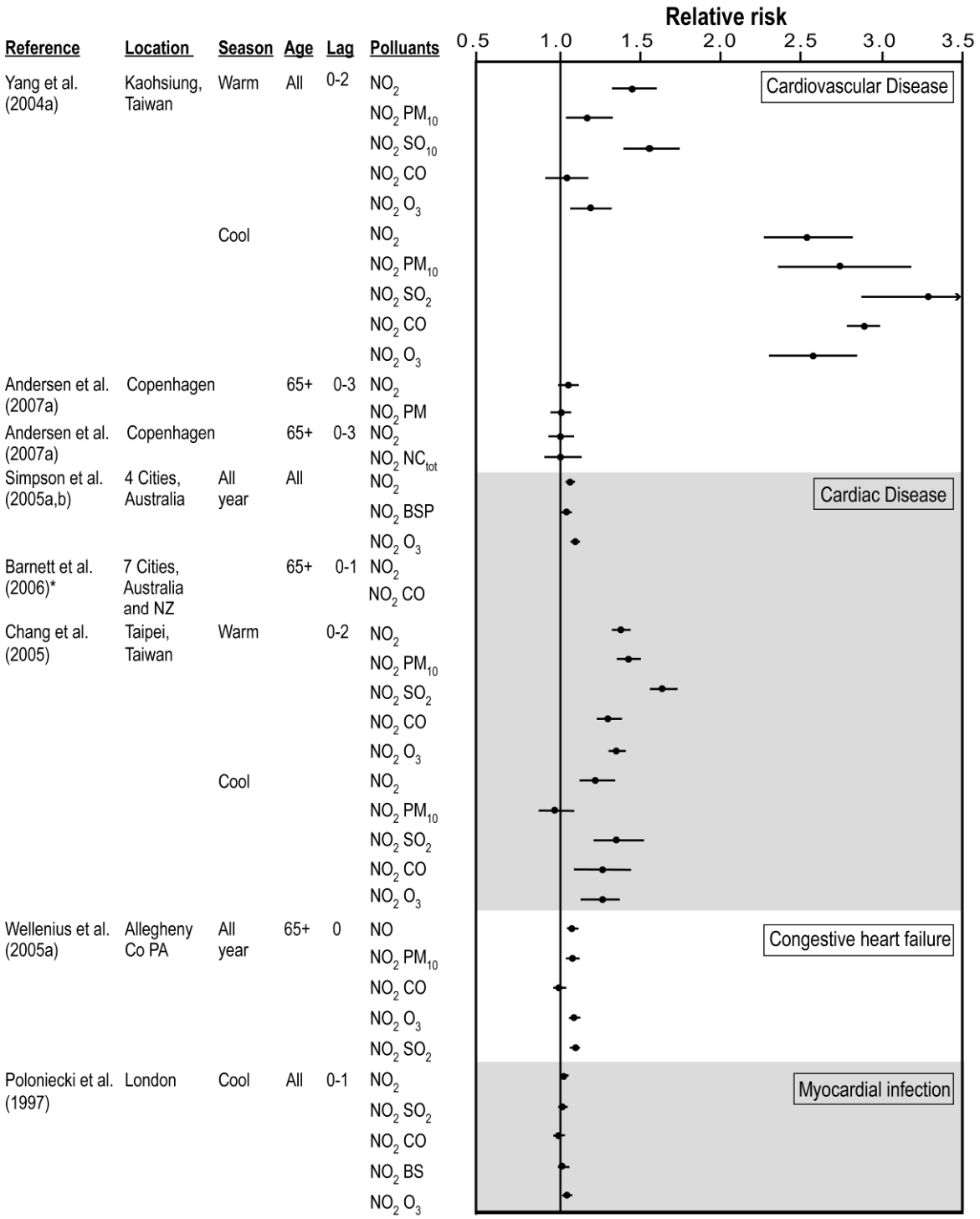


Figure AX6.2-5. Relative risks (95% CI) for associations of 24-h avg NO_2 exposure (per 20 ppb) and daily 1-h max NO_2* (per 30 ppb) with hospitalizations or emergency department visits for CVD. Studies with 2 pollutant model results. Primary author and year of publication, city, stratification variable(s), and lag are listed. Results for lags 0 or 1 are presented as available.

In two additional U.S. studies, investigators provided text descriptions of multipollutant model results and indicated that their analyses were unable to distinguish the effects of NO_2 from PM, CO, and other traffic pollutants (Linn et al., 2000; Mann et al., 2002.) In both studies, CO was more highly correlated with NO_2 than PM. In a Canadian study in which default GAM procedures were used, the significant association of NO_2 with ED visits for cardiac disease was reduced and non-significant in multipollutant models (Stieb et al., 2000). Further, in a study of emergency department visits to Atlanta hospitals, Metzger et al., 2004 observed a diminishment of the effect of NO_2 on visits for cardiovascular disease when CO was modeled with NO_2, while the effect of CO remained robust. This finding was repeated in an analysis that included several additional years of data (Tolbert et al., 2007). In this paper, Tolbert et al. (2007) discussed the limitations of multipollutant models in detail and conclude that these models may help researchers identify the strongest predictor of disease but may not isolate the independent effect of each pollutant. In an Australia study (Jalaludin et al., 2006) and a Spanish multicity study (Ballester et al., 2006) presenting multipollutant results, the association of NO_2 with cardiac disease was not robust to adjustment for other pollutants (CO, SO_2, particles). However, in a European multicity study investigators reported that the effect of NO_2 on cardiac readmissions among MI survivors was not diminished in multipollutant models (Von Klot et al., 2005).

Burnett et al. (1997a) reported robust estimates for cardiac disease hospital admissions and NO_2, whereas the observed association for cardiac hospitalizations and PM were explained by gaseous pollutants. In another multicity study conducted in the same area, associations of NO_2 with cardiac disease were not attenuated when CO, SO_2, and PM variables were included in the models (Burnett et al., 1999).

The association of NO_2 with stroke was not robust to adjustment for CO in a Canadian study (Villeneuve et al., 2006). The association of NO_2 with all cerebrovascular disease was not robust to adjustment for BS and SO_2 in a Spanish single city study (Ballester et al., 2001). Although results from a Taiwanese study indicated that the effect of NO_2 on stroke admissions is not diminished in two-pollutant models, the authors noted that the association of NO_2 with stroke may not be causal if NO_2 is a surrogate other components of the air pollution mixture (Tsai et al., 2003a).

Studies using alternative methods to investigate the influence of copollutants on observed associations of NO_2 with cardiovascular disease are few in number. In an study of emergency admissions for MI and ambient pollution in Boston investigators attempt to distinguish traffic from non-traffic related pollutants through their definition of an exposure metric for non-traffic PM (residuals in model of $PM_{2.5}$ regressed against BC) but found NO_2, $PM_{2.5}$ and non-traffic PM each may trigger MI during the warm season (Zanobetti and Schwartz, 2006). In a study conducted in Hong Kong, investigators looked at the association of NO_2 with CVD during high PM_{10} and high ozone days (Wong et al., 1999). An interaction between NO_2 and ozone was observed (in the single-pollutant model NO_2 associated with heart failure, RR: 1.18 95% CI: 1.10, 1.26 per 20 ppb, lag 0-3).

AX6.2.6. Heart Rate Variability

Liao et al. (2004) investigated short-term associations between ambient pollutants and cardiac autonomic control from the fourth cohort examination (1996 to 1998) of the population-based Atherosclerosis Risk in Communities (ARIC) Study. PM_{10}, NO_2, and other gaseous air pollutants were examined in this study. PM_{10} (24-h avg) and NO_2 (24-h avg) 1 day prior to the randomly allocated examination date were used. The mean ± SD NO_2 level was 21 ± 8 ppb. PM_{10} concentrations measured 1 day prior to the HRV measurements were inversely associated with both frequency- and time-domain HRV indices. Ambient NO_2 concentrations were inversely associated with high-frequency power and SDNN. In single-pollutant models, a 20-ppb increase in ambient NO_2 was associated with a 5% reduction (95% CI: 0.7, 9.2), in mean SDNN. Consistently more pronounced associations were suggested between PM_{10} and HRV among persons with a history of hypertension.

Various measures of HRV have been examined in relation to daily levels of ambient air pollution in other studies (Chan et al., 2005; Wheeler et al., 2006; Holguín et al., 2003; Luttmann-Gibson et al., 2006; Schwartz et al., 2005). Chan et al. (2005) recruited 83 patients from the cardiology section of a hospital in Taiwan. Patients included 39 with coronary heart disease (CHD) and 44 with more than one risk factor for CHD. The authors reported finding significant associations between increases in NO_2 and decline in SDNN (NO_2 lagged 4 to 8 h) and LF (NO_2 lagged 5 or 7 h) (see Annex Table AX6.3-10 for quantitative results). There were no significant associations for r-MSSD or HF and NO_2. None of the other pollutants tested (PM_{10}, CO, SO_2, O_3) were significantly associated with any of the HRV measured. Wheeler et al. (2006) examined HRV and ambient air pollution in Atlanta in 12 patients who had an MI from 3 to 12 months prior to enrollment and 18 COPD patients. The results in the two patient groups were quite different: increasing concentration of NO_2 in the previous 4-h significantly reduced SDNN in MI patients and significantly increased SDNN in COPD patients (see Annex Table AX6.10). Similar significant associations were seen with increases in 4-h ambient $PM_{2.5}$. The $PM_{2.5}$ concentrations were moderately correlated with NO_2 levels (r = 0.4).

In contrast, Holguín et al. (2003) found $PM_{2.5}$ concentrations were moderately correlated with NO_2 levels (v = 0.04) in 34 elderly adults in Mexico City and found no significant associations with increases in NO_2, but did find significant effects of $PM_{2.5}$ on HF, particularly among hypertensive subjects. Similarly, Luttmann-Gibson et al. (2006) also found significant effects of $PM_{2.5}$ and SO_4 on HRV measured in a panel of 32 senior adults in Steubenville, OH, but observed no effect of increasing NO_2. Likewise, Schwartz et al. (2005) found significant effects of increases in $PM_{2.5}$ on measures of HRV, while no associations with NO_2 were observed. A population-based study of air pollutants and HRV was conducted in Boston, MA on 497 men from the VA Normative Aging Study (NAS) (Park et al., 2005). The mean ± SD 24-h avg NO_2 concentration was 22.7 ± 6.2 ppb. Associations with HRV outcomes were observed with a 4-h moving avg of O_3 and $PM_{2.5}$ concentrations, but not with NO_2.

AX6.2.7. Repolarization Changes

A prospective panel study, conducted in East Germany, analyzed 12 repeat ECG recordings for 56 males with IHD (Henneberger et al., 2005). Ambient air pollutants measured at fixed monitoring sites were used to assign individual exposures for 0 to 5, 5 to 11, 12 to 17, 18 to 23, 0 to 23 h and for 2 to 5 days prior to the EEG. Pollutants considered were ultrafine particles (UFP), accumulation mode particle (ACP), $PM_{2.5}$, elemental carbon (EC), organic carbon (OC), SO_2, NO_2, NO, and CO. Associations were observed between (1) QT duration and EC and OC; (2) T-wave amplitude and UFP, ACP and $PM_{2.5}$; and (3) T-wave complexity and PM_{10}, EC, and OC. NO (r = 0.83) and NO_2 (0.76) were highly correlated with UFP but were not associated with repolarization abnormalities.

AX6.2.8. Arrhythmias Recorded on Implantable Cardioverter Defibrilators (ICDs)

In a pilot study, Peters et al. (2000a) abstracted device records for 3 years for each of 100 patients with ICDs. Defibrillator discharge events were positively associated with the previous day and 5-day mean NO_2 concentrations: each 20-ppb increase in the previous day's NO_2 level was associated with an increased risk of a discharge event (OR = 1.55 [95% CI: 1.05, 2.29]) (see Annex Table AX6.3-1 for the increase associated with a 20-ppb increase in NO_2).

Three papers by the same team of investigators examined the association between air pollution and the incidence of ventricular arrhythmias (Dockery et al., 2005; Rich et al., 2005) and PAF episode (Rich et al., 2006b) in Boston. A total of 203 patients with ICDs who lived within 25 miles of the ambient monitoring site were monitored. Data included a total of 635 person-years of follow-up or an average of 3.1 years per subject. The median (IQR) 48-h avg NO_2 concentration was 22.7 (7.7) ppb. In the study by

Dockery et al. (2005), significant positive associations were observed between ventricular arrhythmias within 3 days of a prior event, and a 2-day mean exposure to several air pollutants including $PM_{2.5}$, BC, NO_2, CO, and SO_2. Rich et al. (2005) examined associations between ambient air pollution levels less than 24 h before the occurrence of a ventricular arrhythmia to make use of the precise time definition available from the implantable cardioverter defibrillator (Rich et al., 2005). In single-pollutant models, each 20-ppb increase in the mean NO_2 level over the previous 2 days was associated with an increased likelihood of ventricular arrhythmia, OR = 1.54 (95% CI: 1.11, 2.18). The association with NO_2 was not significant in two-pollutant models with $PM_{2.5}$, but remained marginally significant in models with O_3 (2.0-ppb increase in 24-h moving avg NO_2 was associated with an OR = 1.36 [95% CI: 1.00, 1.80]). There was a strong association between an increase of NO_2 (by 20 ppb) and ventricular arrhythmia in the presence of ventricular arrhythmia within the previous 72 h (OR = 2.09 [95% CI: 1.26, 3.51]). Increased but non-significant associations were observed in this population between NO_2 levels and PAF, as well as fine particles and black carbon (Rich et al., 2006b).

A study conducted in St. Louis, which also examined the association of air pollutant level within 24 h of a ventricular arrhythmia, reports non-significant increases for NO_2 and elemental carbon, while SO_2 was significantly associated with increased occurrence of arrhythmia (Rich et al., 2006a). Metzger et al. (2007) examined the association of ventricular tachyarrhythmias with air pollutants in the largest study to date (N = 518), which was conducted in Atlanta. These investigators reported "suggestive" findings for course particulate but generally no evidence of an association of NO_2 and other pollutants with tachyarrhythmias (Metzger et al., 2007).

AX6.2.9. Markers of Cardiovascular Disease

In a large cross-sectional study of 7,205 office workers in London, Pekkanen et al. (2000) collected blood samples and analyzed the association between plasma fibrinogen, a risk factor for CVD, and ambient levels of air pollution. In models adjusting for weather, demographic, and socioeconomic factors, there was an increased likelihood of blood levels of fibrinogen >3.19 g/l (90th percentile) for each 20-ppb increase in NO_2 lagged by 3 days (OR = 1.14 [95% CI: 1.03, 1.25]). The correlation between daily NO_2 and other traffic-related pollutants were high: daily levels of black smoke (r = 0.75), PM_{10} (r = 0.76), SO_2 (r = 0.62), CO (r = 0.81). The authors proposed that the increased concentrations of fibrinogen, a mediator of cardiovascular morbidity and mortality, may be an indicator of inflammatory reactions caused by air pollution.

Schwartz (2001) examined the association between fibrinogen, platelet count, and white blood cell (WBC) count in the Third National Health and Nutrition Examination Survey (NHANES III). In single-pollutant models NO_2 was associated with platelet counts and fibrinogen. However, in a two-pollutant model with PM_{10} these associations became negative.

Pekkanen et al. (2002) enrolled a panel of 45 adults with coronary heart disease in order to examine associations between heart function as measured by risk of ST-segment depression and particulate pollution. Level of particulate and gaseous pollutants, including NO_2, lagged by 2 days was found to have the strongest effect on risk of ST-segment depression during mild exercise tests (OR = 14.1 [95% CI: 3.0, 65.4] for ST-segment depression of >0.1mV with a 20-ppb increase in NO_2 lagged by 2 days). A large (n = 863) cross-sectional study of resting heart rate (HR) of adults in France found significant associations between elevated levels of NO_2 within 8-h of measurement and resting HR of ≥75 beats per minute (bpm) (OR = 2.7 [95% CI: 1.2, 5.4] for resting HR >75 bpm for each 20-ppb increase in NO_2) (Ruidavets et al., 2005).

In a population based study of participants in the Atherosclerosis Risk in Communities (ARIC) study, Liao et al., 2005 did not observe differences in White Blood Cell (WBC) count, Factor VIII C, fibrinogen, Von Willibrand Factor (VWF) or albumin depending on 24-h avg NO_2 level lagged 1 to 3 days prior to the examination date. However, PM_{10} was associated with factor VIII-C in this cohort. An

association between PM_{10} and serum albumin was observed only among persons with a history of CVD (Liao et al., 2005).

Ruckerl et al. (2006) examined several markers of inflammation, cell adhesion, and coagulation among a panel of 57 male patients with CHD. These authors primary hypothesis was that C-reactive protein (CRP) would be increased with increases in air pollution. They also investigated the effect of air pollution on other markers including serum amyloid A (SAA), E-selectin, von Wildebrand factor antigen, intercellular adhesion molecule 1 (ICAM-1), fibrinogen, factor VII, prothrombin fragment 1+2, and D-dimer. A significant association was observed for NO_2 with CRP greater than the 90th percentile but the strongest effect on CRP was observed for ultrafine particles.

Steinvil et al. (2007) investigated the association of air pollutants with several markers of inflammation (fibrinogen, CRP, and WBC). Significant decreases in fibrinogen associated with increases of 13 ppb in ambient NO_2 were reported among men (all lags 0-7 and 7 day avg) and women (lag 0, 7 day avg). The absolute change in fibrinogen ranged from 7.9 to 16.7 mg/dL (Steinvil et al., 2007). The mean NO_2 level was 19.5 ppb (Steinvil et al., 2007). PM_{10} was significantly associated with increased fibrinogen only at day 7. No correlations with CRP and WBC were observed (Steinvil et al., 2007).

Baccarelli et al. (2007) investigated the effect of ambient NO_2 with prothrombin time (PT) and activated partial thromboplastin time (APTT) in 1218 normal subjects in Italy. Both NO_2 (coefficient = -0.08 95%CI: -0.15, 0.00) and PM_{10} (coefficient = -0.08 95% CI: -0.14, -0.01) on the same day and the average for 30 days prior to the examination were negatively correlated with PT (e.g., PT became shorter indicating hypercoagulability), while no effect on APTT was reported (Baccarelli et al., 2007).

AX6.3. Epidemiologic Studies

Table AX6.3-1. Studies examining exposure to indoor NO_2 and respiratory symptoms.

AUTHOR, YEAR, LOCATION	STUDY DESIGN	EXPOSURE TIME	MEAN (SD)	RANGE (PPB)	OUTCOME & ESTIMATE (95% CI)
Pilotto et al. (2004) Australia	Subjects: 118 asthmatic children Analysis: negative binomial Monitoring Device: passive diffusion badges	6 h	intervention: 16 (7) control: 47 (27)	intervention: 7, 38 control: 12, 116	**difficulty breathing, day** RR 2.44 (1.02, 14.29)* **chest tightness, day** RR 2.22 (1.23, 4.00)* **asthma attacks, day** RR 2.56 (1.08, 5.88)* **difficulty breathing, night** RR 3.12 (1.45, 7.14)*
Pilotto et al. (1997) Australia	Subjects: 388 children Analysis: generalized linear mixed models Monitoring Device: passive diffusion badges	6 h		overall: 4, 132	wheeze (>40 ppb vs. ≤ 40 ppb) OR 1.41 (0.63, 3.15) Dry cough (>40 ppb vs. ≤ 40 ppb) OR 1.08 (0.62, 1.90)

AUTHOR, YEAR, LOCATION	STUDY DESIGN	EXPOSURE TIME	MEAN (SD)	RANGE (PPB)	OUTCOME & ESTIMATE (95% CI)
Nitschke et al. (2006) Australia	Subjects: 174 asthmatic children Analysis: negative binomial Monitoring Device: passive diffusion badges	6 h	home: 20 (22) school: 34 (28)		Wheeze Day: school RR 1.01 (0.97,1.06) home RR 0.98 (0.92, 1.04) Night: school RR 0.99 (0.93, 1.06) home RR 1.00 (0.90, 1.11) difficulty breathing Day: school RR 1.09 (1.03, 1.15) home RR 1.00 (0.98, 1.03) Night: school RR 1.11 (1.05, 1.18) home RR 1.03 (1.01, 1.05) chest tightness Day: school RR 1.08 (0.99, 1.19) home RR 0.97 (0.89, 1.06) Night: school RR 1.12 (1.07, 1.17) home RR 1.02 (0.95, 1.09) Cough Day: school RR 1.01 (0.99, 1.03) home: RR 1.01 (0.97, 1.05) Night: school RR 1.01 (0.98, 1.04) home RR 0.99 (0.96, 1.02) asthma attacks Day: school RR 1.03 (0.98, 1.08) home: RR 1.00 (0.95, 1.05) Night: school RR 1.00 (0.93, 1.08) home RR 1.04 (1.00, 1.07) results given for 10-ppb increase in NO2
Garrett et al. (1998) Australia	Subjects: 148 children (age 7-14) Analysis: multiple logistic regression Monitoring Device: passive monitors	4 days	med 6		Cough Gas stove OR 2.25 (1.13, 4.49) Bedroom OR 1.47 (0.99, 2.18) Shortness of Breath Gas stove OR 1.49 (0.72, 3.08) Bedroom OR 1.23 (0.92, 1.64) wheeze Gas stove OR 1.79 (0.80, 3.99) Bedroom OR 1.15 (0.85, 1.54) asthma attack Gas stove OR 1.73 (0.77, 3.90) Bedroom OR 1.06 (0.77, 1.46) chest tightness Gas stove OR 3.11 (1.07, 9.05) Bedroom OR 1.12 (0.81, 1.56)

AUTHOR, YEAR, LOCATION	STUDY DESIGN	EXPOSURE TIME	MEAN (SD)	RANGE (PPB)	OUTCOME & ESTIMATE (95% CI)
Smith et al. (2000) Australia	Subjects: 125 asthmatic adults/children Analysis: GEE Monitoring Device: passive diffusion badges	4.5 h		overall: 4, 147	children (n = 48, age 0-14) wheeze OR 1.04 (0.89, 1.12) breathlessness OR 0.95 (0.70, 1.31) chest tightness OR 1.29 (1.16, 1.43) Cough OR 1.07 (0.89, 1.29) Asthma attack, day OR 1.13 (1.02, 1.26) Asthma stack, night OR 1.16 (1.03, 1.30) results given for 1 SD (43.8-ppb) increase in NO2
Belanger et al. (2006) Northeast U.S.	Subjects: 728 asthmatic children Analysis: logistic, Poisson regression Monitoring Device: Palmes tubes	2 wks	gas home: 26 (18) elect home: 9 (9)		multifamily housing wheeze RR 1.33 (1.05, 1.68) persistent cough RR 1.07 (0.84, 1.35) breathlessness RR 1.23 (0.95, 1.59) chest tightness RR 1.51 (1.18, 1.91) single-family housing wheeze RR 0.98 (0.78, 1.22) persistent cough RR 0.91 (0.69, 1.20) breathlessness RR 0.86 (0.63, 1.18) chest tightness RR 0.92 (0.68, 1.25)
Chauhan et al. (2003) Southampton, U.K.	Subjects: 114 asthmatic children Monitoring Device: Palmes diffusion tubes	7 d	Exposure tertiles: <7.5; 7.5-14; >14		Increased symptom score for all virus types 3rd vs. 1st tertile: 0.6 (0.01, 1.18) Increased symptom score for RSV only 3rd vs. 1st tertile: 2.1 (0.52, 3.81)
Van Strien et al. (2004) Northeast U.S.	Subjects: 762 infants Analysis: Poisson regression		med: 10		wheeze <5.1 ppb: RR 1.0 5.1, 9.9 ppb: RR 1.15 (0.79, 1.67) 9.9, 17.4 ppb: RR 1.03 (0.69, 1.53) >17.4 ppb: RR 1.45 (0.92, 2.27) persistent cough <5.1 ppb: RR 1.0 5.1, 9.9 ppb: RR 0.96 (0.69, 1.36) 9.9, 17.4 ppb: RR 1.33 (0.94, 1.88) >17.4 ppb: RR 1.52 (1.00, 2.31) shortness of breath <5.1 ppb: RR 1.0 5.1, 9.9 ppb: RR 1.59 (0.96, 2.62) 9.9, 17.4 ppb: RR 1.95 (1.17, 3.27) >17.4 ppb: RR 2.38 (1.31, 4.34)

Unless otherwise noted, results given for 20-ppb increase in NO_2.
*For purpose of comparison, RRs from Pilotto et al. (2004) are shown here as risk of symptoms given greater exposure to NO_2, i.e., control (unflued gas heater) vs intervention (flued or electric replacement heater).
RRs reported by Pilotto et al. (2004) as protective effects for intervention vs. control.

Table AX6.3-2. Studies examining exposure to ambient NO_2 and acute respiratory symptoms using generalized estimating equations (GEE) in the analysis method

AUTHOR, YEAR, LOCATION	SUBJECTS	AVG TIME	MID-RANGE (ppb)	RANGE (ppb)	COPOLLUTANTS & CORRELATIONS	OUTCOME	OR (95% CI)
Children: Multi-City Studies							
Schwartz et al. (1994) 6 U.S. Cities	1844 children	24 h	med 13	p10-p90, 5, 24	PM2.5: r = 0.35 PM10: r = 0.36 O_3: r = -0.28 SO_2: r = 0.51	cough, incidence: lag 1-4 mean	1.61 (1.08, 2.43)
Mortimer et al. (2002) U.S., NCICAS	864 asthmatic children	4 h	med 25	7, 90	O_3: r =0.27	asthma symptoms: lag 1-6 mean	1.48 (1.02, 2.16)
Schildcrout et al. (2006) North America CAMP	990 asthmatic children	24 h	med 23	min p10 to max p90, 10, 37	PM10: r = 0.26, 0.64 O_3: r = 0.04, 0.47 SO_2: r = 0.23, 0.68 CO: r = 0.63, 0.92	asthma symptoms:	
						lag 0	1.06 (1.00, 1.13)
						lag 1	1.04 (0.97, 1.10)
						lag 2	1.09 (1.03, 1.15)
						3-day moving sum	1.04 (1.01, 1.07)
Ward et al. (2002) Birmingham and Sandwell, UK	162 children	24 h	Winter med 18.0 Summer med 13.3	Winter: 4-35 Summer 2-33	O_3, PM10, PM2.5, SO_2, SO_4^{2-}	ΔPEF, morning , lag 0	-0.81 (-3.66, 2.01)(
						ΔPEF, afternoon , lag 1	-1.76 (-4.61, 0.96)
Children: Single-City Studies							
Pino et al. (2004) Chile	504 infants	24 h	mean (sd) 41 (19)	p5-p95, 20, 81		wheezy bronchitis: 6 day lag	1.14 (1.04, 1.30)
Ostro et al. (2001) Southern California	138 asthmatic children, African American	1 h	mean (sd) 80 (4)	20, 220	PM2.5: r = 0.34 PM10: r = 0.63 O_3: r = 0.48	cough, incidence: lag 3	1.07 (1.00, 1.14)
						wheeze, incidence: lag 3	1.05 (1.01, 1.09)
Delfino et al. (2002) Southern California	22 asthmatic children	8 h	mean (sd) 15 (7)	6, 34	PM10: r = 0.55 O_3: r = 0.26	asthma symptoms: lag 0	1.91 (1.07, 3.39)

AUTHOR, YEAR, LOCATION	SUBJECTS	AVG TIME	MID-RANGE (ppb)	RANGE (ppb)	COPOLLUTANTS & CORRELATIONS	OUTCOME	OR (95% CI)
Ségala et al. (1998) Paris	84 asthmatic children	24 h	mean (sd) 30 (8)	13, 65	PM2.5: r = (0.61)* PM10: r = 0.55 SO_2: r = 0.54	asthma symptoms: incidence: lag 0	1.89 (1.13, 3.17)
						lag 1	1.36 (0.70, 2.64)
						lag 4	1.80 (1.07, 3.01)
						nocturnal cough: incidence: lag 3	1.44 (0.99, 2.08)
						lag 4	1.74 (1.20, 2.52)
Delfino et al. (2003a)	24 asthmatic children	1 h	mean (sd) 7 (2)	3, 13	O_3 CO SO_2	lag 0 asthma symptoms	NO_2:12.0 (1.98, 72.7) NO_2+Benzene: 3.58 (0.49, 26.2) NO_2+Toluene: 5.97 (0.83, 43.1) NO_2+xylene: 6.33 (0.72, 55.4)
Linn et al. (1996)	269 children	24 h 1 h	32-42 175-195		PM10: r = 0.48 O_3: r = 0.61	FVC. a.m. FEV1, a.m. FVC, p.m. FEV1, p.m. ΔFVC, p.m.-a.m. ΔFEV1, p.m.-a.m. Total score, a.m. Total score, p.m.	-0.40 (0.16) -0.11 (0.18) -0.18 (0.21) -0.26 (0.19) -0.11 (0.18) -0.39 (0.16) -0.01 (0.022) -0.028 (0.025)
Just et al. (2002) Paris	82 asthmatic children	24 h	mean (sd) 29 (9)	12, 59	PM2.5: r = 0.92* PM10: r = 0.54 O_3: r = 0.09 SO_2: r = 0.69	nocturnal cough: incidence: lag 0	2.11 (1.20, 3.74)
						lag 0-2	1.80 (0.89, 3.84)
						lag 0-4	1.58 (0.73, 3.54)
Jalaludin et al. (2004) Austrailia	148 children with wheeze history	15 h	mean (sd) 15 (6)	3, 79	PM10: r = 0.26 O_3: r = -0.31	Wet cough: lag 0	1.13 (1.00, 1.26)
Adults							
Ségala et al. (2004) Paris	46 nonsmoking adults	24 h	mean (sd) 30 (9)	12, 71	PM2.5: r = 0.82* PM10: r = 0.83	sore throat, cough: lag 0-4	4.05 (1.20, 13.60)

AUTHOR, YEAR, LOCATION	SUBJECTS	AVG TIME	MID-RANGE (ppb)	RANGE (ppb)	COPOLLUTANTS & CORRELATIONS	OUTCOME	OR (95% CI)
Von Klot et al. (2002) Germany	53 asthmatic adults	24 h	med 24	4, 63	PM10: r = 0.74 SO_2: r = 0.36 CO: r = 0.82	wheeze, prev: 5-day mean	1.15 (1.02, 1.31)
						phlegm, prev: 5-day mean	1.22 (1.10, 1.39)
						cough, prev: 5-day mean	1.15 (1.00, 1.31)
						breathing prob in a.m.: 5-day mean	1.25 (1.10, 1.39)

Odds ratios (OR) given for 20 ppb increase in NO_2 with 24-h averaging time, or 30 ppb for 1-h averaging time. (20 ppb increases also used for times between 1 and 24 h.) *BS

Table AX6.3-3. Respiratory health effects of oxides of nitrogen: hospital admissions.

REFERENCE, STUDY LOCATION, & PERIOD	OUTCOMES, DESIGN, & METHODS	MEAN LEVELS & MONITORING STATIONS	COPOLLUTANTS & CORRELATIONS	EFFECTS: RELATIVE RISK OR PERCENT CHANGE & CONFIDENCE INTERVALS (95%)
UNITED STATES				
Moolgavkar (2000a,b,c) Moolgavkar (2003) Multi-city, United States: Chicago, Los Angeles, Maricopa County, (Phoenix). Period of Study: 1987-1995	Outcomes (ICD 9 codes): COPD including asthma (490-496) Age groups analyzed: 0-19, 20-64, 65+ (LA only) Study Design: Time-series Statistical Analyses: Poisson regression, GAM Covariates: Day of wk, temporal trends, temperature, relative humidity Lag: 0-5 days	Chicago Median: 25 ppb IQR: 10 ppb Los Angeles Median: 38 ppb IQR: 18 ppb Maricopa Median: 19 ppb IQR: 12 ppb	Chicago: PM10; r = 0.49 CO; r = 0.63 SO_2; r = 0.44 O_3; r = 0.02 LA: PM2.5; r = 0.73 PM10; r = 0.70 CO; r = 0.80 SO_2; r = 0.74 O_3; r = -0.10 Maricopa: PM10; r = 0.22 CO; r = 0.66 SO_2; r = 0.02 O_3; r = -0.23	Increment: 10 ppb COPD, >65 yrs Chicago 1.7% [CI 0.36, 3.05] lag 0 - GAM default Chicago 2.04% [t = 2.99] lag 0 - GAM-100 Los Angeles 2.5% [CI 1.85, 3.15] lag 0 - GAM default Los Angeles 2.84% [t = 13.32] lag 0 - GAM - 30 Los Angeles 1.80% [t = 9.60] lag 0 - GAM - 100 Los Angeles 1.78% [t = 7.72] lag 0 - NR-100 Phoenix 4.4% [CI 1.07, 7.84] lag 5 Chronic Respiratory Disease Los Angeles 0-19 yrs 4.9% [CI 4.1, 5.7] lag 2 20-64 yrs 1.7% [CI 0.9, 2.1] lag 2 Multi-pollutant model NO_2 and PM10: 1.72% [t = 3.18] lag 0 - GAM-100 NO_2 and PM2.5: 1.51% [t = 2.07] lag 0 - GAM-100

REFERENCE, STUDY LOCATION, & PERIOD	OUTCOMES, DESIGN, & METHODS	MEAN LEVELS & MONITORING STATIONS	COPOLLUTANTS & CORRELATIONS	EFFECTS: RELATIVE RISK OR PERCENT CHANGE & CONFIDENCE INTERVALS (95%)
Moolgavkar*et al. (1997) United States: Minneapolis-St. Paul Period of Study: 1986-1991	Outcomes (ICD 9 codes): COPD including asthma (490-496), Pneumonia (480-487) Age groups analyzed: 65+ Study Design: Time-series Statistical Analyses: Semi-parametric Poisson regression, GAM Covariates: Day of wk, season, temporal trends, temperature Statistical Package: S Plus Lag: 0-3 days	NO_2 24-h avg (ppb) 16.3 ppb IQR: 9.5 ppb	PM10; r = 0.31 SO_2; r = 0.09 CO; r = 0.58	Increment: 10 ppb Sum of Pneumonia and COPD 2.2% [0.2, 4.2] lag 1 Pneumonia Only 3.1% [0.6, 5.6] lag 1, 20 df 1.7% [-0.8, 4.2] lag 1, 130 df
Neidell (2004) California Period of Study: 1992-1998	Outcomes (ICD 9 codes): Asthma Age groups analyzed: <18; 0-1; 1-3; 3-6; 6-12; 12-18 Study Design: Time-series Statistical Analyses: NR Covariates: Temperature, precipitation, influenza epidemic Seasons: Nov-Mar only Lag: 0-4 days	NO_2 (ppb) Mean: 45.947 SD = 17.171	O_3 CO PM10	Increment: NR Age 0-1 Fixed effects: 0.009 (0.014) Controlled for avoidance behavior: 0.009 (0.014) Single-pollutant: 0.001 (0.011) Adjusted for SES: 0.021 (0.017) Interaction with Low SES: -0.017 (0.029) Age: 1-3 Fixed effects: 0.002 (0.016) Controlled for avoidance behavior: 0.002 (0.016) Single-pollutant: 0.009 (0.013) Adjusted for SES: -0.001 (0.020) Interaction with Low SES: -0.004 (0.032) Age 3-6 Fixed effects: 0.006 (0.016) Controlled for avoidance behavior: 0.006 (0.016) Single-pollutant: 0.028 (0.013) Adjusted for SES: 0.020 (0.020) Interaction with Low SES: -0.037 (0.033) Age 6-12 Fixed effects: 0.041 (0.015) Controlled for avoidance behavior: 0.042 (0.015) Single-pollutant: 0.047 (0.012) Adjusted for SES: 0.040 (0.018) Interaction with Low SES: -0.016 (0.031) Age: 12-18 Fixed effects: 0.005 (0.013) Controlled for avoidance behavior: 0.005 (0.013) Single-pollutant: 0.015 (0.010) Adjusted for SES: 0.013 (0.017) Interaction with Low SES: -0.020 (0.026)

REFERENCE, STUDY LOCATION, & PERIOD	OUTCOMES, DESIGN, & METHODS	MEAN LEVELS & MONITORING STATIONS	COPOLLUTANTS & CORRELATIONS	EFFECTS: RELATIVE RISK OR PERCENT CHANGE & CONFIDENCE INTERVALS (95%)
Karr et al. (2006) Southern LA County, CA, United States Period of Study: 1995-2000	Outcomes (ICD 9 codes): Acute bronchiolitis (466.1) Age groups analyzed: 0-1 yr Study Design: Case-crossover N: 19,109 Statistical Analyses: Conditional logistic regression Covariates: Day of wk, temperature, humidity Seasons: Nov-Mar only Lag: 0-4 days	1-h max NO_2 (ppb) Mean: 59 ppb IQR: 26 ppb Number of Stations: 34	CO PM2.5	Increment: 26 ppb (IQR) Acute bronchiolitis OR 0.96 [0.94, 0.99] lag 4 OR 0.97 [0.95, 0.99] lag 1 Stratified by Gestational Age at Birth: 37-44 wks 0.98 [0.95, 1.00] lag 1; 0.97 [0.94, 0.99] lag 4 34-36 wks 0.90 [0.84, 0.97] lag 1; 0.94 [0.88, 1.02] lag 4 29-33 wks 1.01 [0.91, 1.13] lag 1; 0.90 [0.80, 1.01] lag 4 25-28 wks 0.94 [0.78, 1.13] lag 1; 0.90 [0.73, 1.11] lag 4
Linn et al. (2000) Los Angeles, United States Period of Study: 1992-1995	Outcomes (ICD 9 codes): Asthma (493), COPD (APR-DRG 88), Pulmonary diagnoses (APR-DRG 75-101) Age groups analyzed: >30 Study Design: Time-series N: 302,600 Statistical Analyses: Poisson regression, GAM, OLS regression Covariates: day of wk, holiday, max temperature, min temperature, rain days, mean temperature, barometric pressure, season Seasons: Winter (Jan-Mar), Spring (Apr-Jun), Summer (Jul-Sep), Fall (Oct-Dec) Statistical Package: SPSS and SAS Lag: 0, 1 days	All concentrations are in pphm. Winter: 3.4 ± 1.3 Spring: 2.8 ± 0.9 Summer: 3.4 ± 1.0 Autumn: 4.1 ± 1.4 Overall: 3.4 ± 1.3	Winter CO; r = 0.89 PM10; r = 0.88 O_3; r = -0.23 Spring CO; r = 0.92 PM10; r = 0.67 O_3; r = 0.35 Summer CO; r = 0.94 PM10; r = 0.80 O_3; r = 0.11 Winter CO; r = 0.84 PM10; r = 0.80 O_3; r = -0.00	Increment: 10 ppb All pulmonary All seasons: 0.7% ± 0.3% Winter: 1.1% ± 0.5% Spring: 0.7% ± 0.1% Summer: 0.4% ± 0.8% Autumn: 1.2% ± 0.4% Asthma All season: 1.4% ± 0.5% Winter: 2.8% ± 0.1% Spring: NR Summer: NR Autumn: 1.9% ± 0.8% COPD All season: 0.8% ± 0.4% Winter: NR Spring: NR Summer: NR Autumn: 1.6% ± 0.6%
Magas et al. (2007) Oklahoma City, OK Period of Study: 2001-2003	Outcomes (ICD 9 codes): Asthma (493) Age groups analyzed: 0-14 Study Design: Time-series N: 1,270 Statistical Analyses: negative binomial regression Covariates: gender, day of wk, holiday, Lag:	24-h avg: 11.7 ppb Number of monitors: 10	O_3 PM2.5	Qualitative results: ambient concentrations of NO_2 increased pediatric asthma hospitalizations

REFERENCE, STUDY LOCATION, & PERIOD	OUTCOMES, DESIGN, & METHODS	MEAN LEVELS & MONITORING STATIONS	COPOLLUTANTS & CORRELATIONS	EFFECTS: RELATIVE RISK OR PERCENT CHANGE & CONFIDENCE INTERVALS (95%)
Gwynn*et al. (2000) Buffalo, NY United States Period of Study: 1988-1990 Days: 1,090	Outcomes (ICD 9 codes): Respiratory admissions: Acute bronchitis/bronchiolitis (466); Pneumonia (480-4860); COPD and Asthma (490-493, 496) Age groups analyzed: 6 Study Design: Time-series N: 24, Statistical Analyses: Poisson regression with GLM and GAM Covariates: Season, day of wk, holiday, temperature, relative humidity Lag: 0-3 days	24-h avg NO_2 (ppb): Min: 4.0 25th: 15.5 Mean: 20.5 75th: 24.5 Max: 47.5	H+; r = 0.22 SO42-; r = 0.36 PM10; r = 0.44 O_3; r = 0.06 SO_2; r = 0.36 CO; r = 0.65 COH; r = 0.72	Increment: 27 9 ppb (Max-Mean; IQR) NO_2 alone: Max-Mean RR 1.033 (t = 1.32) lag 1 IQR RR 1.01 (t = 1.32) lag 1
Zanobetti and Schwartz (2006) Boston, MA, United States Period of Study: 1995-1999	Outcomes (ICD 9 codes): Pneumonia (480-7) Age groups analyzed: 65+ Special Population: Medicare patients only Study Design: Case-crossover N: 24,857 Statistical Analyses: Conditional logisitic regression Covariates: Apparent temperature, day of wk Seasons: Warm (Apr-Sep), Cool (Oct-Mar) Statistical Package: SAS Lag: 0, 1 days, 0-1 avg	NO_2 median 23.20 ppb; 90-10%: 20.41 ppb; For lag 0-1 2 day avg 90-10% = 16.8 ppb; IQR = 10.83 Number of Stations: 5	PM2.5; r = 0.55 BC; r = 0.70 CO; r = 0.67 O_3; r = -0.14	Increment: 20.41 ppb (90-10%) Pneumonia -0.16% [-4.73, 4.42] lag 0 Increment: 16.78 ppb (90-10%) Pneumonia 2.26% [-2.55, 7.01] lag 0-1
CANADA				
Burnett et al. (1997a) 16 cities Canada Period of Study: 4/1981-12/1991 Days: 3,927	Outcomes (ICD 9 codes): All respiratory admissions (466, 480-6, 490-4, 496) Study Design: Time-series N: 720,519 # of hospitals: 134 Statistical Analyses: Random effects relative risk regression model Covariates: Long-term trend, season, day of wk, hospital, Statistical Package: NR Lag: 0, 1, 2 day	1-h max NO_2 (ppb) Mean: 35.5 SD = 16.5 25th: 25 50th: 33 75th: 43 95th: 62 99th: 87	O_3; r = 0.20 CO SO_2 COH	Increment: 10 ppb Single-pollutant NO_2 and respiratory admissions, p = 0.772 Multipollutant model (adjusted for CO, O_3, SO_2, COH, dew point): RR 0.999 [0.9922, 1.0059] lag 0

REFERENCE, STUDY LOCATION, & PERIOD	OUTCOMES, DESIGN, & METHODS	MEAN LEVELS & MONITORING STATIONS	COPOLLUTANTS & CORRELATIONS	EFFECTS: RELATIVE RISK OR PERCENT CHANGE & CONFIDENCE INTERVALS (95%)
Yang et al. (2003) Vancouver, Canada Period of Study: 1986-1998 Days: 4748	Outcomes (ICD 9 codes): All respiratory admissions (460-519) Study Design: Case-crossover Age groups analyzed: <3, ≥65 Statistical Analyses: Conditional logistic regression Statistical Package: NR Lag: 0-5 days	24-h avg NO_2 (ppb): Mean: 18.74 SD = 5.66 5th: 11.35 25th: 14.88 50th: 17.80 75th: 21.45 100th: 49.00 IQR: 5.57 Number of stations: 30	CO SO_2 O_3; r = -0.32 COH	Increment: 5.57 ppb (IQR) All Respiratory Admissions <3 yrs: NO_2 alone: OR 1.05 [1.02, 1.09] lag 1 NO_2 + O_3: OR 1.05 [1.02, 1.09] lag 1 NO_2 + O_3 + CO + COH + SO_2: OR 1.05 [0.99, 1.11] lag 1 All Respiratory Admissions ≥65 yrs: NO_2 alone: OR 1.05 [1.03, 1.07] lag 1 NO_2 + O_3: OR 1.04 [1.02, 1.07] lag 1 NO_2 + O_3 + CO + COH + SO_2: OR 1.05 [1.01, 1.08] lag 1
Fung et al. (2006) Vancouver, BC, Canada Period of Study: 6/1/95-3/31/99	Outcomes (ICD 9 codes): All respiratory hospitalizations (460-519) Age groups analyzed: 65+ Study Design: (1) Time-series, (2) Case-crossover, (3) DM-models (Dewanji and Moolgavkar 2000, 2002) N: 40,974 Statistical Analyses: (1) Poisson, (2) conditional logistic regression, (3) DM method – analyze recurrent data in which the occurrence of events at the individual level over time is available Covariates: Day of wk Statistical Package: S-Plus and R Lag: Current day, 3 and 5 day lag	NO_2 24-h avg: Mean: 16.83 ppb, SD = 4.34; IQR: 5.43 ppb; Range: 7.22, 33.89	CO; r = 0.74 COH; r = 0.72 SO_2; r = 0.57 PM10; r = 0.54 PM2.5; r = 0.35 PM10-2.5; r = 0.52 O_3; r = -0.32	Increment: 5.43 ppb. (IQR) NO_2 Time-series RR 1.018 [1.003, 1.034] lag 0 RR 1.024 [1.004, 1.044] lag 0-3 RR 1.025 [1.000, 1.050] lag 0-5 RR 1.027 [0.998, 1.058] lag 0-7 NO_2 Case-crossover RR 1.028 [1.010, 1.047] lag 0 RR 1.035 [1.012, 1.059] lag 0-3 RR 1.032 [1.006, 1.060] lag 0-5 RR 1.028 [0.997, 1.060] lag 0-7 NO_2 DM model RR 1.012 [0.997, 1.027] lag 0 RR 1.018 [1.000, 1.037] lag 0-3 RR 1.007 [0.988, 1.026] lag 0-5 RR 1.002 [0.981, 1.023] lag 0-7 DM method produced slightly higher RR estimates on O_3, SO_2, and PM2.5 compared to time-series and case-crossover, and slightly lower RR estimates on COH, NO_2, and PM10, though the results were not significantly different from one another.

REFERENCE, STUDY LOCATION, & PERIOD	OUTCOMES, DESIGN, & METHODS	MEAN LEVELS & MONITORING STATIONS	COPOLLUTANTS & CORRELATIONS	EFFECTS: RELATIVE RISK OR PERCENT CHANGE & CONFIDENCE INTERVALS (95%)
Yang (2005) Vancouver, BC, Canada Period of Study: 1994-1998 Days: 1826	Outcomes (ICD 9 codes): COPD excluding asthma (490-2, 494, 496) Age groups analyzed: 65+ Study Design: Time-series N: 6,027 Statistical Analyses: Poisson regression with GAM (with more stringent criteria) Covariates: Temperature, relative humidity, day of wk, temporal trends, season Statistical Package: S-Plus Lag: 0-6 days, moving avgs	24-h avg: 17.03 ppb, SD = 4.48; IQR: 5.47 ppb; Range: 4.28, 33.89 Winter: 19.20 (4.86) Spring: 15.36 (3.72) Summer: 16.33 (4.57) Fall: 17.27 (3.77) Number of Stations: 31	PM10; r = 0.61 SO_2; r = 0.61 CO; r = 0.73 O_3; r = -0.10	Increment: 5.5 ppb (IQR) COPD >65 yrs, yr round RR 1.05 [1.01, 1.09] lag 0 RR 1.04 [1.00, 1.10] lag 0-1 RR 1.07 [1.01, 1.13] lag 0-2 RR 1.08 [1.02, 1.15] lag 0-3 RR 1.10 [1.03, 1.17] lag 0-4 RR 1.11 [1.04, 1.19] lag 0-5 RR 1.11 [1.04, 1.20] lag 0-6 Two-pollutant model PM10: RR 1.03 [0.90, 1.17] lag 0 CO: RR 1.07 [0.96, 1.20] lag 0-6 O_3: RR 1.12 [1.04, 1.20] lag 0-6 Multipollutant models NO_2, CO, SO_2, O_3, PM10: RR 1.01 [0.88, 1.16] NO_2, CO, SO_2, O_3: RR 1.06 [0.95, 1.19] NO_2 was strongest predictor of hospital admission for COPD among all gaseous pollutants in single-pollutant models.

REFERENCE, STUDY LOCATION, & PERIOD	OUTCOMES, DESIGN, & METHODS	MEAN LEVELS & MONITORING STATIONS	COPOLLUTANTS & CORRELATIONS	EFFECTS: RELATIVE RISK OR PERCENT CHANGE & CONFIDENCE INTERVALS (95%)
Lin* et al. (2004) Vancouver, BC Canada Period of Study: 1987-1991	Outcomes (ICD 9 codes): Asthma (493) Age groups analyzed: 6-12 Study Design: Time-series N: 3,754 (2,331 male, 1,423 female) Statistical Analyses: Semi-parametric Poisson regression with GAM (with default and more stringent criteria) Covariates: Trend, day of wk Statistical package: S-Plus Lag: Cumulative 1-7 day	24-h avg NO_2 (ppb) Mean: 18.65 SD = 5.59 Min: 4.28 25th: 14.82 50th: 17.75 75th: 21.36 Max: 45.36 Number of stations: 30	CO; r = 0.73 SO_2; r = 0.67 O_3; r = -0.03 PM2.5; r = 0.37 PM10; r = 0.55	Increment: 6.54 ppb (IQR) Boys 6-12 yrs by SES status: Low; High Lag 1 RR 1.13 [1.04, 1.23]; 1.04 [0.95, 1.14] Lag 2 RR 1.13 [1.02, 1.24]; 1.06 [0.95, 1.18] Lag 3 RR 1.14 [1.02, 1.27]; 1.06 [0.94, 1.19] Lag 4 RR 1.14 [1.02, 1.28]; 1.05 [0.92, 1.19] Lag 5 RR 1.12 [0.99, 1.27]; 1.10 [0.96, 1.26] Lag 6 RR 1.12 [0.98, 1.28]; 1.07 [0.93, 1.23] Lag 7 RR 1.11 [0.97, 1.28]; 1.09 [0.94, 1.27] Girls 6-12 yrs by SES status: Low; High Lag 1 RR 1.07 [0.96, 1.19]; 1.01 [0.90, 1.13] Lag 2 RR 1.03 [0.91, 1.17]; 0.98 [0.85, 1.12] Lag 3 RR 1.04 [0.91, 1.20]; 0.98 [0.84, 1.13] Lag 4 RR 1.11 [0.95, 1.29]; 1.01 [0.86, 1.19] Lag 5 RR 1.11 [0.94, 1.30]; 0.99 [0.83, 1.17] Lag 6 RR 1.08 [0.91, 1.28]; 1.03 [0.86, 1.24] Lag 7 RR 1.07 [0.90, 1.28]; 1.09 [0.90, 1.32] Multipollutant model (adjusted for SO_2) Boys, Low SES: 1.16 [1.06, 1.28] lag 1 1.18 [1.03, 1.34] lag 4 Results presented are default GAM, but authors state that use of natural cubic splines with a more stringent convergence rate produced similar results.
Chen et al. (2005) Vancouver, BC Period of Study: 6/1995-3/1999	Outcomes (ICD 9 codes): All Respiratory (460-519) Age groups analyzed: 65+ Study Design: Time-series N: 12,869 overall admissions Statistical Analyses: Poisson regression with GLM Covariates: Trend, day of wk, weather Statistical package: S-Plus Lag: 1-7	24-h avg: 16.8 (4.3) ppb Range: 7.2-33.9 IQR: 5.4	PM10; r = 0.54 PM10-2.5; r = 0.54 PM2.5; r = 0.36 CO; r = 0.74 SO_2; r = 0.57 O_3; r = -0.32	No analyses for NO_2

REFERENCE, STUDY LOCATION, & PERIOD	OUTCOMES, DESIGN, & METHODS	MEAN LEVELS & MONITORING STATIONS	COPOLLUTANTS & CORRELATIONS	EFFECTS: RELATIVE RISK OR PERCENT CHANGE & CONFIDENCE INTERVALS (95%)
Lin et al. (2003) Toronto, ON Period of Study: 1981-1993	Outcomes (ICD 9 codes): Asthma (493) Age groups analyzed: 6-12 Study Design: Bi-directional case-crossover N: 7,319 Statistical Analyses: Conditional logistic regression Covariates: Daily maximum and minimum temperatures and avg relative humidity Lag: Cumulative lag of 1-7 days	NO_2 24-h avg: 25.24 ppb, SD = 9.04; IQR: 11 ppb; Range: 3.00, 82.00 Number of Stations: 4	CO; r = 0.55 SO_2; r = 0.54 PM10; r = 0.52 O_3; r = 0.03 PM2.5; r = 0.50 PM10-2.5; r = 0.38	Increment: 11 ppb (IQR) Boys 6-12 yrs; Girls 6-12 yrs Lag 0: OR 1.04 [0.99, 1.10]; 0.99 [0.92, 1.06] Lag 0-1: OR 1.07 [1.00, 1.14]; 1.03 [0.94, 1.12] Lag 0-2: OR 1.09 [1.01, 1.17]; 1.07 [0.96, 1.18] Lag 0-3: OR 1.10 [1.01, 1.20]; 1.09 [0.97, 1.21] Lag 0-4: OR 1.10 [1.00, 1.20]; 1.14 [1.02, 1.28] Lag 0-5: OR 1.12 [1.01, 1.23]; 1.16 [1.02, 1.31] Lag 0-6: OR 1.11 [1.00, 1.24]; 1.16 [1.02, 1.32]
Burnett et al. (1997b) Toronto, Canada Period of Study: 1992-1994	Outcomes (ICD 9 codes): Respiratory tracheobronchitis (480-6), COPD (491-4, 496) Study Design: Time-series Statistical Analyses: Poisson regression, GEE, GAM Covariates: Temperature, dew point temperature, long-term trend, season, influenza, day of wk Seasons: summers only Lag: 0,1,2,3,4 days	Mean NO_2: 38.5 ppb IQR NO_2: 5.75 ppb Range: 12, 81 Number of Stations: 6-11	PM10; r = 0.61 CO; r = 0.25 H+; r = 0.25 SO4; r = 0.34 TP; r = 0.61 FP; r = 0.45 CP; r = 0.57 COH; r = 0.61 O_3; r = 0.07 SO_2; r = 0.46	Increment: 5.75 ppb (IQR) Respiratory - Percent increase 4.4% [CI 2.4, 6.4], lag 0 Copollutant and multipollutant models RR (t-statistic): NO_2, COH: 1.018 (1.36) NO_2, H+: 1.037 (3.61) NO_2, SO4: 1.033 (3.05) NO_2, PM10: 1.039 (2.85) NO_2, PM2.5: 1.037 (3.13) NO_2, PM10-2.5: 1.037 (2.96) NO_2, O_3, SO_2: 1.028 (2.45) NO_2, O_3, SO_2, COH: 1.010 (0.71) NO_2, O_3, SO_2, H+: 1.027 (2.39) NO_2, O_3, SO_2, SO4: 1.027 (2.36) NO_2, O_3, SO_2, PM10: 1.028 (1.77) NO_2, O_3, SO_2, PM2.5: 1.028 (2.26) NO_2, O_3, SO_2, PM10-2.5: 1.022 (1.71)

REFERENCE, STUDY LOCATION, & PERIOD	OUTCOMES, DESIGN, & METHODS	MEAN LEVELS & MONITORING STATIONS	COPOLLUTANTS & CORRELATIONS	EFFECTS: RELATIVE RISK OR PERCENT CHANGE & CONFIDENCE INTERVALS (95%)
Burnett et al. (1999) Metro Toronto, Canada Period of Study: 1980-1994	Outcomes (ICD 9 codes): Asthma (493); Obstructive lung disease (490-2, 496); Respiratory Infection (464, 466, 480-7, 494) Study Design: Time-series Statistical Analyses: Poisson regression model with stepwise analysis Covariates: Long-term trends, season, day of wk, daily maximum temperature, daily minimum temperature, daily avg dew point temperature, daily avg relative humidity Statistical Package: S-Plus, SAS Lag: 0,1,2 days, cumulative	24-h mean: 25.2 ppb, SD = 9.1, CV: 36; IQR: 23 Number of stations: 4	COH; r = NR PM2.5; r = 0.50 PM10-2.5; r = 0.38 PM10; r = 0.52 CO; r = 0.55 SO_2; r = 0.54 O_3; r = -0.03	Increment: 25.2 ppb (Mean) 7.72 excess daily admissions due to pollution of all sorts. 40.4% increase; or 3 excess daily admissions traced to NO_2. Single-pollutant model percent increase (t statistic) Asthma: 3.33% (2.37) lag 0 OLD 2.21% (1.07) lag 1 Respiratory infection: 6.89% (5.53), lag 2 Multipollutant model percent increase (SE) Respiratory infection: NO_2 alone: 4.64 (SE ≥3) NO_2 + SO_2 + O_3 + PM2.5: 4.04 (SE ≥2) NO_2 + SO_2 + O_3 + PM10-2.5: 4.56 (SE ≥3) NO_2 + SO_2 + O_3 + PM10: 4.16 (SE ≥3) NO_2 + O_3 + PM2.5: 4.44 (SE ≥2)
Lin et al. (2005) Toronto, Canada Period of Study: 1998-2001	Outcomes (ICD 9 codes): Respiratory infections (464, 466, 480-487) Age groups analyzed: 0-14 N: 6,782 Study Design: Bidirectional case-crossover Statistical Analyses: Conditional logistic regression Covariates: Temperature, dew point temperature Statistical Package: SAS v 8.2 Lag: 1-7 day exposure averages	24-h avg: 24.54 (7.56) ppb Range: 9.2-53.75 25th: 18.75 50th: 24.00 75th: 29.33 Number of monitors: 7	CO; r = 0.20 SO_2; r = 0.61 O_3; r = 0 PM10; r = 0.54 PM2.5; r = 0.48 PM10-2.5; r = 0.40	Increment: 10.6 ppb (IQR) All children: NO_2 alone: 1.20 [1.08, 1.34] lag 0-5 NO_2 + PM2.5 + PM10-2.5: 1.13 [0.97, 1.31] lag 0-5 Boys: NO_2 alone: 1.13 [0.98, 1.29] lag 0-5 NO_2 + PM2.5 + PM10-2.5: 1.00 [0.83, 1.21] lag 0-5 Girls: NO_2 alone: 1.28 [1.09-1.50] lag 0-5 NO_2 + PM2.5 + PM10-2.5: 1.31 [1.05, 1.63] lag 0-5
Burnett* et al. (2001) Toronto, Canada Period of Study: 1980-1994	Outcomes (ICD 9 codes): Croup (464.4), pneumonia (480-486), asthma (493), acute bronchitis/bronchiolitis (466) Age groups analyzed: <2 yrs Study Design: Time-series Statistical Analyses: Poisson regression with GAM Covariates: temporal trend, day of wk, temperature, relative humidity Statistical Package: S-Plus Lag: 0-5 days	1-h max NO_2 (ppb) Mean: 44.1 CV: 33 5th: 25 25th: 35 50th: 42 75th: 52 95th: 70 99th: 86 100th: 146 Number of stations: 4	O_3; r = 0.52 SO_2 CO PM2.5 PM10-2.5	Increment: NR All respiratory admissions: Single-pollutant: Percent increase: 20.2 (t = 3.43) lag 0-1 Multipollutant (adjusted for O_3): Percent increase: 7.1 (t = 1.09) lag 0-1

REFERENCE, STUDY LOCATION, & PERIOD	OUTCOMES, DESIGN, & METHODS	MEAN LEVELS & MONITORING STATIONS	COPOLLUTANTS & CORRELATIONS	EFFECTS: RELATIVE RISK OR PERCENT CHANGE & CONFIDENCE INTERVALS (95%)
Fung et al. (2007) Ontario, Canada Period of Study: 1996-2000	Outcomes (ICD 9 codes): All respiratory (460-519) Age groups analyzed: 0-4, 5-14, 15-19, 20-24, 25-54, 55-64, 65-74, 75+ Study Design: Statistical Analyses: Covariates: Statistical Package: Lag:	London Mean: 18.10 ppb (7.86) Range: 0-53 Windsor Mean: 23.50 ppb (7.59) Range: 6-50 Sarnia Mean: 16.85 ppb (8.13) Range: 0-52	SO_2 O_3 CO	Not reported
Luginaah et al. (2005) Windsor, ON, Canada Period of Study: 4/1/95-12/31/00	Outcomes (ICD 9 codes): Respiratory admissions (460-519) Age groups analyzed: 0-14, 15-64, 65+, all ages Study Design: (1) Time-series and (2) case-crossover N: 4,214 # of Hospitals: 4 Statistical Analyses: (1) Poisson regression, GAM with natural splines (stricter criteria), (2) conditional logistic regression with Cox proportional hazards model Covariates: Temperature, humidity, change in barometric pressure, day of wk Statistical Package: S-Plus Lag: 1,2,3 days	NO_2 mean 1-h max: 38.9 ppb, SD = 12.3; IQR: 16 Number of stations: 4	SO_2; r = 0.22 CO; r = 0.38 PM10; r = 0.33 COH; r = 0.49 O_3; r = 0.26 TRS; r = 0.06	Increment: 16 ppb (IQR) Time-series, females; males All ages, lag 1 1.035 [0.971, 1.104]; 0.944 [0.886, 1.006] 0-14 yrs, lag 2 1.114 [0.994, 1.248]; 0.955 [0.866, 1.004] 15-65 yr, lag 3 1.121 [0.978, 1.285], 1.012 [0.841, 1.216] 65+ yr, lag 1 1.020 [0.930, 1.119]; 0.9196 [0.832, 1.016] Case-crossover, females; males All ages, lag 1 1.078 [0.995, 1.168]; 0.957 [0.883, 1.036] 0-14 yrs, lag 2 1.189 [1.002, 1.411]; 0.933 [0.810, 1.074] 15-65 yr, lag 3 1.114 [0.915, 1.356]; 0.972 [0.744, 1.268] 65+ yr, lag 1 1.081 [0.964, 1.212]; 0.915 [0.810, 1.034]

REFERENCE, STUDY LOCATION, & PERIOD	OUTCOMES, DESIGN, & METHODS	MEAN LEVELS & MONITORING STATIONS	COPOLLUTANTS & CORRELATIONS	EFFECTS: RELATIVE RISK OR PERCENT CHANGE & CONFIDENCE INTERVALS (95%)
AUSTRALIA/NEW ZEALAND				
Simpson et al. (2005a) Multi-city study, Australia (Sydney, Melbourne, Brisbane, Perth) Period of Study: 1996-1999	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: 15-64 (asthma), 65+ (all respiratory, COPD, asthma, pneumonia with bronchitis) Study Design: Time-series Statistical Analyses: Followed APHEA2 protocol: (1) Single city: (a) GAM with default and more stringent criteria, (b) GLM with default and more stringent criteria, (c) penalized spline models. (2) Multicity meta analysis: random effects meta-analysis Covariates: Temperature, relative humidity, day of wk, holiday, influenza epidemic, brushfire/controlled burn Statistical Package: S-Plus, R Lag: 0,1,2 days	1 h max NO_2 ppb (range) Brisbane: 24.1 (2.1, 63.3) Sydney: 23.7 (6.5, 59.4) Melbourne: 23.7 (4.4, 66.7) Perth: 16.3 (1.9, 41.0)	Brisbane: O_3; r = 0.15 BSP; r = 0.50 Melbourne: O_3; r = 0.30 BSP; r = 0.29 Sidney: O_3; r = 0.24 BSP; r = 0.54 Perth: O_3; r = 0.28 BSP; r = 0.62	Increment: 1 ppb Respiratory ≥65 yrs 1.0027 [1.0015, 1.0039] lag 0-1 COPD and Asthma >65 yrs 1.0020 [1.0003, 1.0037] lag 0-1 Pneumonia and Acute Bronchitis >65 yrs 1.0030 [1.0011, 1.0048] lag 0-1 Multipollutant Model Respiratory ≥65 yrs NO_2 Alone: 1.0027 [1.0015,1.0039] lag0-1 NO_2 + BSP: 1.0023 [1.0009, 1.0038] lag 0-1 NO_2 + O_3: 1.0028 [1.0016, 1.0040] lag 0-1 GAM results from S-Plus and R similar to one another, but different than results from GLM. GAM results from S-Plus presented.

REFERENCE, STUDY LOCATION, & PERIOD	OUTCOMES, DESIGN, & METHODS	MEAN LEVELS & MONITORING STATIONS	COPOLLUTANTS & CORRELATIONS	EFFECTS: RELATIVE RISK OR PERCENT CHANGE & CONFIDENCE INTERVALS (95%)
Barnett et al. (2005) Multicity, Australia/ New Zealand; (Auckland, Brisbane, Canberra, Christchurch, Melbourne, Perth, Sydney) Period of Study: 1998-2001	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 10.2 (1.7, 28.9) Brisbane 7.6 (1.4, 19.1) Canberra 7.0 (0, 22.5) Christchurch 7.1 (0.2, 24.5) Melbourne 11.7 (2, 29.5) Perth 9.0 (2, 23.3) Sydney 11.5 (2.5, 24.5) IQR: 5.1 ppb Daily 1-h max (range): Auckland 19.1 (4.2, 86.3) Brisbane 17.3 (4, 44.1) Canberra 17.9 (0, 53.7) Christchurch 15.7 (1.2, 54.6) Melbourne 23.2 (4.4, 62.5) Perth 21.3 (4.4, 48) Sydney 22.6 (5.2, 51.4) IQR: 9.0 ppb	BS; r = 0.39, 0.63 PM2.5; r = 0.34, 0.68 PM10; r = 0.21, 0.57 CO; r = 0.53, 0.73 SO_2; r = 0.15, 0.58 O_3; r = -0.15, 0.28	Increment: 5.1 ppb (24 h) or per 9 ppb (1-h max). (IQR) 24-h avg NO_2 (5.1 ppb change) Pneumonia and acute bronchitis 0 yrs 3.2% [-1.8, 8.4] lag 0-1 1-4 yrs 4.8% [-1.0, 11.0] lag 0-1 5-14 yrs (sample size too small) Respiratory 0 yrs 3.1% [-1.0, 7.3] lag 0-1 1-4 yrs 2.4% [-0.8, 5.7] lag 0-1 5-14 yrs 5.8% [1.7, 10.1] lag 0-1 Asthma 0 yrs No analysis (poor diagnosis) 1-4 yrs 2.6% [-1.3, 6.6] lag 0-1 5-14 yrs 6.0% [0.2, 12.1] lag 0-1 1 h NO_2 max (9.0 ppb change) Pneumonia and acute bronchitis 0 yrs 2..8% [-1.8, 7.7] lag 0-1 1-4 yrs 4.1% [-2.4, 11.0] lag 0-1 5-14 yrs (sample size too small) Respiratory 0 yrs 2.2% [-1.6, 6.1] lag 0-1 1-4 yrs 2.8% [0.7, 4.9] lag 0-1 5-14 yrs 4.7% [1.6, 7.9] lag 0-1 Asthma 0 yrs No analysis (poor diagnosis) 1-4 yrs 2.5% [-0.2, 5.2] lag 0-1 5-14 yrs 2.6% [-2.2, 7.6] lag 0-1
Erbas et al. (2005) Melbourne, Australia Period of Study : 2000-2001	Outcomes (ICD 10): Asthma (J45, J46) Age groups analyzed: 1-15 Study Design: Time-series N: 8,955 # of Hospitals: 6 Statistical Analyses: Poisson regression, GAM and GEE Covariates: Day of wk Dose-response investigated?: Yes Statistical Package: NR Lag: 0,1,2 days	1-h mean NO_2: 16.80 ppb, SD = 8.61; Range: 2.43, 63.00	PM10 O_3	Increment: 90th-10th percentile Inner Melbourne; increment = 25.54 ppb RR 0.83 [0.68, 0.98] lag 0 Western Melbourne; increment = 28.86 ppb RR 1.15 [1.03, 1.27] lag 2 Eastern Melbourne; increment = 17.67 ppb RR 1.07 [0.93, 1.22] lag 0 South/Southeastern; increment = 17.74 ppb RR 0.98 [0.79, 1.18] lag 1

REFERENCE, STUDY LOCATION, & PERIOD	OUTCOMES, DESIGN, & METHODS	MEAN LEVELS & MONITORING STATIONS	COPOLLUTANTS & CORRELATIONS	EFFECTS: RELATIVE RISK OR PERCENT CHANGE & CONFIDENCE INTERVALS (95%)
Hinwood et al. (2006) Perth, Australia Period of Study: 1992-1998	Outcomes (ICD 9): COPD (490-496, excluding 493); Pneumonia (480-489.99); Asthma (493) Age groups analyzed: <15, 65+, all ages Study Design: Case-crossover, time-stratified Statistical Analyses: Conditional logistic regression Covariates: Temperature, change in temperature, maximum humidity, holiday, day of wk Statistical Package: NR Lag: 0,1,2,3 days or cumulative 0-2 and 0-3 days	24-h mean [Std. Dev] (10th and 90th percentile) All yr 10.3 [5.0] (4.4, 17.1) Summer 9.6 [4.8] (4.3, 15.7) Winter 11.1 [5.1] (4.8, 18.0) Daily 1-h max Mean [Std. Dev] All yr 24.8 [10.1] (13.3, 37.5) Summer 24.9 [8.9] (12.4, 39.2) Winter 24.7 [11.1] (14.4, 35.7) Number of stations: 3	O_3; r = -0.06 CO; r = 0.57 BS; r = 0.39 PM10 PM2.5	Increment: 1 ppb (all values were estimated from the graphs) All respiratory NO_2 (24 h) ≥65 yrs OR: 1.005 [1.001, 1.011] lag 1 All ages OR: 1.002 [0.998, 1.004] lag 1 Pneumonia NO_2 (24 h) ≥65 yrs OR: 1.006 [0.999, 1.014] lag 1 All ages OR: 1.002 [0.998, 1.010] lag 1 COPD NO_2 (24 h) ≥65 yrs OR: 1.004 [0.990, 1.012] lag 2 All ages OR: 1.001 [0.995, 1.010] lag 2 Asthma NO_2 (24 h) 0-14 yrs OR: 1.002 [0.998, 1.004] lag 0 ≥65 yrs OR: 0.996 [0.988, 1.002] lag 0 All ages OR: 1.001 [0.999, 1.003] lag 0
Morgan et al. (1998a) Sydney, Australia Period of Study: 1990-1994	Outcomes (ICD 9): COPD (490-492, 494, 496); Asthma (493) Age groups analyzed: 1-14, 15-64, 65+, all ages Study Design: Time-series # of hospitals: 27 Statistical Analyses: APHEA protocol, Poisson regression, GEE Covariates: Long-term trend, temperature, dew point, day of wk, holiday Statistical Package: SAS Lag: 0,1,2 days and cumulative	24-h daily mean: 15 ppb, SD = 6, Range: 0, 52, IQR: 11, 90-10th percentile: 17 Mean daily 1-h max: 29 ppb, SD = 3, Range: 0, 139, IQR: 15, 90-10th percentile: 29 # of stations: 3-14, r = 0.52	24-h avg NO_2: PM(24 h); r = 0.53 PM (1 h); r = 0.51 O_3; r = -0.9 1-h max NO_2: PM(24 h); r = 0.45 PM (1 h); r = 0.44 O_3; r = 0.13	Increment: 90-10th percentile 24-h avg (17 ppb) Asthma: 1-14 yrs 3.28% [-1.72, 8.54] lag 0 15-64 yrs 2.29% [-2.97, 7.83] lag 0 COPD: >65 yrs 4.30% [-0.75, 9.61] lag 1 Daily 1-h max (29 ppb) Asthma: 1-14 yrs 5.29% [1.07, 9.68] lag 0 15-64 yrs. 3.18% [-1.53, 8.11] lag 0 COPD: 65+ yrs. 4.60% [-0.17, 9.61] lag 1 Multipollutant model (29 ppb) Asthma: 1-14 yrs. 5.95% [1.11, 11.02] lag 0 COPD: 65+ yrs. 3.70% [-1.03, 8.66] lag 1

REFERENCE, STUDY LOCATION, & PERIOD	OUTCOMES, DESIGN, & METHODS	MEAN LEVELS & MONITORING STATIONS	COPOLLUTANTS & CORRELATIONS	EFFECTS: RELATIVE RISK OR PERCENT CHANGE & CONFIDENCE INTERVALS (95%)
Petroeschevsky et al. (2001) Brisbane, Australia Period of Study: 1987-1994 Days: 2922	Outcomes (ICD 9): All respiratory (460-519); Asthma (493) Age groups analyzed: 0-4, 5-14, 15-64, 65+, all ages Study Design: Timeseries 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	Mean (range) 24-h avg: Cumulative: 0-2, 0-4 Overall: 139 (12, 497) Summer: 97 (20, 331) Autumn: 129 (33, 319) Winter: 179 (12, 454) Spring: 153 (35, 497) Mean (range) 1-h max Overall: 282 (35, 1558) Summer: 206 (35, 580) Autumn: 256 (70, 585) Winter: 354 (35, 805) Spring: 321 (35, 1558) # of stations: 3, r = 0.43, 0.53	BSP O_3 SO_2	Increment: 10 ppb Respiratory (1-h max): 0-4 yrs 1.015 [0.996, 1.035] lag 3 5-14 yrs 0.985 [0.950, 1.021] lag 0 All ages 0.989 [0.977, 1.002] lag 1 Respiratory (24-h avg): 15-64 yrs 1.027 [0.984, 1.071] lag 0 >65 yrs 0.903 [0.851, 0.959] lag 5 Asthma (1-h max): 0-4 yrs 0.975 [0.947, 1.004] lag0 5-64 yrs 0.983 [0.949, 1.018] lag 1 All ages 0.962 [0.936, 0.989] lag 0-2
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	Outcomes (ICD 9): COPD - unspecified bronchitis (490), chronic bronchitis (491), emphysema (492), chronic airways obstruction (496) Study Design: Time-series Statistical Analyses: APHEA protocol, Poisson regression, meta-analysis Covariates: Trend, season, day of wk, holiday, influenza, temperature, humidity Season: Cool, Oct-Mar; Warm, Apr-Sep Statistical Package: NR Lag: 0,1,2 days and 0-3 cumulative	24-h all yr avg: (μg/m^3) Amsterdam: 50 Barcelona: 53 London: 67 Paris: 42 Rotterdam: 52 1-h max: Amsterdam: 75 Barcelona: 93 London: 67 Paris: 64 Rotterdam: 78	SO_2 BS TSP O_3	Increment: 50 μg/m^3 Meta-analytic results - Weighted mean values from 6 cities COPD-Warm season 24 h 1.03 [1.00, 1.06] lag 1 1 h 1.02 [1.00, 1.05] lag 1 COPD-Cool season 24 h 1.01 [0.99, 1.03] 1 h 1.02 [0.99, 1.05] COPD-All Year 24 hr 1.019 [1.002, 1.047] lag 1 24 hr 1.026 [1.004, 1.036] lag 0-3, cumulative 1 hr 1.013 [1.003, 1.022] lag 1 1 hr 1.014 [0.976, 1.054] lag 0-3, cumulative
Atkinson et al. (2001) Multicity, Europe (Barcelona, Birmingham, London, Milan, Netherlands, Paris, Rome, Stockholm) Period of study: 1998-1997	Outcomes (ICD 9): Asthma (493), COPD (490-496), All respiratory (460-519) Study Design: Time-series Statistical Analyses: APHEA protocol, Poisson regression, meta-analysis Covariates: Season, temperature, humidity, holiday, influenza Statistical Package: NR Lag: NR	1-h max of NO_2 (μg/m^3) Barcelona: 94.4 Birmingham: 75.8 London: 95.9 Milan: 147.0 Netherlands: 50.1 Paris: 87.2 Rome: 139.7 Stockholm: 35.6	SO_2, O_3, CO, BS PM10; r = Barcelona: 0.48 B'gham: 0.68 London: 0.70 Milan: 0.72 Netherlands: 0.64 Paris: 0.44 Rome: 0.32 Stockholm: 0.30	Increment: 10 μg/m^3 for PM10; change in NO_2 not described. Asthma, 0 to 14 yrs: For PM10: 1.2% [0.2, 2.3] For PM10 + NO_2: 0.1 [-0.8, 1.0] Asthma, 15 to 64 yrs: For PM10: 1.1% [0.3, 1.8] For PM10 + NO_2: 0.4 [-0.5, 1.3] COPD + Asthma, ≥65 yrs For PM10: 1.0% [0.4, 1.5] For PM10 + NO_2: 0.8 [-0.6, 2.1] All Respiratory, ≥65 yrs of age For PM10: 0.9% [0.6, 1.3] For PM10 + NO_2: 0.7 [-0.3, 1.7]

REFERENCE, STUDY LOCATION, & PERIOD	OUTCOMES, DESIGN, & METHODS	MEAN LEVELS & MONITORING STATIONS	COPOLLUTANTS & CORRELATIONS	EFFECTS: RELATIVE RISK OR PERCENT CHANGE & CONFIDENCE INTERVALS (95%)
Sunyer et al. (1997) Multicity, Europe (Barcelona, Helsinki, Paris, London) Period of Study: 1986-1992	Outcomes (ICD 9): Asthma (493) Age groups analyzed: <15, 15-64 Study Design: Time-series Statistical Analyses: APHEA protocol, Poisson regression, GEE; meta-analysis Covariates: Humidity, temperature, influenza, soybean, long-term trend, season, day of wk Season: Cool, Oct-Mar; Warm: Apr-Sep Statistical Package: NR Lag: 0,1,2,3 and cumulative 1-3	24-h median (range) (μg/m^3) Barcelona: 53 (5, 142) Helsinki: 35 (9, 78) London: 69 (27, 347) Paris: 42 (12, 157) # of stations: Barcelona: 3 London: 2 Paris: 4 Helsinki: 8	SO_2 black smoke O_3	Increment: 50 μg/m^3 of 24-h avg for all cities combined Asthma 15-64 yrs 1.029 [1.003, 1.055] lag 0-1 1.038 [1.008-1.068] lag 0-3, cumulative <15 yrs 1.026 [1.006, 1.049] lag 2 1.037 [1.004, 1.067] lag 0-3, cumulative 1.080 [1.025, 1.140] – Winter only Two-pollutant models: NO_2/Black smoke 15-64 yrs 1.055 [1.005, 1.109] lag 0-1 15-64 yrs 1.088 [1.025, 1.155] cumulative 0-3 <15 yrs 1.036 [0.956, 1.122] NO_2/SO_2 <15 yrs 1.034 [0.988, 1.082]
Schouten et al. (1996) Multicity, The Netherlands (Amsterdam, Rotterdam) Period of Study: 04/01/77-09/30/89	Outcomes (ICD 9): All respiratory (460-519), COPD (490-2, 494, 496), Asthma (493) Age groups analyzed: 15-64, 65+, all ages Study Design: Time-series Statistical Analyses: APHEA protocol, Poisson regression Covariates: Long-term trend, season, influenza, day of wk, holiday, temperature, humidity Season: Cool, Nov-Apr; Warm: May-Oct Statistical Package: NR Lag: 0,1,2 days; and cumulative 0-1 and 0-3 day lags	24-h avg NO_2 Amsterdam Mean/Med: 50/50 μg/m^3 Rotterdam Mean: 54/52 μg/m^3 Daily max 1 h Amsterdam Mean/Med: 75/75 μg/m^3 Rotterdam Mean/Med: 82/78 μg/m^3 # of stations: 1 per city	SO_2 BS O_3	Increment: 100 μg/m^3 increment All respiratory, Amsterdam 24 h mean; 1-h max 15-64 yrs RR 0.890 [0.783, 1.012]; 0.894 [0.821, 0.973] lag 1 >65 yrs RR 1.023 [0.907, 1.154]; 0.996 [0.918, 1.080] lag 2 All respiratory, Rotterdam 24 h mean; 1-h max (1985-89) 15-64 yrs RR 0.965 [0.833, 1.118]; 1.036 [0.951, 1.129] lag 1 >65 yrs RR 1.172 [0.990, 1.387]; 1.073 [0.970, 1.186] lag 0 COPD, Amsterdam, 24-h mean, All ages RR 0.937 [0.818, 1.079] lag 1 Asthma Amsterdam, 24-h mean, All ages RR 1.062 [0.887, 1.271] lag 2 COPD, Rotterdam 24-h mean All ages RR 1.051 [0.903, 1.223] lag 2

REFERENCE, STUDY LOCATION, & PERIOD	OUTCOMES, DESIGN, & METHODS	MEAN LEVELS & MONITORING STATIONS	COPOLLUTANTS & CORRELATIONS	EFFECTS: RELATIVE RISK OR PERCENT CHANGE & CONFIDENCE INTERVALS (95%)
Ponce de Leon et al. (1996) London, England Period of Study: 04/1987-1988; 1991-02/1992	Outcomes (ICD 9): All respiratory (460-519) Age groups analyzed: 0-14, 15-64, 65+, all ages Study Design: Timeseries 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	NO_2 24-h avg: 37.3 ppb, Med: 35 SD = 13.8 IQR: 14 ppb 1-h max: 57.4 ppb, Med: 51 SD = 26.4 IQR: 21 ppb # of stations: 2	SO_2; r = 0.45 BS; r = 0.44 O_3	Increment: 90th-10th percentile (24-h avg: 27 ppb) All yr All ages 1.0114 [1.006, 1.0222] lag 2 0-14 yrs 1.0104 [0.9943, 1.0267] lag2 15-64 yr 1.0113 [0.9920, 1.0309] lag 1 ≥65 yr 1.0216 [1.0049, 1.0386] lag 2 Warm season All ages 1.0276 [1.0042, 1.0515] lag 2 0-14 yrs 1.038 [1.0009, 1.0765] lag 2 15-64 yr 1.0040 [0.9651, 1.0445] lag 1 >65 yr 1.0326 [0.9965, 1.0699] lag 2 Cool season All ages 1.0060 [0.9943, 10177] lag2 0-14 yrs 1.0027 [0.9855, 1.0202] lag2 15-64 yr 1.0136 [0.9920, 1.0357] lag 1 >65 yr 1.0174 [0.9994, 1.0358] lag 2
Atkinson et al. (1999a) London, England Period of Study: 1992 to 1994 Days: 1096	Outcomes (ICD 9): All respiratory (460-519), Asthma (493), Asthma + COPD (490-6), Lower respiratory disease (466, 480-6) Age groups analyzed: 0-14, 15-64, 65+, all ages Study Design: Time-series N: 165,032 Statistical Analyses: APHEA protocol, Poisson regression 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, 0-1, 0-2, 0-3 cum. avg.	NO_2 1-h mean: 50.3 ppb, SD = 17.0, Range: 22.0, 224.3 ppb, 10th percentile: 34.3, 90th percentile: 70.3 # of stations: 3; r = 0.7, 0.96	O_3, CO, PM10, BS, SO_2	Increment: 36 ppb (90th-10th centile) All ages Respiratory 1.64% [0.14, 3.15] lag 1 Asthma 1.80% [-0.77, 4.44] lag 0 0-14 yrs Respiratory 1.94% [-0.39, 4.32] lag 2 Asthma 1% [-1.42, 5.77] lag 3 15-64 yrs Respiratory 1.61% [-0.82, 4.09] lag 1 Asthma 5.08% [0.81, 9.53] lag 1 65+ yrs Respiratory 2.53% [0.58, 4.52] lag 3 Asthma 4.53% [-2.36, 11.91] lag 3 COPD 3.53% [0.64, 6.50] lag 3 Lower Resp. 3.47% [0.08, 6.97] lag 3

REFERENCE, STUDY LOCATION, & PERIOD	OUTCOMES, DESIGN, & METHODS	MEAN LEVELS & MONITORING STATIONS	COPOLLUTANTS & CORRELATIONS	EFFECTS: RELATIVE RISK OR PERCENT CHANGE & CONFIDENCE INTERVALS (95%)
Spix et al. (1998) Multi-city (London, Amsterdam, Rotterdam, Paris), Europe Period of Study: 1977 and 1991	Hospital Admissions Outcomes (ICD 9 codes): All respiratory (460-519); Asthma (493) Age groups analyzed: 15-64, 65+ Study Design: Time-series # of Hospitals: Statistical Analyses: Poisson regression following APHEA protocol. Pooled meta-analysis adjusted for heterogeneity Covariates: Trend, seasonality, day of wk, holiday, temperature, humidity, unusual events (strikes, etc.) Statistical Package: Lag: 1 to 3 days	NO_2 daily mean (μg/m^3) London 35 Amsterdam 50 Rotterdam 53 Paris 42	SO_2, O_3, BS, TSP	Increment: 50 μg/m^3. All cities, yr round 15-64 yrs RR 1.010 [0.985, 1.036] Warm RR 1.00 [0.96, 1.04] Cold RR 1.01 [0.98, 1.04] ≥65 yrs RR 1.019 [0.982, 1.060] Warm RR 1.02 [0.99, 1.06] Cold RR 1.00 [0.98, 1.03]
Wong* et al. (2002) London England and Hong Kong Period of Study: London: 1992-1994 Hong Kong: 1995-1997 Days: 1,096	Outcomes (ICD 9): All respiratory admissions (460-519); asthma (493) Age groups analyzed: 15-64, 65+, all ages Study Design: Time-series Statistical Analyses: APHEA protocol, Poisson regression with GAM Covariates: Long-term trend, season, influenza, day of wk, holiday, temperature, humidity, thunderstorms Season: Cool, Oct-Mar; Warm: Apr-Sep Dose-Response Investigated?: Yes Statistical Package: S-Plus Lag: 0,1,2,3,4 days, 0-1 cum. avg	24 h NO_2 μg/m^3 Hong Kong Mean: 55.9 Warm: 48.1 Cool: 63.8 SD = 19.4 Range: 15.3, 151.5 10th: 31.8 50th: 53.5 90th: 81.8 London Mean: 64.3 Warm: 62.6 Cool: 66.1 SD = 20.4 Range: 23.7, 255.8 10th: 42.3 50th: 61.2 90th: 88.8 # of stations: Hong Kong: 7; r = 0.65, 0.90 London: 3; r = 0.80	Hong Kong PM10; r = 0.82 SO_2; r = 0.37 O_3; r = 0.43 London PM10; r = 0.68 SO_2; r = 0.71 O_3; r = -0.29	Increment: 10 μg/m^3 Asthma, 15-64 yrs Hong Kong ER -0.6 [-2.1, 1.0] lag 0-1 ER -1.3 [-2.6, 0.1] lag 1 Warm: ER -0.5 [-2.7, 1.6] lag 0-1 Cool: ER -0.6 [-2.8, 1.6] lag 0-1 London ER 1.0 [0.0, 2.1] lag 0-1 ER 1.1 [0.2, 2.0] lag 2 Warm: ER 0.6 [-0.8, 2.0] lag 0-1 Cool: ER 1.3 [-0.1, 2.8] lag 0-1 Respiratory 65+ yrs Hong Kong ER 1.8 [1.2, 2.4] lag 0-1 ER 1.3 [0.8, 1.8] lag 0 Warm: ER 0.8 [0.1, 1.6] lag 0-1 Cool: ER 3.0 [2.1, 3.9] lag 0-1 +O_3: ER 1.6 [1.0, 2.3] lag 0-1 +PM10: ER 1.7 [0.8, 2.7] lag 0-1 +SO_2: ER 1.6 [0.8, 2.4] lag 0-1 London ER -0.1 [-0.6, 0.5] lag 0-1 ER 0.9 [0.5, 1.3] lag 3 Warm: ER 0.6 [-0.2, 1.4] lag 0-1 Cool: ER -0.7 [-1.4, 0.0] lag 0-1 +O_3: ER -0.1 [-0.5, 0.6] lag 0-1 +PM10: ER -0.4 [-1.2, 0.4] lag 0-1 +SO_2: ER -0.2 [-0.9, 0.5] lag 0-1

REFERENCE, STUDY LOCATION, & PERIOD	OUTCOMES, DESIGN, & METHODS	MEAN LEVELS & MONITORING STATIONS	COPOLLUTANTS & CORRELATIONS	EFFECTS: RELATIVE RISK OR PERCENT CHANGE & CONFIDENCE INTERVALS (95%)
Anderson et al. (1998) London, England Period of Study: Apr 1987-Feb 1992 Days: 1,782	Outcomes (ICD 9): Asthma (493) Age groups analyzed: <15, 15-64, 65+ Study Design: Time-series N: 16 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 Dose-Response Investigated?: Yes Statistical Package: S Lag: 0,1,2 days	24-h avg NO_2 (ppb) Mean: 37.2 SD = 12.3 Range: 14, 182 5th: 22 10th: 25 25th: 30 50th: 36 75th: 42 90th: 50 95th: 58 1-h max NO_2 (ppb) Mean: 57.2 SD = 23.0 Range: 21, 370 5th: 35 10th: 38 25th: 44 50th: 52 75th: 64 90th: 81 95th: 98 Number of stations: 2	O_3 SO_2 BS	Increment: 10 ppb in 24-h NO_2 0-14 yrs Whole yr RR 1.25 [0.3, 2.2] lag 2; RR 1.77 [0.39, 3.18] lag 0-3 + O_3 lag 2 RR 1.13 [-0.10, 2.36] + SO_2 lag 2 RR 0.97 [-0.05, 1.99] + BS lag 2 RR 2.26 [0.83, 3.71] Warm season RR 1.42 [-0.3, 3.17] lag 2; RR 3.01 [3.8, 5.72] lag 0-3 Cool season RR 1.18 [0.02, 2.35] lag 2; RR 1.22 [-0.48, 2.96] lag 0-3 15-64 yrs Whole yr RR 0.95 [-0.26, 2.17] lag 0; RR 0.99 [-0.36, 3.36] lag 0-1 Warm RR 0.46 [-1.70, 2.67] lag 0; RR 0.05[-2.45, 2.61] lag 0-1 Cool season RR 1.21 [-0.22, 2.5] lag 0; RR 1.43 [-0.18, 3.06] lag 0-1 65+ yrs Whole yr RR 2.96 [0.67, 5.31] lag 2; RR 3.14 [-0.04, 6.42] lag 0-3 + O_3 lag 2 RR 4.51 [1.43, 7.69] + SO_2 lag 2 RR 2.49 [-0.25, 5.31] + BS lag 2 RR 1.88 [-1.49, 5.36] Warm lag 2; RR 1.89 [-2.41, 6.38] RR -1.76 [-7.27, 4.07] lag 0-3 Cool season RR 3.52 [0.81, 6.30] lag 2; RR 5.57 [1.85, 9.43] lag 0-3

REFERENCE, STUDY LOCATION, & PERIOD	OUTCOMES, DESIGN, & METHODS	MEAN LEVELS & MONITORING STATIONS	COPOLLUTANTS & CORRELATIONS	EFFECTS: RELATIVE RISK OR PERCENT CHANGE & CONFIDENCE INTERVALS (95%)
Anderson et al. (1998) (cont'd)				+ O_3 lag 2 RR 5.14 [0.69, 9.79] + SO_2 lag 2 RR 2.10 [-1.08, 5.39] + BS lag 2 RR 4.47 [-0.04, 9.19] All ages Whole yr RR 1.25 [0.49, 2.02] lag 2; RR 2.05 [0.96, 3.15] lag 0-3 + O_3 lag 2 RR 1.08 [0.12, 2.05] + SO_2 lag 2 RR 0.99 [0.18, 1.81] + BS lag 2 RR 1.23 [0.47, 2.00] Warm RR 1.15 [-0.25, 2.57] lag 2; RR 1.54 [-0.54, 3.67] lag 0-3 Cool season RR 1.30 [0.38, 2.23] lag 2; RR 2.26 [0.94, 3.59] lag 0-3 + O_3 lag 2 RR 0.50 [-0.79, 1.81] + SO_2 lag 2 RR 1.10 [0.12, 2.08] + BS lag 2 RR 1.29 [0.37, 2.22]
Anderson et al. (2001) West Midlands conurbation, United Kingdom Period of Study: 10/1994-12/1996	Hospital Admissions: Outcomes (ICD 9 codes): All respiratory (460-519), Asthma (493), COPD (490-496, excluding 493) Age groups analyzed: 0-14, 15-64, 65+ Study Design: Time-series Statistical Analyses: Followed APHEA 2 protocol, GAM Covariates: Season, temperature, humidity, epidemics, day of wk, holidays Statistical Package: S-Plus 4.5 Pro Lag: 0,1,2,3, 0-1, 0-2, 0-3	1-h max avg: 37.2 ppb, 15.1 (SD) Min: 10.7 ppb Max: 176.1 ppb 10th: 22.9 ppb 90th: 51.7 ppb # of monitors: 5	PM10; r = 0.62 PM2.5; r = 0.61 PM2.5-10; r = 0.25 BS; r = 0.65 SO4; r = 0.30 SO_2; r = 0.52 O_3; r = 0.08 CO; r = 0.73	Increment: 25.5 ppb (90th – 10th) All respiratory All ages 1.7% [-0.2, 3.7] lag 0-1 0-14 yrs 2.3% [-0.6, 5.3] lag 0-1 15-64 yrs 0.0% [-3.7, 3.8] lag 0-1 ≥65 yrs 1.0% [-1.8, 3.9] lag 0-1 COPD with asthma 0-14 yrs 4.0% [-2.0, 10.2] lag 0-1 15-64 yrs -3.3% [-10.4, 4.4] lag 0-1 ≥65 yrs 2.5% [-2.1, 7.3] lag 0-1
Prescott et al. (1998) Edinburgh, United Kingdom Period of Study: 10/92-6/95	Outcomes (ICD 9): Pneumonia (480-7), COPD + Asthma (490-496) Age groups analyzed: <65, 65+ Study Design: Time-series Statistical Analyses: Poisson log linear regression Covariates: Trend, seasonal and wkly variation, temperature, wind speed, day of wk Lag: 0,1 or 3 day rolling avg	NO_2: 26.4 ± 7.0 ppb Min: 9 ppb Max: 58 ppb IQR: 10 ppb # of Stations: 1	CO PM10 SO_2 O_3 BS	Increment: 10 ppb Respiratory admissions >65 yrs 3.1 [-4.6, 11.5] rolling 3-day avg <65 yrs -0.2% [-7.5, 7.7] rolling 3-day avg

REFERENCE, STUDY LOCATION, & PERIOD	OUTCOMES, DESIGN, & METHODS	MEAN LEVELS & MONITORING STATIONS	COPOLLUTANTS & CORRELATIONS	EFFECTS: RELATIVE RISK OR PERCENT CHANGE & CONFIDENCE INTERVALS (95%)
Thompson et al. (2001) Belfast, Northern Ireland Period of Study: 1993-1995	Outcomes: Asthma ICD9: NR Age groups analyzed: 0-14 Study Design: Time-series N: 1,095 Number of hospitals: 1 Statistical Analyses: Poisson regression Covariates: Season, long-term trend, temperature, day of wk, holidays Season: Warm (May-Oct), Cold (Nov-Apr) Statistical Package: Stata Lag: 0,1,2,3 days	24-h mean: Warm: 19.2 (7.9) ppb; Range: 13-23 Cold: 23.3 (9.0) ppb; Range: 18-28	SO_2; r = 0.82 PM10; r = 0.77 CO; r = 0.69 O_3; r = -0.62 NO_X; r = 0.93 log (NO); r = 0.84 log (CO); r = 0.69	Increment: 10 ppb All seasons RR 1.08 [1.03, 1.13] lag 0 RR 1.11 [1.05, 1.17] lag 0-1 RR 1.10 [1.04, 1.17] lag 0-2 RR 1.12 [1.03, 1.02] lag 0-3 Warm season RR 1.14 [1.04, 1.26] lag 0-1 Cold season RR 1.10 [1.03, 1.17] lag 0-1 NO_2 + Benzene RR 0.99 [0.87, 1.13] lag 0-1 *Model made no allowance for possible autocorrelation in the data or for extra-Poisson variation.
Hagen et al. (2000) Drammen, Norway Period of Study: 1994-1997	Outcomes (ICD 9): All respiratory admissions (460-519) Age groups analyzed: All ages Study Design: Time-series Number of hospitals: 1 Statistical Analyses: Poisson regression with GAM (adhered to HEI phase 1.B report) Covariates: Time trends, day of wk, holiday, influenza, temperature, humidity Lag: 0,1,2,3 days	NO_2 24-h avg (μg/m^3): 36.15, SD = 16 IQR: 16.92 μg/m^3 # of Stations: 2	PM10; r = 0.61 SO_2; r = 0.58 Benzene; r = 0.31 NO; r = 0.70 O_3; r = -0.47 Formaldehyde; r = 0.68 Toluene; r = 0.65	Increment: NO_2: 16.92 μg/m^3 (IQR); NO: 29μg/m^3 (IQR) Single-pollutant model Respiratory disease only NO_2: RR 1.058 [0.994, 1.127] NO: 1.048 [1.013, 1.084] All disease NO_2: RR 1.011 [0.988, 1.035] Two-pollutant model with PM10 NO_2: 1.044 [0.966, 1.127] NO: 1.045 [1.007, 1.084] Three-pollutant model with PM10 + Benzene NO_2: 1.015 [0.939, 1.097] NO: 1.031 [0.986, 1.077]
Oftedal et al. (2003) Drammen, Norway Period of Study: 1994-2000	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: 33.8 μg/m^3 SD = 16.2 IQR: 20.8 μg/m^3	PM10 SO_2 O_3 Benzene Formaldehyde Toluene	Increment: 20.8 μg/m^3 (IQR) All respiratory disease Single-pollutant model RR 1.060 [1.017, 1.105] lag 3 Two-pollutant model Adjusted for PM10 RR 1.063 [1.008, 1.120] Adjusted for benzene RR 1.046 [1.002, 1.091]

REFERENCE, STUDY LOCATION, & PERIOD	OUTCOMES, DESIGN, & METHODS	MEAN LEVELS & MONITORING STATIONS	COPOLLUTANTS & CORRELATIONS	EFFECTS: RELATIVE RISK OR PERCENT CHANGE & CONFIDENCE INTERVALS (95%)
Pönkä (1991) Helsinki, Finland Period of Study: 1987-1989	Outcomes (ICD 9 codes): Asthma (493) Age groups analyzed: 0-14; 15-64; ≥65 yrs Study Design: Time-series N: 4,209 Statistical Analyses: Correlations and partial correlations Covariates: Minimum temperature Statistical Package: Lag: 0-1	24-h avg: 38.6 (16.3) μg/m^3 Range: 4.0-169.6 Number of Monitors: 4	SO_2; r = 0.4516 NO; r = 0.6664 O_3; r = -0.2582 TSP; r = 0.1962 CO	Correlations between hospital admissions (HA) for asthma and pollutants and temperature by ages. 0-14 yrs HA: -0.0166 Emergency HA: 0.0061 15-64 yrs HA: 0.1648 p < 0.0001 Emergency HA: 0.1189 p < 0.0001 ≥65 yrs HA: 0.1501 p < 0.0001 Emergency HA: 0.1392 p < 0.0001 Partial correlations between admissions for asthma and SO_2 were standardized for temperature. HA: 0.1830 p < 0.0001 Emergency HA: 0.1137 p = 0.0004
Pönkä and Virtanen (1994) Helsinki, Finland Period of Study: 1987-1989 Days: 1096	Outcomes (ICD 9): Chronic bronchitis and emphysema (491-492) 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: 39 μg/m^3 SD = 16.2; Range: 4, 170 # of stations: 2	SO_2 O_3 TSP	Increment: NR Chronic bronchitis and emphysema ≥65 yrs RR 0.87 [0.71, 1.07] lag 0 RR 1.07 [0.86, 1.33] lag 1 RR 1.16 [0.93, 1.46] lag 2 RR 1.08 [0.86, 1.35] lag 3 RR 0.94 [0.76, 1.18] lag 4 RR 0.90 [0.72, 1.12] lag 5 RR 1.31 [1.03, 1.66] lag 6 RR 0.82 [0.67, 1.01] lag 7 <65 yrs NR
Pönkä and Virtanen, (1996) Helsinki, Finland Period of study: 1987-1989	Hospital Admissions Outcomes (ICD 9 codes): Asthma (493) Age groups analyzed: 0-14, 15-64, 65+ Study Design: Time-series Statistical Analyses: Covariates: Long-term trend, season, epidemics, day of wk, holidays, temperature, relative humidity Statistical Package: Lag: 0-2	24-h avg (μg/m^3): Winter: 38 Spring: 44 Summer: 39 Fall: 34	SO_2 O_3 TSP	No results presented for NO_2 because they were not statistically significant

REFERENCE, STUDY LOCATION, & PERIOD	OUTCOMES, DESIGN, & METHODS	MEAN LEVELS & MONITORING STATIONS	COPOLLUTANTS & CORRELATIONS	EFFECTS: RELATIVE RISK OR PERCENT CHANGE & CONFIDENCE INTERVALS (95%)
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: 13.4 μg/m^3 Range: 0-69 1-hr max: 38.5 μg/m^3 Range: 0-154 # of Monitoring Stations: 4	NO_2; r = 0.48 TSP; H2S	Pearson correlation coefficients ED asthma visits and same day SO_2: r = 0.20 p < 0.001 lag 0 Weekly ED asthma visits and same wk SO_2: r = 0.42 p < 0.001 Weekly ED asthma visits and previous wk SO_2: r = 0.58 p < 0.001 Multi-pollutant (NO_2; TSP; H2S) Regression coefficient: All yr: ≥ = 0.209, p = 0.034 Winter: ≥ = 0.201, p = 0.014 Summer: ≥ = 0.041, p = 0.714
Andersen et al. (2007a) Copenhagen, Denmark Period of Study: 1999-2004	Outcomes (ICD 10): chronic bronchitis (J41-42), emphysema (J43), COPD (J44), asthma (J45), status asthmaticus (J46) Age groups analyzed: 5-18, 65+ Number of hospitals: 9 Study Design: Time-series Statistical Analyses: Poisson regression with GAM Covariates: Temperature, long-term trend, seasonality, influenza, day of wk, public holidays, school holidays Lag: 0, 1, 2, 3, 4, 5, 0-4, 0-5 days	24-h avg: 12 (5) ppb Statistical package: R IQR: 7 25th: 8 75th: 15	PM10; r = 0.42 PM10–biomass; r = 0.41 PM10–Secondary; r = 0.43 PM10–Oil; r = 0.42 PM10–Crustal; r = 0.24 PM10–Sea salt; r = -0.19 PM10–Vehicle; r = 0.65 CO; r = 0.74	Increment: 7 ppb (IQR): All respiratory disease (65+): NO_2: 1.040 [1.009, 1.072] lag 5 day moving avg NO_2 + PM10: 1.014 [0.978, 1.051] lag 5 day ma Asthma (5-18 yrs): NO_2: 1.128 [1.029, 1.235] lag 6 day ma NO_2+PM10: 1.032 [0.917-1.162] lag 6 day ma
Andersen et al. (2007b) Copenhagen, Denmark Period of Study: 5/15/2001-12/31/2004	Outcomes (ICD 10): chronic bronchitis (J41-42), emphysema (J43), COPD (J44), asthma (J45), status asthmaticus (J46) Age groups analyzed: 5-18, 65+ Number of hospitals: 9 Study Design: Time-series Statistical Analyses: Poisson regression with GAM Covariates: Temperature, long-term trend, seasonality, influenza, day of wk, public holidays, school holidays Lag: 0, 1, 2, 3, 4, 5, 0-4, 0-5 days	24-h avg: 11 (5) ppb Statistical package: R IQR: 6 25th: 8 50th: 11 75th: 14 99th: 28	PM10 PM2.5 CO O_3	Increment: 6 ppb (IQR): All respiratory disease (65+): NO_2: 1.06 [1.01, 1.12] lag 0-4 moving avg NO_2 + NCtot: 1.06 [0.99, 1.13] lag 0-4 ma Asthma (5-18 yrs): NO_2: 1.04 [0.92, 1.18] lag 0-5 ma NO_2+NCtot: 0.97 [0.83-1.14] lag 0-5 ma

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Dab* et al. (1996) Paris, France Period of Study: 1/1/87-9/30/92	Outcomes (ICD 9): All respiratory (460-519), Asthma (493), COPD (490-496) Age groups analyzed: All ages Study Design: Time-series Number of hospitals: 27 Statistical Analyses: Poisson regression, followed APHEA protocol Covariates: Temperature, relative humidity, influenza, long-term trend, season, holiday, medical worker strike Lag: 0,1,2 days, 0-3 cumulative	NO_2 24-h avg: 45 µg/m^3 5th: 22, 99th: 108.3 Daily maximum 1-h Concentration: 73.8 µg/m^3 5th: 37.5, 99th: 202.7	SO_2 O_3 PM13 BS	Increment: 100 µg/m^3 All respiratory (1987-1990) 24-h avg NO_2: RR 1.043 [0.997, 1.090] lag 0 1-h max NO_2: RR 1.015 [0.993, 1.037] lag 0 Asthma (1987-1992) 24-h avg: RR 1.175 [1.059, 1.304] lag 0-1 1-h max: RR 1.081 [1.019, 1.148] lag 0-1 COPD 24-h avg: RR 0.974 [0.898, 1.058] lag 2 1-h max: RR 0.961 [0.919, 1.014] lag 2
Linares et al. (2006) Madrid, Spain Period of Study: 1995-2000	Outcomes (ICD 9): All respiratory (460-519), bronchitis (460-496), pneumonia (480-487) Age groups analyzed: <10 Study Design: Time-series Number of hospitals: 1 Statistical Analyses: Poisson regression Covariates: Temperature, pressure, relative humidity Statistical Package: S Plus 2000 Lag:	24-h avg: 64.8 (17.1) ug/m^3 Range: 23-144 Number of monitors: 24	PM10; r = 0.71 O_3; r = -0.41 SO_2; r = 0.63	Qualitative results suggest linear relationship without threshold for NO_2 concentration and respiratory hospital admissions.
Llorca et al. (2005) Torrelavega, Spain Period of Study: 1992-1995 Days: 1,461	Outcomes (ICD 9): All respiratory admissions (460-519) Age groups analyzed: All ages Study Design: Time-series Number of hospitals: 1 Statistical Analyses: Poisson regression Covariates: Short and long-term trends Statistical Package: Stata Lag: NR	24-h avg NO_2: 21.3 µg/m^3, SD = 16.5 24-h avg NO: 12.2 µg/m^3, SD = 15.2 # of Stations: 3	SO_2; r = 0.588 NO; r = 0.855 TSP; r = -0.12 SH2; r = 0.545	Increment: 100 µg/m^3 Single-pollutant model All cardio-respiratory admissions NO_2: RR 1.37 [1.26, 1.49] NO: RR 1.33 [1.22, 1.46] Respiratory admissions NO_2: RR 1.54 [1.34, 1.76] NO: RR 1.35 [1.17, 1.56] 5-pollutant model All cardio-respiratory admissions NO_2: RR 1.20 [1.05, 1.39] NO: RR 0.93 [0.79, 1.09] Respiratory admissions NO_2: RR 1.69 [1.34, 2.13] NO: RR 0.87 [0.67, 1.13]

REFERENCE, STUDY LOCATION, & PERIOD	OUTCOMES, DESIGN, & METHODS	MEAN LEVELS & MONITORING STATIONS	COPOLLUTANTS & CORRELATIONS	EFFECTS: RELATIVE RISK OR PERCENT CHANGE & CONFIDENCE INTERVALS (95%)
Migliaretti and Cavallo (2004) Turin, Italy Period of Study: 1997-1999	Outcome(s) (ICD 9): Asthma (493) Age groups analyzed: <4, 4-15 Study Design: Case-control Controls: Age matched with other respiratory disease (ICD9: 460-7, 490-2, 494-6, 500-19) N: Cases = 734, controls = 25,523 Statistical Analyses: Logistic regression Covariates: Seasonality, temperature, humidity, solar radiation Seasons: Cold: Oct-Mar; Warm: Apr-Sep Statistical Package: SPSS Lag: 0-3 days and cumulative	Controls: Mean: 113.3 μg/m^3, SD = 30.5 Cases: Mean: 117.4 μg/m^3, SD = 29.7	TSP	Increment: 10 μg/m^3 <4 yrs 2.8% [0.03, 5.03] lag 1-3 cumulative 4-15 yrs 2.7% [-0.01, 6.06] lag 1-3 cumulative All ages 2.8% [0.07, 4.09] lag 1-3 cumulative Two-pollutant model adjusted for TSP NO_2 2.1% [-0.1, 5.6]
Farchi et al. (2006) Rome, Italy Period of Study: 11/94-2/95	Outcome(s) (ICD 9): All respiratory conditions (381-382, 460-466, 480-493); acute upper respiratory tract infections (380-382, 460-465); lower respiratory tract conditions including asthma (466, 480-493) Age groups analyzed: 6-7 Study Design: Cohort (SIDRIA) N: 2,947 Statistical Analyses: Cox regression models, GAM Covariates: Gender, paternal education, paternal smoking Statistical Package: STATA 8.0	Mean: 46.9 μg/m^3 (10.2) IQR: 17 Range: 24-66	Traffic	Increment: 10 μg/m^3 All respiratory conditions: HR: 1.28 [0.98-1.68] 1st Quartile (24-35 μg/m^3): 1.00 2nd Quartile (35-47 μg/m^3): 1.06 [0.45-2.53] 3rd Quartile (47-52 μg/m^3): 1.57 [0.59-4.13] 4th quartile (52-66 μg/m^3): 1.95 [0.81-4.71] Acute URT infections: HR: 1.56 [0.96-2.56] 1st Quartile (24-35 μg/m^3): 1.00 2nd Quartile (35-47 μg/m^3): 0.55 [0.08-3.61] 3rd Quartile (47-52 μg/m^3): 1.25 [0.25-6.24] 4th quartile (52-66 μg/m^3): 3.04 [0.67-13.79] Acute LRT infections and asthma: HR: 1.10 [0.80-1.51] 1st Quartile (24-35 μg/m^3): 1.00 2nd Quartile (35-47 μg/m^3): 1.34 [0.51-3.21] 3rd Quartile (47-52 μg/m^3): 1.58 [0.35-4.10] 4th quartile (52-66 μg/m^3): 1.24 [0.64-3.08]

REFERENCE, STUDY LOCATION, & PERIOD	OUTCOMES, DESIGN, & METHODS	MEAN LEVELS & MONITORING STATIONS	COPOLLUTANTS & CORRELATIONS	EFFECTS: RELATIVE RISK OR PERCENT CHANGE & CONFIDENCE INTERVALS (95%)
Fusco* et al. (2001) Rome, Italy Period of Study: 1/1/95-10/31/97	Outcomes (ICD 9): All respiratory (460-519 excluding 470-478), Asthma (493), COPD (490-492, 494-496), Respiratory infections (460-466, 480-486) Age groups analyzed: 0-14, all ages Study Design: Time-series Statistical Analyses: Semi-parametric Poisson regression with GAM Covariates: Influenza, day, temperature, humidity, day of wk, holiday Season: Warm (Apr-Sep), Cold (Oct-Mar) Statistical Package: S-Plus 4 Lag: 0-4 days	NO_2 24-h avg (μg/m^3): 86.7, SD = 16.2 IQR: 22.3 μg/m^3 # of stations: 5; r = 0.66-0.79	PM10: All yr; r = 0.35 Cold; r = 0.50 Warm; r = 0.25 SO_2: All yr; r = 0.33 Cold; r = 0.40 Warm; r = 0.68 CO: All yr; r = 0.31 Cold; r = 0.41 Warm; r = 0.59 O_3: All yr; r = 0.19 Cold; r = 0.19 Warm; r = 0.13	Increment: 22.3 μg/m^3 (IQR) All respiratory All ages: 2.5% [0.9, 4.2] lag 0 0-14 yrs: 4.0% [0.6, 7.5] lag 0 Respiratory infections All ages: 4.0% [1.6, 6.5] lag 0 0-14 yrs: 4.0% [0.2, 8.0] lag 0 Asthma All ages: 4.6% [-0.5, 10.0] lag 0 0-14 yrs: 10.7% [3.0, 19.0] lag 1 COPD ≥65 yrs: 2.2% [-0.7, 5.2] lag 0 Multipollutant models All respiratory (NO_2 + CO) All ages: 0.9% [-0.8, 2.8] lag 0 0-14 yrs: 3.3% [-0.2, 6.9] lag 0 Acute infections (NO_2 + CO) All ages: 3.9% [1.3, 6.7] lag 0 0-14 yrs: 2.9% [-1.0, 7.0] lag 0 Asthma (NO_2 + CO) All ages: 1.4% [-3.9, 7.1] lag 0 0-14 yrs: 8.3% [-0.1, 17.4] lag 1 COPD (NO_2 + CO) ≥65 yrs: -1.0%[-4.1, 2.2] lag 0
Pantazopoulou et al. (1995) Athens, Greece Period of Study: 1988	Outcomes: All respiratory admissions ICD9: NR Age groups analyzed: All ages Study Design: Time-series N: 15,236 Number of hospitals: 14 Statistical Analyses: Multiple linear regression Covariates: Season, day of wk, holiday, temperature, relative humidity Season: Warm (3/22-9/21), Cold (1/1-3/21 and 9/22-12/31) Lag: NR	NO_2 24-h avg Winter: 94 μg/m^3, SD = 25 5th: 59, 50th: 93, 95th: 135 Summer: 111 μg/m^3, SD = 32 5th: 65, 50th: 108, 95th: 173 # of stations: 2	CO BS	Increment: 76 μg/m^3 in winter and 108 μg/m^3 in summer (95th-5th) Respiratory disease admissions Winter: Percent increase: 24% [6.4, 43.5] Summer: Percent increase: 9.3% [-14.1, 24.4]

REFERENCE, STUDY LOCATION, & PERIOD	OUTCOMES, DESIGN, & METHODS	MEAN LEVELS & MONITORING STATIONS	COPOLLUTANTS & CORRELATIONS	EFFECTS: RELATIVE RISK OR PERCENT CHANGE & CONFIDENCE INTERVALS (95%)
LATIN AMERICA				
Gouveia and Fletcher, (2000a) São Paulo, Brazil Period of Study: 11/92-9/94	Outcomes (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	1-h max NO_2 (µg/m^3) Mean: 174.3 SD = 101.3 Range: 26.0, 692.9 5th: 62.0 25th: 108.8 50th: 151.7 75th: 210.0 95th: 388.0 # of stations: 4	SO_2; r = 0.37 PM10; r = 0.40 CO; r = 0.35 O_3; r = 0.25	Increment: 319.4 µg/m^3 (90th-10th) All Respiratory <5 yrs: RR 1.063 [0.999, 1.132] lag 0 <5 yrs + O_3: RR 1.050 [0.985, 1.120] <5 yrs + PM10: RR 1.043 [0.972, 1.119] <5 yrs + O_3+ PM10: RR 1.035 [0.963, 1.113] <5 yrs Cool: RR 1.04 [0.96, 1.11] (estimated from graph) <5 yrs Warm: RR 1.09 [1.01, 1.16] (estimated from graph) Pneumonia <5 yrs: RR 1.093 [1.016, 1.177] lag 0 <1 yr: RR 1.091 [0.996, 1.193] lag 0 Asthma <5 yrs: RR 1.107 [0.940, 1.300] lag 2
Braga* et al. (1999) Sao Paulo, Brazil Period of Study: 10/1992-10/1993	Hospital Admissions Outcomes (ICD 9 codes): All respiratory (466,480-486,491-492,496) Age groups analyzed: <13 yrs Study Design: Time-series N: 68,918 # of Hospitals: 112 Statistical Analyses: Multiple linear regression models (least squares). Also used Poisson regression techniques. GLM and GAM using LOESS for smoothing. Covariates: Season, temperature, humidity, day of wk Statistical Package: SPSS, S-Plus Lag: 1,2,3,4,5,6,7 moving avgs	24-h avg 174.84 (101.38) µg/m^3 Min: 26.0 Max: 668.3 # of monitors: 13	PM10; r = 0.53 CO; r = 0.42 SO_2; r = 0.53 O_3; r =	Due to problems with NO_2 monitors, this pollutant could not be included in the analysis.
Braga* et al. (2001) São Paulo, Brazil Period of Study: 1/93-11/97	Outcomes (ICD 9): All respiratory admissions (460-519) Age groups analyzed: 0-19, #2, 3-5, 6-13, 14-19 Study Design: Time-series Statistical Analyses: Poisson regression with GAM Covariates: Long-term trend, season, temperature, relative humidity, day of wk, holiday Statistical Package: S-Plus 4.5 Lag: 0-6 moving avg	NO_2 mean: 141.4 µg/m^3, SD = 71.2 IQR: 80.5 µg/m^3 Range: 25, 652.1 # of stations: 5-6	PM10; r = 0.62 SO_2; r = 0.54 CO; r = 0.58 O_3; r = 0.34	Increment: 80.5 µg/m^3 (IQR) All Respiratory admissions <2 yrs 9.4% [6.2, 12.6] lag 5 3-5 yrs 1.6% [-6.4, 9.6] 6-13 yrs 2.3% [-5.9, 10.4] 14-19 yrs -3.0% [-15.7, 9.7] All ages 6.5% [3.3, 9.7]

REFERENCE, STUDY LOCATION, & PERIOD	OUTCOMES, DESIGN, & METHODS	MEAN LEVELS & MONITORING STATIONS	COPOLLUTANTS & CORRELATIONS	EFFECTS: RELATIVE RISK OR PERCENT CHANGE & CONFIDENCE INTERVALS (95%)
Braga* et al. (2001) São Paulo, Brazil Period of Study: 1/93-11/97	Outcomes (ICD 9): All respiratory admissions (460-519) Age groups analyzed: 0-19, #2, 3-5, 6-13, 14-19 Study Design: Time-series Statistical Analyses: Poisson regression with GAM Covariates: Long-term trend, season, temperature, relative humidity, day of wk, holiday Statistical Package: S-Plus 4.5 Lag: 0-6 moving avg	NO_2 mean: 141.4 µg/m^3, SD = 71.2 IQR: 80.5 µg/m^3 Range: 25, 652.1 # of stations: 5-6	PM10; r = 0.62 SO_2; r = 0.54 CO; r = 0.58 O_3; r = 0.34	Increment: 80.5 µg/m^3 (IQR) All Respiratory admissions <2 yrs 9.4% [6.2, 12.6] lag 5 3-5 yrs 1.6% [-6.4, 9.6] 6-13 yrs 2.3% [-5.9, 10.4] 14-19 yrs -3.0% [-15.7, 9.7] All ages 6.5% [3.3, 9.7]
Farhat* et al. (2005) São Paulo, Brazil Period of Study: 8/96-8/97 Days: 396	Outcomes (ICD 9): Pneumonia/bronchiopheumonia (480-6), asthma (493), bronchiolitis (466), Obstructive disease 493, 466) Age groups analyzed: <13 Study Design: Time-series N: 1,021 Number of hospitals: 1 Statistical Analyses: Poisson regression with GAM Covariates: Time, temperature, humidity, day of wk, season Statistical package: S-Plus Lag: 0-7 days, 2,3,4 day moving avg	Mean: 125.3 µg/m^3 SD = 51.7 IQR: 65.04 µg/m^3 Range: 42.5, 369.5	PM10; r = 0.83 SO_2; r = 0.66 CO; r = 0.59 O_3; r = 0.47	Increment: 65.04 µg/m^3 (IQR) Single-pollutant models (estimated from graphs) Lower respiratory tract disease: NO_2 alone: –18% [13, 24] lag 0-3 NO_2 + PM10 16.1% [5.4, 26.8] lag 0-2 NO_2 + SO_2 24.7% [18.2, 31.3] lag 0-2 NO_2 + CO 19.2% [11.8, 26.6] lag 0-2 NO_2 + O_3 16.1% [9.5, 22.7] lag 0-2 Multipollutant model (PM10, SO_2, CO, O_3) 18.4% [3.4, 33.5] 2 day avg Pneumonia: NO_2 alone: –17.5% [3, 32.5] lag 0-2 NO_2 + PM10 8.1% [-11.4, 27.6] lag 0-2 NO_2 + SO_2 13.1% [-3.4, 29.7] lag 0-2 NO_2 + CO 14.6% [-4.9, 34.1] lag 0-2 NO_2 + O_3 12.4% [-5.6, 30.4] lag 0-2 Multipollutant model (PM10, SO_2, CO, O_3) 1.8% [-23.9, 27.6] 2 day avg Asthma or Bronchiolitis NO_2 alone: 30.5% [9, 56] lag 0-1 NO_2 + PM10 47.7% [1.15, 94.2] lag 0-2 NO_2 + SO_2 33.1% [5.7, 60.5] lag 0-2 NO_2 + CO 28.8% [-0.2, 57.9] lag 0-2 NO_2 + O_3 28.0% [-1.0, 57.0] lag 0-2 Multipollutant model (PM10, SO_2, CO, O_3) 39.3% [-14.9, 93.5] 2 day avg

REFERENCE, STUDY LOCATION, & PERIOD	OUTCOMES, DESIGN, & METHODS	MEAN LEVELS & MONITORING STATIONS	COPOLLUTANTS & CORRELATIONS	EFFECTS: RELATIVE RISK OR PERCENT CHANGE & CONFIDENCE INTERVALS (95%)
Arbex et al., 2007 Araraquara, Brazil Period of Study: 3/2003-7/2004	Outcomes (ICD 10): asthma (J15) Age groups analyzed: <13 Study Design: Ecological Time-series N: 1,021 Number of hospitals: 1 Statistical Analyses: Poisson regression with GLM Covariates: Long-term trend, weather Statistical package: S-Plus Lag: 0-7 days, 2,3,4 day moving avg	TSP (μg/m^3)		Increment: 10 μg/m^3 Asthma hospital admissions: 11.6% [5.4, 17.7] lag 1-5
ASIA				
Lee et al. (2006) Hong Kong, China Period of Study: 1997-2002 Days: 2,191	Outcomes (ICD 9): Asthma (493) Age groups analyzed: #18 Study Design: Time-series N: 26,663 Statistical Analyses: Semi-parametric Poisson regression with GAM (similar to APHEA 2) Covariates: Long-term trend, temperature, relative humidity, influenza, day of wk, holiday Statistical package: SAS 8.02 Lag: 0-5 days	NO_2 24-h mean: 64.7 μg/m^3, SD = 20.9 IQR: 27.1 μg/m^3 25th: 49.7, 75th: 76.8 # of stations: 9-10, r = 0.53, 0.94, Mean: 0.78	PM10; r = 0.78 PM2.5; r = 0.75 SO_2; r = 0.49 O_3; r = 0.35	Increment: 27.1 μg/m^3 (IQR) Asthma Single-pollutant model 4.37% [2.51, 6.27] lag 0 5.88% [4.00, 7.70] lag 1 7.19% [5.37, 9.04] lag 2 9.08% [7.26, 10.93] lag 3 7.64% [5.84, 9.48] lag 4 6.40% [4.60, 8.22] lag 5 Multipollutant model – including PM, SO_2, and O_3 5.64% [3.21, 8.14] lag 3 Other lags NR
Chew et al. (1999) Singapore Period of Study: 1990-1994	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: 18.9 μg/m^3, SD = 15.0, Max < 40 # of Stations: 15	SO_2; r = -0.22 O_3; r = 0.17 TSP; r = 0.23	Categorical analysis (via ANOVA) p-value and Pearson correlation coefficient (r) using continuous data comparing daily air pollutant levels and daily number of hospital admissions. Age Group: 3-12 13-21 Lag 0 r = 0.13 r = 0.05 p = 0.013 p < 0.18 Lag 1 r = 0.13 r = 0.02 P = 0.02 p = 0.75 Lag 2 r = 0.13 r = 0.07 p = 0.35 p = 0.012

REFERENCE, STUDY LOCATION, & PERIOD	OUTCOMES, DESIGN, & METHODS	MEAN LEVELS & MONITORING STATIONS	COPOLLUTANTS & CORRELATIONS	EFFECTS: RELATIVE RISK OR PERCENT CHANGE & CONFIDENCE INTERVALS (95%)
Tsai et al. (2006) Kaohsiung, Taiwan Period of Study: 1996-2003 Days: 2922	Outcomes (ICD 9): Asthma (493) Study Design: Case-crossover N: 17,682 Statistical Analyses: Conditional logistic regression Covariates: Temperature, humidity Season: Warm (≥25ºC); Cool (<25ºC) Statistical package: SAS Lag: 0-2 days cumulative	NO_2 24-h mean: 27.20 ppb IQR: 17 ppb Range: 4.83, 63.40 # of stations: 6	PM10 SO_2 O_3 CO	Increment: 17 ppb (IQR) Seasonality Single-pollutant model >25°C 1.259 [1.111, 1.427] lag 0-2 <25°C 2.119 [1.875, 2.394] lag 0-2 Dual-pollutant model Adjusted for PM10 >25°C 1.082 [0.913, 1.283] lag 0-2 <25°C 2.105 [1.791, 2.474] lag 0-2 Adjusted for CO >25°C 0.949 [0.792, 1.137] lag 0-2 <25°C 2.30 [1.915, 2.762] lag 0-2 Adjusted for SO_2 >25°C 1.294 [1.128, 1.485] lag 0-2 <25°C 2.627 [2.256, 3.058] lag 0-2 Adjusted for O_3 >25°C 1.081 [0.945, 1.238] lag 0-2 <25°C 2.096 [1.851, 2.373] lag 0-2
Chen et al. (2006) Taiwan Period of Study: 1/1998-12/2001	Outcomes (ICD 9): Asthma (493) Age Groups: 0-4, 5-14, 15-44, 45-64, 65+ Study Design: Time-series N: 126,671 Statistical Analyses: Spearman Rank Correlations Covariates: Season: Statistical package: SPSS Lag:	Mean monthly NO_2 averaged across 55 monitors: 37.64 (4.89) ppb Min: 29.52 25th: 33.72 50th: 37.07 75th: 40.63 Max: 47.65	PM10; r = SO_2; r = CO; r = O_3; r =	Spearman rank correlations show that seasonal variations in adult asthma admissions are significantly correlated with levels of NO_2 (r = 0.423, p = 0.003).
Lee* et al. (2002) Seoul, Korea Period of Study: 12/1/97-12/31/99 Days: 822	Outcomes (ICD 10): Asthma (J45 – J46) Age groups analyzed: <15 Study Design: Time-series N: 6,436 Statistical Analyses: Poisson regression, log link with GAM Covariates: Time, day of wk, temperature, humidity Season: Spring (Mar-May), Summer (Jun-Aug), Fall (Sep-Nov), Winter (Dec-Feb) Statistical package: NR Lag: 0-2 days cumulative	24-h NO_2 (ppb) Mean: 31.5 SD = 10.3 5th: 16.0 25th: 23.7 50th: 30.7 75th: 38.3 95th: 48.6 # of stations: 27	SO_2; r = 0.72 O_3; r = -0.07 CO; r = 0.79 PM10; r = 0.74	Increment: 14.6 ppb (IQR) Asthma NO_2: RR 1.15 [1.10, 1.20] lag 0-2 NO_2 + PM10: RR 1.13 [1.07, 1.19] lag 0-2 NO_2 + SO_2: RR 1.20 [1.11, 1.29] lag 0-2 NO_2 + O_3: RR 1.14 [1.09, 1.20] lag 0-2 NO_2 + CO: RR 1.12 [1.03, 1.22] lag 0-2 NO_2 + O_3 + CO + PM10 + SO_2: RR 1.098 [1.002, 1.202]

REFERENCE, STUDY LOCATION, & PERIOD	OUTCOMES, DESIGN, & METHODS	MEAN LEVELS & MONITORING STATIONS	COPOLLUTANTS & CORRELATIONS	EFFECTS: RELATIVE RISK OR PERCENT CHANGE & CONFIDENCE INTERVALS (95%)
Yang et al. (2007) Taipei, Taiwan Period of Study: 1996-2003	Outcomes (ICD 9): Asthma (493) Age groups analyzed: All Study Design: Case-crossover N: 25,602 Number of hospitals: 47 Statistical Analyses: Conditional logistic regression Covariates: Temperature, humidity Statistical package: SAS Lag: 0-2	24-h avg: 30.77 ppb Range: 3.84-77.97 25th: 25.55 50th: 30.31 75th: 35.60 Number of monitors: 6	SO_2 PM10 CO O_3	Increment: 10.05 ppb (IQR) NO_2 alone: ≥25 EC: 1.178 [1.113, 1.247] lag 0-2 <25 EC: 1.128, 1.076, 1.182] lag 0-2 NO_2 + PM10: ≥25 EC: 1.328 [1.224, 1.441] lag 0-2 <25 EC: 1.144 [1.077, 1.215] lag 0-2 NO_2 + SO_2: ≥25 EC: 1.224 [1.140, 1.314] lag 0-2 <25 EC: 1.219 [1.150, 1.291] lag 0-2 NO_2 + CO: ≥25 EC: 1.084 [0.999, 1.176] lag 0-2 <25 EC: 1.198 [1.111, 1.291] lag 0-2 NO_2 + O_3: ≥25 EC: 1.219 [1.142, 1.301] lag 0-2 <25 EC: 1.156 [1.102, 1.212] lag 0-2
Yang and Chen (2007) Taipei, Taiwan Period of Study: 1996-2003	Outcomes (ICD 9): COPD (493) Age groups analyzed: Study Design: Case-crossover N: 25,602 Number of hospitals: 47 Statistical Analyses: Conditional logistic regression Covariates: Temperature, humidity Statistical package: SAS Lag: 0-2	24-h avg: 30.77 ppb Range: 3.84-77.97 25th: 25.55 50th: 30.31 75th: 35.60 Number of monitors: 6	SO_2 PM10 CO O_3	Increment: 10.05 ppb (IQR) NO_2 alone: ≥20 EC: 1.193 [1.158, 1.230] lag 0-2 <20 EC: 0.972 [0.922, 1.024] lag 0-2 NO_2 + PM10: ≥20 EC: 1.183 [1.137, 1.231] lag 0-2 <20 EC: 0.920 [0.862, 0.982] lag 0-2 NO_2 + SO_2: ≥20 EC: 1.302 [1.254, 1.351] lag 0-2 <20 EC: 0.895 [0.837, 0.956] lag 0-2 NO_2 + CO: ≥20E C: 1.154 [1.102, 1.208] lag 0-2 <20 EC: 0.972 [0.892, 1.059] lag 0-2 NO_2 + O_3: ≥20 EC: 1.163 [1.126, 1.200] lag 0-2 <20 EC: 0.952 [0.901, 1.006] lag 0-2

REFERENCE, STUDY LOCATION, & PERIOD	OUTCOMES, DESIGN, & METHODS	MEAN LEVELS & MONITORING STATIONS	COPOLLUTANTS & CORRELATIONS	EFFECTS: RELATIVE RISK OR PERCENT CHANGE & CONFIDENCE INTERVALS (95%)
Ko et al. (2007a) Hong Kong Period of Study	Outcomes (ICD 9): Age groups analyzed: # of hospitals: Study Design: Statistical Analyses: Covariates: Statistical package: Lag:			
Lee et al. (2006) Hong Kong, China Period of Study: 1997-2002	Outcomes (ICD 9): asthma (493) Age groups analyzed: <18 N: 26,663 Study Design: Time-series Statistical Analyses: Poisson regression with GAM Covariates: Temperature, humidity, influenza, day of wk, holidays Statistical package: SAS v 8.02 Lag: 0, 1, 2, 3, 4, 5	24-h avg: 64.7 (20.9) μg/m^3 25th: 49.7 50th: 63.5 75th: 76.8 IQR: 27.1 Number of monitors: 10	SO_2; r = 0.49 PM10; r = 0.78 PM2.5; r = 0.75 O_3; r = 0.35	Increment: 27.1 μg/m^3 (IQR) Lag 0: 4.37% [2.51, 6.27] Lag 1: 5.88% [4.00, 7.70] Lag 2: 7.19% [5.37, 9.04] Lag 3: 9.08% [7.26, 10.93] Lag 4: 7.64% [5.84, 9.48] Lag 5: 6.40% [4.60, 8.22] NO_2 alone: 9.08% [7.26, 10.93] lag 3 NO_2 + SO_2 + PM10 + PM2.5 + O_3: 5.64% [3.21, 8.14] lag 3
Lee et al. (2007) Kaohsiung, Taiwan Period of Study: 1996-2003	Outcomes (ICD 9): COPD (490-492, 494, 496) Age groups analyzed: All # of hospitals: 63 N: 25,108 Study Design: Case-crossover Statistical Analyses: Conditional logistic regression Covariates: Temperature, humidity Season: Warm: >25 EC, cool: <25 EC Statistical package: SAS v 8.2 Lag: 0-2 cumulative avg	24-h avg: 27.2 ppb Range: 4.83-63.40 25th: 18.4 50th: 27.17 75th: 35.40 # of monitors: 6	SO_2 PM10 CO O_3	Increment : 17 ppb (IQR) NO_2 alone: ≥25 C: 1.241 [1.117, 1.379] lag 0-2 <25 C: 1.975 [1.785, 2.186] lag 0-2 NO_2 + PM10: ≥25 C: 1.083 [0.939, 1.249] lag 0-2 <25 C: 1.957 [1.709, 2.241] lag 0-2 NO_2 + SO_2: ≥25 C: 1.264 [1.127, 1.418] lag 0-2 <25 C: 2.378 [2.095, 2.700] lag 0-2 NO_2 + CO: ≥25 C: 0.984 [0.848, 1.141] lag 0-2 <25 C: 2.035 [1.746, 2.373] lag 0-2 NO_2 + O_3: ≥25 C: 1.076 [0.961, 1.205] lag 0-2 <25 C: 1.946 [1.755, 2.157] lag 0-2

REFERENCE, STUDY LOCATION, & PERIOD	OUTCOMES, DESIGN, & METHODS	MEAN LEVELS & MONITORING STATIONS	COPOLLUTANTS & CORRELATIONS	EFFECTS: RELATIVE RISK OR PERCENT CHANGE & CONFIDENCE INTERVALS (95%)
Wong et al. (1999) Hong Kong, China Period of Study: 1994-1995	Outcomes (ICD 9): All respiratory admissions (460-6, 471-8, 480-7, 490-6); Asthma (493), COPD (490-496), Pneumonia (480-7) Age groups analyzed: 0-4, 5-64, ≥65, all ages # of hospitals: 12 Study Design: Time-series Statistical Analyses: Poisson regression (followed APHEA protocol) Covariates: Trend, season, day of wk, holiday, temperature, humidity Statistical package: SAS 8.02 Lag: days 0-3 cumulative	Median 24-h NO_2: 51.39 μg/m^3 Range: 16.41, 122.44 25th: 39.93, 75th: 66.50 # of stations: 7, r = 0.68, 0.89	O_3 SO_2 PM10; r = 0.79	Increment = 10 μg/m^3 Overall increase in admissions: 1.020 [1.013, 1.028] lag 0-3 Respiratory Relative Risks (RR) 0-4 yrs: 1.020 [1.010, 1.030] lag 0-3 5-64yrs: 1.023 [1.011, 1.034] lag 0-3 >65 yrs: 1.024 [1.014, 1.035] lag 0-3 Cold Season: 1.004 [0.988, 1.020] NO_2 + high PM10: 1.009 [0.993, 1.025] NO_2 + high O_3: 1.013 [0.999, 1.026] Asthma: 1.026 [1.01, 1.042] lag 0-3 COPD: 1.029 [1.019, 1.040] lag 0-3 Pneumonia: 1.028 [1.015, 1.041] lag 0-3
Wong et al. (2001a) Hong Kong, China Period of Study: 1993-1994	Outcomes (ICD 9): Asthma (493) Age groups analyzed: #15 N: 1,217 # of hospitals: 1 Study Design: Time-series Statistical Analyses: Poisson regression (followed APHEA protocol) Covariates: Season, temperature, humidity Season: Summer (Jun-Aug), Autumn (Sep-Nov), Winter (Dec-Feb), Spring (Mar-May) Lag: 0, 1, 2, 3, 4, 5 days; and cumulative 0-2 and 0-3 days	24-h avg NO_2 mean: 43.3 μg/m^3, SD = 16.6 Range: 9, 106 μg/m^3 Autumn: 51.7 (17.6) Winter: 46.6 (15.5) Spring: 40.7 (11.8) Summer: 32.6 (13.7) # of stations: 9	PM10 SO_2	Increment: 10 μg/m^3 Asthma All yr: 1.08 p = 0.001 Autumn: 1.08 p = 0.017 Winter: NR Spring: NR Summer: NR

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

Table AX6.3-4. Respiratory Health Effects of Oxides of Nitrogen: Emergency Department Visits

STUDY	METHODS	MEAN LEVELS OF NO_2 & MONITORING STATIONS	COPOLLUTANT CORRELATIONS	EFFECTS AND INTERPRETATION: RELATIVE RISK & CONFIDENCE INTERVALS (95%)
UNITED STATES				
Jaffe et al. (2003) 3 cities, Ohio, (Cleveland, Columbus, Cincinnati) Period of Study: 7/91-6/96	Outcome (ICD-9): Asthma (493) Age Groups Analyzed: 5-34 Study Design: Time-series N: 4,416 Statistical Analyses: Poisson regression using a standard GAM approach Covariates: City, day of wk, wk, yr, minimum temperature, overall trend, dispersion parameter Season: Jun to Aug only Dose-response investigated: Yes Statistical Package: NR Lag: 0-3 days	Cincinnati: 24-h avg: 50 ppb, SD = 15 Cleveland: 24-h avg: 48 ppb, SD = 16 NO_2 was not monitored in Columbus due to relatively low levels	Cincinnati: PM10; r = 0.36 SO_2; r = 0.07 O_3; r = 0.60 Cleveland: PM_{10}; 0.34 SO_2; r = 0.28 O_3; r = 0.42 No multipollutant models were utilized.	Increment: 10 ppb Cincinnati: 6% [-1.0, 13] lag 1 Cleveland: 4% [-1, 8] lag 1 All cities: 3% [-1.0, 7] Attributable risk from NO_2 increment: Cincinnati 0.72 (RR 1.06) Cleveland 0.44 (RR 1.04) Regression diagnostics for Cincinnati showed significant linear trend during entire study period and for each wk (6/1-8/31). No trends observed for Cleveland. Regression Models assessing exposure thresholds showed a possible dose-response for NO_2 (percent increase after 40 ppb). No increased risk until minimum concentration of 40 ppb was reached.
Ito et al. (2007) New York, NY	Outcome (ICD-9): Asthma (493) Age Groups Analyzed: All ages Study Design: Time-series N: 1,460 Statistical Analyses: Poisson's Generalized Linear Model Covariates: temporal trends, day of wk, weather, over-dispersion Season: all year; warm (April to September), cold (October to March) Statistical Package: NR Lag: 0-1 day	All year 24-h avg: 31.1 SD = 8.7 Warm season 24-h avg: 30.4 SD = 8.8 Cold season 24-h avg: 31.8 SD = 31.8	$PM_{2.5}$: r = 0.91 O_3: r = 0.89 SO_2: r = 0.74 CO: r = 0.60	All Year: Increment : 24 ppb 24-h avg, lag 0 RR 1.14 (1.09, 1.19) Warm Months: Increment : 25 ppb 24-h avg, lag 0 RR 1.32 (1.23, 1.42)

STUDY	METHODS	MEAN LEVELS OF NO_2 & MONITORING STATIONS	COPOLLUTANT CORRELATIONS	EFFECTS AND INTERPRETATION: RELATIVE RISK & CONFIDENCE INTERVALS (95%)
NYDOH (2006) Bronx and Manhattan, NY Period of Study: 1/1999-11/2000	Outcome (ICD-9): Asthma (493) Age Groups Analyzed: All ages Study Design: Time-series Statistical Analyses: Poisson regression Covariates: temporal cycles, temperature, day of wk Season: All year Dose-response investigated: Yes Statistical Package: NR Lag: 0-4 days	24-h avg: 34 ppb	$PM_{2.5}$ SO_2 O_3	Increment : 20 ppb lag 0-4 24-h avg Bronx NO_2 : 1.06 (1.01, 1.10) $NO_2 + O_3$: 1.05 (1.00, 1.10) NO_2 + FRM $PM_{2.5}$: 1.03 (0.98, 1.08) $NO_2 + PM_{2.5}$ max : 1.02 (0.98, 1.08) $NO_2 + SO_2$: 1.01 (0.96, 1.07) Manhattan NO_2 : 0.97 (0.82, 1.14) $NO_2 + O_3$: 0.95 (0.80, 1.12) NO_2 + FRM $PM_{2.5}$: 0.90 (0.41, 1.10) $NO_2 + PM_{2.5}$ max : 0.90 (0.41, 1.11) $NO_2 + SO_2$: 0.97 (0.80, 1.17)
Norris* et al. (1999) Seattle, WA, United States Period of Study: 1995-1996	Outcome (ICD-9): Asthma (493) Age groups analyzed: <18 yrs Study Design: Time-series N: 900 ER visits Statistical Analyses: Semi parametric Poisson regression using GAM Covariates: day of wk, time trends, temperature, dew point temperature Dose-response investigated: Yes Statistical Package: NR Lag: 0,2 days	24 h: 20.2 ppb, SD = 7.1 IQR: 9 ppb 1-h max: 34.0 ppb, SD = 11.3 IQR: 12 ppb	CO; r = 0.66 PM; r = 0.66 SO_2; r = 0.25	Increment: IQR 24-h avg (9-ppb increment) RR 0.99 [0.90, 1.08] lag 2 1-h max (12-ppb increment) RR 1.05 [0.99, 1.12] lag 0 Age and hospital utilization (high and low) segregation (<5, 5-11, and 12-17 yrs) did not figure significantly in the association between emergency room visits and asthma.
Lipsett et al. (1997) Santa Clara County, California, United States Period of Study: 1988-1992	Outcome(s): Asthma ICD-9 Code(s): NR Age groups analyzed: All Study Design: Time-series Statistical Analyses: Poisson Regression; GEE repeated with GAM Covariates: Minimum temperature, day of study, precipitation, hospital, day of wk, yr, overdispersion parameter Season: Winters only Statistical Package: SAS, S Plus, Stata Lag: 0-5 days	NO_2 1-h mean: 69 ppb, SD = 28 Range: 29, 150 ppb	PM10; r = 0.82 COH; r = 0.8 No multipollutant model due to high correlation between pollutants	Same day NO_2 was associated with ER visits for asthma (≥ = 0.013, p = 0.024) Absence of association between lagged or multiday specifications of NO_2 and asthma ER visits (data not shown) suggest that same day association may be artifact of covariation with PM10.

STUDY	METHODS	MEAN LEVELS OF NO_2 & MONITORING STATIONS	COPOLLUTANT CORRELATIONS	EFFECTS AND INTERPRETATION: RELATIVE RISK & CONFIDENCE INTERVALS (95%)
Peel et al. (2005) Atlanta, GA, United States Period of Study: 1/93-8/2000	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, 2-18 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: 45.9 ppb, SD = 17.3	O_3; r = 0.42 SO_2; r = 0.34 CO; r = 0.68 PM10; r = 0.46 Evaluated multipollutant models (data not shown)	Increment: 20 ppb All respiratory RR 1.016 [1.006, 1.027] lag 0-2, 3-day moving avg Upper Respiratory Infection (URI) RR 1.019 [1.006, 1.031] lag 0-2, 3-day moving avg Asthma All: 1.014 [0.997, 1.030] lag 0-2, 3-day moving avg 2-18: 1.027 [1.005, 1.050] lag 0-2, 3-day moving avg Pneumonia RR 1.000 [0.983, 1.019] lag 0-2, 3-day moving avg COPD RR 1.035 [1.006, 1.065] lag 0-2, 3-day moving avg
Tolbert et al. (2000) Atlanta, GA, United States Period of Study: 1993-1995	Outcome(s) (ICD-9): Asthma (493), wheezing (786.09), Reactive airways disease (RADS) (519.1) Age groups analyzed: 0-16; 2-5, 6 10, 11-16 Study Design: Case-Control N: 5,934 Statistical Analyses: Ecological GEE analysis (Poisson model with logit link) and logistic regression Covariates: Day of wk, day of summer, yr, interaction of day of summer and yr Season: Summers only Statistical Package: SAS Lag: 1 day (a priori)	NO_X 1-h max continuous Mean: 81.7 ppb, SD = 53.8 Range = 5.35, 306 Number of stations: 2	PM10; r = 0.44 O_3; r = 0.51	Increment: 50 ppb Age 0-16: RR 1.012 [0.987, 1.039] lag 1
Tolbert et al. (2007) Atlanta, GA Period of Study: 1993-2004	Outcome(s) (ICD-9): Combined respiratory diseases (493, 786.07, 786.09, 491, 492, 496, 460-465, 477, 480-486, 466.1, 466.11, 466.19) Age groups analyzed: All Study Design: Time-series N: 1,072,429 Number of hospitals: 41 Statistical Analyses: Poisson regression with GLM Covariates: Day of wk, season, hospital, holiday, temperature, dew point Statistical Package: SAS vs. 9.1 Lag: 0-2 (a priori)	1-h max: 43.2 ppb Range: 1.0-181.0 10th: 22.0 25th: 31.0 50th: 41.0 75th: 54.0 90th: 66.0	PM10; r = 0.53 O_3; r = 0.44 SO_2; r = 0.36 CO; r = 0.70 $PM_{2.5}$; r = 0.47 PM10-2.5; r = 0.48 $PM_{2.5}$sulfate; r = 0.14 $PM_{2.5}$EC; r = 0.64 $PM_{2.5}$OC; r = 0.62 OHC; r = 0.24	Increment: 23 ppb (IQR) RR 1.015 [1.004, 1.025] lag 0-2

STUDY	METHODS	MEAN LEVELS OF NO_2 & MONITORING STATIONS	COPOLLUTANT CORRELATIONS	EFFECTS AND INTERPRETATION: RELATIVE RISK & CONFIDENCE INTERVALS (95%)
Cassino* et al. (1999) New York City, NY United States Period of Study: 1/1989-12/1993	Outcome(s) (ICD-9): Asthma (493); COPD (496), bronchitis (490), emphysema (492), bronchiectasis (494) Study Design: Time-series N: 1,115 # of Hospitals: 11 Statistical Analyses: Time-series regression, Poisson regression with GLM and GAM; Linear regression, Logistic regression with GEE Covariates: Season, trend, day of wk, temperature, humidity Statistical Package: S Plus and SAS Lag: 0-3 days	24-h avg NO_2: Mean: 45.0 ppb Median: 43 ppb 10% 31 ppb 25% 37 ppb 75% 53 ppb 90% 63 ppb	O_3 CO SO_2	Increment: 15 ppb (IQR) RR 0.97 [0.85, 1.09] lag 0 RR 1.04 [0.92, 1.18] lag 1 RR 1.06 [0.94, 1.2] lag 2 RR 0.97 [0.86, 1.09] lag 3

STUDY	METHODS	MEAN LEVELS OF NO_2 & MONITORING STATIONS	COPOLLUTANT CORRELATIONS	EFFECTS AND INTERPRETATION: RELATIVE RISK & CONFIDENCE INTERVALS (95%)
CANADA				
Bates et al. (1990) Vancouver Region, BC, Canada Period of Study: 7/1/1984-10/31/1986	Outcome(s) (ICD 9): Asthma (493); Pneumonia (480-486); Chronic bronchitis (491,492,496); Other respiratory (466) Age groups analyzed: All; 15-60 Study Design: # of Hospitals: 9 Statistical Analyses: Pearson correlation coefficients were calculated between asthma visits and environmental variables Season: Warm (May-Oct); Cool (Nov-Apr) Covariates: NR Statistical Package: NR Lag: 0, 1, 2	May-Oct SO_2 1-h max: Range: 0.0337-0.0458 ppm Nov-Apr Range: 0.0364-0.0455 ppm Number of stations: 11	May-Oct. O_3; r = 0.35 SO_2; r = 0.67 CoH; r = 0.53 SO4; r = 0.50 Nov-Apr O_3; r = 0.31 SO_2; r = 0.61 CoH; r = 0.69 SO4; r = 0.49	Correlation Coefficients: Warm Season (May-Oct) Asthma (1-14 yrs) NR lag 0 NR lag 1 NR lag 2 Respiratory (1-14) NR lag 0 NR lag 1 NR lag 2 Total (1-14) NR lag 0 NR lag 1 NR lag 2 Asthma (15-60 yrs) NR lag 0 NR lag 1 NR lag 2 Respiratory (15-60 yrs) r = 0.120 lag 0 p < 0.01 NR lag 1 NR lag 2 Total (15-60 yrs) NR lag 0 NR lag 1 NR lag 2 Asthma (61+ yrs) NR lag 0 NR lag 1 NR lag 2 Respiratory (61+ yrs) NR lag 0 NR lag 1 NR lag 2

STUDY	METHODS	MEAN LEVELS OF NO_2 & MONITORING STATIONS	COPOLLUTANT CORRELATIONS	EFFECTS AND INTERPRETATION: RELATIVE RISK & CONFIDENCE INTERVALS (95%)
Bates et al. (1990) (cont'd)				Total (61+ yrs) NR lag 0 NR lag 1 NR lag 2 Cool Season (Nov - Apr) Asthma (1-14 yrs) NR lag 0 NR lag 1 NR lag 2 Respiratory (1-14) NR lag 0 NR lag 1 NR lag 2 Total (1-14) NR lag 0 NR lag 1 NR lag 2 Asthma (15-60 yrs) NR lag 0 NR lag 1 NR lag 2 Respiratory (15-60 yrs) r = 0.120 lag 0 p < 0.01 NR lag 1 NR lag 2 Total (15-60 yrs) NR lag 0 NR lag 1 NR lag 2 Asthma (61+ yrs) NR lag 0
Bates et al. (1990) (cont'd)				NR lag 1 NR lag 2 Respiratory (61+ yrs) r = 0.132 lag 0 p < 0.01 r = 0.176 lag 1 p < 0.001 r = 0.178 lag 2 p < 0.001 Total (61+ yrs) NR lag 0 NR lag 1 NR lag 2

STUDY	METHODS	MEAN LEVELS OF NO_2 & MONITORING STATIONS	COPOLLUTANT CORRELATIONS	EFFECTS AND INTERPRETATION: RELATIVE RISK & CONFIDENCE INTERVALS (95%)
Kesten et al. (1995) Toronto, ON Period of Study: 7/1/1991-6/30/1992	Outcome(s): Asthma Age groups analyzed: All Study Design: Time-series N: 854 # of Hospitals: 1 Statistical analysis: Autoregressive technique Statistical Package: SAS v 6.04 Lag: 0,1	24-h avg NO_2: Range: 2.20-3.75 H 0.01 ppm	SO_2 O_3	Lag 0: "No statistically discernible regression coefficients" Lag 0-6: "No statistically discernible regression coefficients" Mean weekly indices lagged 1 wk behind weekly mean number of visits: p = 0.005
Stieb et al. (1996) St. John, New Brunswick, Canada Period of Study: 1984-1992	Outcome(s): Asthma (May-Sept only) ICD-9 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 NO_2 (ppb) Mean: 25.2 Range: 0, 120 95th: 60	O_3; r = 0.16 SO_2; r = -0.03 SO42-; r = 0.16 TSP; r = 0.15	Increment: NR $NO_2 + O_3$: ≥ = -0.0037 (0.0023) lag 2
Stieb* et al. (2000) Saint John, New Brunswick, Canada Period of Study: Retrospective: 7/92-6/94 Prospective: 7/94-3/96	Outcome(s): Asthma; COPD; Respiratory infection (bronchitis, bronchiolitis, croup, pneumonia); All respiratory ICD-9 Codes: NR Age groups analyzed: All Study Design: Time-series N: 19,821 Statistical Analyses: Poisson regression, GAM Covariates: Day of wk, selected weather variables in each model Seasons: All yr, summer only Dose-response investigated: Yes Statistical Package: S-Plus Lag: all yr = 0; summer only = 8	Annual mean: 8.9 ppb Spring/fall mean: 10.0 ppb Max: 82	O_3; r = -0.02 SO_2; r = 0.41 TRS; r = 0.16 PM10; r = 0.35 $PM_{2.5}$; r = 0.35 H+; r = 0.25 SO42-; r = 0.33 COH; r = 0.49 Assessed multipollutant models	Increment: 8.9 ppb (IQR) Respiratory visits: -3.8%, p = 0.070 lag 0 May to Sept: 11.5%, p = 0.17 lag 8 Multipollutant model (NO_2, O_3, SO_2) -3.6% [-7.5, 0.5] lag 0 Multipollutant model (ln(NO_2), O_3, SO_2 COH) May to Sep: 4.7% [0.8 to 8.6] lag 8 Non-linear effect of NO_2 on summertime respiratory visits observed and log transformation strengthened the association.

STUDY	METHODS	MEAN LEVELS OF NO_2 & MONITORING STATIONS	COPOLLUTANT CORRELATIONS	EFFECTS AND INTERPRETATION: RELATIVE RISK & CONFIDENCE INTERVALS (95%)
EUROPE and MIDDLE-EAST				
Sunyer et al. (1997) Multi-city, Europe (Barcelona, Helsinki, Paris, London) Period of Study: 1986-1992	Outcomes (ICD-9): Asthma (493) Age groups analyzed: <15, 15-64 Study Design: Time-series Statistical Analyses: APHEA protocol, Poisson regression, GEE; meta-analysis Covariates: Humidity, temperature, influenza, soybean, long-term trend, season, day of wk Season: Cool, Oct-Mar; Warm: Apr-Sep Statistical Package: NR Lag: 0,1,2,3 and cumulative 1-3	24-h median (range) ($\mu g/m^3$) Barcelona: 53 (5, 142) Helsinki: 35 (9, 78) London: 69 (27, 347) Paris: 42 (12, 157) # of stations: Barcelona: 3 London: 2 Paris: 4 Helsinki: 8	SO_2 black smoke O_3	Increment: 50 $\mu g/m^3$ of 24-h avg for all cities combined Asthma 15-64 yrs 1.029 [1.003, 1.055] lag 0-1 1.038 [1.008, 1.068] lag 0-3, cumulative <15 yrs 1.026 [1.006, 1.049] lag 2 1.037 [1.004, 1.067] lag 0-3, cumulative 1.080 [1.025, 1.140] - Winter only Two-pollutant models: NO_2/Black smoke 15-64 yrs 1.055 [1.005, 1.109] lag 0-1 15-64 yrs 1.088 [1.025, 1.155] cumulative 0-3 <15 yrs 1.036 [0.956, 1.122] NO_2/SO_2 <15 yrs 1.034 [0.988, 1.082]
Atkinson et al. (1999b) London, United Kingdom Period of Study: 1/92-1294	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	1-h max: 50.3 ppb, SD = 17.0 # of Stations: 3; r = 0.70, 0.96	NO_2, O_3 (8 h), SO_2 (24 h), CO (24 h), PM10 (24 h), BS	Increment: 36 ppb in 1-h max Single-pollutant model Asthma Only 0-14 yrs 8.97% [4.39, 13.74] lag 1 15-64 yrs 4.44% [0.14, 8.92] lag 1 All ages 4.37% [1.32, 7.52] lag 0 All Respiratory 0-14 yrs 2.17% [-0.49, 4.91] lag 1 15-64 yrs 1.87% [-0.69, 4.49] lag 2 ≥65 yrs 3.97% [0.51, 7.55] lag 0 All Ages 1.20% [-0.57, 3.00] Two-pollutant model Asthma Only 0-14 yrs: SO_2: 5.75% [0.39, 11.40] lag 1 CO: 8.34% [3.61, 13.29] lag 0 PM10: 6.95% [1.96, 12.19] lag 2 BS: 8.32% [3.56, 13.30] lag 2 O_3: 9.68% [5.02, 14.54] lag 0

STUDY	METHODS	MEAN LEVELS OF NO_2 & MONITORING STATIONS	COPOLLUTANT CORRELATIONS	EFFECTS AND INTERPRETATION: RELATIVE RISK & CONFIDENCE INTERVALS (95%)
Buchdahl et al. (1996) London, United Kingdom Period of Study: 3/1/92-2/28/93	Outcomes: Daily acute wheezy episodes ICD-9: NR Age groups analyzed: ≥16 Study Design: Case-control N: 1,025 cases, 4,285 controls Number of hospitals: 1 Statistical Analyses: Poisson regression Covariates: Season, temperature, wind speed Season: Spring (Apr-Jun), Summer (Jul-Sep), Autumn (Oct Dec), Winter (Jan-Mar) Statistical Package: Stata Lag: 0-7 days	NO_2 24-h yr round mean: 60 μg/m^3, SD = 17 IQR: 17 μg/m^3 Spring: 59 (19) Summer: 55 (18) Fall: 66 (13) Winter: 61 (17)	SO_2 r = 0.62 O_3 r = -0.18	Increment: 17 μg/m^3 (IQR) No adjustments to model RR 1.07 [1.01, 1.14] lag not specified Adjusted for temperature and season. RR 1.02 [0.96, 1.09] lag not specified
Thompson et al. (2001) Belfast, Northern Ireland Period of Study: 1993-1995	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 NO_2 (ppb): Mean: 19.20; SD = 7.90; IQR: 13.0, 23.0 NO_X (ppb): Mean: 35.50; SD = 25.50; IQR: 21.0, 40.0 NO (ppb): Mean: 16.4; SD = 19.70; IQR: 7.0, 17.0 Cold Season NO_2 (ppb): Mean: 23.30; SD = 9.00; IQR: 18.0, 28.0 NO_X (ppb): Mean: 50.50; SD = 50.50; IQR: 26.0, 56.0 NO (ppb): Mean: 27.30; SD = 43.10; IQR: 9.0, 28.0	NO_2: PM10; r = 0.77 SO_2; r = 0.82 NO_X; r = 0.93 NO; r = 0.84 O_3; r = -0.62 CO; r = 0.69 Benzene; r = 0.83 NO_X: PM10; r = 0.73 SO_2; r = 0.83 NO_2; r = 0.92 NO; r = 0.97 O_3; r = -0.73 CO; r = 0.74 Benzene; r = 0.86 NO: PM10; r = 0.65 SO_2; r = 0.76 NO_X; r = 0.97 NO_2; r = 0.84 O_3; r = -0.76 CO; r = 0.71 Benzene; r = 0.82	NO_2 Increment: 10 ppb NO_X Increment: per doubling NO Increment: per doubling NO_2 Lag 0 RR 1.08 [1.03, 1.13] Lag 0-1 RR 1.11 [1.05, 1.17] Lag 0-2 RR 1.10 [1.04, 1.17] Lag 0-3 RR 1.12 [1.03, 1.20] Warm only Lag 0-1 RR 1.14 [1.04, 1.26] Cold only Lag 0-1 RR1.10 [1.03, 1.17] Adjusted for Benzene Lag 0-1 RR 0.99 [0.87, 1.13] NO_X Lag 0 RR 1.07 [1.02, 1.12] Lag 0-1 RR 1.10 [1.05, 1.16] Lag 0-2 RR 1.10 [1.03, 1.17] Lag 0-3 RR 1.11 [1.04, 1.20] Warm only Lag 0-1 RR 1.13 [1.03, 1.24] Cold only Lag 0-1 RR 1.09 [1.02, 1.16] Adjusted for Benzene Lag 0-1 RR 0.89 [0.77, 1.03] NO Lag 0 RR 1.04 [1.01, 1.07] Lag 0-1 RR 1.07 [1.03, 1.11] Lag 0-2 RR 1.06 [1.02, 1.11] Lag 0-3 RR 1.08 [1.02, 1.14] Warm only Lag 0-1 RR 1.08 [1.01, 1.16] Cold only Lag 0-1 RR 1.06 [1.01, 1.11] Adjusted for Benzene Lag 0-1 RR 0.93 [0.85, 1.01]

STUDY	METHODS	MEAN LEVELS OF NO_2 & MONITORING STATIONS	COPOLLUTANT CORRELATIONS	EFFECTS AND INTERPRETATION: RELATIVE RISK & CONFIDENCE INTERVALS (95%)
Boutin-Forzano et al. (2004) Marseille, France Period of Study: 4/97-3/98	Outcome(s): Asthma ICD-9 Code(s): NR Age groups analyzed: 3-49 Study Design: Case-crossover N: 549 Statistical Analyses: Logistic regression Covariates: Minimal daily temperature, maximum daily temperature, minimum daily relative humidity, maximum daily relative humidity, day of wk Statistical Package: NR Lag: 0-4 days	Mean NO_2: 34.9 μg/m^3 Range: 3.0, 85	SO_2; r = 0.56 O_3; r = 0.58	Increment: 10 μg/m^3 Increased ER visits OR 1.0067 [0.9960, 1.0176] lag 0
Castellsague et al. (1995) Barcelona, Spain Period of Study: 1986-1989	Outcome(s): Asthma ICD-9 Code(s): NR Age groups analyzed: 15-64 Study Design: Time-series # of Hospitals: 4 Statistical Analyses: Poisson regression Covariates: long-time trend, day of wk, temperature, relative humidity, dew point temperature Seasons: Winter: Jan-Mar; Summer: Jul-Sep Dose-Response investigated: Yes Statistical Package: NR Lag: 0, 1-5 days and cumulative Summer: lag 2 days Winter: lag 1 day	Mean NO_2 (μg/m^3) Summer: 104.0 Winter: 100.8 IQR (μg/m^3): Summer: 48 Winter: 37 # of Stations: 15 manual, 3 automatic	SO_2; r = NR O_3; r = NR	Increment: 25 μg/m^3 Seasonal differences Summer: 1.071 [1.101, 1.130] lag 0-5 cumulative 1.045 [1.009, 1.081] lag 0 Winter: 1.072 [1.010, 1.137] lag 0-2 cumulative 1.056 [1.011, 1.104] lag 0 Asthma visits increased across quartiles of NO_2 in summer; a positive but less consistent increase across quartiles was observed in winter.
Tobías et al. (1999) Barcelona, Spain Period of Study: 1986-1989	Outcome(s): Asthma ICD-9: NR Age groups analyzed: >14 Study Design: Time-series Statistical Analyses: Poisson regression, followed APHEA protocol Covariates: temperature, humidity, long-term trend, season, day of wk Statistical Package: NR Lag: NR	24-h avg NO_2 μg/m^3 Non-epidemic days: 54.7 (20.8) Epidemic days: 58.9 (26.7)	BS SO_2 O_3	≥ H 104 (SE H 104) using Std Poisson Without modeling asthma epidemics: 11.25 (11.79) p > 0.1 Modeling epidemics with 1 dummy variable: 1.18 (7.59) p > 0.1 Modeling epidemics with 6 dummy variables: 13.60 (7.79) p < 0.1 Modeling each epidemic with dummy variable: 14.40 (7.44) p < 0.1 ≥ H 104 (SE H 104) using Autoregressive Poisson Without modeling asthma epidemics: 13.65 (11.81) p > 0.1 Modeling epidemics with 1 dummy variable: 3.28 (7.77) p > 0.1 Modeling epidemics with 6 dummy variables: 16.49 (8.01) p < 0.05 Modeling each epidemic with dummy variable: 18.18 (8.01) p < 0.1

STUDY	METHODS	MEAN LEVELS OF NO_2 & MONITORING STATIONS	COPOLLUTANT CORRELATIONS	EFFECTS AND INTERPRETATION: RELATIVE RISK & CONFIDENCE INTERVALS (95%)
Galán et al. (2003) Madrid, Spain Period of Study: 1995-1998	Outcome(s) (ICD-9): Asthma (493) Age groups analyzed: All Study Design: Time-series N: 4,827 Statistical Analyses: Poisson regression, (1) classic APHEA protocol and (2) GAM with stringent criteria Covariates: trend, yr, season, day of wk, holidays, temperature, humidity, influenza, acute respiratory infections, pollen Statistical Package: NR Lag: 0-4 days	24-h mean: 67.1 μg/m^3 SD = 18.0 IQR: 20.5 Max: 147.5 # of Stations: 15	PM10; r = 0.717 SO_2; r = 0.610 O_3; r = -0.209	Increment: 10 μg/m^3 Asthma: RR 1.013 [0.991, 1.035] lag 0 RR 1.011 [0.989, 1.032] lag 1 RR 1.013 [0.992, 1.034] lag 2 RR 1.033 [1.013, 1.054] lag 3 RR 1.026 [1.006, 1.047] lag 4 Multipollutant model: NO_2/SO_2 1.031 [1.004, 1.059] lag 3 NO_2/PM10 1.001 [0.971, 1.031] lag 3 NO_2/Pollen 1.024 [1.004, 1.044] lag 3 NO_2/Pollen/O_3 1.024 [1.005, 1.045] Poisson NO_2/Pollen/O_3 1.022 [1.005, 1.040] GAM
Tenías et al. (1998) Valencia, Spain Period of Study: 1993-1995 Seasons: Cold: Nov-Apr Warm: May-Oct	Outcome(s): Asthma ICD-9 Code(s): NR Age groups analyzed: >14 Study Design: Time-series N: 734 Statistical Analyses: Poisson regression, APHEA protocol Covariates: Seasonality, temperature, humidity, long-term trend, day of wk, holidays, influenza Seasons: Cold: Nov-Apr; Warm: May-Oct Dose-Response Investigated: Yes Statistical Package: NR Lag: 0-3 days	24 h: 57.7 μg/m^3 Cold: 55.9 Warm: 59.4 1-h max: 101.1 μg/m^3 Cold: 97.3 Warm: 102.8 # of Stations: 2	24 h: O_3; r = -0.304 SO_2 (24 h); r = 0.265 SO_2 (1 h); r = 0.261 1 h: O_3; r = -0.192 SO_2 (24 h); r = 0.199 SO_2 (1 h); r = 0.201	Increment: 10 μg/m^3 NO_2 24-h avg All yr 1.076 [1.020, 1.134] lag 0 Cold: 1.083 [1.022, 1.148] lag 0 Warm: 1.066 [0.989, 1.149] lag 0 NO_2 1-h max All yr 1.037 [1.008, 1.066] lag 0 Cold: 1.034 [1.004, 1.066] lag 0 Warm: 1.044 [1.002, 1.088] lag 0
Tenías et al. (2002) Valencia, Spain Period of Study: 1994-1995	Outcome(s): COPD ICD-9 Code(s): NR Age groups analyzed: >14 Study Design: Time-series N: 1,298 # of Hospitals: 1 Statistical Analyses: Poisson regression, APHEA protocol; basal models and GAM Covariates: Seasonality, annual cycles, temperature, humidity, day of wk, feast days Seasons: Cold: Nov-Apr; Warm: May-Oct Dose-Response Investigated: Yes Statistical Package: NR Lag: 0-3 days	NO_2 24-h avg: 7.7 μg/m^3; Range: 12, 135 1-h max: 100.1 μg/m^3; Range: 31, 305 # of Stations: 6 manual and 5 automatic; r = 0.87	BS; r = 0.246 SO_2; r = 0.194 CO; r = 0.180 O_3; r = -0.192	Increment: 10 μg/m^3 24-h avg NO_2 All yr RR 0.979 [0.943, 1.042] lag 0 Cold: 24-h avg: RR 0.991 [0.953, 1.030] lag 0 Warm: 24-h avg: RR 0.961 [0.900, 1.023] lag 0 1-h max NO_2 All yr RR 0.986 [0.966, 1.007] lag 0 Cold: 24-h avg: RR 0.996 [0.975, 1.018] lag 0 Warm: 24-h avg: RR 0.968 [0.935, 1.003] lag 0 Possibility of a linear relationship between pollution and risk of emergency cases could not be ruled out.

STUDY	METHODS	MEAN LEVELS OF NO_2 & MONITORING STATIONS	COPOLLUTANT CORRELATIONS	EFFECTS AND INTERPRETATION: RELATIVE RISK & CONFIDENCE INTERVALS (95%)
Migliaretti et al. (2005) Turin, Italy Period of Study: 1997-1999	Outcome (ICD-9): Asthma (493) Age groups analyzed: <15, 15-64, >64 Study Design: Case-Control Controls: age matched with other respiratory disease (ICD-9: 460 487, 490-2, 494-6, 500-19) or heart disease (ICD-9: 390-405, 410-429) N: cases = 1,401 controls = 201,071 Statistical Analyses: Logistic regression Covariates: Seasonality, temperature, humidity, solar radiation, wind velocity, day of wk, holiday, gender, age, education level Seasons: Cold: Oct-Mar; Warm: Apr-Sep Statistical Package: NR Lag: 0-3 days and cumulative	All Participants: 24-h mean: 112.7 μg/m^3, SD = 30.2, Median: 107.7 Cases: 24-h mean: 117.1 μg/m^3, SD = 30.0, Median: 113.0 Controls: 24-h mean: 112.7 μg/m^3, SD = 30.2, Median: 107.7 # of Stations: 10; r = 0.79	TSP; r = 0.8 Two-pollutant model adjusted for TSP	Increment: 10 μg/m^3 Single-pollutant (NO_2): <15 yrs 2.3% [0.3, 4.40] 15-64 yrs 3.10% [-0.01, 7.70] >64 yrs 7.70% [0.20, 15.20] All ages 2.40% [0.5, 4.30] Copollutant (NO_2 and TSP) <15 yrs 1.71% [-0.02, 5.00] 15-64 yrs 1.20% [-0.06, 6.50] >64 yrs 0.91% [-0.08, 5.91] All ages 1.10% [-0.02, 3.82]
Bedeschi et al. (2007) Reggio Emilia, Italy Period of Study: 03/2001-03/2002	Outcome (ICD-9): Respiratory disorders, asthma or asthma-like disorders, other respiratory disorders Age groups analyzed: <15 Study Design: Time-series N: 854 children, 1051 visits Statistical Analyses: Poisson regression with GAM Covariates: Weekday, festivity day, humidity, precipitation, temperature, flu epidemic, pollen concentrations Statistical Package: R software Lag: 0-5 days and cumulative	24-h avg: NO_2 (μg/m^3) Mean: 49 (13.8) Range: 21.6-107.5 Median: 47.5	SO_2; r = 0.56 CO;r = 0.77 TSP; r = 0.58 PM10; r = 0.57 O_3; r = -0.50	Increment: 10 μg/m^3 All Respiratory Disorders: Italians: 9% [1.0, 17.6] lag 4 Foreigners: 17.6% [3.9, 33.0] lag 4 All: 11.0% [3.6, 18.8] lag 4
Vigotti et al. (2007) Pisa, Italy Period of Study: 2000	Outcome (ICD-9): Respiratory complaints (493, 468, 466) Age groups analyzed: <10, >65 Study Design: Ecologic N: 966 Number of hospitals: 1 Statistical Analyses: Robust poisson regression in GAM model Covariates: Day of study, temperature, humidity, rain, influenza epidemics, day of wk, holidays Statistical Package: NR Lag: up to 5 d	24-h avg: 45.6 (11.0) μg/m^3 Range: 21.3-74.0 50th: 44.8 Number of monitors: 3	PM10; r = 0.58 CO; r = 0.62	Increment: 10 μg/m^3 Children: 1.118 [1.014, 1.233] lag 0-2 65+: 1.06 [0.967, 1.162] lag 0-2

STUDY	METHODS	MEAN LEVELS OF NO_2 & MONITORING STATIONS	COPOLLUTANT CORRELATIONS	EFFECTS AND INTERPRETATION: RELATIVE RISK & CONFIDENCE INTERVALS (95%)
Pantazopoulou et al. (1995) Athens, Greece Period of Study : 1988	Outcomes: All respiratory visits ICD-9: NR Age groups analyzed: All ages Study Design: Time-series N: 213,316 Number of hospitals: 14 Statistical Analyses: Multiple linear regression Covariates: Season, day of wk, holiday, temperature, relative humidity Season: Warm (3/22-9/21), Cold (1/1-3/21 and 9/22-12/31) Lag: NR	NO_2 24-h avg Winter: 94 µg/m^3, SD = 25 5th: 59, 50th: 93, 95th: 135 Summer: 111 µg/m^3, SD = 32 5th: 65, 50th: 108, 95th: 173 # of stations: 2	CO BS	Increment: 76 µg/m^3 in winter and 108 µg/m^3 in summer (95th-5th) Respiratory disease admissions Winter: Percent increase: ≥ = 66.8 [19.6, 113.9] Summer: Percent increase: ≥ = 21.2 [-35.1, 77.5]
Garty et al. (1998) Tel Aviv, Israel 1993	Outcome(s): Asthma ICD-9 Code(s): NR Age groups analyzed: 1-18 Study Design: Descriptive study with correlations N: 1,076 Statistical Analyses: Pearson correlation and partial correlation coefficients Covariates: Maximum and minimum ambient temperatures, relative humidity, and barometric pressure Statistical Package: Statistix	24-h mean of NO_X (estimated from histogram): 60 µg/m^3; Range: 50, 250		Correlation between NO_X and ER visits for asthma: All Yr: Daily data r = 0.30 Running mean for 7 days r = 0.62 Excluding Sept: Daily data r = 0.37 Running mean for 7 days r = 0.74 38% of variance in number of ER visits explained by fluctuations in NO_X. Increases to 55% when Sept. is omitted from analyses.
LATIN AMERICA				
Farhat* et al. (2005) São Paulo, Brazil Period of Study: 1996-1997	Outcome(s) (ICD-9): 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	Mean: 125.3 µg/m^3 SD = 51.7 IQR: 65.04 µg/m^3 # of Stations: 6	PM10; r = 0.83 SO_2; r = 0.66 CO; r = 0.59	Increment: IQR of 65.04 µg/m^3 Single-pollutant models (estimated from graphs): LRD ~17.5% [12.5, 24] Multipollutant models: Adjusted for: PM10 16.1% [5.4, 26.8] 4 day avg SO_2 24.7% [18.2, 31.3] 4 day avg CO 19.2% [11.8, 26.6] 4 day avg Multipollutant model 18.4% [3.4, 33.5] 4 day avg

STUDY	METHODS	MEAN LEVELS OF NO_2 & MONITORING STATIONS	COPOLLUTANT CORRELATIONS	EFFECTS AND INTERPRETATION: RELATIVE RISK & CONFIDENCE INTERVALS (95%)
Martins* et al. (2002) São Paulo, Brazil Period of Study: 5/96-9/98	Outcome(s) (ICD-10): Chronic Lower Respiratory Disease (CLRD) (J40-J47); includes chronic bronchitis, emphysema, other COPDs, asthma, bronchiectasia Age groups analyzed: >64 Study Design: Time-series N: 712 # of Hospitals: 1 Catchment area: 13,163 total ER visits Statistical Analyses: Poisson regression and GAM - no mention of more stringent criteria Covariates: Weekdays, time, minimum temperature, relative humidity, daily number of non-respiratory emergency room visits made by elderly Statistical Package: S-Plus Lag: 2-7 days and 3 day moving avgs	NO_2 max 1-h avg ($\mu g/m^3$): 117.6, SD = 53.0, Range: 32.1, 421.6 IQR: 62.2 $\mu g/m^3$ # of Stations: 4	O_3; r = 0.44 SO_2; r = 0.67 PM10; r = 0.83 CO; r = 0.62	Increment: IQR of 62.2 $\mu g/m^3$ Percent increase: 4.5% [-6.5, 15] lag 3 day moving avg (estimated from graph)

STUDY	METHODS	MEAN LEVELS OF NO_2 & MONITORING STATIONS	COPOLLUTANT CORRELATIONS	EFFECTS AND INTERPRETATION: RELATIVE RISK & CONFIDENCE INTERVALS (95%)
Ilabaca et al. (1999) Santiago, Chile Period of Study: 2/1/95 – 8/31/96	Outcome(s) (ICD-9): Upper respiratory illness (460 465, 487); Days: 578 Lower respiratory illness (466, 480-486, 490-494, 496, 519.1, 033.9); Pneumonia (480 486) Age groups analyzed: <15 Study Design: Time-series # of Hospitals: 1 Statistical Analyses: Poisson regression Covariates: Long-term trend, season, day of wk, temperature, humidity, influenza epidemic Season: Warm (Sep-Apr), Cool (May-Aug) Statistical Package: NR Lag: 0-3 days	24-h avg NO_2: Warm: Mean: 97.0 Median: 91.5 SD = 34.6 Range: 37.2, 246 5th: 54.3 95th: 163.0 Cool: Mean: 160.2 Median: 154.4 SD = 59.5 Range: 60.1, 397.5 5th: 74.4 95th: 266.0 # of stations: 4, r = 0.70, 0.88	Warm: SO_2; r = 0.66 O_3; r = 0.15 PM10; r = 0.71 $PM_{2.5}$; r = 0.70 Cool: SO_2; r = 0.74 O_3; r = 0.22 PM10; r = 0.82 $PM_{2.5}$; r = 0.80	Increment: IQR All respiratory Cool Lag 2 IQR: 56.4 RR 1.0378 [1.0211, 1.0549] Lag 3 IQR: 56.4 RR 1.0294 [1.0131, 1.0460] Lag avg 7 IQR: 33.84 RR 1.0161 [1.0000, 1.0325] Warm Lag 2 IQR: 30.08 RR 1.0208 [0.9992, 1.0428] Lag 3 IQR: 30.08 RR 1.0395 [1.0181, 1.0612] Lag avg 7 IQR: 22.56 RR 1.0251 [0.9964, 1.0548] Upper respiratory Cool Lag 2 IQR: 56.4 RR 1.0569 [1.0339, 1.0803] Lag 3 IQR: 56.4 RR 1.0318 [1.0095, 1.0545] Lag avg 7 IQR: 33.84 RR 1.0177 [0.9960, 1.0399] Warm Lag 2 IQR: 30.08 RR 1.0150 [0.9881, 1.0426] Lag 3 IQR: 30.08 RR 1.0425 [1.0157, 1.0699] Lag avg 7 IQR: 22.56 RR 0.9944 [0.9591, 1.0311] Pneumonia Cool Lag 2 IQR: 56.4 RR 1.0824 [1.0300, 1.1374] Lag 3 IQR: 56.4 RR 1.0768 [1.0273, 1.1287] Lag avg 7 IQR: 33.84 RR 1.0564 [1.0062, 1.1092] Warm Lag 2 IQR: 30.08 RR 1.1232 [1.0450, 1.2072] Lag 3 IQR: 30.08 RR 1.0029 [0.9332, 1.0779] Lag avg 7 IQR: 22.56 RR 1.1084 [1.0071, 1.2200]

STUDY	METHODS	MEAN LEVELS OF NO_2 & MONITORING STATIONS	COPOLLUTANT CORRELATIONS	EFFECTS AND INTERPRETATION: RELATIVE RISK & CONFIDENCE INTERVALS (95%)
Lin et al. (1999) São Paulo, Brazil Period of Study: May 1991 - Apr 1993 Days: 621	Outcome(s): Respiratory disease, Upper respiratory illness, Lower respiratory illness, Wheezing ICD-9 Code(s): NR Age groups analyzed: <13 Study Design: Time-series # of Hospitals: 1 Statistical Analyses: Gaussian and Poisson regression Covariates: Long-term trend, seasonality, day of wk, temperature, humidity Statistical Package: NR Lag: 5-day lagged moving avgs	NO_2 µg/m^3: Mean: 163 SD = 85 Range: 2, 688 Number of stations: 3	SO_2; r = 0.38 CO; r = 0.35 PM10; r = 0.40 O_3; r = 0.15	Increment: NR All respiratory illness NO_2 alone: RR 1.003 [1.001, 1.005] 5-day moving avg NO_2 + PM10 + O_3 + SO_2 + CO: RR 0.996 [0.994, 0.998] Lower respiratory illness NO_2 alone: RR 0.999 [0.991, 1.007] 5-day moving avg NO_2 + PM10 + O_3 + SO_2 + CO: RR 0.990 [0.982, 0.998] Upper respiratory illness NO_2 alone: RR 1.003 [0.999, 1.007] 5-day moving avg NO_2 + PM10 + O_3 + SO_2 + CO: RR 0.996 [0.992, 1.000] Wheezing NO_2 alone: RR 0.996 [0.990, 1.002] 5-day moving avg NO_2 + PM10 + O_3 + SO_2 + CO: RR 0.991 [0.983, 0.999]
ASIA				
Kim et al. (2007) Seoul, Korea Period of Study: 2002	Outcome(s) (ICD-10): Asthma (J45, J46) Age groups analyzed: All Study Design: Case-crossover N: 92,535 Statistical Analyses: Conditional logistic regression Covariates: Time trend, weather conditions, seasonality Statistical Package: NR Lag: 0, 1, 2, 3, 4, 2-4 ma	24-h avg: 36.0 (14.7) ppb Range: 2.3-108.0 50th: 34.3 IQR: 20.1	PM10 CO SO_2 O_3	Increment: 20.1 ppb Stratified by individual SES: Highest SES quintile: 1.06 [1.02, 1.10] lag 2-4 2nd Quintile: 1.06 [1.02, 1.09] lag 2-4 3rd Quintile: 1.03 [0.99, 1.06] lag 2-4 4th Quintile: 1.06 [1.02, 1.10] lag 2-4 Lowest SES quintile: 1.05 [1.00, 1.10] lag 2-4 Stratified by Regional SES: Highest SES quintile: 0.96 [0.90, 1.02] lag 2-4 2nd Quintile: 1.08 [1.04, 1.13] lag 2-4 3rd Quintile: 1.03 [1.00, 1.07] lag 2-4 4th Quintile: 1.06 [1.02, 1.10] lag 2-4 Lowest SES quintile: 1.06 [1.02, 1.09] lag 2-4 Overall: 1.05 [1.03, 1.06] Relative Effect Modification for Interaction Terms: Stratified by individual SES H air pollution: Highest SES quintile: 1.00 [referent] 2nd Quintile: 0.99 [0.95, 1.04] 3rd Quintile: 0.96 [0.92, 1.01] 4th Quintile: 1.00 [0.95, 1.05] Lowest SES quintile: 0.99 [0.93, 1.05] Stratified by Regional SES H air pollution:
Kim et al. (2007) (cont'd)				Highest SES quintile: 1.00 [referent] 2nd Quintile: 1.11 [1.03, 1.20] 3rd Quintile: 1.07 [1.00, 1.15] 4th Quintile: 1.09 [1.02, 1.17] Lowest SES quintile: 1.09 [1.02, 1.16]

STUDY	METHODS	MEAN LEVELS OF NO_2 & MONITORING STATIONS	COPOLLUTANT CORRELATIONS	EFFECTS AND INTERPRETATION: RELATIVE RISK & CONFIDENCE INTERVALS (95%)
Sun et al. (2006) Central Taiwan Period of Study: 2004	Outcome(s) (ICD-9): asthma (493) Age groups analyzed: <16, 16-55 Study Design: Cross-sectional Number of hospitals: 4 Statistical Analyses: Multiple correlation coefficients/multiple regression analysis Covariates: Statistical Package: SPSS v 12.0 Lag:	Number of monitors: 11	SO_2 O_3 CO PM10	Children: r = 0.72, p = 0.004 Adults: r = 0.428, p = 0.083 Emergency visits for asthma increased with increased levels of NO_2 for children but not for adults.
Chew et al. (1999) Singapore Period of Study: 1990-1994	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: 18.9 μg/m^3, SD = 15.0, Max < 40 # of Stations: 15	SO_2; r = -0.22 O_3; r = 0.17 TSP; r = 0.23	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 = 0.10 r = 0.09 p = 0.0019 p < 0.001 Lag 1 r = 0.12 r = 0.04 p < 0.001 p = 0.0014 Lag 2 r = 0.14 r = 0.03 p < 0.001 p = 0.0066
Hwang and Chan (2002) Taiwan Period of Study: 1998	Outcome(s) (ICD-9): Lower Respiratory Disease (LRD) (466, 480-6) including acute bronchitis, acute bronchiolits, pneumonia Age groups analyzed: 0-14, 15-64, ≥65, all ages Study Design: Time-series Catchment area: Clinic records from 50 communities Statistical Analyses: Linear regression, GLM Covariates: Temperature, dew point temperature, season, day of wk, holiday Statistical Package: NR Lag: 0,1,2 days and avgs	24-hr avg: 23.6 ppb, SD = 5.4, Range: 13.0, 34.1	SO_2 PM10 O_3 CO No correlations for individual pollutants Colinearity of pollutants prevented use of multipollutant models	Increment: 10% change in NO_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 1.3% [1.0, 1.6] lag 0 15-64 yrs 1.5% [1.3, 1.8] lag 0 ≥65 yrs 1.8% [1.4, 2.2] lag 0 All ages 1.4% [1.2, 1.6] lag 0

STUDY	METHODS	MEAN LEVELS OF NO_2 & MONITORING STATIONS	COPOLLUTANT CORRELATIONS	EFFECTS AND INTERPRETATION: RELATIVE RISK & CONFIDENCE INTERVALS (95%)
Tanaka et al. (1998) Kushiro, Japan Period of Study: 1992-1993	Outcome(s): Asthma ICD-9 Code(s): NR Age groups analyzed: 15-79 Study Design: Time-series N: 102 # of Hospitals: 1 Statistical Analyses: Poisson regression Covariates: Temperature, vapor pressure, barometric pressure, relative humidity, wind velocity, wind direction at maximal velocity Statistical Package: NR	NO_2 24-h avg 9.2 ± 4.6 ppb in fog 11.5 ± 5.7 in fog free days Max NO_2 24-h avg <30 ppb	NO_2; r = NR SO_2; r = NR SPM (TSP); r = 0.70 O_3; r = NR	Increment: 15 ppb Nonatopic OR 0.62 [0.45, 0.84] Atopic OR 0.81 [0.67, 0.97]

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

Table AX6.3-5. Respiratory Health Effects of Oxides of Nitrogen: General Practitioner/Clinic Visits

REFERENCE, STUDY LOCATION, & PERIOD	OUTCOMES, DESIGN, & METHODS	MEAN LEVELS & MONITORING STATIONS	COPOLLUTANTS CORRELATIONS	EFFECTS: RELATIVE RISK & CONFIDENCE INTERVALS (95%)
NORTH AMERICA				
Sinclair and Tolsma (2004) Atlanta, GA Period of Study: 8/1998-8/2000	Outcome(s) (ICD9): Asthma (493), URI (460-466, 477), LRI (466.1, 480-486) Age groups analyzed: <18, >18 Study Design: Time-series N: 232,350 Statistical Analyses: Poisson regression with GLM Covariates: Season, day of wk, federal holiday, study month, long-term trend Statistical Package: SAS v 8.02 Lag: 0-2, 3-5, 6-8	1-h max: 51.22 (18.54) ppb Monitors: 1 ARIES monitor in downtown Atlanta	$PM_{2.5}$, PM10-2.5 PM10 $PM_{2.5}$ components PMuf Polar VOCs O_3 SO_2	No NO_2 results presented because they were not statistically significant for any lag periods examined.

REFERENCE, STUDY LOCATION, & PERIOD	OUTCOMES, DESIGN, & METHODS	MEAN LEVELS & MONITORING STATIONS	COPOLLUTANTS CORRELATIONS	EFFECTS: RELATIVE RISK & CONFIDENCE INTERVALS (95%)
Hernández-Garduño et al. (1997) Mexico City, Mexico Period of Study: May 15, 1992 - January 31, 1993	Outcome(s): Respiratory illness ICD9: NR Age groups analyzed: <15, 15+, all ages (0-92) Study Design: Time-series N: 24,113 Number of Clinics: 5 Statistical Analyses: Cross-correlation, linear regression and autoregressive error model analyses Covariates: Long-term trend, day of wk, temperature, humidity Statistical Package: SAS Lag: 0-6	Number of Stations: 5	SO_2 O_3 CO NO_X	Increment: Max NO_2 concentration of all days-Mean NO_2 concentration of all days <14 yrs: NO_2 lag 0: RR 1.29 ± 0.09 ($p < 0.01$) NO_2 lag 6: RR 1.18 ± 0.09 ($p > 0.05$) 15+ yrs: NO_2 lag 0: RR 1.14 ± 0.07 ($p < 0.05$) NO_2 lag 6: RR 1.10 ± 0.06 ($p > 0.05$) All ages: NO_2 lag 0: RR 1.43 ± 0.15 ($p < 0.01$) NO_2 lag 6: RR 1.29 ± 0.15 ($p > 0.05$)
Villeneuve et al. (2006) Toronto, ON, Canada Period of Study: 1995-2000 Days: 2,190	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: 25.4 ppb, SD = 7.7 IQR: 10.3 ppb, Range 9.2, 71.7 Number of stations: 9	SO_2 O_3 CO $PM_{2.5}$ PM10-2.5 PM10	Increment: 10.3 ppb (IQR) All results estimated from Stick Graph: All Yr: Mean Increase: 1.9% [-0.2, 3.8] lag 0 Warm: Mean Increase: 0.1% [-3.2, 3.8] lag 0 Cool: Mean Increase: 1.4% [0.0, 5.9] lag 0

REFERENCE, STUDY LOCATION, & PERIOD	OUTCOMES, DESIGN, & METHODS	MEAN LEVELS & MONITORING STATIONS	COPOLLUTANTS CORRELATIONS	EFFECTS: RELATIVE RISK & CONFIDENCE INTERVALS (95%)
EUROPE				
Hajat et al. (1999) London, United Kingdom Period of Study: 1992-1994	Outcome (ICD9): Asthma (493); Lower respiratory disease (464, 466, 476, 480-3, 490-2, 485-7, 4994-6, 500, 503-5, 510-5) Age groups analyzed: 0-14; 15-64; 65+; all ages Study Design: Time-series analysis Statistical Analysis: Poisson regression, APHEA protocol Covariates: Long-term trends, seasonality, day of wk, temperature, humidity Seasons: Warm, Apr-Sep; Cool, Oct-Mar; All yr Dose-response investigated?: Yes Statistical package: SAS Lag: 0-3 days, cumulative	All yr 24-h avg: 33.6 ppb, SD = 10.5 Warm: 32.8 (19.8) Cool: 34.5 (10.1) 10th-90th all yr percentile: 24 ppb	SO_2; r = 0.61 BS; r = 0.70 CO; r = 0.72 PM10; r = 0.73 O_3; r = -0.10	Increment: 24 ppb (90th-10th percentile) Asthma All ages 2.1% [-0.7, 4.9] lag 0; 3.1% [-0.4, 6.7] lag 0-1 0-14 yrs 6.1% [1.2, 11.3] lag 1; 6.9% [1.7, 12.4] lag 0-1 Warm: 13.2% [5.6, 21.3] lag 1 Cool: -0.1% [-6.3, 6.5] lag 1 15-64 yrs 3.0% [-0.7, 6.7] lag 0; 3.1% [-1.6, 7.9] lag 0-3 Warm: 3.3% [-2.0, 8.9] lag 0 Cool: 2.6% [-2.3, 7.7] lag 0 65+ yrs 9.9% [1.6, 18.7] lag 2; 5.3% [-3, 14.3] lag 0-3 Warm: 18.6% [6.3, 32.4] lag 2 Cool: -0.5% [-9.6, 11.8] lag 2 Lower Respiratory disease All ages 1.3% [-0.4, 3.0] lag 1; 1.2% [-0.7, 3.1] lag 0-2 0-14 yrs 4.8% [1.3, 8.3] lag 2; 4.5% [0.4, 8.7] lag 0-3 Warm: 1.4% [-3.8, 6.9] lag 2 Cool: 7.2% [2.8, 11.6] lag 2 15-64 yrs 1.1% [-1.1, 3.4] lag 2; 0.8% [-1.8, 3.5] lag 0-2 Warm: 2.3% [-1.2, 5.9] lag 2 Cool: 0.2% [-2.6, 3.1] lag 2 65+ -1.7% [-4.3, 1.1] lag 0 Warm: -1.7% [-5.9, 2.6] lag 0 Cool: -1.6% [-4.8, 1.8] lag 0 Two-pollutant model-Asthma NO_2 alone: 5.2% [0.8, 9.8] NO_2/O_3: 6.7% [2.2, 11.4] NO_2/SO_2: 3.9% [-1.2, 9.2] NO_2/PM10: 5.3% [-0.6, 11.6]
Hajat et al. (1999) (cont'd)				Two-pollutant model - Lower Respiratory disease NO_2 alone 4.2% [1.1, 7.3] NO_2/O_3 4.9% [1.8, 8.2] NO_2/SO_2 2.5% [-1.1, 6.2] NO_2/PM10 3.5% [0.1, 6.9]

REFERENCE, STUDY LOCATION, & PERIOD	OUTCOMES, DESIGN, & METHODS	MEAN LEVELS & MONITORING STATIONS	COPOLLUTANTS CORRELATIONS	EFFECTS: RELATIVE RISK & CONFIDENCE INTERVALS (95%)
Hajat* et al. (2001) London, United Kingdom Period of Study: 1992-1994	Outcome (ICD9): Allergic Rhinitis (477) Age groups analyzed: 0-14; 15-64; 65+; all ages Study Design: Time-series analysis N: 4,214 Statistical Analysis: Poisson regression, GAM Covariates: Long-term trends, seasonality, day of wk, temperature, humidity, variation in practice population, counts for lagged allergic pollen measures, daily number of consultations for influenza Dose-response investigated? Yes Statistical package: S-Plus Lag: 0-6 days, cumulative	NO_2 24-h avg: 33.6 ppb, SD = 10.5 # of Stations: 3, r = 0.7-0.96	SO_2; r = 0.61 BS; r = 0.70 CO; r = 0.72 PM10; r = 0.73 O_3; r = -0.10	Increment: 24 ppb (90th-10th percentile) Single-pollutant model <1 to 14 yrs 11.0% [3.8, 18.8] lag 4 12.6% [4.6, 21.3] lag 0-4 15 to 64 yrs 5.5% [2.0, 9.1] lag 6 11.1% [6.8, 15.6] lag 0-6 >64 yrs - too small for analysis Two-pollutant models <1 to 14 yrs NO_2 & O_3: 7.9% [0.6, 15.8] NO_2 & SO_2: -3.8% [11.8, 5.0] NO_2 & PM10: 10.8% [0.1, 22.7] 15 to 64 yrs NO_2 & O_3: 4.8% [1.0, 8.8] NO_2 & SO_2: 1.0% [-3.7, 5.8] NO_2 & PM10: 0.5% [-4.9, 6.3]
Hajat* et al. (2002) London, United Kingdom Period of Study: 1992-1994	Outcome (ICD9): Upper Respiratory Disease, excluding Rhinitis (460-3, 465, 470-5, 478) Age groups analyzed: 0-14; 15-64; 65+; all ages Study Design: Time-series analysis Statistical Analysis: Poisson regression, GAM Covariates: Long-term trends, seasonality, day of wk, holidays, temperature, humidity, variation in practice population, counts for lagged allergic pollen measures, daily number of consultations for influenza Seasons: Warm: Apr-Sep; Cool: Oct-Mar Dose-response investigated?: Yes Statistical package: S-Plus Lag: 0,1,2,3 days	NO_2 24-h avg: 33.6 ppb, SD = 10.5 Warm: (Apr-Sep) Mean: 32.8 ppb, SD = 10.1 Cool: (Oct-Mar) Mean: 34.5 ppb, SD = 10.1 # of Stations: 3	SO_2; r = 0.61 BS; r = 0.70 CO; r = 0.72 PM10; r = 0.73 O_3; r = -0.10	Increment (90th-10th percentile): All yr: 24 ppb; Warm season: 25.8 ppb; Cool season: 22.1 ppb Single-pollutant model All yr 0-14 yr 2.0% [-0.3, 4.3] lag 3 15-64 yrs 5.1% [2.0, 8.3] lag 2 >65 yrs 8.7% [3.8, 13.8] lag 2 Warm 0-14 yrs 2.5% [-0.9, 6.1] lag 3 15-64 yrs 6.7% [3.7, 9.8] lag 2 ≥65 yrs 6.6% [-1.1, 14.9] lag 2 Cool 0-14 yrs 1.7% [-1.1, 4.6] lag 3 15-64 yrs 1.2% [-1.3, 3.9] lag 2 >65 yrs 9.4% [2.8, 16.4] lag 2 Two-pollutant models 0-14 yrs NO_2 & O_3: 1.7% [-0.6, 3.9] NO_2 & SO_2: 2.2% [-0.4, 5.0] NO_2 & PM10: 1.5% [-1.7, 4.8] For 15-64 yrs NO_2 & O_3: 4.4% [2.2, 6.8] NO_2 & SO_2: 4.4% [1.6, 7.2] NO_2 & PM10: 2.7% [-0.5, 5.9] For >65 yrs NO_2 & O_3: 8.1% [3.0, 13.6] NO_2 & SO_2: 8.6% [2.1, 15.4] NO_2 & PM10: 4.3% [-2.8, 11.8]

REFERENCE, STUDY LOCATION, & PERIOD	OUTCOMES, DESIGN, & METHODS	MEAN LEVELS & MONITORING STATIONS	COPOLLUTANTS CORRELATIONS	EFFECTS: RELATIVE RISK & CONFIDENCE INTERVALS (95%)
Chardon et al. (2007) Greater Paris, France Period of Study: 2000-2003	Outcome (ICD9): Asthma, URD, LRD 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, counts for lagged allergic pollen measures, daily number of consultations for influenza Seasons: Warm: Apr-Sep; Cool: Oct-Mar Dose-response investigated?: Yes Statistical package: R software Lag: 0, 1, 2, 3, 0-1, 0-2, 0-3 days	24-h avg: 44.4 (14.92) μg/m^3 Median: 43.6 IQR: 33.7-53.2 Range: 12.3-132.8 Number of monitors: 12-15	PM10; r = 0.68 $PM_{2.5}$; r = 0.68	Increment: 10 μg/m^3 URD: 0.7% [-0.9, 2.3] lag 0-3 LRD: 1.1% [-0.7, 2.9], lag 0-3 Asthma: -0.3% [-3.3, 2.7], lag 0-3

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

Table AX6.3-6. Human Health Effects of Oxides of Nitrogen: CVD Hospital Admissions and Visits: United States and Canada

REFERENCE, STUDY LOCATION, & PERIOD	OUTCOMES, DESIGN, & METHODS	MEAN LEVELS & MONITORING STATIONS	COPOLLUTANTS (CORRELATIONS)	EFFECTS: RELATIVE RISK OR PERCENT CHANGE & CONFIDENCE INTERVALS ([95% LOWER, UPPER])
Burnett et al. (1997a) Metropolitan Toronto (Toronto, North York, East York, Etobicoke, Scarborough, York), Canada Study period: 1992-1994, 388 days, summers only	Outcome(s) (ICD9): IHD 410-414; Cardiac Dysrhythmias 427; Heart failure 428. All Cardiac 410-414, 427, 428. Obtained from hospital discharge data. Population: 2.6 Million residents Study design: Time-series Age groups analyzed: all # Hospitals: NR Statistical analysis: Relative risk regression models, GEEs. Covariates: Adjusted for long-term trends, seasonal and subseasonal variation, day of the wk, temperature, dew point Seasons: Summer only Dose response: Figures presented Statistical package: NR Lag: 1-4 days	NO_2 daily 1-h max (ppb): Mean: 38.5 CV: 29 Min: 12 25th percentile: 31 50th percentile: 38 75th percentile: 45 Max: 81 # of Stations: 6-11 (Results are reported for additional metrics including 24-h avg and daytime avg (day))	H+ (0.25) SO4 (0.34) TP (0.61) FP (0.45) CP (0.61) COH (0.61) O_3 (0.07) SO_2 (0.46) CO (0.25)	Results reported for RR for an IQR increment increase in NO_2. T ratio in parentheses. All Cardiac Disease Single-pollutant model 1.049 (3.13), daily avg over 4 days, lag 0 Multipollutant model 1.30 (1.68), w/ NO_2, O_3, SO_2, Objective of study was to evaluate the role of particle size and chemistry on cardio and respiratory diseases. NO_2 attenuated the effect of particulate in this study.

REFERENCE, STUDY LOCATION, & PERIOD	OUTCOMES, DESIGN, & METHODS	MEAN LEVELS & MONITORING STATIONS	COPOLLUTANTS (CORRELATIONS)	EFFECTS: RELATIVE RISK OR PERCENT CHANGE & CONFIDENCE INTERVALS ([95% LOWER, UPPER])
Burnett et al. (1999) * Metropolitan Toronto (Toronto, North York, East York, Etobicoke, Scarborough, York), Canada Study Period: 1980-1995, 15 yr	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 with LOESS smoothers to remove temporal and weather related trends, stepwise regression used to select minimum number of air pollutants in multipollutant models. Covariates: Long-term trends, seasonal variation, day of wk, temperature, and humidity. Statistical Package: SPLUS, SAS Lag(s): 0-2 day	NO_2 daily avg (ppb) Mean: 25.2 5th percentile: 13 25th percentile: 19 50th percentile: 24 75th percentile: 30 95th percentile: 42 Max: 82 Multiple day avgs used in models	$PM_{2.5}$ (0.50) PM10-2.5 (0.38) PM10 (0.52) CO (0.55) SO_2 (0.55) O_3 (-0.04)	Results reported for % increase in hospital admissions for an increment increase in NO_2 equal to the mean value. Single-Pollutant Models: Dysrhythmias: 5.33 (1.73) 3-day avg, lag 0 Heart Failure: 9.48 (6.33), 1 day, lag 0 IHD: 9.73 (8.4) 2-day avg, lag 0 Cerebrovascular disease: 1.98 (1.34), 1 day, lag 0 Peripheral circulation: 3.57 (1.78), 1-day, lag 0 Multipollutant Models: Heart failure 6.89 (w/ CO) 6.68 (w/ CO, $PM_{2.5}$) 6.33 (w/ CO, $PM_{2.5}$, PM10-2.5) 6.45 (w/ CO, $PM_{2.5}$, PM10-2.5, PM10) IHD 8.34 (w/ CO, SO_2) 7.76 (w/ CO, SO_2, $PM_{2.5}$) 8.41 (w/ CO, SO_2, $PM_{2.5}$, PM10-2.5) 8.52 (w/ CO, SO_2, $PM_{2.5}$, PM10-2.5, PM10) In multipollutant models, gaseous pollutants were selected by stepwise regression. PM variables were then added to the model.
Morris et al. (1995) US (Chicago, Detroit, LA, Milwaukee, NYC, Philadelphia) Study Period: 1986-1989, 4 yr	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 day	NO_2 1 h-max (ppm) Mean: (SD) LA: 0.077 (0.028) Chicago: 0.045 (0.013) Philadelphia: 0.054 (0.017) New York: 0.064 (0.022) Detroit: 0.041 (0.015) Houston: 0.041 (0.017) Milwaukee: 0.040 (0.014)	SO_2 1-h max O_3 1-h max CO 1-h max Correlations of NO_2 with other pollutants strong. Multipollutant models run.	Results reported for RR of admission for CHF associated with an incremental increase in NO_2 of 10 ppb. CHF: LA: 1.15 (1.10, 1.19) Chicago: 1.17 (1.07, 1.27) Philadelphia: 1.03 (0.95, 1.12) New York: 1.07 (1.02, 1.13) Detroit: 1.04 (0.92, 1.18) Houston: 0.99 (0.88, 1.10) Milwaukee: 1.05 (0.89, 1.23) RR diminished in multipollutant models (4 copollutants) for all cities with the exception of New York.

REFERENCE, STUDY LOCATION, & PERIOD	OUTCOMES, DESIGN, & METHODS	MEAN LEVELS & MONITORING STATIONS	COPOLLUTANTS (CORRELATIONS)	EFFECTS: RELATIVE RISK OR PERCENT CHANGE & CONFIDENCE INTERVALS ([95% LOWER, UPPER])
Dales et al (2006) Canada (11 largest cities) Study period: January 1, 1986-December 31, 2000.	Outcomes (ICD-9): Asphyxia (799.0), respiratory failure (799.1), dyspnea and respiratory abnormalities (786.0), respiratory distress syndrome (769), unspecificed birth asphyxia in live-born infant (768.9), other respiratory problems after birth (770.8) and pneumonia (486) Data from: Canaidian Institutue for Health Information: 9542 records for patients aged birth to 27 days Study Design: Time series Statistical analysis: Random-effects regression model Statitsitical Software: S-PLUS	NO_2 24-hour mean levels (ppb): Calgary: 25.6 Edmonton: 24.6 Halifax: 15.1 Hamilton: 20.8 London: 20.0 Ottawa: 21.2 Saint John: 9.2 Toronto: 25.1 Vancouver: 19.0 Windsor: 24.9 Winnipeg: 15.2 Population weighted avg: 21.8	Range of Pearson pairwise correlations PM10: -0.26 to 0.69 O_3: -0.55 to 0.05 SO_2: 0.20 to 0.67 CO: 0.13 to 0.76	Pooled estimate of % increase in neonatal resipartory hospital admissions (95% CI): Interquartile range: 10.0 Single-pollutant model: 2.94 (1.93 to 3.95) Multi pollutant model: 2.85 (1.68 to 4.02) Multipollutant model restricted to days with PM10 measures: 2.48 (1.18 to 3.80)
Wellenius et al. (2005b) Birmingham, Chicago, Cleveland, Detroit, Minneapolis, New Haven, Pittsburgh, Seattle Study Period: Jan 1986-Nov 1999 (varies slightly depending on city)	Outcome(s) IS, primary diagnosis of acute but ill-defined cerebrovascular disease or occlusion of the cerebral arteries; HS, primary diagnosis of intracerebral hemorrhage. ICD codes not provided. Hospital admissions ascertained from the Centers for Medicare and Medicaid Services. Cases determined from discharge data were admitted from the ER to the hospital. N IS: 155,503 N HS: 19,314 Study Design: Time-stratified case-crossover. Control days chosen such that they fell in same mo and same day of wk. Design controls for seasonality, time trends, chronic and other slowly varying potential confounders. Statistical Analysis: 2-stage hierarchical model (random effects), conditional logistic regression for city effects in the first stage. Software package: SAS Covariates: Lag(s): 0-2, unconstrained distributed lags	NO_2 24-h (ppb) 10th: 13.71 25th: 18.05 Median: 23.54 75th: 29.98 90th: 36.54 NO_2 data not available for Birmingham, Salt Lake, and Seattle.	PM10 (0.53) CO, SO_2 Correlation only provided for PM because study hypothesis involves PM	Results reported for percent increase in stroke admissions for an incremental increase in NO_2 equivalent to one IQR (11.93). Ischemic Stroke: 2.94 (1.78, 4.12), lag 0 Hemorrhagic Stroke: 0.38 (-2.66, 3.51), lag 0 Multipollutant models not run.

REFERENCE, STUDY LOCATION, & PERIOD	OUTCOMES, DESIGN, & METHODS	MEAN LEVELS & MONITORING STATIONS	COPOLLUTANTS (CORRELATIONS)	EFFECTS: RELATIVE RISK OR PERCENT CHANGE & CONFIDENCE INTERVALS ([95% LOWER, UPPER])
Fung et al. (2005) Windsor, Ontario, Canada Study Period: Apr 1995-Jan 2000	Outcome(s) (ICD9): CHF 428; IHD 410-414; dysrhythmias 427. 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 yr Statistical Software: SPLUS Lag(s): lag 0, 2, 3 day avg	NO_2 1-h max (ppb): Mean (SD): 38.9 (12.3) Min: 0 Max: 117	SO_2 (0.22) CO (0.38) O_3 (0.26) COH (0.39) PM10 (0.33)	Results expressed as percent change associated with an incremental increase in NO_2 equivalent to the IQR (16 ppb) Cardiac: <65 age group: 0.7 (-5.5, 6.6) 2.1 (-3.7, 8.2) 3.7 (-2.9, 10.7) 65+ age group: 0.8 (-2.2, 3.9), lag 0 0.9 (-2.7, 4.6), 2-day avg (lag 0-1) 0.8 (-3.3, 5.0), 3-day avg (lag 0-2) Effect for NO_2 not observed in these data. Association of SO_2 with cardiac admissions observed.
Linn et al. (2000) Metropolitan Los Angeles, USA Study Period: 1992-1995	Outcome(s): All Patient Refined Diagnosis Related Groups (based on medicare diagnosis related groups). CVD APR-DRG 103-144; Cerebrovascular APR-DRG 14-17 and 22; CHF APR-DRG 127; MI APR-DRG 111, 115, 121; cardiac ARR APR-DRG 138; Occlusive Stroke APR-DRG 14. Hospital admission records used to ascertain cases. Study Design: Time-series Statistical Analyses: Poisson regression, cubic spline smooth on time, indicator variables to adjust for temperature and rain. Covariates: Day of wk, holidays, long-term trend, seasonal variation, temperature, humidity Lag(s): 0-1 Seasons: Winter, Spring, Summer, Autumn Statistical Software: SPSS, SAS	NO_2 24-h (ppm) Winter Mean: (SD) 3.4 (1.3) Range: 1.1, 9.1 Spring Mean (SD): 2.8 (0.9) Range: 1.1, 6.1 Summer Mean (SD): 3.4 (1.0) Range: 0.7, 6.7 Autumn Mean (SD): 4.1 (1.4) Range: 1.6, 8.4	CO (0.84, 0.92) O_3 (-0.23, 0.11) PM10 (-0.67, 0.8) Range in correlations depends on the season, independent effects of pollutants could not be distinguished. # Stations: 6+	Results reported as increase % increase in admission for a 10 ppb increase in NO_2. SD in parentheses. CVD, lag 0 All Seasons: 1.4 (0.2) Winter: 1.6 (0.4) Spring: 0.1 (0.6) Summer: 1.1 (0.5) Autumn: 1.4 (0.3) Cerebrovascular, lag 0 All Seasons: 0.4 (0.4) Winter: -1.3 (0.7) Spring: 4.2 (1.2) Summer: 0.9 (1.2) Autumn: 0.7 (0.6) MI, lag 0 (yr round) 1.1 (0.5) CHF, lag 0 (yr round) 1.0 (0.5), winter 1.9 (0.9) Cardiac Arrhythmia, lag 0 (yr round) 0.6 (0.5) Occlusive stroke, lag 0 (yr round) 2.0 (0.5), winter 2.7 (1.0), autumn 0.1 (0.05) Significant effects observed in fall for occlusive stroke and winter for CHF.

REFERENCE, STUDY LOCATION, & PERIOD	OUTCOMES, DESIGN, & METHODS	MEAN LEVELS & MONITORING STATIONS	COPOLLUTANTS (CORRELATIONS)	EFFECTS: RELATIVE RISK OR PERCENT CHANGE & CONFIDENCE INTERVALS ([95% LOWER, UPPER])
Lippmann et al. (2000*; reanalysis Ito, 2003, 2004) Windsor Ontario (near Detroit MI) Study period: 1992-1994 (hospital admissions – mortality study spanned longer period)	Outcome(s): IHD 410-414; dysrhythmias 427; heart failure 428; stroke 431-437. Study Design: Time-series Statistical Analysis: Poisson regression GAM. Results of reanalysis by Ito 2003, 2004 with GLM are presented. Lag(s): 0-3 day	NO_2 24-h avg (ppb) 5th %: 11 25th %: 16 50th %: 21 75th %: 26 95th %: 36 Mean: 21.3	PM10 (0.49) $PM_{2.5}$ (0.48) PM10-2.5 (0.32) H+ (0.14) SO4 (0.35) O_3 (0.14) SO_2 (0.53) CO (0.68)	Results reported for RR for incremental increase in NO_2 of 5th to 95th percentile (28 ppb). IHD (0.94, 1.10), lag 0 0.98 (0.90, 1.06), lag 1 Dysrhythmias 0.98 (0.86, 1.12), lag 0 1.03 (0.90, 1.06), lag 1 Heart Failure 1.00 (0.91, 1.09), lag 0 1.07 (0.98, 1.17), lag 1 Stroke 0.99 (0.90, 1.09), lag 0 0.98 (0.89, 1.08), lag 1
Mann et al. (2002) South coast air basin of CA, United States Study Period: 1988-1995, 8 yr	Outcome(s) IHD 410-414; or IHD with accompanying diagnosis of CHF 428; or Arrhythmia 426, 427; Ascertained through health insurance records. Study Design: Time-series N: 54,863 IHD admissions Age groups analyzed: #40; 40-59; ≥60. Statistical Analysis: Poisson regression, GAM with cubic splines, results pooled across air basins using inverse variance weighting as no evidence of heterogeneity was observed Covariates: Study day, temperature, relative humidity, day of wk Lag(s): 0-2, 2-4 day moving avg Software: SPLUS Seasons: Some analyses restricted to Apr-Oct	NO_2 24-h avg (ppb): Exposure assigned for each air basin based on health insurance participant's zip code. Mean (SD): 37.2 (15.7) Range: 3.69, 138 Median: 34.8 # Stations: 25-35	O_3 8 h-max (-0.16, 0.54) CO 8-h max (0.64, 0.86) PM10 24-h avg (0.36, 0.60) Range depends on air basin. No multipollutant models run. Traffic pollution generally implicated in findings.	Results reported for percent increase in admissions for a 10-ppb incremental increase in NO_2. All IHD: 1.68 (1.08, 2.28), lag 0 MI: 1.04 (1.05, 3.02), lag 0 Other acute IHD: 1.75 (0.72, 2.78), lag 0 IHD w/ secondary diagnosis of Arrhythmia: 1.81 (0.78, 2.85), lag 0 IHD w/ secondary diagnosis of CHF: 2.32 (0.69, 3.98), lag 0 IHD w/ no secondary diagnosis: 0.46 (-0.81, 1.74), lag 0 Effect of secondary diagnosis strongest in the 40-59 age group. Group with secondary CHF may be sensitive subpopulation or their vulnerability may be due to greater prevalence of MI as the primary diagnosis.

REFERENCE, STUDY LOCATION, & PERIOD	OUTCOMES, DESIGN, & METHODS	MEAN LEVELS & MONITORING STATIONS	COPOLLUTANTS (CORRELATIONS)	EFFECTS: RELATIVE RISK OR PERCENT CHANGE & CONFIDENCE INTERVALS ([95% LOWER, UPPER])
Metzger et al. (2004) Atlanta, GA Period of Study: Jan 1993-Aug 31 2000, 4 yr	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/day # 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 day	NO_2 1-h max (ppb): Median: 26.3 10th-90th percentile Range: 25, 68	PM10 24 h (0.49) O_3 8-h max (0.42) SO_2 (0.34) CO 1 h (0.68) 1998-2000 Only $PM_{2.5}$ (0.46) Course PM (.46) Ultrafine PM (.26) Water-soluble metals (.32) Sulfates (.17) OC (0.63) EC (.37) OHC (0.3) Multipollutant models used. All models specified a priori.	Results presented for RR of an incremental increase in 1-h max NO_2 equivalent to 20 ppb (1 SD). All CVD: 1.025 (1.012, 1.039) Dysrhythmia: 1.019 (0.994, 1.044) CHF: 1.010 (0.981, 1.040) IHD: 1.029 (1.005, 1.053) PERI: 1.041 (1.013, 1.069) Finger wounds: 1.010 (0.993, 1.027) Lag is 3-day moving avg for results above. NO_2 effect was generally attenuated in two-pollutant models. The attenuation was strongest in the period after 1998.
Moolgavkar (2000a,b,c)* 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/day # 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	NO_2 24-h avg (ppb) Cook County: Min: 7 Q1: 20 Median: 25 Q3: 30 Max: 58 NO_2 24-h avg (ppb) LA County: Min: 10 Q1: 30 Median: 38 Q3: 48 Max: 102 NO_2 24-h avg (ppb) Maricopa County: Min: 2 Q1: 14 Median: 19 Q3: 26 Max: 56	PM10 (0.22-0.70) $PM_{2.5}$ (0.73) (LA only) CO (0.63-0.80) SO_2 (0.02- 0.74) O_3 (-0.23-0.02) Two-pollutant models (see results)	Results reported for percent change in hospital admissions per 10-ppb increase in 24-h avg NO_2. T statistic in parentheses. CVD, 65+: Cook County 2.9 (10.2), lag 0 2.3 (6.7), lag 0, two-pollutant model (PM10) 2.9 (8.1), lag 0, two-pollutant model (CO) 2.8 (8.8), lag 0, two-pollutant model (SO_2) LA County 2.3 (16.7), lag 0 -0.1 (-0.5), lag 0, two-pollutant model (CO) 1.7 (8.0), lag 0, two-pollutant model (SO_2) Maricopa County 2.9 (4.1), lag 0 -0.3 (-0.3), lag 0, two-pollutant model (CO) 2.6 (3.6), lag 0, two-pollutant model (SO_2) Cerebrovascular Disease, 65+: Cook County 1.6 (3.6) LA County 1.1 (5.7) Effect size generally diminished with increasing lag time. Increase in hospital admissions (1.3 for CVD and 1.9 for cerebrovascular) also observed for the 20-64 age group.

REFERENCE, STUDY LOCATION, & PERIOD	OUTCOMES, DESIGN, & METHODS	MEAN LEVELS & MONITORING STATIONS	COPOLLUTANTS (CORRELATIONS)	EFFECTS: RELATIVE RISK OR PERCENT CHANGE & CONFIDENCE INTERVALS ([95% LOWER, UPPER])
Moolgavkar (2003)* Cook County, IL, Los Angeles County, CA, Maricopa County, AZ 1987-1995	Outcome(s) (ICD9): CVD 390-429; Cerebrovascular disease 430-448 was not considered in the reanalysis. Hospital admissions from CA department of health database. Age groups analyzed: 20-64, 65+ yrs Study Design: Time-series N: 118 CVD admissions/day # Hospitals: NR Statistical Analysis: Poisson regression, GAM with strict convergence criteria (10-8), GLM using natural splines Covariates: Adjustment for day of wk, long-term temporal trends, relative humidity, temperature Statistical Package: SPLUS Lag: 0-5 days	NO_2 24-h avg (ppb) Cook County: Min: 7 Q1: 20 Median: 25 Q3: 30 Max: 58 NO_2 24-h avg (ppb) LA County: Min: 10 Q1: 30 Median: 38 Q3: 48 Max: 102 NO_2 24-h avg (ppb) Maricopa County: Min: 2 Q1: 14 Median: 19 Q3: 26 Max: 56	PM10 (0.22-0.70) $PM_{2.5}$ (0.73) (LA only) CO (0.63-0.80) SO_2 (0.02-0.74) O_3 (-0.23-0.02) Two-pollutant models (see results)	Results for CVD not shown but use of stringent criteria in GAM did not alter results substantially. However, increased smoothing of temporal trends attenuated results for all gases.
Peel et al. (2007) Atlanta, GA Study Period: Jan 1993-Aug 2000	Outcome(s) (ICD9): IHD 410-414; dysrhythmia 427; CHF 428; peripheral vascular and cerebrovascular disease 433-437, 440, 443, 444, 451-453. Computerized billing records for ED visits. Comorbid conditions: Hypertension 401-405; diabetes 250; dysrhythmia 427, CHF 428; atherosclerosis 440; COPD 491, 492, 496; pneumonia 480-486; upper respiratory infection 460-465, 466.0; asthma 493, 786.09. # Hospitals: 31 N: 4,407,535 visits Study Design: Case-crossover. CVD outcomes among susceptible groups with Comorbid conditions. Statistical Analyses: Conditional logistic regression. Covariates: Cubic splines for temperature and humidity included in models. Time independent variables controlled through design. Statistical Software: SAS Lag(s): 3-day avg, lagged 0-2 day	NO_2 1-h max (ppb): Mean (SD): 45.9 (17.3) 10th: 25.0 90th: 68.0	PM10 24-h avg O_3 8-h max SO_2 1-h max CO 1-h max Correlations not reported	Results expressed as OR for association of CVD admissions with a 20-ppb incremental increase in NO_2. Comorbid Hypertension: IHD: 1.036 (0.997, 1.076) Dysrhythmia: 1.095 (1.030, 1.165) PERI: 1.031 (0.987, 1.076) CHF: 1.037 (0.985, 1.090) Comorbid Diabetes: IHD: 1.003 (0.95, 1.059) Dysrhythmia: 1.158 (1.046, 1.282) PERI: 1.012 (0.947, 1.082) CHF: 1.017 (0.959, 1.078)

REFERENCE, STUDY LOCATION, & PERIOD	OUTCOMES, DESIGN, & METHODS	MEAN LEVELS & MONITORING STATIONS	COPOLLUTANTS (CORRELATIONS)	EFFECTS: RELATIVE RISK OR PERCENT CHANGE & CONFIDENCE INTERVALS ([95% LOWER, UPPER])
Schwartz, (1997) * Tucson, AZ Study Period: Jan 1988-Dec 1990	Outcome(s) (ICD9): CVD 390-429. Ascertained from hospital discharge records. Study Design: Time-series Statistical Analysis: Poisson regression, GAM Age groups analyzed: 65+ Covariates: Long-term and seasonal trends, day of the wk, temperature, dew point Statistical Software: SPLUS	NO_2 24-h avg (ppb): Mean: 19.3 10th: 9.9 25th: 13.2 50th: 19 75th: 24.6 90th: 29.8	PM10 (0.326) O_3 (-0.456) SO_2 (0.482) CO (0.673)	Results reported as a percent increase in admission for an increment in NO_2 equivalent to the IQR (11.4 ppb). CVD 0.69% (-2.3, 3.8) Tucson selected to minimize correlations between pollutants. Since there was no association between NO_2 and admissions, author suggests results for CO not confounded by NO_2.
Stieb et al. (2000) * Saint John, New Brunswick Canada Study Period: 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, LOESS smooth for temporal and weather related variables N: 19,821 ER visits # Hospitals: 2 Lag(s): 1-8 days	NO_2 24-h avg (ppb) Mean (SD): 8.9 (5.5) 95th: 19 Max: 35 NO_2 max (ppb) Mean (SD): 20.2 95th: 39 Max: 82	CO (0.68) H2S (-0.07) O_3 (-0.02) SO_2 (0.41) PM10 (0.35) $PM_{2.5}$ (0.35) H+ (-0.25) SO4 (0.33) COH (0.49)	Results reported for percent change in admissions based on a single-pollutant model for incremental increase in NO_2 equivalent to 1 IQR (8.9 ppb) Cardiac visits: -3.9, p-value = 0.136, lag 2, all yr 10.1, p-value = 0.051, lag 5, May-Sept For specific CVD diagnoses, ARR and CHF approached significance. NO_2 was not a focus of this paper.
Tolbert et al. (2007) Atlanta, GA Study Period: 1993-2004	Outcome(s) (ICD9): All CVD including IHD 410-414; cardiac dysrhythmias 427; CHF 428; peripheral vascular and cerebrovascular disease 433-437, 440 443-445, 451-453. Emergency visits primary and secondary diagnostic codes. Study Design: Time-series Statistical Analysis: GLM, cubic splines with monthly knots, indicators for season, day of wk, holiday, excluded days with missing exposure data Statistical Software: SAS Lag(s): 3 day moving avg (0-2 d)	NO_2 1-h max (ppb): Mean: 43.2 Min: 1.0 10th: 22 25th: 31 Median: 41 75th: 54 90th: 66 Max: 181	PM10 (0.53) O_3 (0.44) CO (0.70) SO_2 (0.36) Course PM (0.70) $PM_{2.5}$ (0.47) $PM_{2.5}$ SO4 (0.14) $PM_{2.5}$ EC (0.64) $PM_{2.5}$ OC (0.62) $PM_{2.5}$ TC (0.65) $PM_{2.5}$ water sol metals (0.32) OHC (0.24)	Results reported for RR based on incremental increase of NO_2 equivalent to 1 IQR (23 ppb): Single-pollutant model results: CVD 1.015 (1.004, 1.025), lag 0-2 NO_2 effect diminished in multipollutant models containing CO and $PM_{2.5}$TC (shown in figure).

REFERENCE, STUDY LOCATION, & PERIOD	OUTCOMES, DESIGN, & METHODS	MEAN LEVELS & MONITORING STATIONS	COPOLLUTANTS (CORRELATIONS)	EFFECTS: RELATIVE RISK OR PERCENT CHANGE & CONFIDENCE INTERVALS ([95% LOWER, UPPER])
Villeneuve et al. (2006) Edmonton, Canada Study Period: Apr 1992-Mar 2002	Outcome(s) (ICD9): Acute ischemic stroke 434, 436; hemorrhagic stroke 430, 432; transient ischemic attack (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	NO_2 24 h ppb: All yr Mean (SD): 24 (9.8) Median: 22.0 25th: 16.5 75th: 30.0 IQR: 13.5 Summer Mean (SD): 18.6 (6.4) Median: 17.5 25th: 14.0 75th: 22.0 IQR: 8 Winter Mean (SD): 29.4 (9.6) Median: 28.5 25th: 22.5 75th: 35.5 IQR: 13.0	O_3 24-h max (-0.33) O_3 24-h avg (-0.51) SO_2 25-h avg (0.42) CO 24-h avg (0.74) PM10 24-h avg (0.34) $PM_{2.5}$ 24-h avg (0.41) All yr correlations summarized.	Results reported for an incremental increase in NO_2 equivalent to one IQR NO_2. Ischemic Stroke, Summer 1.17 (1.05, 1.31), lag 0 1.18 (1.05, 1.31), lag 1 1.26 (1.09, 1.46), 3-day avg Hemorrhagic stroke, Summer 1.16 (0.99, 1.37) 1.14 (0.97, 1.35) 1.18 (0.95, 1.46) TIA not associated with increase in NO_2. Above results are strongest effects, which were observed during summer. Authors attribute NO_2 effect to vehicular traffic since NO_2 and CO are highly correlated.
Wellenius et al. (2005a) Allegheny County, PA (near Pittsburgh) Study Period: Jan 1987-Nov 1999	Outcome(s): CHF 428. Cases are Medicare patients admitted from ER with discharge of CHF. Study Design: Case-crossover, control exposures same mo and day of wk, controlling for season by design. Statistical Analysis: Conditional logistic regression N: 55,019 admissions, including repeat admissions, 86% admitted #5 times Age groups analyzed: 65+ yrs (Medicare recipients) Covariates: Temperature and pressure. Effect modification by age, gender, secondary diagnosis arrhythmias, atrial fibrillation, COPD, hypertension, type 2 diabetes, AMI within 30 days, angina pectoris, IHD, acute respiratory infection. Statistical Software: SAS Lag(s): 0-3	NO_2 24-h avg (ppb): Mean (SD): 26.48 (8.02) 5th: 15.10 25th: 20.61 Median: 25.70 75th: 31.30 95th: 4102 # Stations: 2	PM10 (0.64) CO (0.70) O_3 (-0.04) SO_2 (0.52)	Results reported for the percent increase in admissions for an increment of NO_2 equivalent to one IQR (11 ppb). CHF, single-pollutant model 4.22 (2.61, 5.85), lag 0 CHF, two-pollutant model 4.05 (1.83, 6.31), adjusted for PM10 -0.37 (-2.59, 1.89), adjusted for CO 3.73 (2.10, 5.39), adjusted for O_3 3.79 (1.93, 5.67), adjusted for SO_2 CHF admission was 3x higher among those with history of MI.

REFERENCE, STUDY LOCATION, & PERIOD	OUTCOMES, DESIGN, & METHODS	MEAN LEVELS & MONITORING STATIONS	COPOLLUTANTS (CORRELATIONS)	EFFECTS: RELATIVE RISK OR PERCENT CHANGE & CONFIDENCE INTERVALS ([95% LOWER, UPPER])
Zanobetti and Schwartz (2006) Boston, MA 1995-1999	Outcome(s) (ICD9): MI 410. Admissions through the emergency room from Medicare claims. Age group analyzed: 65+ yrs Study Design: Case-crossover, control days matched yr, mos and temperature Statistical Analysis: Conditional logistic regression N: 15,578 Covariates: Temperature (regression spline), day of wk Seasons: Hot (Apr-Sept) and cold Software: SAS Lags: 0, 0-1 previous day avg	NO_2 24-h avg ppb 5th: 12.59 25th: 18.30 Median: 23.20 75th: 29.13 95th: 90th-10th: 20.41 # Stations: 4	O_3 (-0.14) BC (0.70) CO (0.67) $PM_{2.5}$ (0.55) PM non-traffic (0.14) (residuals from model of $PM_{2.5}$ regressed on BC)	Results reported for percent increase in admissions for incremental increase in NO_2 equivalent to the 90th-10th percentiles (20.41 or 16.80 for 0-1, previous day avg). MI 10.21 (3.82, 15.61), lag 0 12.67 (5.82, 18.04), lag 0-1, previous day avg Results suggest traffic exposure is responsible for the observed effect. Effects more pronounced in the summer season.

*Default GAM
AMI Acute Myocardial Infarction
ARR Arrhythmia
BC Black Carbon
COH coefficient of haze
CP Course Particulate
CVD Cardiovascular Disease
EC Elemental Carbon
FP Fine Particulate
HS Hemorrhagic Stroke
ICD9 International Classification of Disease, 9th Revision
IHD Ischemic Heart Disease
IS ischemic stroke
MI Myocardial Infarction
OC Organic Carbon
OHC Oxygenated Hydrocarbons
PERI Peripheral Vascular and Cerebrovascular Disease
PM Particulate Matter
PIH primary intracerebral hemorrhage
PNC Particle Number Concentration
SHS Subarachnoid hemorrhagic stroke
TP Total Particulate
UBRE Unbiased Risk Estimator

Table AX6.3-7. Human Health Effects of Oxides of Nitrogen: CVD Hospital Admissions and Visits: Australia and New Zealand

REFERENCE, STUDY LOCATION, & PERIOD	OUTCOMES, DESIGN, & METHODS	MEAN LEVELS & MONITORING STATIONS	COPOLLUTANTS (CORRELATIONS)	EFFECTS: RELATIVE RISK OR PERCENT CHANGE & CONFIDENCE INTERVALS ([95% LOWER, UPPER])
Barnett et al. (2006) Australia and New Zealand: Brisbane, Canberra, Melbourne, Perth, Sydney Period of Study: 1998-2001	Outcome(s) (ICD9): All CVD 390-459; ARR 427; Cardiac disease 390-429; Cardiac failure 428; IHD 410-413; MI 410; Stroke 430-438. Ages groups analyzed: 15-64 yrs, ≥65yrs Study Design: Time stratified, case-crossover, multicity study # of Hospitals: All ER admissions from state government health departments Statistical Analyses: Random effects meta analysis, heterogeneity assessed using I2 statistic. Covariates: Matched analysis controlling for long-term trend, seasonal variation, and respiratory epidemics. Temperature (current-previous day) and relative humidity, pressure, extremes of hot and cold, days of wk, holidays, day after holiday, rainfall in some models. Matched on copollutants. Statistical Package: SAS Lag: 0-3	NO_2 (ppb), Mean (range) Auckland 1-h max: 19.1 (4.2-86.3) 24-h avg: 10.2 (1.7-28.9) Brisbane 1-h max: 17.3 (4-44.1) 24-h avg: 7.6 (1.4-19.1) Canberra 1-h max: 17.9 (0-53.7) 24-h avg: 7.0 (0-22.5) Christchurch 1-h max: 15.7 (1.2-54.6) 24-h avg: 7.1 (0.2-24.5) Melbourne 1-h max: 23.2 (4.4-48) 24-h avg: 11.7 (2-29.5) Perth 1-h max: 21.3 (4.4-48) 24-h avg: 9.0 (2-23.3) Sydney 1-h max: 22.6 (5.2-51.4) 24-h avg: 11.5 (2.5-24.5) 24 h avg IQR: 5.1 # of Stations: 1-13 depending on the city	PM10 24 h CO 24 h SO_2 24 h O_3 8 h BS 24 h Matched analysis conducted to control for copollutants	Results reported for % change in hospital admissions associated with one IQR increase in 24-h avg NO_2, lag 0-1. Arrhythmia ≥65: 0.4 (-1.8, 2.6) 15-64: 5.1 (2.2, 8.1) Cardiac ≥65: 3.4 (1.9, 4.9) 15-64: 2.2 (0.9, 3.4) Cardiac failure ≥65: 6.9 (2.2, 11.8) 15-64: 4.6 (0.1, 6.1) IHD ≥65: 2.5 (1.0, 4.1) 15-64: 0.7 (-1.0, 2.4) MI ≥65: 4.4 (1.0, 8.0) 15-64: 1.7 (-1.1, 2.4) All CVD ≥65: 3.0 (2.1, 3.9) 15-64: 1.7 (0.6, 2.8) NO_2 association became smaller when matched with CO. Authors hypothesize that NO_2 is a good surrogate for PM, which may explain these associations.

REFERENCE, STUDY LOCATION, & PERIOD	OUTCOMES, DESIGN, & METHODS	MEAN LEVELS & MONITORING STATIONS	COPOLLUTANTS (CORRELATIONS)	EFFECTS: RELATIVE RISK OR PERCENT CHANGE & CONFIDENCE INTERVALS ([95% LOWER, UPPER])
Simpson et al. (2005a) Australia (Brisbane, Melbourne, Perth, Sydney). Study Period: Jan 1996-Dec 1999	Outcome(s) (ICD9): Cardiac disease 390-429; IHD 410-413; stroke 430-438. Study Design: Time-series. Statistical analysis: APHEA2 protocol, GAM (did not indicate use of stringent convergence criteria), GLM with natural splines, penalized splines. Random effects meta-analysis with tests for homogeneity. Age groups analyzed: All, 15-64, 65+ Covariates: long-term trend, temperature, humidity, day of wk, holidays, influenza epidemics Software package: SPLUS, R Lag(s): 1-3 days	NO 1-h max (ppb): Mean (range): Brisbane: 21.4 (2.1, 63.3) Sydney: 23.7 (6.5, 59.4) Melbourne: 23.7 (4.4, 66.7) Perth: 16.3 (1.9, 41.0)	PM10 24 h $PM_{2.5}$ BS 24 h (0.29, 0.62) O_3 1 h CO 8 h Not all correlations reported. NO_2 affect attenuated slightly when modeled with BS but not with O_3. May be confounding of NO_2 effect by particulate.	Single-city results reported for percent increase for an increment in 1-h max NO_2 equivalent to one IQR. Pooled results reported for an increment of 1 ppb NO_2. Cardiac All ages: 1.0023 (1.0016, 1.0030), lag 0-1 15-64: 1.0015 (1.0006, 1.0025), lag 0 ≥65: 1.0018 (1.0011, 1.0025), lag 0-1 IHD All ages: 1.0019 (1.0010, 1.0027) ≥65: 1.0017 (1.0007, 1.0027) No effect observed/reported for stroke. Multipollutant results (65+ age group): Cardiac: 1.0032 (1.0006, 1.0022), w/ BS, lag 0-1 1.0032 (1.0024, 1.0039), w/ O_3, lag 0-1 Heterogeneity in CVD results among cities, probably due to different pollutant mixtures, may have affected the results.
Hinwood et al. (2006) Perth, Australia Study Period: 1992-1998	Outcome(s): All CVD unscheduled admissions. Obtained from discharge records using ICD9 Codes. Age groups analyzed: All ages, 65+ Study design: Case-crossover, time-stratified with 3-4 controls within same mo Statistical Analysis: conditional logistic regression N: 26.5 daily CVD admissions Seasons: Nov-Apr, May-Oct	NO_2 24-h (ppb) Mean: 10.3 SD = 5 10th percentile: 4.4 90th percentile: 17.1 NO_2 1-h max (ppb) Mean: 24.8 SD = 10.1 10th percentile: 13.3 90th percentile: 37.5 # of Stations: 3	O_3 1 h, 8 h (-.06) CO 8 h (.57) BSP 24 h (.39)	Results reported for OR per incremental increase of 1 ppb NO_2. All CVD (estimated from graph) NO_2 24 h 65+: 1.005 (1.001, 1.006), lag 1 NO_2 24 h all ages: 1.003 (1.001, 1.007), lag 1

REFERENCE, STUDY LOCATION, & PERIOD	OUTCOMES, DESIGN, & METHODS	MEAN LEVELS & MONITORING STATIONS	COPOLLUTANTS (CORRELATIONS)	EFFECTS: RELATIVE RISK OR PERCENT CHANGE & CONFIDENCE INTERVALS ([95% LOWER, UPPER])
alaludin 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).	NO_2 daily 1-h avg Mean: 32.2 SD = 7.4 Min: 5.2 Q1: 18.2 Median: 23 Q3: 27.5 Max: 59.4 # of Stations: 14	BS 24-h avg (0.35) PM10 24-h avg (0.44) $PM_{2.5}$ 24-h avg (0.45) CO 8-h avg (0.55) O_3 1-h avg (0.45) SO_2 24-h avg (0.56) Two-pollutant models to adjust for copollutants	Results reported for % change in hospital admissions associated with one IQR increase in 1-h avg NO_2. All CVD 2.32 (1.45, 3.19), lag 0 0.45 (-0.52, 1.42), lag 1 1.31 (0.28, 2.35), lag 0-1 Cardiac Disease 2.00 (0.81, 3.20), lag 0 0.91 (-0.26, 2.09), lag 1 1.78 (0.54, 3.04), lag 0-1 IHD 2.11 (0.34, 3.91), lag 0 0.76 (-0.97, 2.52), lag 1 1.73 (-0.10, 3.59), lag 0-1 Stroke -1.66 (-3.80, 0.51) lag 0 -1.11 (-3.19, 1.02), lag 1 -1.68 (-3.90, 0.60), lag 0-1 Effect of NO_2 attenuated when CO was included in the model. NO_2 effect most prominent during the cool season.
Morgan et al. (1998a) Sydney, Australia Study Period: Jan 1990-Dec 1994	Outcome(s) (ICD9): Heart Disease 410, 413, 427, 428. Inpatient statistics database for New South Wales Health Department. Study Design: Time-series Statistical Analysis: Poisson regression, GEE # Hospitals: 27 Covariates: Daily mean temperature, dew point temperature Lag(s): 0-2 days, cumulative Statistical Software: SAS	NO_2 24-h avg (ppb): Mean (SD): 15 (6) IQR: 11 ppb 10th-90th: 17 NO_2 1-h max (ppb): Mean (SD): 29 (3) 10-90th: 29 ppb NO_2 24-h max: 52 NO_2 1-h max: 139 # Stations: 3-14 (1990-1994)	O_3 1-h max (-0.086) PM (0.533, 0.506) Correlations for 24-h avg NO_2 concentrations Multipollutant models	Results reported as percent increase in admissions associated with an incremental increase in 1-h max NO_2 and 24-h avg equivalent to the 10th-90th percentile. Heart Disease: 24-h avg, lag 0 All ages: 7.52 (5.21, 9.88) 65+: 8.39 (5.41, 11.46) 0-64: 5.81 (1.63, 10.17) 1-h max, lag 0 All ages: 6.08 (3.63, 8.59) 65+: 6.71 (4.25, 9.23) 0-64: 4.79 (1.18, 8.53) 65+: 6.68 (3.61, 9.84) Particulate, O_3 Results lost precision but did not change substantially when stratified by age or when 24-h averaging time was used.

REFERENCE, STUDY LOCATION, & PERIOD	OUTCOMES, DESIGN, & METHODS	MEAN LEVELS & MONITORING STATIONS	COPOLLUTANTS (CORRELATIONS)	EFFECTS: RELATIVE RISK OR PERCENT CHANGE & CONFIDENCE INTERVALS ([95% LOWER, UPPER])
Petroeschevsky et al. (2001) Brisbane, Australia Study Period: Jan 1987-Dec 1994, 2,922 days	Outcome(s) (ICD9): CVD 390-459. Hospital admissions, non-residents excluded. Study Design: Time-series Statistical Analyses: Poisson regression, APHEA protocol, linear regression and GEEs Age groups analyzed: 15-64, 65+ Covariates: Temperature, humidity, rainfall. Long-term trends, season, flu, day of wk, holidays. Statistical Software: SAS Lag(s): lag 0-4, 3-day avg, 5 day avg	NO_2 1-h max (pphm) Summer Mean: 206 Min: 0.35 Max: 5.8 Fall Mean: 2.56 Min: 0.70 Max: 5.85 Winter Mean: 3.54 Min: 0.35 Max: 8.05 Spring Mean: 3.12 Min: 0.55 Max: 15.58 Overall Mean: 2.82 Min: 0.35 Max: 15.58	BSP O_3 SO_2 Correlation between pollutants not reported.	Results reported for RR for CVD emergency admissions associated with a one-unit increase in NO_2 1-h max. CVD 15-64 yrs 0.986 (0.968, 1.005), lag 3 CVD 65+ yrs 0.990 (0.977, 1.003) CVD all ages 0.987 (0.976, 0.998)

*Default GAM
AMI Acute Myocardial Infarction
ARR Arrhythmia
BC Black Carbon
COH coefficient of haze
CP Course Particulate
CVD Cardiovascular Disease
EC Elemental Carbon
FP Fine Particulate
HS Hemorrhagic Stroke
ICD9 International Classification of Disease, 9th Revision
IHD Ischemic Heart Disease
IS ischemic stroke
MI Myocardial Infarction
OC Organic Carbon
OHC Oxygenated Hydrocarbons
PERI Peripheral Vascular and Cerebrovascular Disease
PM Particulate Matter
PIH primary intracerebral hemorrhage
PNC Particle Number Concentration
SHS Subarachnoid hemorrhagic stroke
TP Total Particulate
UBRE Unbiased Risk Estimator

Table AX6.3-8. Human health effects of oxides of nitrogen: cvd hospital admissions and visits: Europe

REFERENCE, STUDY LOCATION, & PERIOD	OUTCOMES, DESIGN, & METHODS	MEAN LEVELS & MONITORING STATIONS	COPOLLUTANTS (CORRELATIONS)	EFFECTS: RELATIVE RISK OR PERCENT CHANGE & CONFIDENCE INTERVALS ([95% LOWER, UPPER])
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 day	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 fixed effect model. Tested linearity by modeling pollutant in linear and non-linear way (spline smoothing). Linear model provided best results 55% of time but used in all cases to facilitate comparability. Covariates: temperature, humidity and influenza, day of wk unusual events, seasonal variation and trend of the series Seasons: Hot: May to Oct; Cold: Nov to Apr Statistical Package: SPLUS Lag: 0-3	NO_2 24-h avg (µg/m2): Mean: 51.5 10th percentile: 29.5 90th percentile: 74.4 # of Stations: Depends on the city Correlation among stations: NR	CO 8-h max (0.58) O_3 8-h max (-0.03) SO_2 24 h (0.46) BS 24 h (0.48) TSP 24 h (0.48) PM10 24 h (0.40) Two-pollutant models used to adjust for copollutants.	Results reported for % change in hospital admissions associated with 10 µg/m2 increase in NO_2. All CVD 0.38% (0.07%, 0.69%), lag 0-1 Heart Diseases: 0.86% (0.44%, 1.28%) Effect of NO_2 was diminished in two-pollutant models.

REFERENCE, STUDY LOCATION, & PERIOD	OUTCOMES, DESIGN, & METHODS	MEAN LEVELS & MONITORING STATIONS	COPOLLUTANTS (CORRELATIONS)	EFFECTS: RELATIVE RISK OR PERCENT CHANGE & CONFIDENCE INTERVALS ([95% LOWER, UPPER])
Lanki et al. (2006) Europe (Augsburg, Helsinki, Rome, Stockholm) Study period: 1992-2000	Outcome(s) (ICD9): AMI 410. Ascertained from discharge records or AMI registry data depending on the city. Study Design: Time-series Statistical Analysis: Poisson regression, for non-linear confounders – penalized splines in GAM chosen to minimize UBRE score. Random-effects model for pooled estimates. N: 26,854 hospitalizations Statistical Software: R package Covariates: Barometric pressure, temperature, humidity. Lag(s): 0-3 day	NO_2 (μg/m^3) Augsburg 25th: 40.2 50th: 49.2 75th: 58.9 98th: 88.7 Barcelona 25th: 34.8 50th: 45.0 75th: 60.0 98th: 86.0 Helsinki 25th: 21.8 50th: 28.7 75th: 37.6 98th: 64.7 Rome 25th: 61.9 50th: 70.6 75th: 80.4 98th: 102.5 Stockholm 25th: 16.3 50th: 22.2 75th: 28.6 98th: 45.9	PM10 (0.29, 0.64) CO (0.43, 0.75) O_3 (0.17, 0.38) Range in correlations depends on the city. Two-pollutant models for PNC with O_3 and PM10 only.	Results reported as RR associated with an incremental increase in NO_2 equivalent to the IQR (8 μg/m2). Pooled results for 5 Cities: First MI: 0.996 (0.988, 1.015), lag 0 0.998 (0.986, 1.010), lag 1 1.003 (0.994, 1.011), lag 2 1.001 (0.989, 1.014), lag 3 No significant results observed for analyses stratified by age or season for lag 0/1.

REFERENCE, STUDY LOCATION, & PERIOD	OUTCOMES, DESIGN, & METHODS	MEAN LEVELS & MONITORING STATIONS	COPOLLUTANTS (CORRELATIONS)	EFFECTS: RELATIVE RISK OR PERCENT CHANGE & CONFIDENCE INTERVALS ([95% LOWER, UPPER])
Von Klot et al. (2005) Europe (Augsburg, Barcelona, Helsinki, Rome, Stockholm) Study Period: 1992-2000	Outcome(s) (ICD9): Re-admission for AMI 410; angina pectoris 411 and 413; Cardiac diseases including AMI angina pectoris, dysrhythmia (427), heart failure (428). Hospital admissions database used to identify cases. Population: Incident cases of MI during 1992-2000 among those ≥35 yrs old. N Augsburg: 1560 N Barcelona: 1134 N Helsinki: 4026 N Rome: 7384 N Stockholm: 7902 Study Design: Prospective Cohort Statistical Analyses: Poisson regression, at risk period from the 29th day after the index event until the event of interest, death, migration, or loss to follow-up. GLM models, penalized spline functions for continuous confounders. City results pooled using random-effects model. Heterogeneity assessed. Sensitivity analyses conducted varying the smooth functions, convergence criteria, and how confounders were specified. Statistical Software: R package Covariates: Daily mean temperature, dew point temperature, barometric pressure, relative humidity, vacations or holidays. Lag: 0-3 days	NO_2 24-h avg (µg/m2): Augsburg Mean: 49.6 5th: 30 25th: 39.7 75th: 57.2 95th: 75.3 Barcelona Mean: 47.7 5th: 18 25th: 34.0 75th: 60 95th: 83 Helsinki Mean: 30.1 5th: 13 25th: 21.2 75th: 36.7 95th: 52.9 Rome Mean: 15.8 5th: 5.4 25th: 10.1 75th: 21.7 95th: 25.9 Stockholm Mean: 22.8 5th: 10.3 25th: 16 75th: 28 95th: 39.4 # Stations: 1-5	CO 24 h (0.44, 0.75) O_3 8 h (-0.2, -0.13) PM10 (.29, .66) PNC (.44, .83) Two-pollutant models but NO_2, CO, and PNC not modeled together because they were too highly correlated.	Results reported for RR for incremental increases in same day NO_2 equivalent to the mean of the city specific IQR's multiplied by 0.05 (8 µg/m^3). Pooled results are below: MI 1.028 (0.997, 1.060), lag 0 Angina Pectoris 1.032 (1.006, 1.058), lag 0 Cardiac Diseases 1.032 (1.014, 1.051), lag 0 Two-pollutant models show that the effect of NO_2 independent of PM10 and O_3. Traffic exhaust may be associated with cardiac re-admission.

REFERENCE, STUDY LOCATION, & PERIOD	OUTCOMES, DESIGN, & METHODS	MEAN LEVELS & MONITORING STATIONS	COPOLLUTANTS (CORRELATIONS)	EFFECTS: RELATIVE RISK OR PERCENT CHANGE & CONFIDENCE INTERVALS ([95% LOWER, UPPER])
Andersen et al. (2007a) Copenhagen, Denmark Study Period: 1999-2004	Outcome(s) (ICD10): angina pectoris I20; acute and subsequent MI I21-22; other acute IHD I24; chronic IHD I25; pulmonary embolism I26; cardiac arrest I46; cardiac arrhythmias I48-49; hear failure I50. Hospital admissions from Danish Hospital Register. # Hospitals: 9 (within 15 km of monitoring station) Study Population: 65 + Catchment area: 1.5 million Study Design: Time-series Statistical Analysis: Principal components analysis for source apportionment. Poisson GAM, smoothing splines for weather, long-term trends/seasonality, indicator variables for influenza, holidays Software: mgcv package, R Lag(s): 0-5 d, 0-3 d avg	24-h avg NO_2 (ppb) Mean (SD): 12 (5) 25th: 8 75th: 15 IQR: 7	PM10 (0.45) CO (0.74) Source Specific PM10 Biomass (0.41) Secondary (0.43) Oil (0.42) Crustal (0.24) Sea Salt (-0.19) Vehicle (0.65)	Results reported for RR associated with an incremental increase in NO_2 equivalent to one IQR (7 ppb). Single-pollutant 1.013 (0.993, 1.033), lag 0-3 avg 2-pollutant, NO_2 with PM10 1.000 (0.975, 1.026)
Andersen et al. (2007b) Copenhagen, Denmark Study Period: 2001-2004	Outcome(s) (ICD10): Angina pectoris I20; acute and subsequent MI I21-22; other acute IHD I24; chronic IHD I25; pulmonary embolism I26; cardiac arrest I46; cardiac arrhythmias I48-49; heart failure I50. Hospital admissions from Danish Hospital Register. # Hospitals: 9 (within 15 km of monitoring station) Study Population: 65 + Catchment area: 1.5 million Study Design: Time-series Statistical Analysis: Poisson GAM, smoothing splines for weather, long-term trends/seasonality, indicator variables for influenza, holidays Software: mgcv package, R Lag(s): 0-5 d, 0-3 d avg	24-h avg NO_2 (ppb) Mean (SD): 11 (5) 25th: 8 50th: 11 75th: 14 99th: 28 IQR: 6 24-h avg NO_X (ppb) Mean (SD): 15 (8) 25th: 9 50th: 12 75th: 18 99th: 46 IQR: 9 24-h avg NO_X curbside (ppb) Mean (SD): 83 (36) 25th: 58 50th: 76 75th: 103 99th: 207 IQR: 45	NCtot w/ NO_2 (0.68) NCtot w/ NO_X (0.66) NCa57 w/ NO_2 (0.57)	Results reported for associations of a 6-ppb increase equivalent to one IQR of NO_2 with all CVD. One-pollutant model: 1.0 (0.98, 1.03), lag 0-3 Two-pollutant model with NCtot 1.0 (0.96, 1.03)

REFERENCE, STUDY LOCATION, & PERIOD	OUTCOMES, DESIGN, & METHODS	MEAN LEVELS & MONITORING STATIONS	COPOLLUTANTS (CORRELATIONS)	EFFECTS: RELATIVE RISK OR PERCENT CHANGE & CONFIDENCE INTERVALS ([95% LOWER, UPPER])
Atkinson et al. (1999b) London, England Period of Study: 1992-1994, N = 1,096 day	Outcome(s) (ICD9): All CVD 390-459; IHD 410-414. Emergency admissions obtained from the Hospital Episode Statistics (HES) database. Ages groups analyzed: 0-14 yr, 15-64 yr, 0-64 yr, 65+ yr, 65 74 yr, 75+ yr Study Design: Time-series, hospital admission counts N: 189, 109 CVD admissions Catchment area: 7 million residing in 1600 Km2 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, quadratic, piece-wise, spline) Seasons: 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	1-h max (ppb) Mean: 50.3 SD = 17.0 Min: 22.0 Max: 224.3 10th-90th percentile: 36 # of Stations: 3, results averaged across stations Correlation among stations: 0.7-0.96	PM10 24 h CO 24 h SO_2 24 h O_3 8 h BS 24 h Correlations of NO_2 with CO, SO_2, O_3, BS ranged from 0.6-0.7 Correlation of NO_2 with O_3 negative Two-pollutant models used adjust for copollutants	Results reported for % change in hospital admissions associated with 10th-90th percentile increase in NO_2 (36 ppb) All CVD Ages 0-64: 1.20% (-0.62%, 3.05%), lag 0 Ages 65+: 1.68% (0.32%, 3.06%), lag 0 IHD Ages 0-64: 1.53% (-1.22%, 4.37%), lag 0 Ages 65+: 3.03% (0.87%, 5.24), lag 0 NO_2 was associated with increased CVD admissions for all ages but this association was stronger among those 65+ yrs old. Similar increase associated with IHD among those 65+ yrs old. Monitors close to roadways were not used in the study. Correlations for NO_2 between urban monitoring sites were high. Authors suggest that the pollution levels are uniform across the study area. Authors did not investigate the interaction between meteorological variables and air pollution. In two-pollutant models, O_3 had little impact on NO_2. BS moderated the association of NO_2 with CVD among the 65+ age group. Suggestion that NO_2 associations were non-linear.
Ballester et al. (2001) Valencia, Spain Period of Study: 1992-1996	Outcome(s) (ICD9): All CVD 390-459; heart diseases 390-459; 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 with parametric smoothers, APHEA/ Spanish EMECAM protocol. Both Linear and non parametric 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, wk days, flu, special events, air pollution. Seasons: Hot season May to Oct; Cold season Nov to Apr Statistical Package: SAS Lag: 0-4	1-h max (µg/m2) Mean: 116.1 SD = NR Min: 21.1 Max: 469.0 Median: 113.2 # of Stations: 14 manual, 5 automatic Correlation among stations: 0.3-0.62 for BS, 0.46-0.78 for gaseous pollutants	CO 24 h (0.03) SO_2 24 h (0.33) O_3 8 h (-0.26) BS (0.33) Two-pollutant models used to adjust for copollutants.	Results reported for RR corresponding to a 10 µg/m2 increase in NO_2 All CVD 1.0302 (1.0042, 1.0568), lag 0 Heart Disease 1.0085 (0.9984, 1.0188), lag 2 Cerebrovascular Disease 1.0362 (1.0066, 1.0667), lag 4 Clear association of NO_2 with cerebrovascular disease observed. Association persisted after Inclusion of BS and SO_2 in two-pollutant models with NO_2. Cases of digestive disorders served as a control group - null association with NO_2 observed.

REFERENCE, STUDY LOCATION, & PERIOD	OUTCOMES, DESIGN, & METHODS	MEAN LEVELS & MONITORING STATIONS	COPOLLUTANTS (CORRELATIONS)	EFFECTS: RELATIVE RISK OR PERCENT CHANGE & CONFIDENCE INTERVALS ([95% LOWER, UPPER])
D'Ippoliti et al. (2003) Rome, Italy Study Period: Jan 1995- Jun 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 yrs, ≥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.	NO_2 24 h (μg/m^3) Mean (SD): 86.4 (15.8) 25th: 74.9 50th: 86.0 75th: 96.9 IQR: 22 # Stations: 5	TSP 24 h (0.37) SO_2 24 h (0.31) CO 24 h (0.03) No multipollutant models	Results presented for OR associated with incremental increase in NO_2 equivalent to one IQR. AMI 1.026 (1.002, 1.052), lag 0 1.026 (0.997, 1.057), lag 0-2 Association observed for NO_2 but TSP association more consistent. Authors think that TSP, CO, and NO_2 cannot be distinguished from traffic-related pollution in general.
Llorca et al. (2005) Torrelavega, Spain Study period: 1992-1995	Outcome(s) (ICD): CVD (called cardiac in paper) 390-459. Emergency admissions, excluding non residents. Obtained admissions records from hospital admin office. Study design: Time-series Statistical analyses: Poisson regression, APHEA protocol Covariates: rainfall, temperature, wind speed direction N: 18,137 admissions Statistical software: STATA Lag(s): not reported	NO_2 24 h μg/m^3 Mean (SD): 21.3 (16.5)	TSP (-0.12) SO_2 (0.588) SH2 (0.545) NO (0.855) Multipollutant models	Results reported for RR of hospital admissions for 100 μg/m^3 increase in NO_2. CVD admissions: 1.27 (1.14, 1.42), 1-pollutant model 1.10 (0.92, 1.32), 5-pollutant model Effect of NO_2 diminished in multipollutant model.
Pantazopoulou et al. (1995) Athens, Greece Study Period: 1988 (Winter and Summer)	Outcome(s): Cardiac Disease ICD codes not provided. Cases ascertained from National Center for Emergency Service database. Cases diagnosed at time of admission so they are ED visits and were not necessarily admitted to the hospital. Study design: Time-series Statistical Analyses: Linear regression (not well described) Covariates: Dummy variables for winter mos with Jan as referent. Dummy variables for summer mos with Apr as referent. Day of the wk, holidays, temperature, relative humidity, N: 25,027 cardiac admissions. Lag(s): NR	NO_2 1-h max (μg/m^3): Winter Mean (SD): 94 (25) 5th: 59 50th: 93 95th: 135 Summer Mean (SD): 111 (32) 5th: 65 50th: 108 95th: 173 # Stations: 2	CO, BS No correlations provided	Results reported for regression coefficients based on an incremental increase in NO_2 of 76 μg/m^3 in winter and 108 μg/m^3 in summer (5th to 95th percentile). Winter (regression coefficient) 11.2 (3.3, 19.2) Summer (regression coefficient) -0.06 (-6.6, 6.5)

REFERENCE, STUDY LOCATION, & PERIOD	OUTCOMES, DESIGN, & METHODS	MEAN LEVELS & MONITORING STATIONS	COPOLLUTANTS (CORRELATIONS)	EFFECTS: RELATIVE RISK OR PERCENT CHANGE & CONFIDENCE INTERVALS ([95% LOWER, UPPER])
Poloniecki et al. (1997) London, UK Study Period: Apr 1987-Mar 1994, 7 yrs	Outcome(s): All CVD 390-459; MI 410; Angina pectoris 413; other IHD 414; ARR 427; congestive heart failure 428; cerebrovascular disease 430-438. Hospital Episode Statistics (HES) data on emergency hospital admissions. Study Design: Time-series N: 373, 556 CVD admissions Statistical Analyses: Poisson regression, linear and quadratic terms to adjust for long-term trends. 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 day	NO_2 24 h ppb: Min: 8 10%: 23 Median: 35 90%: 53 Max: 198	Black Smoke CO 24 h SO_2 24 h O_3 8 h Correlations between pollutants high but not specified.	Results expressed as a relative rate (RR) for an incremental increase of NO_2 equivalent to 30 ppb (10th-90th percentile). AMI: 1.0274 (1.0084, 1.0479) Angina Pectoris: 1.0212 (0.9950, 1.0457) Other IHD: 0.99 (0.0067, 1.0289) Cardiac ARR: 1.0274 (1.0006, 1.0984) Heart Failure: 0.9970 (0.9769, 1.0194) Cerebrovascular Disease: 0.9851 (0.9684, 1.0045) Other Circulatory: 1.0182 (1.0000, 1.0398) All CVD: 1.0243 (1.0054, 1.0448) No attenuation of NO_2 association with MI in two-pollutant model (cool season).
Pönkä and Virtanen (1996) Helsinki, Finland Study Period: 1987-1989, 3 yrs	Outcome(s) (ICD9): IHD 410-414; MI 410; TIA 411; Cerebrovascular diseases 430-438; Cerebral ischemia due to occlusion of extracerebral vessels 433; Cerebral ischemia due to occlusion of cerebral vessels 434; Transient ischemic cerebral attack 435. Case ascertainment was for both emergency admission and hospital admissions – done via registry system. Study Design: Time-series Statistical Analyses: Poisson regression, pollutant concentrations log transformed N: 12,664 all IHD admissions; 7005 IHD ED admissions; 7232 cerebrovascular hospital admissions; 3737 cerebrovascular ED admissions. Covariates: Weather, day of wk, long-term trends, influenza Lag(s): 1-7 days	NO_2 8 h ($\mu g/m^3$) Mean (SD): 39 (16.2) Range: 4, 170 NO 8 h $\mu g/m^3$ Mean (SD): 91 (61) Range: 7, 467 # Stations: 2	SO_2 8 h NO 8 h TSP 8 h O_3 8 h NO_2 highly correlated with SO_2 and TSP.	Results reported are regression coefficients and standard errors (SE). NO_2 with ED admissions for transient short term ischemic attack -0.056 (0.105), p = 0.59, lag 1 NO_2 with ED admissions for cerebrovascular disease -0.025 (0.057), p = 0.657, lag 1 NO with IHD, all admissions 0.097 (0.023), p < 0.001, lag 1 NO with IHD, ED admissions 0.111 (0.030), p < 0.001, lag 1 Significant increase in admissions for transient short-term ischemic attack and cerebrovascular diseases for lag 6 associated with NO_2 exposure.
Prescott et al. (1998) * Edinburgh, UK Study period: Oct 1992-June 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 wkday variation, temperature, and wind speed. Lag(s): 0, 1, 3 day moving avg	NO_2 24 h (ppb) Mean (SD): 26.4 (7.0) Range: 9, 58 IQR: 10 ppb	O_3, 24 h PM, 24 h SO_2, 24 h CO, 24 h Correlations not reported.	Results reported for percent change in admissions based on an incremental increase in NO_2 equivalent to the IQR of 10 ppb. <65 yrs, CVD admissions -0.05 (-5.2, 4.5), 3 day moving avg 65+ yrs, CVD admissions -0.9 (-8.2, 7.0), 3 day moving avg Data for lag 1 not presented.

REFERENCE, STUDY LOCATION, & PERIOD	OUTCOMES, DESIGN, & METHODS	MEAN LEVELS & MONITORING STATIONS	COPOLLUTANTS (CORRELATIONS)	EFFECTS: RELATIVE RISK OR PERCENT CHANGE & CONFIDENCE INTERVALS ([95% LOWER, UPPER])
Yallop et al. (2007) London, England Study Period: Jan. 1988-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, PM10: daily avg used for all copollutants High O_3 levels correlate with low NO, low CO, increased wind speeds and low humidity and each was associated with admission for pain. Not possible to distinguish associations in analysis.	Results reported are cross-correlation coefficients. NO inversely correlated with admission for acute pain in SCD. CFF: -0.063, lag 0

*Default GAM
AMI Acute Myocardial Infarction
ARR Arrhythmia
BC Black Carbon
COH coefficient of haze
CP Course Particulate
CVD Cardiovascular Disease
EC Elemental Carbon
FP Fine Particulate
HS Hemorrhagic Stroke
ICD9 International Classification of Disease, 9th Revision
IHD Ischemic Heart Disease
IS ischemic stroke
MI Myocardial Infarction
OC Organic Carbon
OHC Oxygenated Hydrocarbons
PERI Peripheral Vascular and Cerebrovascular Disease
PM Particulate Matter
PIH primary intracerebral hemorrhage
PNC Particle Number Concentration
SHS Subarachnoid hemorrhagic stroke
TP Total Particulate
UBRE Unbiased Risk Estimator

Table AX6.3-9. Human health effects of oxides of nitrogen: cvd hospital admissions and visits: Asia

REFERENCE, STUDY LOCATION, & PERIOD	OUTCOMES, DESIGN, & METHODS	MEAN LEVELS & MONITORING STATIONS	COPOLLUTANTS (CORRELATIONS)	EFFECTS: RELATIVE RISK OR PERCENT CHANGE & CONFIDENCE INTERVALS ([95% LOWER, UPPER])
Chan et al. (2006) Taipai, Taiwan Period of Study: Apr 1997-Dec 2002, 2090 days	Outcome(s) (ICD9): Cerebrovascular disease 430-437; stroke 430-434; hemorrhagic stroke 430-432; ischemic stroke 433-434. Emergency admission data collected from National Taiwan University Hospital. Ages groups analyzed: Age >50 included in study Study Design: Time-series N: 7341 Cerebrovascular admissions among those >50 yrs old # of Hospitals: Catchment area: Statistical Analyses: Poisson regression, GAMs used to adjust for non-linear relation between confounders and ER admissions. Covariates: Time-trend variables: yr, mo, and day of wk, daily temperature difference, and dew point temperature. Linearity: Investigated graphically by using the LOESS smoother. Statistical Package: NR Lag: 0-3, cumulative lag up to 3 days	NO_2 24-h avg (ppb): Mean: 29.9 SD = 8.4 Min: 8.3 Max: 77.1 IQR: 9.6 ppb # of Stations: 16 Correlation among stations: NR	PM10 24 h; r = 0.50 $PM_{2.5}$ 24 h; r = 0.64 CO 8-h avg; r = 0.77 SO_2 24 h; r = 0.64 O_3 1-h max; r = 0.43 Two-pollutant models to adjust for copollutants.	Results reported for OR for association of emergency department admissions with an IQR increase in NO_2 (9.3 ppb) Cerebrovascular: 1.032 (0.991, 1.074), lag 0 Stroke: 0.994 (0.914, 1.074), lag 0 Ischemic stroke: 1.025 (0.956, 1.094), lag 0 Hemorrhagic stroke: 0.963 (0.884, 1.042), lag 0 No significant associations for NO_2 reported. Lag 0 shown but similar null results were obtained for lags 1-3. NO_2 highly correlated with PM and CO.
Chang et al. (2005) Taipei, Taiwan Study Period: 1997-2001, 5 yrs	Outcome(s) (ICD9): CVD 410-429. Daily clinic visits or hospital admission from computerized records of National Health Insurance. Discharge data. Source Population: 2.64 Million N: 40.8 admissions/day, 74,509/5 yrs # Hospitals: 41 Study Design: Case-crossover, referent day 1 wk before or after index day Statistical Analyses: Conditional logistic regression. Covariates: Same day temperature and humidity. Season: Warm/cool (stratified by temperature cutpoint of 20 ºC) Lag(s): 0-2 days	NO_2 24-h avg (ppb): Mean: 31.54 Min: 8.13 25th: 26.27 50th: 31.03 75th: 36.22 Max: 77.97 # of Stations: 6	CO 24-h avg O_3 24-h avg SO_2 24-h avg PM10 24-h avg Correlations not reported. Two-pollutant models to adjust for copollutants	OR for the association of CVD admissions with an incremental increase in 24-h avg NO_2 equivalent to one IQR, 9.95 ppb. Warm (≥20 ºC) 1.177 (1.150, 1.205), lag 0-2 Cool (<20 ºC) 1.112 (1.058, 1.168), lag 0-2 NO_2 effect remained in all warm season two-pollutant models. Effect remained in cool season two-pollutant models with the exception of the model that included PM10.

REFERENCE, STUDY LOCATION, & PERIOD	OUTCOMES, DESIGN, & METHODS	MEAN LEVELS & MONITORING STATIONS	COPOLLUTANTS (CORRELATIONS)	EFFECTS: RELATIVE RISK OR PERCENT CHANGE & CONFIDENCE INTERVALS ([95% LOWER, UPPER])
Hosseinpoor et al. (2005) Tehran, Iran Study period: Mar 1996-Mar 2001, 5 yrs	Outcome(s) (ICD9): Angina pectoris 413. Primary discharge diagnosis from registry databases or records. Study Design: Time-series Statistical Methods: Poisson regression # Hospitals: 25 Covariates: Long-term trends, seasonality, temperature, humidity, holiday, post-holiday, day of wk. Lag(s): 0-3	NO_2 24-h avg (μg/m^3) Mean (SD): 60.01 (39.69) Min: 0.30 25th: 29.39 Median: 47.42 75th: 84.55 Max: 324.78	NO_2 CO O_3 PM10 Correlations not reported	Results reported for relative risk in hospital admissions per increment of 10 μg/m^3 SO_2. Angina 1.00618 (1.00261, 1.00976), lag 1 In a multipollutant model only CO (lag 1) was significantly associated with angina pectoris related hospital admissions.
Lee et al. (2003a)* Seoul, Korea Study period: Dec 1997-Dec 1999, 822 days, 184 days in summer	Outcome(s) (ICD10): IHD: Angina pectoris 120; Acute or subsequent MI 121-123; other acute IHD 124. Electronic medical insurance data used. Study Design: Time-series Statistical Methods: Poisson regression, GAM with default convergence criteria. Age groups analyzed: all ages, 64+ Covariates: long-term trends LOESS smooth, temperature, humidity, day of wk. Season: Presented results for summer (June, July, Aug) and entire period. Lag(s): 0-6	NO_2 24 h (ppb): 5th: 16 10th: 23.7 Median: 30.7 75th: 38.3 95th: 48.6 Mean (SD): 31.5 (10.3) IQR: 14.6	PM10; r = 0.73, 0.74 SO_2; r = 0.72, 0.79 O_3; r = -0.07, 0.63 CO; r = 0.67, 0.79 Range depends on summer vs. entire period. Two-pollutant models	Results reported for RR of IHD hospital admission for an incremental increase in NO_2 equivalent to one IQR. 64+, entire study period: 1.08 (1.03, 1.14), lag 5 64+, summer only: 1.25 (1.11, 1.41), lag 5 Results for lag 5 presented above. Lag 0 or 1 results largely null - presented graphically. Confounding by PM10 was not observed in these data using two-pollutant models.
Tsai et al. (2003a) Kaohsiung, Taiwan Study period: 1997-2000	Outcome(s) (ICD9): All cerebrovascular 430-438; SHS 430; PIH 431-432; IS 433-435; Other 436-438. Ascertained from National Health Insurance Program computerized admissions records. Study Design: Case-crossover Statistical Analysis: Conditional logistic regression. Statistical Software: SAS Seasons: ≥20 ºC; <20 ºC. N: 23,179 stroke admissions # Hospitals: 63 Lag(s): 0-2, cumulative lag up to 2 previous days	24-h avg NO_2 (ppb) Min: 6.25 25th: 19.25 Median: 28.67 75th: 36.33 Max: 63.40 Mean: 28.17	PM10 SO_2 CO O_3	Results reported as OR for the association of admissions with an incremental increase of NO_2 equivalent to the IQR of 17.1 ppb PIH admissions Warm: 1.56 (1.32, 1.84), lag 0-2 Cool: 0.81 (0.0, 1.31), lag 0-2 IS admissions: Warm: 1.55 (1.40, 1.71), lag 0-2 Cool: 1.16 (0.81, 1.68), lag 0-2 Effects persisted after adjustment for PM10, SO_2, CO, and O_3. PIH: 1.31 (1.03, 1.66) NO_2 w/ PM10 1.66 (1.38, 2.00), NO_2 w/ SO_2 1.60 (1.25, 2.05) NO_2 w/ CO 1.51 (1.26, 1.80) NO_2 w/ O_3 IS: 1.39 (1.20, 1.60) NO_2 w/ PM10 1.62 (1.45, 1.81), NO_2 w/ SO_2 1.54 (1.33, 1.79), NO_2 w/ CO 1.53 (1.37, 1.71), NO_2 w/ O_3

REFERENCE, STUDY LOCATION, & PERIOD	OUTCOMES, DESIGN, & METHODS	MEAN LEVELS & MONITORING STATIONS	COPOLLUTANTS (CORRELATIONS)	EFFECTS: RELATIVE RISK OR PERCENT CHANGE & CONFIDENCE INTERVALS ([95% LOWER, UPPER])
Wong et al. (1999) Hong Kong, China Study Period: 1994-1995	Outcome(s) (ICD9): CVD: 410-417, 420-438, 440-444; CHF 428; IHD 410-414; Cerebrovascular Disease 430-438. Hospital admissions through ER departments via Hospital Authority (discharge data). Study Design: Time-series Statistical Analyses: Poisson regression, linear and quadradic terms for long-term trends, 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	NO_2 24-h avg (μg/m^3) Min: 16.41 25th: 39.93 Median: 51.39 75th: 51.39 Max: 122.44	PM10; r = 0.79 SO_2 O_3 Range for other pollutants: r = 0.68, 0.89.	Results reported for RR associated with incremental increase in NO_2 equal to 10 μg/m^3. CVD 5-64 yrs: 1.008 (0.998, 1.018), lag 0-1 65+ yrs: 1.016 (1.009, 1.023), lag 0-1 All ages: 1.013 (1.007, 1.020), lag 0-1 CHF 1.044 (1.25, 1.063), lag 0-3 IHD 1.010 (0.999, 1.020), lag 0-1 Cerebrovascular Disease 1.008 (0.998, 1.018), lag 0-1 Interaction of NO_2 with O_3 observed
Wong et al. (2002)* Hong Kong London Study Period: 1995-1997	Outcome(s) (ICD9): Cardiac disease 396-429; IHD 410-414. Admissions through the emergency department, general outpatient, or direct to inpatient wards. Study design: Statistical analysis: Poisson regression, GAMs, nonparametric smooth functions (LOESS) Covariates: Statistical Software: SPlus	24-h avg NO_2 Hong Kong Mean (warm/cool): 55.9 (48.1/63.8) Min: 15.3 10th: 31.8 50th: 53.5 90th: 81.8 Max: 151.5 Hong Kong Mean (warm/cool): 64.3 (62.6.1/66.1) Min: 23.7 10th: 42.3 50th: 61.2 90th: 88.8 Max: 255.8	Hong Kong SO_2; r = 0.37 PM10; r = 0.82 O_3; r = 0.43 London SO_2; r = 0.71 PM10; r = 0.68 O_3; r = -0.29	Results reported for excess risk associated with a 10 μg/m^3 change in mean concentration Single-pollutant model. Hong Kong: 1.8 (1.2, 2.4), lag 0-1 London: -0.1 (-0.6, 0.5), lag 0-1 Multipollutant results Hong Kong: 1.6 (1.0, 1.3), lag 0-1, adjusted for Ozone 1.7 (0.8, 2.7), lag 0-1, adjusted for PM10 1.6 (0.8, 2.4), lag 0-1, adjusted for SO_2 London: 0.1 (-0.5, 0.6), lag 0-1, adjusted for Ozone -0.4 (-1.2, 0.4), lag 0-1, adjusted for PM10 -0.2 (-0.9, 0.5), lag 0-1, adjusted for SO_2

REFERENCE, STUDY LOCATION, & PERIOD	OUTCOMES, DESIGN, & METHODS	MEAN LEVELS & MONITORING STATIONS	COPOLLUTANTS (CORRELATIONS)	EFFECTS: RELATIVE RISK OR PERCENT CHANGE & CONFIDENCE INTERVALS ([95% LOWER, UPPER])
Yang et al. (2004b) Kaohsiung, Taiwan Period of Study: 1997-2000	Outcome(s) (ICD9): All CVD: 410-429 *(All CVD typically defined to include ICD9 codes 390-459) N: 29,661 Study Design: Case-crossover Statistical Analysis: Poisson time-series regression models, APHEA protocol # of Hospitals: 63 Seasons: Authors indicate not considered because the Taiwanese climate is tropical with no apparent seasonal cycle Covariates: Stratified by warm (≥25º) and cold (<25º) days, temperature and humidity measurements included in the model Statistical Package: SAS Lag: 0-2 days	24-h avg (ppb) Min: 6.25 25%: 19.25 50%: 28.67 75%: 36.33 Max: 63.40 Mean: 28.17 # of Stations: 6 Correlation among stations: NR	PM10 CO SO_2 O_3 8 Two-pollutant models used to adjust for copollutants Correlations NR	OR's for the association of one IQR (17.08 ppb) increase in NO_2 with daily counts of CVD hospital admissions are reported. All CVD (ICD9: 410-429), one-pollutant model ≥25º: 1.380 (1.246, 1.508) <25º: 2.215 (2.014, 2.437) All CVD (ICD9: 410-429), two-pollutant models Adjusted for PM10: ≥25º: 1.380 (1.246, 1.508) <25º: 2.215 (2.014, 2.437) Adjusted for SO_2: ≥25º: 1.149 (1.017, 1.299) <25º: 2.362 (2.081, 2.682) Adjusted for CO: ≥25º: 1.039 (0.919, 1.176) <25º: 2.472 (2.138, 2.858) Adjusted for O_3: ≥25º: 1.159 (1.051, 1.277) <25º: 2.243 (2.037, 2.471) Association of CVD admissions with NO_2 attenuated on warm days after adjustment for copollutants. Association persisted on cool days. Kaohsiung is the center of Taiwan's heavy industry.
Ye et al. (2001) Tokyo, Japan Study Period: Jul-Aug, 1980-1995	Outcome(s): Angina 413; Cardiac insufficiency 428; Hypertension 401-405; MI 410. Diagnosis made by attending physician for hospital emergency transports. Age groups analyzed: 65+ yrs male and female Statistical analysis: GLM Covariates: Maximum temperature, confounding by season minimal since only 2 summer mos included in analysis Statistical Software: SAS Lag(s): 1-4 days	NO_2 24-h avg (ppb) Min: 5.3 Max: 72.2 Mean (SD): 25.4 (11.4)	O_3; r = 0.183 PM10; r = 0.643 SO_2; r = 0.333 CO; r = 0.759	Results reported for model coefficient and 95% CI. Angina: 0.007 (0.004, 0.009) Cardiac insufficiency: 0.006 (0.003, 0.01) MI: 0.006 (0.003, 0.01)

REFERENCE, STUDY LOCATION, & PERIOD	OUTCOMES, DESIGN, & METHODS	MEAN LEVELS & MONITORING STATIONS	COPOLLUTANTS (CORRELATIONS)	EFFECTS: RELATIVE RISK OR PERCENT CHANGE & CONFIDENCE INTERVALS ([95% LOWER, UPPER])

* Default GAM
AMI Acute Myocardial Infarction
ARR Arrhythmia
BC Black Carbon
COH coefficient of haze
CP Course Particulate
CVD Cardiovascular Disease
EC Elemental Carbon
FP Fine Particulate
HS Hemorrhagic Stroke
ICD9 International Classification of Disease, 9th Revision
IHD Ischemic Heart Disease
IS ischemic stroke
MI Myocardial Infarction
OC Organic Carbon
OHC Oxygenated Hydrocarbons
PERI Peripheral Vascular and Cerebrovascular Disease
PM Particulate Matter
PIH primary intracerebral hemorrhage
PNC Particle Number Concentration
SHS Subarachnoid hemorrhagic stroke
TP Total Particulate
UBRE Unbiased Risk Estimator

Table AX6.3-10. Studies examining exposure to ambient NO_2 and heart rate variability as measured by standard deviation of normal-to-normal intervals (SDNN).

AUTHOR, YEAR, LOCATION	STUDY DESIGN	AVG TIME	NO_2 CONC (PPB)		COPOLLUTANT CORRELATION	OUTCOME	% CHANGE (95% CI)
			MEAN (SD)	RANGE			
Liao et al. (2004) US, ARIC study	Subjects: 4,390 adults Analysis Method: multivariable linear regression	24 h	21 (8)		none	lag 1	-5.0% (-9.2, --7)
Chan et al. (2005) Taiwan	Subjects: 83 adults recruited from cardiology Analysis Method: linear mixed effects regression	1 h	33 (15)	1, 110	PM_{10}: 0.4 O_3: -0.4 SO_2: 0.5 CO: 0.7	4-h lag	-4.5% (-8.1, --30)
						8-h lag	-6.9% (-12.0, -1.8)
Wheeler et al. (2006) Atlanta	Subjects: 30 adults (12 MI + 22 COPD) Analysis Method: linear mixed models	4 h	18 (no sd given)	p10-p20, 7, 30	$PM_{2.5}$: 0.4 CO: 0.5	MI patients [N = 12] 4-h lag	-26.0% (-42.1, -8.6)
						COPD patients [N = 22] 4-h lag	16.6% (0.2, 34.3)

AUTHOR, YEAR, LOCATION	STUDY DESIGN	AVG TIME	NO_2 CONC (PPB)		COPOLLUTANT CORRELATION	OUTCOME	% CHANGE (95% CI)
			MEAN (SD)	RANGE			
Luttmann-Gibson et al. (2006) Steubenville	Subjects: 32 adults (>50 yrs) Analysis Method: mixed models	24 h	10 (no sd given)	p25-p75, 6, 13	$PM_{2.5}$: 0.4 O_3: -0.3 SO_2: 0.3	lag 1	0.3% (-6.0, 6.6)
Schwartz et al. (2005) Boston	Subjects: 28 elderly adults Analysis Method: hierarchical models	24 h	med 18	p25-p75, 14, 23	$PM_{2.5}$: :0.3 O_3: 0.02 CO: 0.6	lag 1	-1.6% (-7.8, 5.1)

Table AX6.3-11. Studies examining exposure to ambient NO_2 and heart rate variability as measured by variables recorded on implantable cardioverter defibrillators (ICDs).

AUTHOR, YEAR, LOCATION	SUBJECTS	ANALYSIS METHOD	NO_2 CONC (PPB)		COPOLLUTANT CORRELATION	OUTCOME	OR (95% CI)
			MEAN (SD)	RANGE			
Peters et al. (2000a) Eastern MA	100 cardiac outpatients	logistic regression, fixed effects	23 (no sd given)	11, 65	$PM_{2.5}$: 0.6 O_3: -0.3 SO_2: 0.3 CO: 0.7	Risk of ICD-recorded ventricular arrhythmias	
						lag 1	1.55 (1.05, 2.29)
						lag 0-4	1.88 (1.01, 3.49)
Rich et al. (2005) Boston	203 cardiac outpatients	case-crossover	med 22	p25-max, 18, 62		All patients lag 0-1	1.54 (1.11, 2.18)
						Patients with recent arrhythmia (<3 days) lag 0-1	2.09 (1.26, 3.51)
Dockery et al. (2005) Boston	307 cardiac outpatients	logistic regression, GEE	med 23	p25-p95, 19, 34	$PM_{2.5}$ > 0.4 O_3 < -0.4 SO_2 > 0.4 CO: 0.6	Patients with recent arrhythmia (<3 days) lag 0-1	2.14 (1.14, 4.03)
Pekkanen et al. (2002) Finland	45 cardiac patients	linear regression, GAM	med 16	p25-max, 12, 36	$PM_{2.5}$: 0.4 CO: 0.3	lag 2	14.1 (3.0, 65.4)
Ruidavets et al. (2005) France	863 adults	polytomous logistic regression	16 (6)	2, 48	O_3: -0.3 SO_2: 0.7	lag 8h	2.7 (1.2, 5.4)

l results given for 20-ppb increase in NO_2 with 24-h averaging time.

Table AX6.3-12. Birth weight and long-term NO_2 exposure studies

AUTHOR, YEAR, LOCATION	STUDY DETAILS	CONC RANGE (PPB)			CORRELATION WITH OTHER POLLUTANTS	OUTCOMES	ODDS RATIO (95% CI)
		LOW	MID-RANGE	HIGH			
Lin et al. (2004) Taiwan	Subjects: 92,288 birth cert Years: 1995-1997 Group: Term LBW Analysis method: Logistic regression Distance 3 km	<26.1	26.1, 32.9	>32.9		Pregnancy	
						Medium NO_2	1.06 (0.93, 1.22)
						High NO_2	1.06 (0.89, 1.26)
		<24.3	24.3, 34.7	>34.7		Trimester 1	
						Medium NO_2	1.10 (0.96, 1.27)
						High NO_2	1.09 (0.89, 1.32)
		<24.0	24.0, 34.4	>34.4		Trimester 2	
						Medium NO_2	0.87 (0.76, 1.00)
						High NO_2	0.93 (0.77, 1.12)
		<23.8	23.8, 34.2	>34.2		Trimester 3	
						Medium NO_2	1.01 (0.88, 1.16)
						High NO_2	0.86 (0.71, 1.03)
Lee et al. (2003b) Seoul, Korea	Subjects: 388,105 birth cert Years: 1996-1998 Group: Term LBW model (GAM) , Interquartile Averaging time: 24h Analysis method: Generalized additive	25	31.4	39.7	PM_{10}: 0.66 SO_2: 0.75 CO: 0.77	Pregnancy	1.04 (1.00, 1.08)
					PM_{10}: 0.81 SO_2: 0.77 CO: 0.78	Trimester 1	1.02 (0.99, 1.04)
					PM_{10}: 0.8 SO_2: 0.76 CO: 0.82	Trimester 2	1.03 (1.01, 1.06)
						Trimester 3	0.98 (0.96, 1.00)

AUTHOR, YEAR, LOCATION	STUDY DETAILS	CONC RANGE (PPB)			CORRELATION WITH OTHER POLLUTANTS	OUTCOMES	ODDS RATIO (95% CI)
		LOW	MID-RANGE	HIGH			
Bobak M. (2000) Czech	Subjects: 69,935 birth cert Year: 1991 Group: LBW adjusted for GA Averaging time: 24 h Analysis method: Logistic regression, 50 µg increase	12.2	20	31.1	SO_2: 0.53	Trimester 1	0.98 (0.81, 1.18)
					SO_2: 0.62	Trimester 2	0.99 (0.80, 1.23)
					SO_2: 0.63	Trimester 3	0.97 (0.80, 1.18)
Gouveia et al. (2004) Sao Paulo city, Brazil	Subjects: 179,460 live births Group: Ministry of Health, Brazil Year: 1997 Analysis method: GAM models	43.5	117.9	399.6		First Trimester	
						1Q	1
						2Q	1.060 (0.971-1.157)
						3Q	1.197 (0.885-1.619)
						4Q	1.126 (0.812-1.560)
						Second Trimester	
						1Q	1
						2Q	0.986 (0.902-1.076)
						3Q	1.008 (0.871-1.167
						4Q	1.034 (0.861-1.243)
						Third trimester	
						1Q	1
						2Q	0.992 (0.913-1.078)
						3Q	1.041 (0.927-1.169
						4Q	1.046 (0.889-1.231)
Maroziene and Grazuleviciene (2002) Kaunas, Lithuania	Subjects: 3,988 birth cert Group: LBW adjusted for GA Year: 1998 Analysis method: Logistic regression, 10 µg increase					Pregnancy	1.28 (0.97, 1.68)
			6.2 (5.7)			Medium NO_2	0.96 (0.47, 1.96)
						High NO_2	1.54 (0.80, 2.96)

AUTHOR, YEAR, LOCATION	STUDY DETAILS	CONC RANGE (PPB)			CORRELATION WITH OTHER POLLUTANTS	OUTCOMES	ODDS RATIO (95% CI)
		LOW	MID-RANGE	HIGH			
						Trimester 1	0.91 (0.53, 1.56)
						Trimester 2	0.93 (0.61, 1.41)
						Trimester 3	1.34 (0.94, 1.92)
Liu et al. (2003) Vancouver	Subjects: 229,085 birth cert Years: 1986-1998 Group: LBW adjusted for GA Averaging time: 24 h Analysis method: Logistic regression, 10 ppb increase	15.1	18.1	22.3	O_3: -0.25 SO_2: 0.61 CO: 0.72	First mo	0.98 (0.90, 1.07)
						Last mo	0.94 (0.85, 1.04)
Salam et al. (2005) Southern CA	Subjects: 3,901 birth cert Group Term LBW, CHS: Years: 1975-1987 Analysis method: Logistic regression Distance: 5 km or 3 within 50 km, within county		36.1 (15.4)		PM_{10}: 0.55 O_3: -0.1 CO: 0.41	Pregnancy	0.8 (0.4, 1.4)
			IQR 25			Trimester 1	0.9 (0.5, 1.5)
						Trimester 2	1.0 (0.6, 1.6)
						Trimester 3	0.6 (0.4, 1.1)
Bell et al. (2007) CT and MA	Subjects: 358,504 birth cert Group: LBW adjusted for GA Years: 1999-2002 Analysis method: logistic regression, interquartile linear regression, difference in gms per IQR		17.4 (5.0)		$PM_{2.5}$: 0.64 PM_{10}: 0.55	Pregnancy	1.027 (1.002, 1.051)
			IQR 4.8			Black mothers	-12.7 (-18.0, -7.5)
						White mothers	-8.3 (-10.4, -6.3)
Slama et al. (2007) Munich	Subjects: 1016 non-premature births Group: LISA Analysis method: Poisson Regression	0.52	0.75	0.90		Adjusted 1Q	1
						Adjusted 2Q	0.80 (0.52-1.28)
						Adjusted 3Q	1.32 (0.86-2.09)
						Adjusted 4Q	1.16 (0.71-1.71)
						Continuous coding	1.21 (0.86-1.68)

AUTHOR, YEAR, LOCATION	STUDY DETAILS	CONC RANGE (PPB)			CORRELATION WITH OTHER POLLUTANTS	OUTCOMES	ODDS RATIO (95% CI)
		LOW	MID-RANGE	HIGH			

Table AX6.3-13. Preterm delivery and long-term NO_2 exposure studies

AUTHOR, YEAR, LOCATION	STUDY DETAILS	CONC RANGE (PPB)			CORRELATION WITH OTHER POLLUTANTS	OUTCOME	ODDS RATIO (95% CI)
		LOW	MID-RANGE	HIGH			
Bobak (2000) Czech	Subjects: 69,935 birth cert Group: Preterm Years: 1991 Avg time: 24 h Analysis Method: Logistic regression, 50 µg increase	12.2	20	31.1	SO_2: 0.62	Trimester 1	1.10 (1.00, 1.21)
						Trimester 2	1.08 (0.98, 1.19)
						Trimester 3	1.11 (1.00, 1.23)
Liu S. et al. (2003) Vancouver	Subjects: 229,085 birth cert Group: Preterm Years: 1986-1998 Avg time: 24 h Distance: 13 monitors Analysis Method: 10 ppb increase	15.1	18.1	22.3	O_3: -0.25 SO_2: 0.61 CO: 0.72	First mo	1.01 (0.94, 1.07)
						Last mo	1.08 (0.99, 1.17)
Maroziene and Grazuleviciene R. (2002) Kaunas, Lithuania	Subjects: 3,988 birth cert Group: Preterm Analysis Method: Logistic regression					Pregnancy	1.25 (1.07, 1.46)
			6.2 (5.7)			Medium NO_2	1.14 (0.77, 1.68)
						High NO_2	1.68 (1.15, 2.46)
						Trimester 1	1.67 (1.28, 2.18)
						Trimester 2	1.13 (0.90, 1.40)
						Trimester 3	1.19 (0.96, 1.47)

AUTHOR, YEAR, LOCATION	STUDY DETAILS	CONC RANGE (PPB)			CORRELATION WITH OTHER POLLUTANTS	OUTCOME	ODDS RATIO (95% CI)
		LOW	MID-RANGE	HIGH			
Ritz et al. (2000) Southern CA	Subjects: 97,158 birth cert Group: Preterm Years: 1989-1993 Avg time: 24 h Analysis Method: Logistic regression Distance: Zip code within 2 miles	32	40.9	50.4	PM_{10}: 0.74 O_3: -0.12 CO: 0.64	Frst mo	No effects for any preg period
						6 wks before birth	No effects for any preg period
Leem et al. (2006) Inchon, Korea	Subjects: 52,113 birth cert Group: Preterm Years: 2001-2002 Analysis Method: Log binomial regression	15.78	22.93	29.9	PM_{10}: 0.37 SO_2: 0.54 CO: 0.63	Trimester 1 Q2	1.13 (0.99, 1.27)
						Trimester 1 Q3	1.07 (0.94, 1.21)
						Trimester 1 Q4	1.24 (1.09, 1.41) Trend .02
						Trimester 3 Q2	1.06 (0.93, 1.20)
						Trimester 3 Q3	1.14 (1.01, 1.29)
						Trimester 3 Q4	1.21 (1.07, 1.37) Trend <.001
Hansen et al. (2006) Brisbane	Subjects: 28,200 birth cert Group: Preterm Years: 2000-2003 Avg time: 24 h Analysis Method: Logistic regression		8.8 (4.1)		PM_{10}: 0.32 O_3: 0.13	Trimester 1	0.93 (0.78, 1.12)
						90 days before birth	1.03 (0.86, 1.23)

Table AX6.3-14. Fetal growth and long-term NO_2 exposure studies

AUTHOR, YEAR, LOCATION	STUDY DETAILS	CONC RANGE (PPB)			CORRELATION WITH OTHER POLLUTANTS	OUTCOME	ODDS RATIO (95% CI)
		LOW	MID-RANGE	HIGH			
Salam et al. (2005) Southern CA, CHS	Subjects: 3,901 birth cert Group: Term SGA, <15% of data Years: 1975-1987 Avg time: 24 h Analysis Methods: Linear mixed model, IQR = 25 Distance: 5 km or 3 monitors within 50 km		36.1 (15.4)		PM_{10}: 0.55 O_3: -0.1 CO: 0.69	Pregnancy	1.1 (0.9, 1.3)
						Trimester 1	1.2 (1.0, 1.4)
						Trimester 2	1.0 (0.8, 1.2)
						Trimester 3	1.0 (0.8, 1.2)
Mannes et al. (2005) Sydney	Subjects: 51,460 birth cert Group: SGA, >2sd below national data Years: 1998-2000 Avg time: 1-h max Analysis Methods: Logistic regression, 1 ppb Distance: 5 km	18	23	27.5	$PM_{2.5}$: 0.66 PM_{10}: 0.47 O_3: 0.29 CO: 0.57	Trimester 1	1.06 (0.99, 1.14)
			23.2 (7.4)			Trimester 2	1.14 (1.07, 1.22)
						Trimester 3	1.13 (1.05, 1.21)
						1 mo before birth	1.07 (1.00, 1.14)
Liu et al. (2003) Vancouver	Subjects: 229,085 birth cert Group: Term SGA, <10% national Years: 1986-1998 Avg time: 24 h Analysis Methods: Logistic regression, 10 ppb Distance: 13 monitors Avg	15.1	18.1	22.3	SO_2: 0.61 O_3: -0.25 CO: 0.72	Trimester 1	1.03 (0.98, 1.10)
						Trimester 2	0.94 (0.88, 1.00)
						Trimester 3	0.98 (0.92, 1.06)
						First mo	1.05 (1.01, 1.10)
						Last mo	0.98 (0.92, 1.03)

Table AX6.3-15. Lung function and long-term NO_2 exposure.

AUTHOR, YEAR, LOCATION	STUDY DETAILS	CONC RANGE (ppb)			CORRELATION WITH OTHER POLLUTANTS	OUTCOME	ODDS RATIO (95% CI)
		LOW	MID-RANGE	HIGH			
Gauderman (2004) Southern CA	Subjects: 1757 children age 10-18, CHS Group: Lung function, Longitudinal Avg Time: 24-h annual Anlaysis Method: 2-stage linear Regression, 34.6 ppb Distance: Study monitors in 12 towns				$PM_{2.5}$: 0.79 PM_{10}: 0.67 O_3: -0.11	Difference in lung growth	
						FVC	-95 (-183.4, -0.6)
						FEV_1	-101.4 (-164.5, -38.4)
						MMEF	-211 (-377.6, -44.4)
Moseler et al. (1994) Frieberg, Germany	Subjects: 467 children age 9-16 Group: Lung function Avg Time: Median wkly Anlaysis Method: Linear regression, Parameter estimates		21.28 threshold			with asthma symp	
						FEV_1	0.437
						lnMEF75%	-0.011
						lnMEF50%	-0.022
						lnMEF25%	-0.029
						no asthma symp	
						FEV_1	-0.049
						lnMEF75%	0.003
						lnMEF50%	0.004
						lnMEF25%	0.003
Ackermann-Liebrich et al. (1997) Switzerland	Subjects: 3,115 adults, 3-yr residents, nonsmokers, SAPALDIA Group: Lung function Avg Time: 24-h annual Anlaysis Method: 2-stage linear Regression Distance: Monitors in 8 Study areas		18.9 (8.5)		PM_{10}: 0.91 O_3 : -0.78 SO_2: 0.86	FVC	-0.0123 (-0.0152, -0.0094)
						FEV_1	-0.0070 (-0.0099, -0.0041)

AUTHOR, YEAR, LOCATION	STUDY DETAILS	CONC RANGE (ppb)			CORRELATION WITH OTHER POLLUTANTS	OUTCOME	ODDS RATIO (95% CI)
		LOW	MID-RANGE	HIGH			
Schindler et al. (1998) Switzerland	Subjects: 560 adults, 3-yr residents, SAPALDIA Group: Lung function Avg Time: Wkly avg Anlaysis Method: Linear regression Distance: Personal and Home monitors					FVC home	% change -0.59 (-1)
						FVC personal	
						FEV home	
						FEV personal	
Peters et al. (1999a) Southern CA	Subjects: 3,293 children, CHS Group: Lung function Avg Time: 24 h Anlaysis Method: Linear regression Distance: Study monitors in 12 towns					FVC all: 1986-1990	-42.6 (13.5)
						FVC girls: 1986-1990	-58.5 (15.4)
						FEV_1 all: 1986-1990	-23.2 (12.5)
						FEV_1 girls: 1986-1990	-39.9 (13.9)
						FVC all: 1994	-46.2 (16.0)
						FVC girls: 1994	-56.7 (19.8)
						FEV_1 all: 1994	-22.3 (14.8)
						FEV_1 girls: 1994	-44.1 (16.1)
Tager et al. (2005) Southern & Northern CA	Subjects: 255 students UC Berkeley Group: Lung function Avg Time: Anlaysis Method: Linear regression	(MEN)					
		22	30	40	O_3: 0.57	lnFEF75 men	-0.029 (0.003)
		(WOMEN)					
		21	27	40		lnFEF75 women	-0.032 (0.002)

Table AX6.3-16. Asthma and long-term NO_2 exposure.

AUTHOR, YEAR, LOCATION	STUDY DESIGN	ANALYSIS METHOD	CORRELATION WITH OTHER POLLUTANTS	CONC RANGE (PPB)			STUDY FACTOR	ODDS RATIO (95% CI)
				LOW	MID-RANGE	HIGH		
Garrett et al. (1999) Latrobe Valley, Australia	Subjects: 148 children ages 7-14 Years: 1994-1995 Distance: In home Study Group: Asthma, Monash Q	Logistic regression 10 µg			6			
							Bedroom NO_2	1.01 (0.75, 1.37)
							Indoor mean	1.00 (.075, 1.31)
							winter	0.99 (0.84, 1.16)
							summer	2.52 (0.99, 6.42)
Hirsch et al. (1999) Dresden, Germany	Subjects: 5,421 children ages 5-7, 9-11 Years: 1995-1996, 12 mo residence Distance: 4 monitors within 1 km Study Group: Asthma, ISAAC	Logistic regression 10 µg		29.3	33.8	37.8		
							Home address	1.16 (0.94, 1.42)
							Home & school	1.14 (0.86, 1.51)
Peters et al. (1999b) Southern CA, CHS	Subjects: 3,676 children Age 9-16 Years: 1994 Avg time: 24 h Distance: Study monitors in 12 towns Study Groups: Asthma, Questionnaire	Logistic regression IQR = 25 ppb			21.5 mean			
							all children	1.21 (0.850, 1.71)
							boys	1.25 (0.90, 1.75)
							girls	1.07 (0.57, 2.02)

AUTHOR, YEAR, LOCATION	STUDY DESIGN	ANALYSIS METHOD	CORRELATION WITH OTHER POLLUTANTS	CONC RANGE (PPB)			STUDY FACTOR	ODDS RATIO (95% CI)
				LOW	MID-RANGE	HIGH		
Millstein et al. (2004) Southern CA, CHS	Subjects: 2,034 children age 9-11 Years: 1995 Distance: Study monitors in 12 towns Study Groups: Asthma, Medication use	Mixed effects model IQR = 5.74 ppb	$PM_{2.5}$: 0.28 PM_{10}: 0.39				Annual	0.94 (0.71, 1.22)
							Mar-Aug	0.96 (0.68, 1.37)
							Sep-Feb	0.90 (0.66, 1.24)
Pénard-Morand et al. (2005) France 6 towns	Subjects: 4,901 children Age 9-11 Years: 1999-2000, 3 yr residence Avg time: 3 yrs Distance: monitoring sites, school address Study Groups: Asthma, ISAAC	Logistic regression 10 µg	PM_{10}: 0.46 O_3: 0.76 SO_2: 0.35	8.7, 16.0		16.1, 25.7	Lifetime asthma	0.94 (0.83, 1.07)
							Current asthma	0.92 (0.77, 1.10)
Studnicka et al. (1997) 8 communities, Lower Austria	Subjects: 843 children Distance: monitor in each community Avg time: 3 yrs Study Group: Asthma, ISAAC	Logistic regression <.05		8.0, 8.7	11.7, 13.3	14.7, 17.0	Ever asthma low	1.28
							Ever asthma medium	2.14
							Ever asthma high	5.81
							Current asthma low	1.7
							Currrent asthma medium	1.47
							Current asthma high	8.78
Wang et al. (1999) Taiwan	Subjects: 117,080 students age 11-16 Distance: 24 district monitors Study Group: Asthma	Logistic regression Above/below median			28 median		Current asthma	1.08 (1.04, 1.13)

AUTHOR, YEAR, LOCATION	STUDY DESIGN	ANALYSIS METHOD	CORRELATION WITH OTHER POLLUTANTS	CONC RANGE (PPB)			STUDY FACTOR	ODDS RATIO (95% CI)
				LOW	MID-RANGE	HIGH		
Ramadour et al. (2000) 7 communities, France	Subjects: 2,445 children Years: 3-yr residence Age 13-14 Distance: Monitors in each community Study Group: Asthma, ISAAC	Logisitic regression			11-27 mean			Nonsignificant Results
Shima and Adachi et al. (2000) 7 communities, Japan	Subjects: 905 children age 9-10 Distance: In home measurements Monitors near schools Study Groups: Asthma, Prevalence, Incidence	Logistic regression 10-ppb increase		20-29	30-39 7-25 mean Outdoors	≥40	Outdoor 4th grade girls	1.14 (0.65, 2.09)
							Outdoor 5th grade girls	1.14 (0.63, 2.13)
							Outdoor 6th grade girls	0.95 (0.45, 2.05)
							Indoor 4th grade girls	1.63 (1.06, 2.54)
							Indoor 5th grade girls	1.67 (1.06, 2.66)
							Indoor 6th grade girls	1.18 (0.62, 2.18)
							Outdoor	2.10 (1.10, 4.75)
							Indoor	0.87 (0.51, 1.43)

AUTHOR, YEAR, LOCATION	STUDY DESIGN	ANALYSIS METHOD	CORRELATION WITH OTHER POLLUTANTS	CONC RANGE (PPB)			STUDY FACTOR	ODDS RATIO (95% CI)
				LOW	MID-RANGE	HIGH		
Kim et al. (2004a) San Francisco Bay area	Subjects: 1,109 children Age 9-11 Distance: 10 school sites Study Group: Asthma	2-stage Hierarchical model IQR = 3.6 NO_2 IQR = 14.9 NO_X	$PM_{2.5}$: "low" O_3: "low"		24 mean		All children	1.02 (0.97, 1.07)
							All 1 yr residents	1.04 (0.98, 1.10)
							1 yr resident girls	1.09 (1.03, 1.15)
							1 yr resident boys	1.00 (0.94, 1.07)
							All children	1.04 (0.97, 1.11)
							All 1 yr residents	1.07 (1.00, 1.14)
							1 yr resident girls	1.17 (1.06, 1.29)
							1 yr resident boys	1.02 (0.93, 1.11)
Gauderman et al. (2005) Southern CA CHS	Subjects: 208 children Avg time: 4 wk Distance: Outside home Study Group: Asthma	Logistic regression IQR = 5.7			13-51		Lifetime asthma	1.83 (1.04, 3.21)
							Asthma med use	2.19 (1.20, 4.01)
Hwang et al. (2005) Taiwan, National study	Subjects: 32,672 children Distance: Schools within 1 km of monitors Study Group: Asthma, ISAAC	2-stage Hierarchical model 10 ppb NO_X	PM_{10}: 0.34 O_3: -0.39 SO_2: 0.5	21.5	29.6	33.1	Parental atopy	0.99 (0.92, 1.07)
							No parental atopy	1.02 (0.95, 1.10)

Table AX6.3-17. Respiratory symptoms and long-term NO_2 exposure.

STUDY	LOCATION	STUDY GROUP	SUBJECTS	ODDS RATIO (95% CI)	ANALYSIS METHOD	AVG TIME	CONC RANGE (ppb)			CORRE-LATION	DISTANCE
							LOW	MID-RANGE	HIGH		
Karr et al. (2006)	Southern California	Infant Bronchiolitis	18,595 cases; 169,472 controls ages 3 wks to 1 yr	1.03 [0.99, 1.07] per 16 ppb	Conditional logistic regression	Chronic (lifetime avg of 1-h daily max) (ppb)	12	58	204		34 monitors
Karr et al. (2006)	Southern California	Infant Bronchiolitis	18,595 cases; 169,472 controls ages 3 wks to 1 yr	1.04 [1.00, 1.08] per 15 ppb	Conditional logistic regression	Subchronic (avg of 1-h daily max 1 mo prior to hospitalization) (ppb)	12	57	152		34 monitors in home
Garrett et al. (1999)	Latrobe Valley	Symptoms	148 children		Logistic regression			6			
wheeze	Australia	Monash Q	Age 7-14	1.15 (0.85, 1.54)							
cough			1994-1995	1.47 (0.99, 2.18)	10 µg						
short of breath				1.23 (0.92, 1.64)							
chest tightness				1.12 (0.81, 1.56)							
any symptoms				1.24 (0.91, 1.68)	10 µg mean						4 monitors
any symptoms				1.12 (0.93, 1.35)	10 µg winter						
any symptoms				2.71 (1.11, 6.59)	10 µg summer						
Hirsch et al. (1999)	Dresden	Symptoms	5,421 children		Logistic regression		29.3	33.8	37.8		Within 1 km
wheeze home	Germany	ISAAC	Age 5-7, 9 11	1.13 (0.93, 1.37)							
wheeze school			1995-1996	0.95 (0.72, 1.26)	10 µg						
cough home			12 mo residence	1.22 (1.94, 1.44)							
cough school				1.21 (0.96, 1.52)							
cough non-atopic child				1.42 (1.10, 1.84)							
Peters et al. (1999b)	Southern CA	Symptoms	3,676 children		Logistic regression	24 h		21.5 mean			Study monitors in 12 towns

STUDY	LOCATION	STUDY GROUP	SUBJECTS	ODDS RATIO (95% CI)	ANALYSIS METHOD	AVG TIME	CONC RANGE (ppb)			CORRE-LATION	DISTANCE
							LOW	MID-RANGE	HIGH		
wheeze	CHS	Questionnaire	Age 9-16	1.12 (0.86, 1.45)							
cough			1994	1.14 (0.94, 1.39)	IQR = 25 ppb						
wheeze boys				1.54 (1.04, - 2.29)							
wheeze girls				0.86 (0.57, 1.29)							
Millstein et al. (2004)	Southern CA	Symptoms	2,034 children		Mixed effects model	Moly				$PM_{2.5}$: 0.28 PM_{10}: 0.39	Study monitors in 12 towns
wheeze	CHS		Age 9-11	0.93 (0.77, 1.12)							
wheeze Mar-Aug			1995	0.79 (0.40, 1.53)	IQR = 5.74 ppb						
wheeze Sep-Feb				0.85 (0.64, 1.14)							
Pénard-Morand et al. (2005)	France 6 towns	Symptoms	4,901 children		Logistic regression	3 yrs					29 monitoring sites, school address
		ISSAC	Age 9-11								
wheeze past 12 mos.			1999-2000	0.87 (0.75, 1.01)	10 µg		8.7, 16.0		16.1, 25.7	O_3: 0.76 SO_2: 0.35 PM_{10}: 0.46	
			3-yr residence								
Roemer et al. (1993)	Wageningen and Bennekom, Netherlands	Symptoms Questionnaire	73 children grades 3-8 Dec 1990-Mar 1991	No associations	Time series using Yule-Walker estimation method	24 hr avg			127	PM_{10}: 0.57 SO_2: 0.26 BS: 0.65	National Air Quality Monitoring Network
Mukala et al. (1999)	Helsinki	Symptoms	163 children		GEE	Wkly Avg	<8.6	8.6, 14.5	>14.5		Palmes tubes
cough	Finland		Age 3-6	1.23 (0.89, 1.70)	2nd tertile						On outer garment
cough			1991	1.52 (1.00, 2.31)	3rd tertile						
nasal symp winter				0.99 (0.58, 1.68)	2nd tertile						
nasal symp winter				0.89 (0.44. 1.82)	3rd tertile						

STUDY	LOCATION	STUDY GROUP	SUBJECTS	ODDS RATIO (95% CI)	ANALYSIS METHOD	AVG TIME	CONC RANGE (ppb)			CORRE-LATION	DISTANCE
							LOW	MID-RANGE	HIGH		
nasal symp spring				0.76 (0.56, 1.02)	2nd tertile						
nasal symp spring				0.68 (0.46, 1.01)	3rd tertile						
Pikhart et al. (2000)	Prague	Symptoms	3,045 children		Multi-level model		14.8	19	24.1		
wheeze	Czech	SAVIAH	Age 7-10	1.16 (0.95, 1.42)	Individual covariates						
wheeze			1993-1994	1.07 (0.86, 1.33)	Ecological covariates						
wheeze				1.08 (0.86, 1.36)	Both covariates						
Setiani (1996)	6 cities in Japan	Hiroshima Community Health Study	13,836 adult non-smoking women aged 40-59	Logistic regression coefficient (standard error)	Individual multiple linear regression analysis	24 h	graph	graph	graph	SPM: 0.606 OX: -0.337	
Lacrimacy				0.047 (0.046)							
Eye itch				0.036 (0.046							
Runny nose				-0.018 (0.076)							
Sore throat				0.059 (0.042)							
Cough				-0.046 (0.044)							
Plegm				-0.088 (0.049)							
SOB				-0.056 (0.058)							
Sum of cough with phlegm and SOB				-0.035 (0.030)							
Van Strien (2004)	CT and MA	Symptoms	849 children		Poisson regression	10-14 day	5.1	9.9	17.4		In home
wheeze			Age 12 mos	1.15 (0.79, 1.67)	Q2	Avg					
wheeze				1.03 (0.69, 1.53)	Q3						
wheeze				1.45 (0.92, 2.27)	Q4						
cough				0.96 (0.69, 1.36)	Q2						
cough				1.33 (0.94, 1.88)	Q3						

STUDY	LOCATION	STUDY GROUP	SUBJECTS	ODDS RATIO (95% CI)	ANALYSIS METHOD	AVG TIME	CONC RANGE (ppb)			CORRE-LATION	DISTANCE
							LOW	MID-RANGE	HIGH		
cough				1.52 (1.00, 2.31)	Q4						
short of breath				1.59 (0.96, 2.62)	Q2						
short of breath				1.95 (1.17. 3.27)	Q3						
short of breath				2.38 (1.31, 4.34)	Q4						
Nitschke et al. (2006)	Adelaide	Symptoms	174 asthmatic		Zero-inflated negative		School 34 (28)		117 max		9 days in class
Wheeze school	Australia		Children, age 5-13	0.99 (0.93, 1.06)	binomial regression		Home 20 (22)		147 max		3 days at home
Wheeze home			2000	1.00 (0.90, 1.11)							
Cough school				1.01 (0.98, 1.04)	10-ppb increase						
Cough home				0.99 (0.96, 1.02)							
Difficult breath school				1.11 (1.05, 1.18)							
Difficult breath home				1.03 (1.01, 1.05)							
Chest tight school				1.12 (1.07, 1.17)							
Chest tight home				1.02 (0.95, 1.09)							
Hoek and Brukekreef (1993)	Wageningen, Netherlands	Primary school	112 children grades 4-7	No association	Individual linear regression analysis and distribution of individual regression slopes	24-h			127	PM_{10}: 0.55 SO_2: 0.28 BS: 0.65	
Delfino et al. (2006)	Southern California	Asthmatic children	45 children ages 9-18		Linear mixed effects models (Verbeke and Molenberghs 2001)	24-h				Personal NO2, personal $PM_{2.5}$: 0.33	Backpack monitor, active sampling system, central site exposure
Personal NO2										Central NO2, personal $PM_{2.5}$: 0.22	
Not taking anti-inflammatory meds				0.80 (-3.01 to 4.61)						Central NO2, central $PM_{2.5}$: 0.25	

STUDY	LOCATION	STUDY GROUP	SUBJECTS	ODDS RATIO (95% CI)	ANALYSIS METHOD	AVG TIME	CONC RANGE (ppb)			CORRE-LATION	DISTANCE
							LOW	MID-RANGE	HIGH		
Taking anti-inflammatory meds				1.67 (0.55 to 2.79)							
Inhaled corticosteroids				1.22 (0.04 to 2.40							
Antileukotrienes ± inhaled corticosteroes				1.73 (-0.70 to 4.16)							
Central site NO2											
Not taking anti-inflammatory meds				0.96 (-1.34 to 3.26)							
Taking anti-inflammatory meds				1.48 (0.47 to 2.50)							
Inhaled corticosteroids				1.32 (0.33 to 2.32)							
Antileukotrienes ± inhaled corticosteroes				-7.5 (-2.83 to 1.32)							
Salome et al. (1996)	Australia	asthmatic	20 (9 adults and 11 children)		ANOVA		0.02 ppm		1.12 ppm		
Day of exposure- room air											
Change in symptom score: adult				0.01 (0.38)							
Change in symptom score: Child				-0.02 (0.26)							
Wk following exposure- room air											
Severity score: adult				4.38 (1.5)							
Severity score: child				4.20 (1.3)							
Pattenden et al. (2006)	Russia, Austria, Italy, Switzerland, Netherlands	PATY	23,955 children ages 6-12		Logistic regression, Cochran $\chi 2$		12.45		50.00		variable
			1993-1999								
Wheeze				1.01 (0.93-1.10)							
Asthma				1.02 (0.94-1.09)							
Bronchitis				0.99 (0.88-1.12)							

STUDY	LOCATION	STUDY GROUP	SUBJECTS	ODDS RATIO (95% CI)	ANALYSIS METHOD	AVG TIME	CONC RANGE (ppb)			CORRE-LATION	DISTANCE
							LOW	MID-RANGE	HIGH		
Phlegm				1.05 (0.95-1.17)							
Nocturnal cough				1.13 (0.94-1.35)							
Morning cough				1.15 (1.01-1.30)							
Sensitivity to inhaled allergens				1.13 (1.01-1.26)							
Hay fever				1.04 (0.98-1.11)							
Itchy rash				1.05 (0.98-1.12)							
Woken by wheeze				1.06 (0.89-1.26)							
Allergy to pets				1.14 (0.99-1.31)							
Chen et al. (1999)	Taiwan	Study on Air Pollution and Health	941 children ages 8-13	Coefficient (standard error)	models		9.2		141.6		
Day avg											
1 day lag- FVC				-2.66 (1.23)							
1 day lag- FEV10				-0.46 (1.16)							
2 day lag- FVC				-3.32 (1.53)							
2 day lag FEV10				-0.93 (1.45)							
7 day lag- FVC				1.39 (1.71)							
7 day lag- FEV10				2.52 (1.61)							
Daytime Peak											
1 day lag- FVC				-0.59 (0.40)							
1 day lag- FEV10				-0.16 (0.37)							
2 day lag- FVC				-1.33 (0.72)							
2 day lag FEV10				-0.36 (0.68)							
7 day lag- FVC				-0.13 (0.87)							
7 day lag- FEV10				0.43 (0.82							

Table AX6.3-18. Lung cancer.

AUTHOR, YEAR, LOCATION	EXPOSURE	STUDY SUBJECTS	CONC RANGE (PPB)			ANALYSIS	ODDS RATIO (95% CI)
			LOW	MID-RANGE	HIGH		
Nyberg et al. (2000) Stockholm, Sweeden	From addresses and traffic	1,042 cases, 2,364 controls men age 40-75	8.1	10.6	13.3	logistic regression	
						30-yr estimated exposure 10 µg	1.05 (0.93, 1.18)
						Q2	1.18 (0.93, 1.49)
						Q3	0.90 (0.71, 1.14)
						Q4	1.05 (0.79, 1.40)
						10-yr estimated exposure 10 µg	1.10 (0.97, 1.23)
						Q2	1.15 (0.91, 1.46)
						Q3	1.01 (0.79, 1.29)
						Q4	1.07 (0.81, 1.42)
						90th percentile	1.44 (1.05, 1.99)
Nafstad (2004) Norway	Home address 1972-1974	16,209 men age 40-49 at entry followed 1972-1998	5.32	10.6	16	Cox proportional	
						lung cancer incidence 10 µg	1.08 (1.02, 1.15)
						Q2	0.90 (0.70, 1.15)
						Q3	1.06 (0.81, 1.38)
						Q4	1.36 (1.01, 1.83)
						non-lung cancer 10 µg	1.02 (0.99, 1.06
						Q2	0.98 (0.88, 1.08)
						Q3	1.05 (0.94, 1.18)
						Q4	1.04 (0.91, 1.18)

Table AX6.3-19. Effects of acute NO_X exposure on mortality. Risk estimates are standardized for per 20 ppb 24-h avg NO_2 increment.

REFERENCE, STUDY LOCATION, AND PERIOD	OUTCOME MEASURE	MEAN NO2 LEVELS	COPOLLUTANTS CONSIDERED	LAG STRUCTURE REPORTED	METHOD/DESIGN	EFFECT ESTIMATES
META ANALYSIS						
Stieb et al. (2002), re-analysis (2003) meta-analysis of estimates from multiple countries.	All cause	24-h avg ranged from 13 ppb (Brisbane, Australia) to 38 ppb (Santiago, Chile). "Representative" concentration: 24 ppb	PM_{10}, O_3, SO_2, CO	The lags and multiday averaging used in these estimates varied	Meta-analysis of Time-series study results	Single-pollutant model (11 estimates): 0.8% (95% CI: 0.2, 1.5); Multipollutant model estimates (3 estimates): 0.4% (95% CI: -0.2, 1.1)
UNITED STATES						
Samet et al. (2000a,b) (reanalysis Dominici et al., 2003) 90 U.S. cities (58 U.S. cities with NO2 data) 1987-1994	All cause; cardiopulmonary	Ranged from 9 ppb (Kansas City) to 39 ppb (Los Angeles), 24-h avg	PM_{10}, O_3, SO_2, CO; two-pollutant models	0, 1, 2	Poisson GAM, reanalyzed with stringent convergence criteria; Poisson GLM. Time-series study.	24-h avg NO2 (per 20 ppb): Posterior means: All cause: Lag 1: 0.50% (0.09, 0.90) Lag 1 with PM_{10} and SO_2: 0.48% (-0.54, 1.51)
Kinney and Özkaynak (1991) Los Angeles County, CA 1970-1979	All cause; respiratory; circulatory	69 ppb, 24-h avg	KM (particle optical reflectance), NO2, SO_2, CO; multipollutant models	1	OLS (Ordinary Least Squares) on high-pass filtered variables. Time-series study.	All cause: Exhaustive multipollutant model: 0.5% (-0.1, 1.2); Two-pollutant with OX: 0.7% (0.5, 1.0)
Kelsall et al. (1997) Philadelphia, PA, 1974-1988	All cause; respiratory; cardiovascular,	39.6 ppb, 24-h avg	TSP, CO, SO_2, O_3	0 (AIC presented for 0 through 5)	Poisson GAM	All cause: Single-pollutant: 0.3% (-0.6, 1.1); With TSP: -1.2% (-2.2, -0.2)
Ostro et al. (2000) Coachella Valley, CA 1989-1998	All cause; respiratory; cardiovascular; cancer; other	20 ppb, 24-h avg	PM_{10}, $PM_{2.5}$, PM_{10}-2.5, O_3, CO	0-4	Poisson GAM with default convergence criteria. Time-series study.	Lag 0 day: All cause: 5.5% (1.0, 10.3) Respiratory: 1.8% (-10.3, 15.5) Cardiovascular: 3.7% (-1.7, 9.3)
Fairley (1999; reanalysis Fairley, 2003) Santa Clara County, CA 1989-1996	All cause; respiratory; circulatory	28 ppb, 24-h avg	PM_{10}, $PM_{2.5}$, PM_{10}-2.5, SO42-, coefficient of haze, NO_3-, O_3, SO_2;	0, 1	Poisson GAM, reanalyzed with stringent convergence criteria; Poisson GLM. Time-series study.	Lag 1: All cause: 1.9% (0.2, 3.7); Cardiovascular: 1.4% (-1.7, 4.5); Respiratory: 4.8% (-0.3, 10.2)

REFERENCE, STUDY LOCATION, AND PERIOD	OUTCOME MEASURE	MEAN NO2 LEVELS	COPOLLUTANTS CONSIDERED	LAG STRUCTURE REPORTED	METHOD/DESIGN	EFFECT ESTIMATES
Gamble (1998) Dallas, TX 1990-1994	All cause; cardiopulmonary	15 ppb, 24-h avg	PM_{10}, O_3, SO_2, CO; two-pollutant models	Avg 4-5	Poisson GLM. Time-series study.	All cause: 4.4% (0.0, 9.0) Cardiovascular: 1.9% (-4.6, 9.0) Respiratory: 13.7% (-2.0, 32.0)
Dockery et al. (1992) St. Louis, MO and Eastern Tennessee 1985-1986	All cause	St. Louis: 20 ppb; Eastern Tennessee: 12.6 ppb, 24-h avg	PM_{10}, $PM_{2.5}$, SO4, H+, O_3, SO_2	Lag 1	Poisson with GEE. Time-series study.	All cause: St. Louis, MO: 0.7% (-3.5, 5.1) Eastern Tennessee: 3.9% (-8.7, 18.2)
Moolgavkar (2003) Cook County, IL and Los Angeles County, CA, 1987 1995	All cause; cardiovascular	Cook County: 25 ppb; Los Angeles: 38 ppb, 24-h avg	$PM_{2.5}$, PM_{10}, O_3, SO_2, CO; two-pollutant models	0, 1, 2, 3, 4, 5	Poisson GAM with default convergence criteria. Time-series study.	All cause: Lag 1: Cook County: Single-pollutant: 2.2% (1.3, 3.1); with PM_{10}: 1.8% (0.7, 3.0); Los Angeles: Single-pollutant: 2.0% (1.6, 2.5); with $PM_{2.5}$: 1.8% (0.1, 3.6).
Moolgavkar (2000a,b,c); re-analysis (2003). Cook County, IL; Los Angeles County, CA, and Maricopa County, AZ, 1987-1995	Cardiovascular; cerebrovascular; COPD	Cook County: 25 ppb; Los Angeles: 38 ppb; Maricopa County: 19 ppb, 24-h avg	$PM_{2.5}$, PM_{10}, O_3, SO_2, CO; two- and three-pollutant models	0, 1, 2, 3, 4, 5	Poisson GAM with default convergence criteria in the original Moolgavkar (2000); GAM with stringent convergence criteria and GLM with natural splines in the 2003 re-analysis. The 2000 analysis presented total death risk estimates only in figures.	GAM, Lag 1: Cardiovascular: Cook County: 1.1% (-0.5, 2.8); Los Angeles: 2.8% (2.0, 3.6); Maricopa Co.: 4.6% (0.5, 9.0); Re-analysis, GLM: Total deaths: 2.5% (1.5, 3.6)
Lippmann et al. (2000); reanalysis Ito, (2003, 2004) Detroit, MI 1985-1990 1992-1994	All cause; respiratory; circulatory; cause-specific	1985-1990: 23.3 ppb, 24-h avg 1992-1994: 21.3 ppb, 24-h avg	PM_{10}, $PM_{2.5}$, PM_{10}-2.5, SO42-, H+, O_3, SO_2, CO; two-pollutant models	0, 1, 2, 3, 0-1, 0-2, 0-3	Poisson GAM, reanalyzed with stringent convergence criteria; Poisson GLM. Numerical NO2 risk estimates were not presented in the re-analysis. Time-series study.	Poisson GAM: All cause: Lag 1: 1985-1990: 0.9% (-1.2, 3.0) 1992-1994: 1.3% (-1.5, 4.2)
Lipfert et al. (2000) Seven counties in Philadelphia, PA area 1991-1995	All cause; respiratory; cardiovascular; all ages; age 65+ yrs; age <65 yrs; various subregional boundaries	20.4 ppb, 24-h avg	PM_{10}, $PM_{2.5}$, PM_{10}-2.5, SO4, O_3, other PM indices, NO2, SO_2, CO; two-pollutant models	0-1	Linear with 19-day weighted avg Shumway filters. Time-series study. Numerous results.	All-cause, avg of 0- and 1-day lags, Philadelphia: 2.2% ($p > 0.05$)

REFERENCE, STUDY LOCATION, AND PERIOD	OUTCOME MEASURE	MEAN NO2 LEVELS	COPOLLUTANTS CONSIDERED	LAG STRUCTURE REPORTED	METHOD/DESIGN	EFFECT ESTIMATES
Chock et al. (2000) Pittsburgh, PA 1989-1991	All cause; age <74 yrs; age 75+ yrs	Not reported.	PM_{10}, NO2, SO_2, CO; two-, five-, and six-pollutant models	0, plus minus 3 days	Poisson GLM. Time-series study. Numerous results	All cause, lag 0, age 0-74: 0.5% (-2.4, 3.5); age 75+: 1.0% (-1.9, 4.0)
De Leon et al. (2003) New York City, NY 1985-1994	Circulatory and cancer with and without contributing respiratory causes	40.6 ppb, 24-h avg	PM_{10}, O_3, SO_2, CO; two-pollutant models	0 or 1	Poisson GAM with stringent convergence criteria; Poisson GLM. Time-series study.	Gaseous pollutants results were given only in figures. Circulatory: Age < 75: ~1% Age 75+: ~2%
Klemm and Mason (2000); Klemm et al. (2004) Atlanta, GA Aug 1998-July 2000	All cause; respiratory; cardiovascular; cancer; other; age <65 yrs; age 65+ yrs	51.3 ppb, max 1-h.	$PM_{2.5}$, PM_{10}-2.5, EC, OC, O_3, SO42-, NO_3, SO_2, CO	0-1	Poisson GLM using quarterly, moly, or biweekly knots for temporal smoothing. Time-series study.	All cause, age 65+ yrs: avg 0-1 days Quarterly knots: 1.0% (-4.2,6.6); Moly knots: 3.1% (-3.0, 9.7); Bi-wkly knots: 0.9% (-5.9, 8.2)
Gwynn et al. (2000) Buffalo, NY Time-series study.	All cause; respiratory; circulatory	24-h avg 21 ppb	PM_{10}, CoH, O_3, SO_2, CO, H+, SO42-		Poisson GAM with Default convergence criteria.	All cause (lag 3): 2.1% (-0.3, 4.6); Circulatory (lag 2): 1.3% (-2.9, 5.6); Respiratory (lag 1): 6.4% (-2.5, 16.2)
CANADA						
Burnett et al. (2004) 12 Canadian cities 1981-1999	All cause	24-h avg ranged from 10 (Saint John) to 26 (Calgary) ppb.	$PM_{2.5}$, PM_{10}-2.5, O_3, SO_2, CO	1, 0-2	Poisson GLM. Time-series study.	Lag 0-2, single-pollutant: 2.0% (1.1, 2.9); with O_3: 1.8% (0.9, 2.7) Days when PM indices available, lag 1, single-pollutant: 2.4% (0.7, 4.1); with $PM_{2.5}$: 3.1% (1.2, 5.1)
Burnett et al. (2000); re-analysis (2003) 8 Canadian cities 1986-1996	All cause	24-h avg ranged from 15 (Winnipeg) to 26 (Calgary) ppb.	$PM_{2.5}$, PM_{10}, $PM_{2.5}$-10, SO_2, O_3, CO	0, 1, 0-2	Poisson GAM with default convergence criteria. Time-series study. The 2003 re-analysis did not consider gaseous pollutants.	Days when PM indices available, lag 1, single-pollutant: 3.6% (1.6, 5.7); with $PM_{2.5}$: 2.8% (0.5, 5.2)
Burnett et al. (1998a), 11 Canadian cities 1980-1991	All cause	24-h avg ranged from 14 (Winnipeg) to 28 (Calgary) ppb.	SO_2, O_3, CO	0, 1, 2, 0-1, 0-2 examined but the best lag/averaging for each city chosen	Poisson GAM with default convergence criteria. Time-series study.	Single-pollutant: 4.5% (3.0, 6.0); with all gaseous pollutants: 3.5% (1.7, 5.3)
Burnett et al. (1998b), Toronto, 1980-1994	All cause	24-h avg 25 ppb	SO_2, O_3, CO, TSP, COH, estimated PM_{10}, estimated $PM_{2.5}$	0, 1, 0-1	Poisson GAM with default convergence criteria. Time-series study.	Single-pollutant (lag 0): 1.7% (0.7, 2.7); with CO: 0.4% (-0.6, 1.5)

REFERENCE, STUDY LOCATION, AND PERIOD	OUTCOME MEASURE	MEAN NO2 LEVELS	COPOLLUTANTS CONSIDERED	LAG STRUCTURE REPORTED	METHOD/DESIGN	EFFECT ESTIMATES
Vedal et al. (2003) Vancouver, British Columbia, Canada 1994-1996	All cause; respiratory; cardiovascular	17 ppb, 24-h avg	PM_{10}, O_3, SO_2, CO	0, 1, 2	Poisson GAM with stringent convergence criteria. Time-series study. By season.	Results presented in figures only. NO2 showed associations in winter but not in summer.
Villeneuve et al. (2003) Vancouver, British Columbia, Canada 1986-1999	All cause; respiratory; cardiovascular; cancer; socioeconomic status	19 ppb, 24-h avg	$PM_{2.5}$, PM_{10}, PM_{10}-2.5, TSP, coefficient of haze, SO42-, SO_2, O_3, CO	0, 1, 0-2	Poisson GLM with natural splines. Time-series study.	All yr: All cause Lag 1: 4.0% (0.9, 7.2) Respiratory: Lag 0: 2.1% (-3.0, 7.4) Cardiovascular: Lag 0: 4.3% (-4.2, 13.4)
Goldberg et al. (2003) Montreal, Quebec, Canada 1984-1993	Congestive Heart Failure (CHF) as underlying cause of death vs. those classified as having congestive heart failure 1 yr prior to death	22 ppb, 24-h avg	$PM_{2.5}$, coefficient of haze, SO42-, SO_2, O_3, CO	0, 1, 0-2	Poisson GLM with natural splines. Time-series study.	CHF as underlying cause of death: Lag 1: 1.0% (-5.1, 7.5) Having CHF 1 yr prior to death: Lag 1: 3.4% (0.9, 6.0)
EUROPE						
Samoli et al. (2006) 30 APHEA2 cities. Study periods vary by city, ranging from 1990 to 1997	All cause, respiratory; cardiovascular	1-h max ranged from 24 (Wroclaw) to 81 (Milan) ppb	BS, PM_{10}, SO_2, O_3	01	Poisson model with penalized splines.	All-cause: single: 1.8% (1.3, 2.2); with SO_2: 1.5% (1.0, 2.0) Cardiovascular: single: 2.3% (1.7, 3.0); with SO_2: 1.9% (1.1, 2.7) Respiratory: single: 2.2% (1.0, 3.4); with SO_2: 1.1% (-0.4, 2.6)
Samoli et al. (2005) 9 APHEA2 cities. Period not reported.	All-cause	The selected cities had 1-h max medians above 58 ppb and the third quartiles above 68.	None	01	Poisson model with either non-parametric or cubic spline smooth function in each city, and combined across cities.	No numeric estimate presented. The concentration-response was approximately linear.

REFERENCE, STUDY LOCATION, AND PERIOD	OUTCOME MEASURE	MEAN NO2 LEVELS	COPOLLUTANTS CONSIDERED	LAG STRUCTURE REPORTED	METHOD/DESIGN	EFFECT ESTIMATES
Touloumi et al. (1997) Six European cities: London, Paris, Lyon, Barcelona, Athens, Koln. Study periods vary by city, ranging from 1977 to 1992	All cause	Ranged from 37 (Paris) to 70 (Athens) ppb, 1-h max	BS, O_3; two-pollutant models	0, 1, 2, 3, 0-1, 0-2, 0-3 (best lag selected for each city)	Poisson autoregressive. Time-series study.	All-cause: Single-pollutant model: 1.0% (0.6, 1.3); With BS: 0.5% (0.0, 0.9).
Zmirou et al. (1998) Four European cities: London, Paris, Lyon, Barcelona Study periods vary by city, ranging from 1985-1992	Respiratory; cardiovascular	Ranged from 24 (Paris) to 37 (Athens) ppb in cold season and 23 (Paris) to 37 (Athens) ppb in warm season, 24-h avg	BS, TSP, SO_2, O_3	0, 1, 2, 3, 0-1, 0-2, 0-3 (best lag selected for each city)	Poisson GLM. Time-series study.	Western Europe: Respiratory: 0.0% (-1.1, 1.1) Cardiovascular: 0.8% (0.0, 1.5)
Biggeri et al. (2005) 8 Italian cities, Period variable between 1990-1999	All cause; respiratory; cardiovascular	24-h avg ranged from 30 (Verona) to 51 (Rome) ppb	Only single-pollutant models; O_3, SO_2, CO, PM_{10}	0-1	Poisson GLM. Time-series study.	All cause: 3.6% (2.3, 5.0) Respiratory: 5.6% (0.2, 11.2) Cardiovascular: 5.1% (3.0, 7.3)
Anderson et al. (1996) London, England 1987-1992	All cause; respiratory; cardiovascular	37 ppb, 24-h avg	BS, O_3, SO_2; two-pollutant models	0, 1	Poisson GLM. Time-series study.	All cause (Lag 1): 0.6% (-0.1, 1.2); Respiratory (lag 1): -0.7% (-2.3, 1.0) Cardiovascular: 0.5% (-0.4, 1.4)
Bremner et al. (1999) London, England 1992-1994	All cause; respiratory; cardiovascular; all cancer; all others; all ages; age specific (0-64, 65+, 65-74, 75+ yrs)	34 ppb, 24-h avg	BS, PM_{10}, O_3, SO_2, CO; two-pollutant models	Selected best from 0, 1, 2, 3, (all cause); 0, 1, 2, 3, 0-1, 0-2, 0-3 (respiratory, cardiovascular)	Poisson GLM. Time-series study.	All cause (lag 1): 0.9% (0.0, 1.9) Respiratory (lag 3): 1.9% (-0.3, 4.2) Cardiovascular (lag 1): 1.9% (0.6, 3.2)
Anderson et al. (2001) West Midlands region, England 1994-1996	All cause; respiratory; cardiovascular.	37 ppb, 1-h max	PM_{10}, $PM_{2.5}$, $PM_{2.5}$-10, BS, SO42-, O_3, SO_2, CO	0-1	Poisson GAM with default convergence criteria. Time-series study.	All cause: 1.7% (-0.5, 3.8) Respiratory: 3.3% (-1.9, 8.8) Cardiovascular: 3.1% (-0.2, 6.4)
Prescott et al. (1998) Edinburgh, Scotland 1992-1995	All cause; respiratory; cardiovascular; all ages; age <65 yrs; age ≥ 65 yrs	26 ppb, 24-h avg	BS, PM_{10}, O_3, SO_2, CO; two-pollutant models	0	Poisson GLM. Time-series study.	Results presented as figures only. Essentially no associations in all categories. Very wide confidence intervals.

REFERENCE, STUDY LOCATION, AND PERIOD	OUTCOME MEASURE	MEAN NO2 LEVELS	COPOLLUTANTS CONSIDERED	LAG STRUCTURE REPORTED	METHOD/DESIGN	EFFECT ESTIMATES
Le Tertre et al. (2002) Le Havre, Lyon, Paris, Rouen, Strasbourg, and Toulouse, France Study periods vary by city, ranging from 1990-1995	All cause; respiratory; cardiovascular	Ranged from 15 (Toulouse) to 28 (Paris) ppb, 24-h avg	BS, O_3, SO_2	0-1	Poisson GAM with default convergence criteria. Time-series study.	Six-city pooled estimates: All cause: 2.9% (1.6, 4.2) Respiratory: 3.1% (-1.7, 8.0) Cardiovascular: 3.5% (1.1, 5.9)
Zeghnoun et al. (2001) Rouen and Le Havre, France 1990-1995	All cause; respiratory; cardiovascular	24-h avg 18 ppb in Rouen; 20 ppb in Le Havre	SO_2, BS, PM13, O_3	0, 1, 2, 3, 0-3,	Poisson GAM with default convergence criteria. Time-series study.	All cause in Rouen (lag 1): 5.5% (0.2, 11.1) ; in Le Havre (lag 1): 2.4% (-3.4, 8.5)
Dab et al. (1996) Paris, France 1987-1992	Respiratory	24 ppb, 24-h avg	BS, PM13, O_3, SO_2, CO	0	Poisson autoregressive. Time-series study.	Lag1: 2.1% (3.1, 7.7)
Zmirou et al. (1996) Lyon, France 1985-1990	All cause; respiratory; cardiovascular; digestive	37 ppb, 24-h avg	PM13, SO_2, O_3	Selected best from 0, 1, 2, 3	Poisson GLM. Time-series study.	All cause (lag 1): 1.5% (-1.5, 4.6) Respiratory (lag 2): -2.3% (-15.6, 13.0) Cardiovascular (lag 1): 0.8% (-2.7, 4.3)
Sartor et al. (1995) Belgium Summer 1994	All cause; age <65 yrs; age 65+ yrs	24-h avg NO2: Geometric mean: During heat wave (42 day period): 17 ppb Before heat wave (43 day period): 15 ppb After heat wave (39 day period): 13 ppb	TSP, NO, O_3, SO_2	0, 1, 2	Log-linear regression for O_3 and temperature. Time-series study.	Only correlation coefficients presented for NO2. Unlike O_3, NO2 was not particularly elevated during the heat wave.
Hoek et al. (2000); reanalysis Hoek, (2003) The Netherlands: entire country, four urban areas 1986-1994	All cause; COPD; pneumonia; cardiovascular	24-h avg median: 17 ppb in the Netherlands; 24 ppb in the four major cities	PM_{10}, BS, SO42-, NO_3-, O_3, SO_2, CO; two-pollutant models	1, 0-6	Poisson GAM, reanalyzed with stringent convergence criteria; Poisson GLM. Time-series study.	Poisson GLM: All cause: Lag 1: 1.9% (1.2, 2.7) Lag 0-6: 2.6% (1.2, 4.0); with BS: 1.3% (-0.9, 3.5); Cardiovascular (lag 0 6): 2.7% (0.7, 4.7). COPD (lag 0-6): 10.4% (4.5, 16.7). Pneumonia (lag 0-6): 19.9% (11.5, 29.0).

REFERENCE, STUDY LOCATION, AND PERIOD	OUTCOME MEASURE	MEAN NO2 LEVELS	COPOLLUTANTS CONSIDERED	LAG STRUCTURE REPORTED	METHOD/DESIGN	EFFECT ESTIMATES
Hoek et al. (2001); reanalysis Hoek, (2003) The Netherlands 1986-1994	Total cardiovascular; myocardial infarction; arrhythmia; heart failure; cerebrovascular; thrombosis-related	24-h avg median: 17 ppb in the Netherlands; 24 ppb in the four major cities	PM_{10}, O_3, SO_2, CO	1	Poisson GAM, reanalyzed with stringent convergence criteria; Poisson GLM. Time-series study.	Poisson GLM: Total cardiovascular: 2.7% (0.7, 4.7) Myocardial infarction: 0.3% (-2.6, 3.2) Arrhythmia: 1.7% (-6.6, 10.6) Heart failure: 7.6% (1.4, 14.2) Cerebrovascular: 5.1% (0.9, 9.6) Thrombosis-related: -1.2% (-9.6, 8.1)
Roemer and van Wijinen (2001) Amsterdam, The Netherlands 1987-1998	All cause	24-h avg: Background sites: 24 ppb Traffic sites: 34 ppb	BS, PM_{10}, O_3, SO_2, CO	1, 2, 0-6	Poisson GAM with default convergence criteria (only one smoother). Time-series study.	Total population using background sites: Lag 1: 3.8% (1.7, 5.9); Traffic pop. using background sites: Lag 1: 5.7% (0.6, 11.0); Total pop. using traffic sites: Lag 1: 1.7% (0.4, 3.0)
Verhoeff et al. (1996) Amsterdam, The Netherlands 1986-1992	All cause; all ages; age 65+ yrs	1-h max O_3: 43 µg/m^3 Max 301	PM_{10}, O_3, CO; multipollutant models NO NO2!!!	0, 1, 2	Poisson. Time-series study.	1-h max O_3 (per 100 µg/m^3) All ages: Lag 0: 1.8% (-3.8, 7.8) Lag 1: 0.1% (-4.7, 5.1) Lag 2: 4.9% (0.1, 10.0)
Fischer et al. (2003) The Netherlands, 1986-1994	All-cause, cardiovascular, COPD, and pneumonia in age groups <45, 45-64, 65-74, 75+	24-h avg median 17 ppb	PM_{10}, BS, O_3, SO_2, CO	0-6	Poisson GAM with default convergence criteria. Time-series study.	Cardiovascular: Age <45: -1.3% (-13.0, 12.1): age 45-64: -0.4% (-4.8, 4.3); age 65 74: 4.4% (0.8, 8.0); age 75 and up: 3.5% (1.4, 5.6)
Spix and Wichman (1996) Koln, Germany 1977-1985	All-cause	24-h avg 24 ppb; 1-h max 38 ppb	TSP, PM7, SO_2	0, 1, 0-1	Poisson GLM. Time-series study.	Lag 1: 0.4% (-0.4, 1.2)

REFERENCE, STUDY LOCATION, AND PERIOD	OUTCOME MEASURE	MEAN NO2 LEVELS	COPOLLUTANTS CONSIDERED	LAG STRUCTURE REPORTED	METHOD/DESIGN	EFFECT ESTIMATES
Peters et al. (2000b) NE Bavaria, Germany 1982-1994 Coal basin in Czech Republic 1993-1994	All cause; respiratory; cardiovascular; cancer	24-h avg: Czech Republic: 17.6 ppb Bavaria, Germany: 13.2 ppb	TSP, PM_{10}, O_3, SO_2, CO	0, 1, 2, 3	Poisson GLM. Time-series study.	Czech Republic: All cause: Lag 1: 2.1% (-1.7, 6.1) Bavaria, Germany: All cause: Lag 1: -0.1% (-3.6, 3.6)
Michelozzi et al. (1998) Rome, Italy 1992-1995	All-cause	24-h avg 52 ppb	PM13, SO_2, O_3, CO	0, 1, 2, 3, 4	Poisson GAM with default convergence criteria. Time-series study.	Lag 2: all-yr: 1.6% (0.4, 2.9); Cold season 0.3% (-1.2, 1.8); Warm season: 4.2% (1.8, -6.6)
Pönkä et al. (1998) Helsinki, Finland 1987-1993	All cause; cardiovascular; age <65 yrs, age 65+ yrs	24-h avg: Median 20 ppb	TSP, PM_{10}, O_3, SO_2	0, 1, 2, 3, 4, 5, 6, 7	Poisson GLM. Time-series study.	No risk estimate presented for NO2. PM_{10} and O_3 were reported to have stronger associations.
Saez et al. (2002) Seven Spanish cities, variable study periods between 1991 and 1996.	All cause; respiratory; cardiovascular	24-h avg mean ranged from 17 ppb in Huelva to 35 ppb in Valencia.	O_3, PM, SO_2, CO	0-3	Poisson GAM with default convergence criteria. Time-series study.	All cause: 2.6% (1.6, 3.6); with all other poll.: 1.7% (0.0, 3.3); Respiratory: 7.1% (-14.0, 33.5) Cardiovascular: 4.4% (-0.2, 9.2)
Garcia-Aymerich et al. (2000) Barcelona, Spain 1985-1989	All cause; respiratory; cardiovascular; general population; patients with COPD	Levels not reported.	BS, O_3, SO_2	Selected best avg lag	Poisson GLM. Time-series study.	All cause: General population: Lag 0-3: 3.3% (0.8, 5.8) COPD patients: Lag 0-2: 10.9% (0.4, 22.6) Respiratory: General population: Lag 0-1: 3.3% (-2.3, 9.2) COPD patients: Lag 0-2: 12.1% (-4.3, 31.4) Cardiovascular: General population: Lag 0-3: 2.4% (-0.9, 5.8) COPD patients: Lag 0-2: 4.3% (-13.6, 25.8)

REFERENCE, STUDY LOCATION, AND PERIOD	OUTCOME MEASURE	MEAN NO2 LEVELS	COPOLLUTANTS CONSIDERED	LAG STRUCTURE REPORTED	METHOD/DESIGN	EFFECT ESTIMATES
Saez et al. (1999) Barcelona, Spain 1986-1989	Asthma mortality; age 2-45 yrs	Levels not reported.	BS, O_3, SO_2	0-2	Poisson with GEE. Time-series study.	RR = 4.1 (0.5, 35.0)
Sunyer et al. (1996) Barcelona, Spain 1985-1991	All cause; respiratory; cardiovascular; all ages; age 70+ yrs	1-h max: Median: Summer: 51 ppb Winter: 46 ppb	BS, SO_2, O_3	Selected best single-day lag	Autoregressive Poisson. Time-series study.	All yr, all ages: All cause: Lag 1: 1.9% (0.8, 3.1) Respiratory: Lag 0: 1.5% (-1.9, 5.0) Cardiovascular: Lag 1: 2.2% (0.5, 3.9) Summer risk estimates larger than winter risk estimates.
Sunyer and Basagāna (2001) Barcelona, Spain 1990-1995	Mortality in a cohort of patients with COPD	Mean not reported IQR 8.9 ppb 24-h avg	PM_{10}, O_3, CO	0-2	Conditional logistic (case-crossover)	7.8% (-2.0, 18.6) with PM_{10}: 3.9% (-12.0, 22.5)
Sunyer et al. (2002) Barcelona, Spain 1986-1995	All cause, respiratory, and cardiovascular mortality in a cohort of patients with severe asthma	1-h max: median 47 ppb; 24-h avg median 27 ppb	PM_{10}, BS, SO_2, O_3, CO, pollen	0-2	Conditional logistic (case-crossover)	Odds Ratio: Patients with 1 asthma admission: All cause: 1.10 (0.80, 1.51) Cardiovascular: 1.70 (0.96, 2.99) Patients with more than 1 asthma admission: All cause: 2.14 (1.10, 4.14) Cardiovascular: 1.53 (0.46, 5.07)
Díaz et al. (1999) Madrid, Spain 1990-1992	All cause; respiratory; cardiovascular	24-h avg Levels not reported.	TSP, O_3, SO_2, CO	1, 4, 10	Autoregressive linear. Time-series study.	Only significant risk estimates were shown. For NO2, only respiratory mortality was significantly ($p < 0.05$) associated with an excess percent risk 8.5%.

REFERENCE, STUDY LOCATION, AND PERIOD	OUTCOME MEASURE	MEAN NO2 LEVELS	COPOLLUTANTS CONSIDERED	LAG STRUCTURE REPORTED	METHOD/DESIGN	EFFECT ESTIMATES
LATIN AMERICA						
Borja-Aburto et al. (1997) Mexico City 1990-1992	All cause; respiratory; cardiovascular; all ages; age <5 yrs; age >65 yrs	1-h max O_3: Median 155 ppb 8-h max O_3: Median 94 ppb 10-h avg O_3 (8 a.m.-6 p.m.): Median 87 ppb 24-h avg O_3: Median 54 ppb	TSP, SO_2, CO; two-pollutant models	0, 1, 2	Poisson iteratively weighted and filtered least-squares method. Time-series study.	1-h max O_3 (per 100 ppb): All ages:
Borja-Aburto et al. (1998) SW Mexico City 1993-1995	All cause; respiratory; cardiovascular; other; all ages; age >65 yrs	37.7 ppb, 24-h avg	$PM_{2.5}$, O_3, SO_2; two-pollutant models	0, 1, 2, 3, 4, 5, and multiday avg	Poisson GAM with default convergence criteria (only one smoother). Time-series study.	Lag 1-5: All cause: 2.3% (-1.0, 5.6); Cardiovascular: 2.8% (-3.2, 9.2); Respiratory: 4.7% (-5.1, 15.5).
Loomis et al. (1999) Mexico City 1993-1995	Infant mortality	24-h avg 38 ppb	$PM_{2.5}$, O_3	0, 1, 2, 3, 4, 5, 3-5	Poisson GAM with default convergence criteria. Time-series study.	Lag 3-5: 11.4% (2.2, 21.4); with $PM_{2.5}$: 2.9% (-10.2, 17.8)
Gouveia and Fletcher (2000b) São Paulo, Brazil 1991-1993	All ages (all cause); age <5 yrs (all cause, respiratory, pneumonia); age 65+ yrs (all cause, respiratory, cardiovascular)	1-h max: 84 ppb	PM_{10}, O_3, SO_2, CO	0, 1, 2	Poisson GLM. Time-series study.	All ages: All cause: Lag 0: -0.1% (-0.7, 0.4) Age 65+: All cause: Lag 1: 0.4% (-0.2, 1.1) Respiratory: Lag 2: 1.0% (-0.6, 2.5) Cardiovascular: Lag 1: -0.5% (-0.4, 1.3)
Pereira et al. (1998) São Paulo, Brazil 1991-1992	Intrauterine mortality	24-h avg 82 ppb	PM_{10}, O_3, SO_2, CO	0-4	Poisson GLM. Time-series study.	Single-pollutant model: 5.1% (2.8, 7.5); With other pollutants: 4.7% (1.6, 7.9)
Saldiva et al. (1994) São Paulo, Brazil 1990-1991	Respiratory; age <5 yrs	24-h avg NO_X 127 ppb	PM_{10}, O_3, SO_2, CO; multipollutant models	0-2	OLS of raw or transformed data. Time-series study.	NO_X slope estimate: 0.007197 deaths/day/ppb (SE 0.003214), p = 0.025

REFERENCE, STUDY LOCATION, AND PERIOD	OUTCOME MEASURE	MEAN NO2 LEVELS	COPOLLUTANTS CONSIDERED	LAG STRUCTURE REPORTED	METHOD/DESIGN	EFFECT ESTIMATES
Saldiva et al. (1995) São Paulo, Brazil 1990-1991	All cause; age 65+ yrs	24-h avg NO_X 127 ppb	PM_{10}, O_3, SO_2, CO; two-pollutant models	0-1	OLS; Poisson with GEE. Time-series study.	NO_X slope estimate: 0.0341 deaths/day/ppb (SE 0.0105)
Cifuentes et al. (2000) Santiago, Chile 1988-1966	All cause	8-h avg 41 ppb	$PM_{2.5}$, PM_{10}-2.5, CO, SO_2, O_3	0, 1, 2, 3, 4, 5, 1-2, 1 3, 1-4, 1-5	Poisson GAM with default convergence criteria; Poisson GLM. Time-series study.	GLM model, lag 1-2: Single-pollutant: 1.7% (0.7, 2.7); with other pollutants: 1.5% (0.3, 2.7) (per 25ppb 8-h avg)
Ostro et al. (1996) Santiago, Chile 1989-1991	All cause	1-h max 56 ppb	PM_{10}, O_3, SO_2; two-pollutant models	1	OLS, Poisson. Time-series study.	Poisson, lag 1: -0.5% (-1.1, 0)
AUSTRALIA						
Simpson Et Al. (2005a,B) Brisbane, Sydney, Melbourne, And Perth, Australia 1996-1999	All Cause, Respiratory, And Cardiovascular In All Ages; Cardiovascular In Age 65+ Yrs	1-H Max Ranged From 16 To 24 ppb	PM_{10}, $PM_{2.5}$, Bsp (Nephelometer), O_3, Co	0, 1, 2, 3, 0-1	Poisson Glm, Gam With Stringent Convergence Criteria. Time-Series Study.	Lag 0-1, Gam, All-Cause, Single-Pollutant: 3.4% (1.1, 5.7); With Bsp: 3.1% (0.3, 5.9); Cardiovascular: 4.3% (0.9, 7.8); Respiratory: 11.4% (3.5, 19.9)
Simpson et al. (2000) Brisbane, Australia 1991-1996	All cause, respiratory, and cardiovascular in all ages; cardiovascular in age 65+ yrs	24-h avg: whole yr: 12 ppb; cool season: 13 ppb; warm season 9 ppb	PM_{10}, $PM_{2.5}$, BSP, O_3, CO	0, 1, 2, 3, 0-1	Poisson, GAM with default convergence criteria. Time-series study.	All-cause (lag 1): 9.7% (4.7, 14.8); respiratory: 18.8% (1.2, 39.6)
Morgan et al. (1998b) Sydney, Australia 1989-1993	All cause; respiratory; cardiovascular	24-h avg 13 ppb; 1-h max 26 ppb	BSP, O_3	0-1	Poisson with GEE. Time-series study.	Lag 0-1, single-pollutant, all-cause: 3.0% (0.1, 6.0); cardiovascular: 2.2% (-1.7, 6.4); respiratory: 8.6% (-0.4, 18.4)
Simpson et al. (1997) Brisbane, Australia 1987-1993	All cause; respiratory; cardiovascular	24-h avg 14 ppb; 1-h max 28 ppb	PM_{10}, TSP, O_3, SO_2, CO	0	Autoregressive Poisson with GEE. Time-series study.	Lag 0-1, single-pollutant, all-cause, all-yr: -1.0% (-5.2, 3.4); summer: -3.6% (-11.2, 4.7); winter: -1.2% (-4.0, 6.9)
ASIA						
Kim et al. (2004b) Seoul, Korea 1995-1999	All cause	24-h avg 33 ppb	PM_{10}, O_3, SO_2, CO; two-pollutant models	1	Poisson GAM with stringent convergence criteria (linear model); GLM with cubic natural spline; GLM with B mode spline (threshold model). Time-series study.	Risk estimates for NO2 not reported.

REFERENCE, STUDY LOCATION, AND PERIOD	OUTCOME MEASURE	MEAN NO2 LEVELS	COPOLLUTANTS CONSIDERED	LAG STRUCTURE REPORTED	METHOD/DESIGN	EFFECT ESTIMATES
Lee et al. (1999) Seoul and Ulsan, Korea 1991-1995	All cause	1-h max O_3: Seoul: 32.4 ppb 10th %-90th % 14-55 Ulsan: 26.0 ppb 10th %-90th % 16-39	TSP, SO_2	0	Poisson with GEE. Time-series study.	1-h max O_3 (per 50 ppb): Seoul: 1.5% (0.5, 2.5) Ulsan: 2.0% (-11.1, 17.0)
Lee and Schwartz (1999) Seoul, Korea 1991-1995	All cause	1-h max O_3: Seoul: 32.4 ppb 10th %-90th % 14-55	TSP, SO_2	0	Conditional logistic regression. Case-crossover with bidirectional control sampling.	1-h max O_3 (per 50 ppb): Two controls -- 1 wk: 1.5% (-1.2, 4.2) Four controls -- 2 wks: 2.3% (-0.1, 4.8)
Kwon et al. (2001) Seoul, Korea 1994-1998	Mortality in a cohort of patients with congestive heart failure	24-h avg 32 ppb	PM_{10}, O_3, SO_2, CO	0	Poisson GAM with default convergence criteria; case-crossover analysis using conditional logistic regression.	Odds ratio in general population: 1.1% (-0.3, 2.5) Congestive heart failure cohort: 15.8% (1.8, 31.7)
Ha et al. (2003) Seoul, Korea 1995-1999	All cause; respiratory; postneonatal (1 mo to 1 yr); age 2 64 yrs; age 65+	24-h avg 33 ppb	PM_{10}, O_3, SO_2, CO	0	Poisson GAM with default convergence criteria. Time-series study.	All cause for postneonates: 0.8% (-5.7, 7.7); age 65+: 3.8% (3.7, 3.9)
Hong et al. (2002) Seoul, Korea 1995-1998	Acute stroke mortality	24-h avg 33 ppb	PM_{10}, O_3, SO_2, CO	2	Poisson GAM with default convergence criteria. Time-series study.	4.3% (1.6, 7.0)
Tsai et al. (2003b) Kaohsiung, Taiwan 1994-2000	All cause; respiratory; cardiovascular; tropical area	24-h avg 29 ppb	PM_{10}, SO_2, O_3, CO	0-2	Conditional logistic regression. Case-crossover analysis.	Odds ratios: All cause: 0.1% (-5.9, 6.6); Respiratory: -1.0% (-22.2, 25.9); Cardiovascular: -1.8% (-14.0, 12.1)
Yang et al. (2004b) Taipei, Taiwan 1994-1998	All cause; respiratory; cardiovascular; subtropical area	24-h avg 31 ppb	PM_{10}, SO_2, O_3, CO	0-2	Conditional logistic regression. Case-crossover analysis.	Odds ratios: All cause: 0.6% (-3.9, 5.2); Respiratory: 2.5% (-13.1, 20.8); Cardiovascular: -1.1% (-9.5, 8.0)

REFERENCE, STUDY LOCATION, AND PERIOD	OUTCOME MEASURE	MEAN NO2 LEVELS	COPOLLUTANTS CONSIDERED	LAG STRUCTURE REPORTED	METHOD/DESIGN	EFFECT ESTIMATES
Wong et al. (2001b) Hong Kong 1995-1997	All cause; respiratory; cardiovascular	24-h avg 25 ppb in warm season; 33 ppb in cold season	PM_{10}, O_3, SO_2; two-pollutant models	0, 1, 2	Poisson GAM with default convergence criteria. Time-series study.	All cause (lag 1): 2.6% (0.9, 4.4); Respiratory (lag 0): 6.1% (-1.8, 10.5); Cardiovascular (lag 2): 5.2% (1.8, 8.7)
Wong et al. (2002) Hong Kong 1995-1998	Respiratory; cardiovascular; COPD; pneumonia and influenza; ischemic heart dis.; cerebrovascular	24-h avg 29 ppb	PM_{10}, O_3, SO_2; two-pollutant models	0, 1, 2, 0-1, 0-2	Poisson GLM. Time-series study.	Respiratory (0-1): 5.1% (1.6, 8.7); Cardiovascular (lag 0-2): 3.1% (-0.2, 6.5)
Hedley et al. (2002) Hong Kong 1985-1995 Intervention July 1990 (switch to low sulfur-content fuel)	All cause; cardiovascular; respiratory; neoplasms and other causes; all ages; age 15-64 yrs; age 65+ yrs	Avg moly NO2: Baseline: 29 ppb 1 yr after intervention: 25 ppb 2-5 yrs after intervention: 28 ppb	SO_2 (main pollutant of interest, 45% reduction observed 5 yrs after intervention), PM_{10}, SO42-, NO2	Moly avgs considered without lags	Poisson regression of moly avgs to estimate changes in the increase in deaths from warm to cool season. Annual proportional change in death rate before and after the intervention was also examined.	Declines observed in all cause (2.1%, p = 0.001), respiratory (3.9%, p = 0.001), and cardiovascular (2.0%, p = 0.020) mortality after the intervention. As NO2 levels did not change before and after the intervention, NO2 likely did not play a role in the decline in observed mortality.
Yang et al. (2004b) Taipei, Taiwan 1994-1998	All cause; respiratory; cardiovascular; subtropical area	24-h avg 31 ppb	PM_{10}, SO_2, O_3, CO	0-2	Conditional logistic regression. Case-crossover analysis.	Odds ratios: All cause: 0.6% (-3.9, 5.2); Respiratory: 2.5% (-13.1, 20.8); Cardiovascular: -1.1% (-9.5, 8.0)

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